



Research Paper

Monitoring of multiple solid-state transformations at tablet surfaces using multi-series near-infrared hyperspectral imaging and multivariate curve resolution



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ABSTRACT

The assessment of the solid-state stability of active pharmaceutical ingredient (API) and/or excipients in solid dosage forms during manufacturing and storage is mandatory for safeguarding quality of the final products. In this work, the solid-state transformations in tablets prepared as blends of piroxicam monohydrate, polyvinylpyrrolidone and the lactose forms monohydrate or anhydrate were studied when the tablets were exposed to the 23–120 °C range. Multi-series near-infrared hyperspectral images were obtained from the surface of each sample for unveiling the local evolution of the solid-state transformations. The preprocessed spectra from the images (dataset) were arranged in augmented matrices, according to the composition of the tablets, and the profile of the overlapped compounds (relative concentration) along the solid-state transformations in the pixels was resolved by using multivariate curve resolution – alternating least squares (MCR-ALS). Therefore, the dehydration of piroxicam and lactose monohydrates could be mapped separately in the samples (explained variances by the models >96%) even when both compounds were being transformed simultaneously (80–120 °C). The images reproduced the same trends obtained from thermogravimetric analysis of the tablets, with the advantage that the pixel-to-pixel heterogeneity of each compound at the surface of the tablets was highlighted.

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1. Introduction

Solid-state transitions during manufacturing of pharmaceuticals are relevant concerns for the industry. The addition/removal of the water of crystallization in critical unit operations (e.g. crystallization, wet granulation, drying, pelletization) or during storage may induce the coexistence of distinct hydrate/anhydrate forms of active pharmaceutical ingredients (APIs) and/or excipients [1]. Crystal hydrates have particular physicochemical properties compared with their anhydrate counterparts that may result in varying solubility and dissolution behavior [2–4]. Therefore, the drug bioavailability may be seriously affected and may compromise the quality of the final product due to undesirable mixtures of different polymorphs [5–7].

Piroxicam (PRX) is a non-steroidal and anti-inflammatory drug that exists at least in three different anhydrate polymorphs (forms I, II and III) and one monohydrate form, with each of them having distinct Raman and NIR spectra [8]. The success on employing

spectroscopic techniques for monitoring solid-state transformations in pharmaceutical solid dosage forms (SDFs) has already been explored with the applicability of near-infrared, Raman [9,10] and Terahertz [11] spectroscopies for studying hydrate/anhydrate transformations in drug hydrates in different conditions. Although conventional single point spectroscopy was capable to detect solid-state transformations in the SDFs along their thermal conditioning, only bulk chemical information of the samples could be obtained. Therefore, the use of hyperspectral imaging (HSI) for solid-state monitoring can be extremely beneficial due to the possibility of unveiling the intensity of the chemical transitions in the sample in which the blend heterogeneity aspects are also being considered.

In HSI the region of interest (ROI) at the surface of a SDF is split in adjustable regular subspaces, denominated pixels that contain their own spectrum. The pixel sizes cannot be lower than few micrometers due to the inherent decreasing of the spectral signal-to-noise ratio even in the modern NIR-microscopes. The data are sorted in a x,y,z array, wherein xy coordinates define the positions of the pixels in the mapped ROI and the spectral variables (λ) are disposed in the z coordinates. The hypercube obtained is

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generally unfolded into a matrix ($xy \times \lambda$) for obtaining chemical information, through the selection of specific wavelengths [12] or by using chemometrics. In HSI-NIR, the highly overlapped bands usually require multivariate data analysis for extracting chemical information in the pixels [13–15]. Thus, principal components analysis (PCA) can be explored for a qualitative interpretation of the images. However, the lack of chemical selectivity in the pixels leads to principal components (PCs) that are describing mixed combination of effects in the sample, thus hampering the exclusively chemical interpretation of the images. Multivariate curve resolution (MCR) methods overcome this drawback by using iterative algorithms (e.g. alternating least squares – ALS) that optimize the resolution of each chemical compound separately in the images. MCR-ALS algorithm is based in the Lambert–Beer law, in which a spectrum from a mixture is considered a sum of the spectra from the corresponding pure-reference compounds weighted by their respective relative concentrations. In image analysis, the spectra of the pixels arranged in the data matrix $\mathbf{D}_{(xy \times \lambda)}$ are resolved with MCR-ALS in the new matrices $\mathbf{C}_{(xy \times n)}$ (relative concentration of the n compounds in the pixels), \mathbf{S} (ALS-resolved pure-reference spectra) and \mathbf{E} (experimental errors) according to the eq. $\mathbf{D} = \mathbf{C}\mathbf{S}^T + \mathbf{E}$. The refolding of \mathbf{C} according to the original position of the pixels results in chemical images expressing the distribution of the resolved compounds on the ROI of the corresponding sample [16–18]. The ALS-optimization of \mathbf{S} results that minor spectral changes due to chemical interactions among the compounds and from physical variability due to scattering effects (that can still be present in the data even after preprocessing) may be handled during the resolution, representing the main advantage of this algorithm for the analysis of spectral data from pharmaceuticals [19]. A relevant drawback of MCR methods is on modeling rank-deficient matrices, i.e. when the profiles of distinct compounds are linearly correlated in all the pixels, resulting in a number of resolved compounds lower than the true number of chemical compounds in the samples. A common strategy for resolving rank-deficient matrices in HSI analysis is the use of augmented arrays, incorporating the unfolded images from similar samples, but differing on the concentrations of the compounds, in a unique column-wise augmented matrix (\mathbf{D}_{AUG}). The extra addition of unfolded pure-reference images in \mathbf{D}_{AUG} and the use of the *correspondence among species* constraint (i.e. by informing the algorithm the pixels of \mathbf{D}_{AUG} where the concentration of the compounds is known *a priori*) minimize the rank-deficiency originally presented in \mathbf{D} , and each compound can be resolved successfully [20].

In this work, a methodology using NIR-HSI and chemometrics was developed for studying the dehydration of tablets containing the model drug piroxicam monohydrate (PRX-MH) and the excipients polyvinylpyrrolidone (PVP) and one of the lactose forms: α -lactose (LAC-AH) or lactose monohydrate (LAC-MH). Tablets varying the proportions of the ingredients were conditioned in a temperature-controlled oven within the range 23–120 °C, and multi-series images were acquired for each sample along the experiment. The processing of the HSI-NIR data using MCR-ALS revealed the profiles of all the compounds during the solid-state transformations in the pixels over the surface of the tablets at different temperatures. The similarities between the trends obtained from the HSI-NIR results and thermogravimetric analysis of the tablets highlighted the potential applicability of NIR-imaging spectroscopy for monitoring dehydration of API and excipients in pharmaceutical SDFs.

2. Experimental

2.1. Materials

Piroxicam anhydrate (P.A. grade) was obtained from Christian Olsen Pharmaceuticals A/S (Gentofte, Denmark).

Polyvinylpyrrolidone K30 (MW 40,000 g mol⁻¹, water $\leq 5.0\%$) and α -lactose monohydrate $\geq 99\%$ were obtained from Sigma–Aldrich (St. Louis, MO, USA). Lactose anhydrate (Pharmatose DCL 21, P.A. grade) was provided by Nomeco A/S (Copenhagen, Denmark).

2.2. Preparation of piroxicam monohydrate

The drug monohydrate form was prepared by dispersing approximately 2.0 g of PRX-AH in 100 ml of deionized water, keeping the dispersion stirring for 72 h at room temperature. Then the PRX-MH (yellow solid) was vacuum-filtered and transferred to a petri dish for drying in ambient conditions during 48 h. The total conversion of the drug to the monohydrate form was confirmed by X-ray powder diffraction analysis (XRPD), Fig. 1 [21]. The XRPD diffractograms were obtained using a PANalytical X'Pert Pro diffractometer in Bragg–Brentano geometry with a PIXcel detector (PANalytical B.V., Almelo, the Netherlands). The radiation was a continuous 2θ scan with non-monochromatic Cu K α_1 ($\lambda = 1.5406$, 40 mA and 45 kV) in the range 5–35° and point resolution of 0.026°.

2.3. Preparation of the tablets

Tablets were prepared from PRX-MH, PVP and one of the lactose forms: LAC-AH or LAC-MH. Six different formulations of tablets varying the proportions of the drug and excipients (Table 1) were dry blended and compacted using an evaluable dye (13 mm diameter) in a manual hydraulic press (PerkinElmer, Waltham, MA, USA) at 5.5 kN. Pure-reference compacts of PRX-AH and from each of the above-mentioned compounds were prepared likewise.

2.4. Acquisition of the hyperspectral images

Hyperspectral images were acquired in the reflectance mode with the Headwall photonics spectrometer (model 1002A-00371) containing a prototype hyperspectral camera kindly provided by FOSS A/S (Hillerød, Denmark), working in the wavelength range of 1000–1700 nm and spectral resolution of 7 nm (total of 142 variables per spectrum). The spectrometer was adapted to a line mapping configuration with pixel dimensions of 250 \times 50 μm^2 . The mapped area (80 \times 40 mm²) included the entire surface of the tablets. Each image was acquired in approximately 5 min, using a non-commercial software provided by the company.

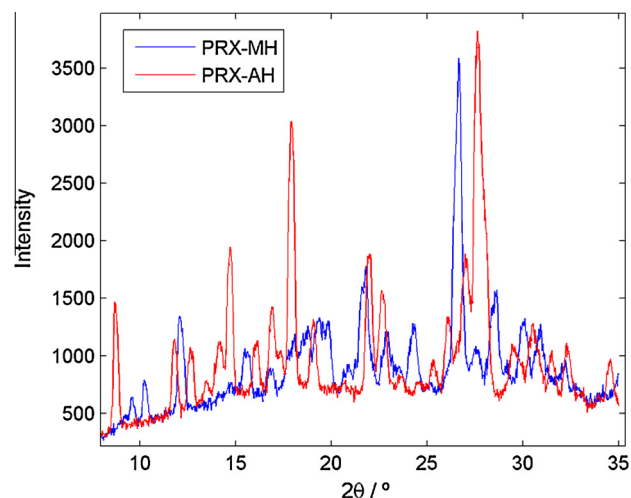


Fig. 1. XRPD patterns of PRX-AH and the PRX-MH prepared according to Section 2.2.

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