Batch Statistical Process Monitoring Approach to a Cocrystallization Process

MAFALDA C. SARRAGUÇA,[1] PAULO R. S. RIBEIRO,[1] ADENILSON O. DOS SANTOS,[2] JOÃO A. LOPES[3]

[1]LAQV/REQUIMTE, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313, Portugal

[2]Centro de Ciências Sociais, Saúde e Tecnologia, Universidade Federal do Maranhão (UFMA), Imperatriz CP:65.900-410, MA, Brazil

[3]iMed, Departamento de Farmácia Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, Lisboa 1649-003, Portugal

ABSTRACT: Cocrystals are defined as crystalline structures composed of two or more compounds that are solid at room temperature held together by noncovalent bonds. Their main advantages are the increase of solubility, bioavailability, permeability, stability, and at the same time retaining active pharmaceutical ingredient bioactivity. The cocrystallization between furosemide and nicotinamide by solvent evaporation was monitored on-line using near-infrared spectroscopy (NIRS) as a process analytical technology tool. The near-infrared spectra were analyzed using principal component analysis. Batch statistical process monitoring was used to create control charts to perceive the process trajectory and define control limits. Normal and non-normal operating condition batches were performed and monitored with NIRS. The use of NIRS associated with batch statistical process models allowed the detection of abnormal variations in critical process parameters, like the amount of solvent or amount of initial components present in the cocrystallization. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4099–4108, 2015

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INTRODUCTION

Cocrystals are an innovative approach to develop pharmaceutical solid forms that can be defined as a multicomponent crystalline structure different from the precursor compounds held together by noncovalent interactions.[1–3] Cocrystals can have enhanced properties comparing with the active pharmaceutical ingredient (API) such as solubility, bioavailability, melting point, hygroscopicity, processability, and physical and/or chemical stability.[4] Adding to the aforementioned advantages, the API bioactivity is maintained and there are possible additional nutritional or health benefits introduced by the coformer.[5]

Furosemide (Fig. 1a) is a loop diuretic drug that acts on the ascending loop of Henle in the kidney allowing the removal of unneeded water and salt from the body into the urine.[6] Furosemide has low solubility in water (0.006 mg mL^{-1}) and low permeability therefore belonging to class IV of the Biopharmaceutics Classification System.[6–8] Nicotinamide (Fig. 1b) is a member of the vitamin B complex group. It is marketed as a medication for acne vulgaris for its anti-inflammatory properties and is used as a food additive. Nicotinamide is a very popular coformer for its high solubility in water and is considered a generally regarded as safe substance.[1,5,9–17] The formation of

cocrystals between furosemide and nicotinamide was studied by Goud et al.[7] and Harriss et al.[2] Goud et al.[7] used liquid assisted grinding to produce cocrystals using acetone, obtaining a 1:1 predominant cocrystal. Harris et al.[2] dissolved furosemide and nicotinamide in ethanol and allowed slow evaporation at room temperature (also obtaining a cocrystal with a stoichiometry of 1:1). Ueto et al.[18] also studied the cocrystallization of furosemide and nicotinamide with the intent of finding cocrystal polymorphs. Five anhydrous polymorphs, one hydrate, and six solvates were found.

The ability to monitor cocrystallization on-line represents a highly useful process that aligns well with the current regulatory guidelines toward continuous monitoring and real-time quality control.[19] Guidelines such as the European Medicines Agency guideline on the use of near-infrared (NIR) spectroscopy (NIRS) in the pharmaceutical industry[20] and the Q8 (R2): Pharmaceutical Development guideline[21] from the International Conference on Harmonization that defines the concept of quality-by-design (QbD), show the importance of monitoring and controlling drug substances synthesis and pharmaceutical products manufacturing processes.

A sound cocrystallization process is the key to ensure that the final product is consistently delivered with target specifications. Critical process parameters must be kept under control in order to ensure consistency on the critical quality attributes (CQA). To achieve this, multivariate statistical process monitoring (MSPM) based on latent variable (LV) models such as principal component analysis (PCA) can be used. To develop a model for process monitoring, the first step is to acquire data that represent the normal operating conditions (NOC), that is, to obtain historical data from when the process was performing
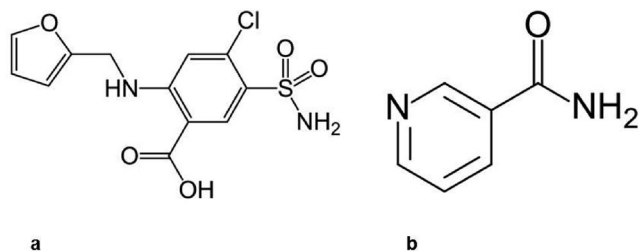
Correspondence to: João A. Lopes (Telephone: +351-217946400; Fax: +351-217946470; E-mail: jlopes@ff.ulisboa.pt)

Figure 1.   Molecular structure of (a) furosemide and (b) nicotinamide.

as expected resulting in a product that is within specification. Batch statistical process monitoring (BSPM) is the batch approach to MSPM. Differently to the continuous case, batch process retains a time-varying trajectory and limited duration. Various multivariate statistics have the potential to be utilized for LVs models-based process real-time monitoring. Hotelling's T^2 and squared prediction error (SPE) from PCA models are within the most commonly used.[22–24]

Accurate on-line measurements of CQA are essential for the successful monitoring and process control. In this context, process analytical technology (PAT) tools play a crucial role.[25–27] Vibrational spectroscopic techniques such as Raman[1] and NIRS[19,28] are good candidates to monitor on-line and in real-time cocrystallization processes because of some of their intrinsic characteristics. These methods are fast, robust, do not require sample preparation, can be easily located in a process without changing the environment and can be fitted with probes allowing a more flexible use. NIRS constitutes one of the most used PAT techniques and may also be used as part of a real-time release testing strategy. When used as such, NIRS is underpinned by the principles of QbD.

The main objective of this study is to apply NIRS and PCA as process statistical monitoring tools to monitor the cocrystallization of furosemide and nicotinamide by solvent evaporation.

Experimental

Materials and Methods

Furosemide (>98% purity) and nicotinamide (>99.5% purity) were acquired from Sigma–Aldrich (St. Louis, Missouri). Acetone (>99.5%) was acquired from Atom Scientific (Manchester, UK).

Cocrystallization of furosemide and nicotinamide was performed by the solvent evaporation method using acetone as the solvent. Equimolar quantities of furosemide (200 mg, 0.6 mmol) and nicotinamide (76.8 mg, 0.6 mmol) were weighted and added to 8 mL of acetone. The solution was stirred at 150 rpm in an orbital stirring table during 16 h until complete solvent evaporation. In total, 10 batches were made, seven of those are nominal batches, that is, were made within the NOC regarding the amounts of acetone, furosemide, and nicotinamide. From those, six were chosen to calibrate the model (B#1 to B#6) and one was used to test the model (B#7). Three non-nominal batches were made. One batch was made with half the amount of acetone (4 mL) (B#8). The other two had only one of the initial components, either furosemide or nicotinamide (B#9 and B#10).

On-Line Process Monitoring

A Fourier transform NIR analyzer (FTLA2000; ABB, Québec, Canada) was used to monitor on-line the cocrystallization process. The spectrophotometer is equipped with an indium–gallium–arsenide (InGaAs) detector. The measurements were made in diffuse reflectance mode using a stainless steel diffuse reflectance probe (SabIR; ThermoNicolet, Madison, Wisconsin) with a 1 cm diameter sapphire window enabling a 0.20 cm^2 illumination area. The spectrum was acquired with a resolution of 8 cm^{-1} over a wavenumber interval between 10,000 and 4000 cm^{-1} as an average of 64 scans. The instrument is controlled via the Grams LT software (version 7; ABB). A background was made before each batch by placing a 100% reflectance certified material (Labsphere, North Sutton, New Hampshire) over the probe tip.

To monitor the process, the probe was set 1 cm over the cocrystallization medium in order to not interfere with the process. A NIR spectrum was taken every 5 min during 16 h, totalizing 193 spectra per batch. All spectra were pre-processed with standard normal variate (SNV) for further analysis.

Product Characterization

Formed cocrystals and crystals were vacuum dried over 1.5 h to remove any residual free solvent. Dried products were characterized by NIRS, mid-infrared (MIR) spectroscopy (MIRS), X-ray powder diffraction (XRPD), and differential scanning calorimetry (DSC).

Near-Infrared Spectroscopy

For the off-line measurements, a Fourier transform NIR analyzer (FTLA2000, ABB, Québec, Canada) was used. The spectrophotometer is equipped with an InGaAs detector and powder sampling accessory (ACC101; ABB) with a 2 cm diameter window enabling diffuse reflectance measurements on a 0.28 cm^2 illumination area. The spectrum was acquired with a resolution of 2 cm^{-1} as an average of 64 spectra in the wavenumber range between 10,000 and 4000 cm^{-1}. The instrument was controlled via the Grams LT software (version 7; ABB). A background was made by using 100% reflectance certified material (polytetrafluoroethylene) (SKG8613G; ABB). For each sample, three spectral replicates were made and the average spectrum considered.

Mid-Infrared Spectroscopy

Mid-infrared spectra were acquired by a Fourier transform spectrophotometer (Frontier; PerkinElmer, Beaconsfield, UK) using an attenuated total reflectance (ATR) accessory (PerkinElmer). Each spectrum was an average of 32 scans with a resolution of 4 cm^{-1} over a wavenumber interval between 4000 and 600 cm^{-1}. The spectrophotometer is equipped with a MIR light source and a deuterated triglycine sulfate detector. The ATR accessory has a pressure arm with force indicator that allows optimal 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 applied in each measurement. The instrument is controlled via the Spectrum software (PerkinElmer). A background was made with the ATR accessory empty. For each sample, three replicates were taken and the average spectrum was considered.