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A PAT approach for the on-line monitoring of pharmaceutical co-crystals formation with near infrared spectroscopy

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ABSTRACT

Cocrystals represent a class of crystalline solids consisting of two or more molecular species usually held together by non-covalent bonds. Pharmaceutical cocrystals can alter the physicochemical properties of the active pharmaceutical ingredient to improve solubility, dissolution rate, particle properties and stability. This work presents a process analytical technology (PAT) approach to monitor on-line the cocrystallization of furosemide and adenine by solvent evaporation using near infrared spectroscopy (NIRS). Furosemide and adenine were added to a small volume of methanol in a beaker and stirred on an orbital stirring table during 8 h at room temperature. The on-line monitoring was performed with a FT-NIR spectrometer fitted with a reflectance fiber optic probe. Monitoring was performed with the probe tip placed 1 cm above the cocrystallization medium to avoid interference with the cocrystallization process. Cocrystals were vacuum dried to remove residual solvent and characterized off-line by NIRS, MIRS, DSC and XRPD. Results demonstrate that it was possible to follow the main cocrystallization events on-line.

1. Introduction

For commercial purposes, pharmaceutical drugs in crystalline form are strongly preferred because they tend to be more stable, reproducible, amenable to purification and easier to scale than other type of solids (Arenas-Garcia et al., 2010; Cheney et al., 2010). However, in general crystalline drugs have poor solubility and bioavailability. Nowadays, more than 80% of the marketed pharmaceutical drugs are solids, most of them produced as tablets. Among these, 40% are known to have poor solubility properties. More alarming, almost 80–90% of the drug molecules at advanced stages of drug development will present solubility problems. In this context, poor aqueous solubility is a major bottleneck in the development of pharmaceutical formulations based on these drugs (Goud et al., 2012). There are several methods that can be used to increase the solubility of drugs, such as complexation (Agarwal et al., 2008), micronization (De Zordi et al., 2012), the use of lipid based formulations (Zvonar et al., 2010), among others. Modifying the drug solid state can also increase solubility. The modification can be made by producing different polymorphic forms, hydrates, solvates, salts or cocrystals (Babu et al., 2010).

Pharmaceutical cocrystals are defined as molecular complexes comprised by an active pharmaceutical ingredient (API) and one cocrystal former, both solids at room temperature. Pharmaceutical coformers are normally referred to as considered generally as safe (GRAS) compounds which do not affect the pharmacological activity of the API (Aitipamula et al., 2010). Pharmaceutical cocrystals are interesting to the pharmaceutical industry since they offer a number of opportunities to modify the chemical and/or physical properties of an API without changing its structure. In this way it is possible to improve the drug physicochemical and mechanical properties as well as in vivo performance such as bioavailability (Alleso et al., 2008; Basavoju et al., 2006). The investigation of cocrystals is particularly attractive since many APIs contain functional groups predisposed to hydrogen bonding that can be exploited to form pharmaceutical cocrystals. Additionally, there are several processes, including solvent crystallization, grinding and melt crystallization that can be used to produce a large range of cocrystals from a specific API.

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Cocrystallization is the process by which a cocrystal is obtained. Understanding and controlling the cocrystallization process is critical to produce a cocrystal with highly reproducible solid state properties. The United State Food and Drug Administration (FDA) has been encouraging process innovation in the pharmaceutical industry through better process understanding by using new technologies to perform timely measurements of critical quality attributes with concepts such as quality-by-design (QbD) and process analytical technology (PAT) (Kelly et al., 2012; Schaefer et al., 2013). Near infrared spectroscopy (NIRS) has become a widely used analytical technique in the pharmaceutical industry due to its many advantages such as: measurements speed, non-destructive nature, virtually no sample preparation requirements and simultaneous capture of chemical and physical information (Bakeev, 2005; De Beer et al., 2011; Sarraguça and Lopes, 2009). Adding to these advantages, fiber optic probes can be used allowing remote measurements. This technique can be used for the real time monitoring of cocrystals formation and solvent evaporation, targeting at the accurate estimation of the seeding point therefore increasing and optimizing the process efficiency.

However, there are not many reported applications of NIRS in cocrystallization processes. The most relevant reported work was the monitoring of ibuprofen–nicotinamide cocrystals formation by extrusion based solvent free continuous crystallization (Kelly et al., 2012).

This study provides a strategy for the implementation of NIRS as a PAT tool for the on-line monitoring of cocrystallization by solvent evaporation processes. The cocrystallization of furosemide with adenine using methanol as solvent was monitored on-line with NIRS resourcing to a fiber optic diffuse reflectance probe.

Furosemide is a widely potent loop diuretic applied in the pharmacotherapy of edematous states associated with hypertension, heart failure, renal failure, nephritic syndrome and cirrhosis (Agarwal et al., 2008; Garnero et al., 2013). Furosemide is a class IV drug in the Biopharmaceutical Classification System (BCS) that has a low solubility (6 mg/L) and poor bioavailability (60–65%) (Ambrogi et al., 2012a,b; Meka et al., 2009). Therefore, furosemide is a good candidate to form cocrystals with improved solubility (Goud et al., 2012; Ueto et al., 2012).

Adenine is a nucleobase with several uses in biochemistry (McHugh and Erxleben, 2011). It is an integral part of both DNA and RNA. Whilst there is limited previous research into adenine complexes, it has been identified as a good cocrystal former (Goud et al., 2012) as it contains a number of strong hydrogen bond donor and acceptor sites and is known to form crystalline complexes, for example with metal ions (Garcia-Teran et al., 2004).

2. Materials and methods

2.1. Process description

Furosemide (p.a. > 98.0%) and adenine (p.a. > 99.9%) were purchase from Sigma–Aldrich. Methanol was HPLC grade and was purchase from Prolab.

The cocrystallization between furosemide and adenine was made by the solvent evaporation method. A 1:1 molar ratio of furosemide (110.0 mg) and adenine (40.00 mg) were added to 8 mL of methanol in a beaker and stirred at 150 rpm in an orbital stirring table during 8 h at room temperature until complete solvent evaporation.

For the on-line monitoring, the tip of a reflectance NIR probe was fixed 1 cm above the cocrystallization medium, in this way the probe did not interfere whatsoever with the cocrystallization process. A NIR spectrum was taken every 5 min over 8 h totalizing 97 NIR spectra per batch. A total of six cocrystallization batches were followed.

Additionally to the cocrystallization batches, two recrystallization batches of furosemide and two recrystallization batches of adenine with methanol were monitored following the same strategy. The goal was the comparison of recrystallized furosemide and adenine with the produced cocrystals when subjected to the same experimental conditions.

Formed cocrystals and crystals were vacuum dried over 1 h to remove any residual solvent. Dried products were characterized by NIRS, mid infrared spectroscopy (MIRS), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

2.2. Near infrared spectroscopy

NIR spectra were recorded on a Fourier transform NIR analyzer (FTLA2000, ABB, Québec, Canada) equipped with an Indium-gallium-arsenide (InGaAs) detector.

For the on-line monitoring, a reflectance probe (SabIR, Thermo Nicolet, Madison, USA) with an illumination area with a diameter of 0.5 cm was used. Each NIR spectrum was recorded over a wavenumber interval between 10,000 cm^{-1} and 4000 cm^{-1}, with resolution and number of scans set to 8 cm^{-1} and 64, respectively.

Off-line NIRS measurements were obtained with a powder sampling accessory (ACC101, ABB, Québec, Canada) enabling diffuse reflectance measurements on a 6 mm diameter sample illumination area. In this case, resolution was set to 2 cm^{-1} over the same wavenumber range and number of scans.

The instrument was controlled via the Bomem Grams software (version 7, ABB). At the beginning of each set of measurements a background spectrum was taken by placing a 100% reflectance reference material PTFE (Teflon) over the probe tip or powder accessory window.

2.3. Mid infrared spectroscopy

Mid infrared spectra were acquired using a FTIR system spectrophotometer (Frontier, PerkinElmer, Beaconsfield, UK) in the ATR mode with an ATR accessory (PerkinElmer) from 4000 to 600 cm^{-1} and a resolution of 4 cm^{-1} and 32 scan co-additions. The spectrometer is equipped with a mid-infrared light source and a deuterated triglycine sulphate (DTGS) detector. The ATR accessory has a pressure arm with force indicator that allows good contact of the sample with the diamond crystal and sample-to-sample reproducibility. Samples were directly applied on the ATR crystal and the same force was always applied in each measurement. For each sample three spectra were taken and the average spectrum considered.

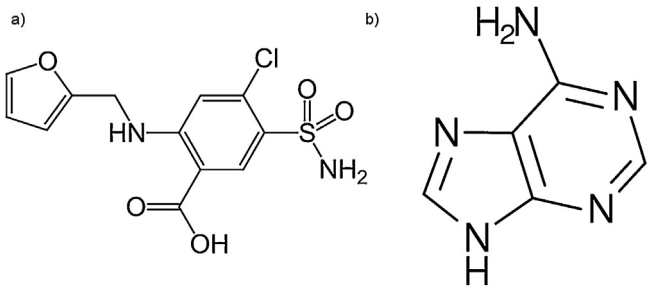

Fig. 1. Molecular structures of (a) furosemide and (b) adenine.

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