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Setting local rank constraints by orthogonal projections for image resolution analysis: Application to the determination of a low dose pharmaceutical compound

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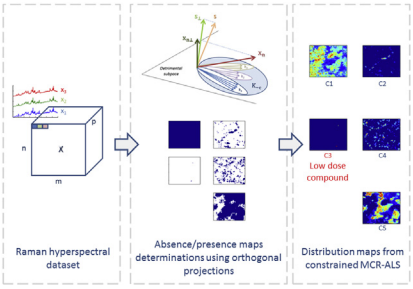
HIGHLIGHTS

- Proposition of a new method to set local rank constraints for multivariate curve resolution-alternating least squares.
- The method is particularly well adapted for a compound distributed in a few pixels with low signal contributions.
- For each product of interest, orthogonal projection is applied to subtract detrimental basis from other compounds.
- The method is used on Raman microscopy to study low dose product distribution in a pharmaceutical drug product.

GRAPHICAL ABSTRACT



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ABSTRACT

Raman chemical imaging provides chemical and spatial information about pharmaceutical drug product. By using resolution methods on acquired spectra, the objective is to calculate pure spectra and distribution maps of image compounds. With multivariate curve resolution-alternating least squares, constraints are used to improve the performance of the resolution and to decrease the ambiguity linked to the final solution. Non negativity and spatial local rank constraints have been identified as the most powerful constraints to be used.

In this work, an alternative method to set local rank constraints is proposed. The method is based on orthogonal projections pretreatment. For each drug product compound, raw Raman spectra are orthogonally projected to a basis including all the variability from the formulation compounds other than the product of interest. Presence or absence of the compound of interest is obtained by observing the correlations between the orthogonal projected spectra and a pure spectrum orthogonally projected to the same basis. By selecting an appropriate threshold, maps of presence/absence of compounds can be set up for all the product compounds. This method appears as a powerful approach to identify a low dose compound within a pharmaceutical drug product. The maps of presence/absence of compounds can be used as local rank constraints in resolution methods, such as multivariate curve resolution-alternating

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least squares process in order to improve the resolution of the system. The method proposed is particularly suited for pharmaceutical systems, where the identity of all compounds in the formulations is known and, therefore, the space of interferences can be well defined.

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1. Introduction

The use of imaging coupled with vibrational spectroscopies has shown a huge interest in research and development environments [1], especially to control the drug product quality during development and beyond post-marketing authorisation [2]. It provides spatial and spectral information associated with the distribution of the different compounds within the sample. Direct interpretation of the acquired images is often not possible and several chemometric tools have previously been published to aid in this task [3]. Qualitative analyses such as principal component analysis (PCA) [4] or independent component analysis (ICA) [5] have already been used as a descriptive method to study compound distributions in a sample by Raman chemical imaging. To extract quantitative information at a global and local pixel level, principal component regression (PCR) and partial least squares regression (PLS-R) have been shown to be powerful chemometric techniques [6]. However, these methods can be time consuming and difficult to implement since they require a calibration step to develop predictive models.

By avoiding the calibration step, resolution methods were identified as a good alternative to study the compound distribution within a pharmaceutical drug product. They provide the distribution maps and pure spectra related to the image compounds of a sample from the information contained in the raw image [7]. Multivariate curve resolution-alternating least squares (MCR-ALS) has been used on Raman hyperspectral images to study the distribution of actives and excipients [8,9]. In order to ensure an accurate resolution, constraints have to be used during the optimization process. In image resolution, non-negativity, spectral normalization and local rank analysis are generally the most successful constraints [10]. Local rank analysis describes the spatial complexity of an image by identifying the rank of a pixel neighbourhood area. Combined with reference spectra of the image compounds, the absence of one or more specific compound in a pixel can be highlighted. To identify where the compounds of the drug product are present or absent in the image, the fixed size image window evolving factor analysis (FSIW-EFA) method can be applied to the data [11]. This method provides the local complexity of a sample by performing singular value decomposition by moving a window of neighbouring pixels across the full image. By comparing the local rank information with reference spectral information, missing compounds on particular pixels can be known. The local complexity and the correct definition of the presence/absence maps are relevant steps of the MCR-ALS algorithm. Indeed, the quality in the resolution of the system depends on the adequacy and correct setting of constraints. If pure compound pixels or pixels with absent compounds are present in the images, both singular value decomposition and identification of missing compounds should led to the identification of the presence or absence of the studied compound and hence should help to provide better MCR-ALS results, less affected by ambiguity.

In the case of a low dose product, it can be assumed that the compound is not homogenously distributed (i.e. it is present in a few pixels at low concentrations). Spatial and spectral information is scarce because only few pixels of the image contain the product of interest and the associated variances are mixed with the other compounds of the formulation. In order to keep the maximum of information during the iterative process, MCR-ALS has to be performed without PCA-based filtering matrix [12] with the appropriate constraints. In cases where the low dose compound has additionally a low spectral response, two problems may arise to obtain proper local rank maps and related maps of presence/absence for this kind of compounds. Firstly, singular value decomposition applied on moving window might encounter some difficulties to extract the variability linked to the low dose compound if the spectral response is low, since the associated variance is weak. Second, since the correlation between pure spectra of the formulation is not null (i.e. spectra are not orthogonal), construction of presence/absence maps, based on the comparison between image spectra and reference pure spectra might be difficult to set up especially if the contribution of the signal of the low dose compound to the pixel spectrum measured is low.

Previous works have been published on the detection of a low dose compound by vibrational spectroscopy within a pharmaceutical drug product [13–15] and some of them focused on the detection limit of the analytical method [16]. The net analyte signal (NAS) concept was used in the pharmaceutical environment to improve the spectral interpretability [17] of model results. It was defined as the part of the signal that is orthogonal to the spectra of the other components [18]. For one component of interest, two definitions were proposed [19,20]. NAS was first defined as “the part of the spectrum of the component of interest that is orthogonal to the spectra of the other components”. Afterwards, the definition evolved into “the part of the raw signal that is useful for prediction of the component of interest”. NAS has a conceptual meaning and is very difficult to measure. It can be viewed as a particular case of preprocessing methods based on orthogonal signal projection approaches [21–23]. The use of NAS pretreatment appeared as an interesting tool to accurately resolve the analyte signal of a low dose compound and allow the construction of a quantitative model [24]. Several adaptations of these approaches can be considered, depending on the spectral basis (i.e. space containing the contributions to be removed) used for projecting the original dataset.

In this article, we propose an alternative procedure to set the presence/absence maps of compounds for later use as local rank constraints. The proposed approach is based on orthogonal projection to a space containing the contributions to be removed (i.e. the interference subspace). Each compound has its proper subspace containing spectral variability due to the environment, acquisition or physical variations. This variability can be viewed as a basis of vectors with an appropriate set of dimensions to build the interference subspace. By orthogonally projecting a spectrum to this basis, interferences are removed and only information of the compound of interest is kept. Since the method is not based on variance decomposition, it should be well adapted for a drug product which contains a low dose compound located in few pixels and with a low spectral response. Spectral comparison between the projected spectrum and a pure projected spectrum of the compound of interest can lead to the presence/

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