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Unveiling multiple solid-state transitions in pharmaceutical solid dosage forms using multi-series hyperspectral imaging and different curve resolution approaches

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ABSTRACT

Solid-state transitions at the surface of pharmaceutical solid dosage forms (SDF) were monitored using multi-series hyperspectral imaging (HSI) along with Multivariate Curve Resolution – Alternating Least Squares (MCR-ALS) and Parallel Factor Analysis (PARAFAC and PARAFAC2). First, the solid-state transformation due to the dehydration of the monohydrate forms of piroxicam and lactose to their respective anhydrate counterparts in tablets were monitored using temperature series NIR-HSI. PARAFAC and MCR-ALS solutions were hampered by the lack of strict trilinearity of the pixels among the unfolded series NIR-images (three-way array) and due to rotational ambiguity (augmented matrix), respectively, while PARAFAC2 resolved satisfactorily the profile of the corresponding compounds in the pixels in the series NIR-images. Next, the amorphous-to-crystalline transitions were monitored in solid dispersion of indomethacin with polyvinylpyrrolidone using time series MIR-HSI. MCR-ALS properly resolved the known solid-state forms of the drug in the pixels of the series MIR-images, while PARAFAC and PARAFAC2 failed to properly resolve all the drug forms in the series MIR-images due to i) strict trilinearity leak in the three-way array and ii) the mandatory constant cross-product $\mathbf{A_k}^T\mathbf{A_k}$ over the k series MIR-images (**A** is the loadings of the shift mode), respectively. The highlighting of the advantages and limitation of the corresponding curve resolution methods stressed their potential applicability when handling multi-series HSI to study solid-state transitions in pharmaceutical SDFs.

1. Introduction

The knowledge of the physicochemical stability of pharmaceutical solid dosage forms (SDFs) is mandatory for guaranteeing its desired pharmacological properties in the organism and the consequent performance of the final medicinal product. However, the stability of drugs and excipients can be seriously susceptible to solid-state transformations during the production and/or on the storage of the SDFs. Typically occurring solid-state transformations during the manufacturing of SDFs are changes in the crystalline state of the ingredients, in particular formation of hydrates, dehydration, amorphous-to-crystalline, crystalline-to-amorphous and polymorphic transformations [1,2]. Several drugs when exposed to water can convert to their respective hydrate forms, as well as complex dehydration processes can be expected [3–7]. Therefore, the monitoring of unit operations, like crystallization, wet granulation and pelletization, drying and the storage conditions of the SDFs are essential steps to avoid undesirable mixtures of hydrates/anhydrous forms in the final products. In the case of the SDFs, the functionality of a product may be seriously affected due to amorphous-to-crystalline transformations and/or interconversion among different crystalline forms [8–10].

Solid-state transformations in SDFs have already been successfully studied using conventional vibrational spectroscopies [11], such as mid-infrared (MIR), near-infrared (NIR) and Raman. NIR spectroscopy and chemometrics were used to monitor the formation of pharmaceutical hydrates during the preparation of SDFs, demonstrating the potential applicability of the spectroscopic techniques in the FDA's Process Analytical Technology (PAT) concepts for on-line monitoring of solid-state transitions triggered by the presence of water [3,12]. Moreover, Raman and MIR spectroscopies have proved to be

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Acronyms

CORCONDIA	core consistency diagnostic
ewfa	evolving window factor analysis
fsiw-efa	fixed size image window – evolving factor analysis
HSI	hyperspectral imaging
IMC	indomethacin
LAC-AH	lactose anhydrate
LAC-MH	lactose monohydrate
MCR-ALS	multivariate curve resolution – alternating least squares
MIR	mid-infrared
NIR	near-infrared
PARAFAC	parallel factor analysis
PAT	process analytical technology
PRX-AH	piroxicam anhydrate
PRX-MH	piroxicam monohydrate
PVP	polyvynilpyrrolidone
RH	relative humidity
ROI	region of interest
SD	solid dispersion
SDF	solid dosage forms
SIMPLISMA	Simple-to-use interactive self-modelling mixture analysis
SVD	singular value decomposition

reliable techniques to understand solid-state transformations, such as amorphous-to-crystalline and polymorphic transitions in pharmaceuticals, since MIR/Raman spectral fingerprinting can usually be assigned to each polymorphic form [8,13,14].

Hyperspectal imaging (HSI) based on vibrational spectroscopy (e.g.; Raman, mid-, -near- and far-infrared) has been increasingly adopted as analytical tool in pharmaceutical solid dosage forms (SDFs) aiming the information about the spatial distribution of the active pharmaceutical ingredient and excipients [15–19]. The great advantage of HSI, comparing with conventional spectroscopy, is that the region of interest (ROI) on the surface of a sample is mapped through the acquisition of spectra in regular adjacent subspaces (pixels), providing the heterogeneity information about this ROI. The hyperspectral image data, initially arranged in a three-way array D(x,y,z) with x and y being the spatial [x,y] variables and z the spectral variable (wavelength, Raman shift, wavenumber position, etc.), are unfolded into a two-way array D′(xy,z), before data analysis using single wavelengths (univariate) or chemometrics.

The applications of HSI in pharmaceutics have not been restricted only to unveil the chemical distributions of the active pharmaceutical ingredient and excipients herein. New approaches involving near-infrared and Raman multi-series HSI, in which images are obtained from the same surface (and ROI) but at different conditions (*e.g.;* time and/or temperature), were presented as a novel analytical strategy to monitor the polymorphic transformations of carbamazepine at the surface of SDFs from temperature series images [9,13]. Due to the possibilities of multi-series images being modelled using both bilinear and trilinear curve resolution methods (a brief theory about the data arrangement in multi-series HSI is presented in the next section), the evolutions of the polymorphic forms of the drug in tablets submitted to heat were resolved in each of the spatial (pixels), spectral and temperature modes using multivariate curve resolution – alternating least squares (MCR-ALS) and parallel factor analysis (PARAFAC).

This work aims to explore different chemometric approaches in two novel applications to monitor solid-state transformations in SDFs using the multi-series HSI framework. In the first part, tablets prepared as blends of the monohydrate forms of piroxicam (PRX-MH) and lactose (LAC-MH) were exposed to thermal conditioning in an oven, and the dehydration of the above-mentioned compounds at the surface of the tablets were studied with temperature series NIR-images. In the second part, amorphous-to-crystalline transitions were studied using time series MIR-imaging from SDFs prepared as solid dispersions (SDs) of the drug indomethacin (IMC) in the hydrophilic polymer polyvinylpyrrolidone (PVP). The profiles of the compounds involved during the solid-state transitions were resolved in the three modes (pixels, spectra and time/temperature) using MCR-ALS and PARAFAC for bilinear and trilinear modeling, respectively. Moreover, the application of the algorithm PARAFAC2 is introduced, for the first time, as a suitable alternative for PARAFAC when handling trilinear disturbance in the three-way array occurring in series-images. The discussions about the performance of the chemometric methods (*i.e.* MCR-ALS, PARAFAC and PARAFAC2) on the modeling of the series-images from the above-mentioned pharmaceutical applications emphasized their main advantages and drawbacks.

2. Data modeling in multi-series HSI

2.1. Multivariate curve resolution – alternating least squares (MCR-ALS)

MCR-methods decompose a data matrix **D** into the bilinear equation $\mathbf{D}=\mathbf{CS^T}+\mathbf{E}$, in which **S** and **C** are the matrices defined by the spectral profiles of the pure-compounds and their relative proportion in the pixels (MCR-scores), respectively, and **E** is the error matrix (non-explained variance by the model). In MCR-ALS, **C** and **S** are resolved iteratively from **D** and an initial estimation of the pure-compounds spectra. However, the rotational ambiguity that is inherent of the $\mathbf{CS^T}$ product requires the use of constraints during the ALS-resolution to achieve feasible solutions, *e.g.;* non-negativity in **C** and/or **S** profiles, closure (*i.e.* the sum of the relative concentration of the pure-compounds equals to 100% in each row of **C**), correspondence among species (*i.e.* previous local rank-information in **D**), and others [20]. Tauler has already proposed a method to estimate the degree of ambiguity in MCR solutions by calculating the maximum and minimum band boundaries of feasible solutions that correspond to the profiles of the resolved compounds. Basically, the relative contribution of the n*th*-compound ($\mathbf{c_n s_n^T}$) to the whole signals ($\mathbf{CS^T}$) is measured by the quotient $fn=||\mathbf{c_n s_n^T}||/||\mathbf{CS^T}||$, with the boundaries of fn values computed for each resolved-compound considering its maximum and minimum solutions that keeps the product $\mathbf{CS^T}$ unchanged (*i.e.* the degree of ambiguity) [21].

The unfolded images from multi-series HSI has to be concatenated into a single column-wise augmented matrix ($\mathbf{D_{AUG}}$) prior to the MCR-ALS initialization for a proper model fitting. The results are a single $\mathbf{S^T}$ matrix, defined by the pure-compounds spectra that is common to all the submatrices (*i.e.* series images), and a $\mathbf{C_{AUG}}$ matrix containing the MCR-scores of the resolved compounds in each pixel of the multi-series images. The appropriate refolding of $\mathbf{C_{AUG}}$ according to the original position of each image in $\mathbf{D_{AUG}}$ reveals the profiles of the resolved-compounds in the pixels mode. Due to the bilinear structure of the MCR-ALS models, the respective profiles in the series mode (*e.g.;* the general profile of an API over the time in time series-HSI of a SDF) has to be computed independently through the average of the MCR-scores (pixels mode) in each image [13]. Indeed, there is no dependency among the spectra from the same pixels over the images while on modeling series images with MCR-ALS, although a single **S** is resolved for all the series images.

2.2. Parallel factor analysis (PARAFAC) and PARAFAC2

Van Benthem et al. [22,23] have already demonstrated the successful use of PARAFAC in series hyperspectral fluorescence-images. The