Journal of Pharmaceutical and Biomedical Analysis 89 (2014) 166–175

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Evaluation of analytical tools and multivariate methods for quantification of co-former crystals in ibuprofen-nicotinamide co-crystals

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ARTICLE INFO

Article history:
Received 16 August 2013
Received in revised form 29 October 2013
Accepted 1 November 2013
Available online 15 November 2013

Keywords:
Co-crystal
Ibuprofen-nicotinamide
Solid state analytical techniques
Multivariate analysis
Partial least squares (PLS)

ABSTRACT

Co-crystals are multicomponent substances designed by the addition of two or more different molecules in a same crystallographic pattern, in which it differs from the crystallographic motif of its co-formers. The addition of highly soluble molecules, like nicotinamide, in the crystallographic pattern of ibuprofen enhances its solubility more than 7.5 times, improving the properties of this widely used drug. Several analytical solid state techniques are used to characterize the ibuprofen-nicotinamide co-crystal, being the most used: mid-infrared (ATR-FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRPD) and Raman spectroscopy. These analytical solid state techniques were evaluated to quantify a mixture of ibuprofen-nicotinamide co-crystal and its co-formers in order to develop a calibration model to evaluate the co-crystal purity after its synthesis. Raman spectroscopy showed better result than all other techniques with a combination of multivariate calibration tools, presenting lower values of calibration and prediction errors. The partial least squares regression model gave a mean error lower than 5% for all components presented in the mixture. DSC and mid-infrared spectroscopy proved to be insufficient for quantification of the ternary mixture. XRPD presented good results for quantification of the co-formers, ibuprofen and nicotinamide, but fair results for the co-crystal. This is the first report of quantification of ibuprofen-nicotinamide co-crystal, among its co-formers. The quantification is of great importance to determine the yield of the co-crystallization reactions and the purity of the product obtained.

1. Introduction

The pharmaceutical industry became more interested in solid state analytical techniques due to the discovery of different crystalline forms for the same active pharmaceutical ingredient (API) [1]. These techniques have become necessary for correct characterization of the API and drug development, and they are usually used when it is necessary to obtain information concerning the crystallographic form of the active pharmaceutical ingredient [2].

Co-crystals are multicomponent molecular crystals that are present in solid state at room temperature, and have a crystallographic pattern distinct from its precursor compounds [3]. In recent years, the co-crystals have been studied as an alternative method to improve the solubility and bioavailability of some API without changing its stability [4].

The ibuprofen [$C_{13}H_{18}O_2$ – (RS)-2-(4-(2-methylpropyl)phenyl) propanoic acid] is a non-steroidal anti-inflammatory drug largely used as antipyretic, analgesic and in the arthritis treatment. It presents an asymmetric carbon, and can assume two distinct isomeric forms, being the S enantiomer the only isomer active in the body [5]. Despite this, the pharmaceutical product presents both forms, so ibuprofen co-crystals have been studied by either racemic mixture or pure (S) isomer [6]. Ibuprofen have a carboxylic group which enables a heterosynthon bond with other drugs that presents amide groups or nitrogen in aromatic rings [7].

Nicotinamide [$C_6H_6N_2O$ – pyridine-3-carboxamide] or niacinamide is an amide produced in vivo from the nicotinic acid (vitamin B3). It is a molecule of the vitamin B group that presents high solubility in water [8]. In its molecular structure, it presents an amide group and a pyridine ring that enables a heterosynthon formation with the carboxylic group of the ibuprofen [9].

Some studies have shown that the interaction between nicotinamide molecules in the crystallographic motif of ibuprofen changes its bioavailability and mechanic stability [10]. Solubility tests have indicated that the solubility of ibuprofen-nicotinamide co-crystal (IBP-NCT) is 7.5 times higher than the solubility of the pure ibuprofen crystal [4].

Several characterization methods were used to characterize the ibuprofen-nicotinamide co-crystal: thermogravimetric analysis (TGA) [10], differential scanning calorimetry (DSC) [4,10–13],

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http://dx.doi.org/10.1016/j.jpba.2013.11.005

powder (XRPD) [4,7,9–13] and single crystal X-ray diffraction (SCXRD) [7,9], mid infrared (FTIR) [4,7,10] and near infrared spectroscopy (NIR) [14], solid state nuclear magnetic resonance (SS-NMR) [4,11], optical microscopy [9] and scanning electron microscopy (SEM) [12].

However, no work in the literature has studied the quantification of ibuprofen-nicotinamide co-crystal in the presence of its co-formers. Such a study is of great importance, because it is possible to determine the fraction of its precursors that were not converted to co-crystals [15]. Then, in this study, four different analytical solid state techniques were used to evaluate the best tool to quantify the co-crystal among its co-formers. The instruments most used for the quantification and characterization of pharmaceutical products: DSC, FTIR, XRPD and Raman [16,17].

The differential scanning calorimetry is a characterization method based on the heat of reaction involved in different thermal events. For the pharmaceutical industry, the DSC is mostly used to obtain melting points of the API and thus, determine its purity [4]. For the co-crystal analysis, there is a clear difference between the melting point of the co-formers and the co-crystal itself. It is a technique that can be used for qualitative and quantitative analysis, because the heat of the reaction is directly proportional to the mass quantity of the compound analyzed [18]. However, by being a destructive technique, the thermal events that occur with the material can interfere in quantitative measurements, essentially on polymorphs and co-crystals.

The X-ray diffraction is one of the most used techniques to determine different crystalline structures [19]. This technique can distinguish the presence of a new crystallographic motif, which can be a polymorph or a co-crystal [20]. It is a non-destructive method and presents diffractions patterns unique for each structure. However, it is a challenging method to implement in PAT systems. Besides, the quantitative analysis can only be made with the internal standard addition method or by mixture analysis, and its data can present problems due to preferential orientation and different crystal granulometry, which make the quantitative analysis difficult to perform [16].

The infrared spectroscopy, like the Raman spectroscopy, presents a great quantity of information about the chemical bonds and interaction [21,22]. It is a fast analysis method, non-destructive and when coupled with ATR (attenuated total reflectance) accessories, needs no sample preparation [23]. Still, analyses using KBr pellets can induce polymorphic transitions or other transformations in solid state due to the high pressure applied to make the pellets.

Raman spectroscopy is an alternative method to identify crystalline arrays of several pharmaceutical drugs [24]. It is a quick technique, non-destructive, presents much chemical information and lower detection limits when compared to XRPD and DSC [25]. However, the fluorescence phenomena can make the analysis of some samples difficult, and micro-Raman usually presents a small laser spot, leading to sampling problems [26].

Some instrumental techniques that present no selectivity, such as XRPD, DSC, FTIR and Raman, usually need multivariate calibration models [15]. Partial least squares (PLS) is a multivariate tool widely used for quantification [27,28]. The PLS is based on a bilinear decomposition of a matrix X (sample data matrix). The latent variables obtained by the matrix X decomposition are distorted in a way to obtain the highest correlation possible with the Y response matrices [29]. Thus, calibration curves are constructed to quantify unknown samples. This model presents advantages over other chemometric calibration tools because PLS considers the information contained in the matrix of responses, Y.

Therefore, the objective of this work is the development of calibration models using multivariate chemometric tools and several characterization techniques: DSC, XRPD, ATR-FTIR and Raman to quantify the co-crystal of ibuprofen-nicotinamide among its forming components.

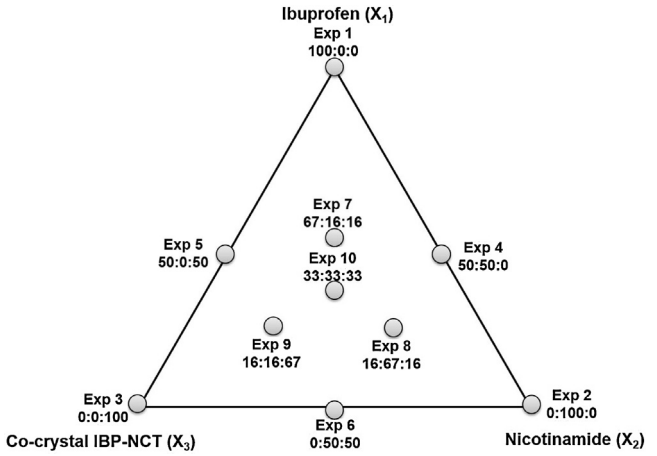

Fig. 1. Mixture design for the calibration curve.

2. Experimental

2.1. Synthesis of IBP-NCT "standard" co-crystal

To synthetize the co-crystal, the methodology developed by Friščič and Jones, and later, used by Berry et al. [9,13] was followed. The procedure is based on complete solubilization of the co-formers in a volatile solvent. The co-crystal grows when all the solvent evaporates. Ibuprofen was used from IOL Chemicals and Pharmaceuticals Ltd., nicotinamide from Aarti Drugs Limited and Methanol, P.A. grade from Quemis.

To obtain 1 mmol of co-crystal, 1 mmol of ibuprofen (206.3 mg), 1 mmol of nicotinamide (122.4 mg) and 1 mL of methanol are necessary. The co-crystal was obtained after complete evaporation of the solvent. The product was characterized by Raman spectroscopy, mid infrared, powder X-ray diffraction (XRPD) and differential scanning calorimetry (DSC). Due to the results obtained from these techniques, which indicated the high pureness of the co-crystal, the product was used as a standard co-crystal.

2.2. IBP-NCT co-crystal quantification

For each sample, different amounts of co-crystal, ibuprofen and nicotinamide were weighed and mixed on a recipient using a vortex, without further sample preparation. A ternary mixture design was used in the preparation of the calibration samples for each analytical technique. The mixture design provided 6 levels of variation for each component resulting in 10 experiments. Fig. 1 illustrates the mixture design used, where each component varies from 0 to 100%, such that:

$$X1 + X2 + X3 = \begin{cases} 50\,\text{mg (for Raman and FTIR)} \\ 10\,\text{mg (for DSC)} \\ 200\,\text{mg (for XRPD)} \end{cases}$$

Fig. 1 shows the preparation of each sample according to the ternary mixture design. To the validation samples, five random samples were prepared with known amounts of each component constraining the final mass for each equipment.

2.3. Raman spectroscopy

An *i*-Raman BWS 415-785H (B&W Tek, Inc., Newark, DE, USA) was used, with a red laser (785 nm) and spectral resolution of