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Direct quantification and distribution assessment of major and minor components in pharmaceutical tablets by NIR-chemical imaging

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ABSTRACT

Near Infrared Chemical Imaging (NIR-CI) is an attractive technique in pharmaceutical development and manufacturing, where new and more robust methods for assessment of the quality of the final dosage products are continuously demanded. The pharmaceutical manufacturing process of tablets is usually composed by several unit operations such as blending, granulation, compression, etc. Having reliable, robust and timely information about the development of the process is mandatory to assure the quality of the final product.

One of the main advantages of NIR-CI is the capability of recording a great amount of spectral information in short time. To extract the relevant information from NIR-CI images, several Chemometric methods, like Partial Least Squares Regression, have been demonstrated to be powerful tools. Nevertheless, these methods require a calibration phase. Developing new methods that do not need any prior calibration would be a welcome development.

In this context, we study the potential usefulness of Classical Least Squares and Multivariate Curve Resolution models to provide quantitative and spatial information of all the ingredients in a complex tablet matrix composed of five components without the development of any previous calibration model. The distribution of the analytes in the surfaces, as well as the quantitative determination of the five components is studied and tested.

1. Introduction

The analytical techniques of hyperspectral imaging, like Near Infrared Chemical Imaging (NIR-CI) or Raman Chemical Imaging (Raman-CI), comprise a group of attractive techniques in the development and manufacturing of pharmaceutical tablets (Chan et al., 2003; Shah et al., 2007; Zhang et al., 2005) where more robust methods are continuously demanded for assessment of the quality of the final products. This attractiveness is due to the capability of the mentioned techniques to obtain a great amount of spectral and spatial information in defined surfaces of pharmaceutical products (Furukawa et al., 2007). The possibility of recording one spectral profile in a wide wavelength range for each defined pixel area of the tablet poses new challenges for the development of robust and reliable methodologies of data analysis to extract all the desirable information.

Basically, the expectations on Chemical Imaging are focused on obtaining quantitative information about the content of each component in the tablet (Chevallier et al., 2006; Zhang et al., 2005) providing at the same time reliable information about the distribution of the component in the surface of the tablet (Furukawa et al., 2007; Lyon et al., 2002) to assure the quality of the final product.

As mentioned above, the great interest of CI techniques relies in the capability to obtain thousand of spectra of a defined surface of the tablet. To extract the quantitative information, powerful mathematical tools are demanded. In this context, several Chemometric methods, like Principal Components Regression (PCR) (Hamilton et al., 2002), Partial Least Squares Regression (PLS) (Burger and Geladi, 2006; Furukawa et al., 2007; Jovanovic et al., 2006; Lied et al., 2000; Roggo et al., 2005; Svensson et al., 2006) or its variant PLS2 (Gendrin et al., 2007; Li et al., 2008), have already been demonstrated to be powerful tools. Nevertheless, these methods require a previous calibration phase, being tedious and time-consuming. Consequently, the development of new methods that do not need any prior calibration stage would be a welcome development.

To overcome the problem of the previous calibration stage, several alternatives can be proposed (Amigo et al., 2008), being

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Classical Least Squares (CLS) (Chan et al., 2005; Gendrin et al., 2007), Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS) (de Juan et al., 2004; Zhang et al., 2005) and MCR-ALS in augmented fashion (Amigo et al., 2008; de Juan et al., 2004) the most promising techniques.

In this context, we study and test the potential usefulness of Classical Least Squares and Multivariate Curve Resolution models to provide quantitative and spatial information about the distribution of each analyte in the surface of a complex pharmaceutical mixture composed of five components without the development of any previous calibration model and by using Near Infrared Chemical Imaging.

2. A brief theoretical background

An exhaustive theoretical background of the proposed models will not be given here but readers are encouraged to look for more information in the supplied references.

When a NIR-Chemical Image is measured for a single tablet, the structure of the obtained dataset is a three-dimensional array known as hyperspectral cube, **D**, whose dimensions are $(X \times Y \times \lambda)$ (Zhang et al., 2005). X and Y refer to the spatial dimensions of the surface; whereas λ refers to the spectral pattern measured in a whole wavelength range for each xyth pixel of the tablet.

The basis of CLS and MCR-ALS could be argued to be the same. Both methods assume that the absorbance follows a linear behaviour with the concentration (Beer–Lambert Law) and that the sum of the individual absorbances for each component equals the total absorbance for each pixel (Eq. (1)).

$$a_{xy\lambda} = c_{1xy}\varepsilon_{1\lambda} + c_{2xy}\varepsilon_{2\lambda} + c_{3xy}\varepsilon_{3\lambda} + \ldots + c_{fxy}\varepsilon_{f\lambda} \quad (1)$$

where $a_{xy\lambda}$ is the absorbance at each xyth pixel dimension and at each wavelength (λ) and, c_{fxy} and $\varepsilon_{f\lambda}$ the concentration and molar absorptivity, respectively, for each f component of the surface.

Mathematically speaking, both are bilinear models. So a previous stage of unfolding is mandatory in order to adapt the three-dimensional structure to bilinear models (Fig. 1). Consequently, the dimensions of the unfolded image **D** are $(XY \times \lambda)$.

The main difference between CLS and MCR-ALS relies in the way of obtaining the quantitative information. CLS is aimed to obtain the concentration of each component by direct regression of **D** by using the pure spectra (Chan et al., 2005; Gendrin et al., 2007). Despite the easiness of calculating this concentration matrix, CLS has one main drawback: it works perfectly if the spectra of the components are known and, what is more important, if there is no other variability source in the sample (for example, interaction between components, distribution of moisture and hydration/adsorption water, etc.) that can promote other features in the sample not related to the pure components. CLS is constrained to model all the variability of the sample by using just the pure spectra. For this question, a more feasible method would be preferred.

Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS) (de Juan and Tauler, 2006; de Juan et al., 2004; Tauler, 1995) decomposes the matrix **D** $(XY \times \lambda)$ into the product of two matrices, **C** $(XY \times F)$, containing the concentration profiles and $\mathbf{S^T}$ $(F \times \lambda)$, containing the spectral profiles for each F component (Eq. (2)):

$$\mathbf{D} = \mathbf{C}\mathbf{S^T} + \mathbf{E} \quad (2)$$

where **E** $(XY \times \lambda)$ contains the experimental error. The main difference from CLS is that MCR-ALS works by iteratively optimizing the matrices **C** and $\mathbf{S^T}$. Thus, the result is not constrained to the pure spectra, allowing MCR-ALS to cope with minor sources of variability that may be in the tablet.

To start the iterations, MCR-ALS needs initial estimates, as well as several constraints based on chemical knowledge of the sample studied. Using the pure spectra of the components (if they are available) as initial estimations becomes one of the most attractive ways of including information about the tablet. Several constraints based on chemical knowledge or on mathematical features of the data can be imposed to the iterations, being the most useful in the quantification of mixtures by means of Chemical Image analysis are: (1) non-negativity in concentration and/or spectral profiles, which imposes that concentration profiles of the components are supposed to be always positives and (2) closure, where each pixel can be supposed to accomplish a constant mass balance of 1, representing 100% of global concentration.

The main disadvantage of MCR-ALS in Chemical Imaging is the lack of selectivity in the surface (Amigo et al., 2008); i.e., to obtain good results, each component must have a selective area in the tablet, accounting for the variability of the concentration in the sample. This lack of selectivity can be associated to a rank-deficiency problem. MCR-ALS only works properly if the rank of

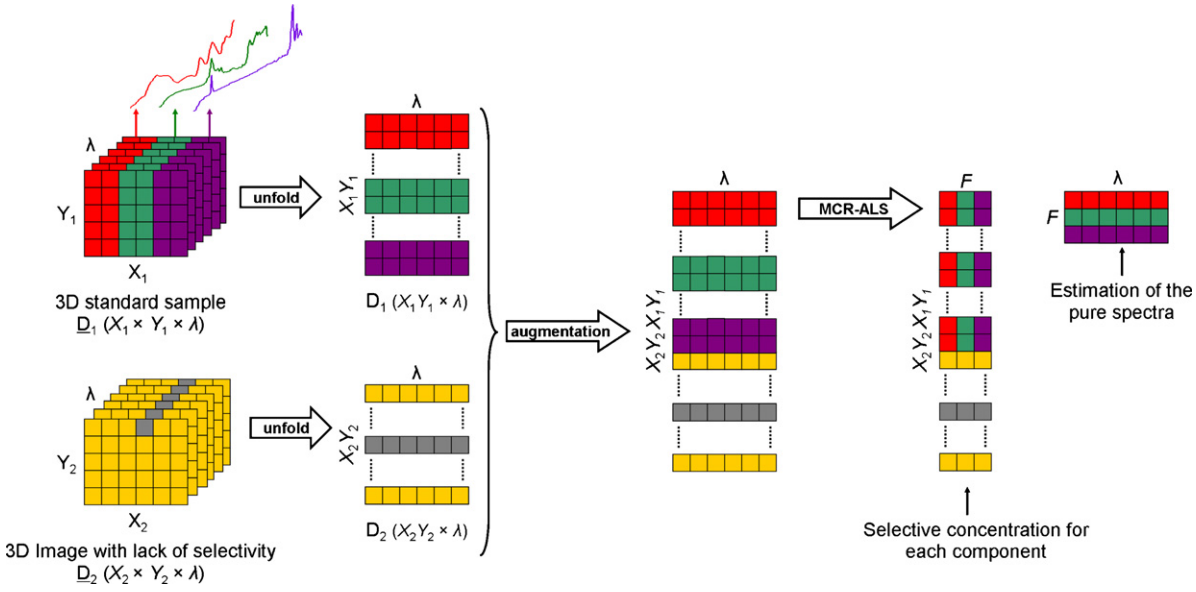

Fig. 1. Augmentation of images and MCR-ALS analysis. The example is illustrated by assuming three components in the samples.