Near infrared chemical imaging study of Aspirin commercial tablets

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Introduction

Near infrared chemical imaging (NIR-CI) is experiencing an increasing interest in the pharmaceutical field because of its ability to obtain relevant information about the composition and distribution of components from tablets.[1] The analysis of the sample by NIR-CI provides a single spectrum at each pixel of the image, and generates a great amount of information that requires chemometric algorithms for treatment.

Multivariate curve resolution-alternating least squares (MCR-ALS) has been successfully applied to extract quantitative information of NIR Images in pharmaceutical samples.[2] This technique presents an alternative to quantify different components in tablets without needing a specific calibration model (only the spectra of pure components are needed).

This work is presented in two different parts. First, the MCR-ALS algorithm is proposed as a quantitative method, to analyse hyperspectral images of different commercial Aspirin tablets. A large range of API concentration, between 82% and 12%, was covered for the chosen samples, which present different compositions depending on the manufacturer.

Second, content uniformity has been determined by MCR-ALS, from a unique image of 10 tablets. Tablets from four different manufactures were selected. The distribution of API and the major excipient in the tablet has been evaluated using concentration maps and pixel histograms.

Methods

Samples

For the first part of this study 10 different brands of commercial Aspirin tablets were purchased at pharmacies. The acetylsalicylic acid (ASA) concentration for the tablets was obtained by dividing the nominal content by the weight of the tablet. The concentration of ASA covered a range from 82% to 12% (w/w).

For the second part of this study 4 different tablet brands, were used (10 tablets per brand) selected according their diameter. The nominal concentrations of ASA in the different tablets covered a range of concentration from 82% to 71%.

Microcrystalline cellulose (MCC) is the main excipient in six preparations, whereas manitol is the main excipient in the other two 2. *Dolmen* and *Aspirina C* are effervescent tablets and also contain ascorbic acid as an active component. Other excipients are citric acid, sodium carbonate and anhydrous sodium bicarbonate. Table 1 shows the main features of each brand tablets.

Table 1. Main features and results obtained for 10 different brands of commercial tablets.

Commercial Brand	Nominal ASA (mg)	Diameter (mm)	Tablet Weight (g)	Nominal concentration (%)	Main Excipient	NIR-CI concentration (%)
A.A.S 100	100	82	0.227	*44.1*	Manitol	53.3
A.A.S 500	500	134	0.864	*57.9*	Manitol	54.9
Bayer 500	500	120	0.609	*82.1*	MCC	81.6
Adiro 100	100	72	0.135	*73.9*	MCC	76.5
Adiro 300	300	102	0.409	*73.3*	MCC	70.9
Aspirina C*	400	258	3.235	*12.4*	–	12.9
Dolmen*	500	242	3.399	*14.7*	–	16.4
Aspirine Nicholas	500	120	0.624	*80.1*	MCC	77.0
Bioplak 250	250	70	0.348	*71.8*	MCC	71.3
Bioplak 125	125	100	0.173	*72.1*	MCC	67.8

*Effervescent tablets.

Instrumentation and software

Hyperspectral images of the tablets were obtained by a "Think Spectrally Roda-25" NIR Hyperspectral Imaging Spectrophotometer (*Think Spectrally*, Valencia, Spain). The dimension image acquires the format of a data-cube [256 × 360 × 130] (Figure 1).

Three-dimensional structure of the hyperspectral data-cube requires a previous unfolding step to a bi-dimensional matrix, adapting the image for further pre-treatments, or any other method.

The spectral pre-treatments were applied by using home-made routines programmed in MATLAB code (MATLAB v 7.0, *The MatWorks*, Massachussetts).[3] Once the images were unfolded standard normal variation (SNV) and also smoothing were applied.

MCR-ALS software from the reference[4] working under MATLAB was used.

MCR-ALS in imaging data

Multivariate curve resolution-alternating least squares (MCR-ALS)[4] decomposes the unfolded matrix $\mathbf{X}$ ($MN \times \lambda$) into the product of two matrices, $\mathbf{C}$ ($MN \times A$), containing the concentration profiles, and $\mathbf{S^T}$ ($A \times \lambda$), containing the spectral profiles for each A component [Figure 1(a) Equation (1)]:

$$\mathbf{X} = \mathbf{CS^T} + \mathbf{E} \tag{1}$$

where $\mathbf{E}$ ($MN \times \lambda$) corresponds to the experimental error matrix.

The ALS optimisation stops when the relative difference in lack of fit (% LOF) values between consecutive iterations is below a threshold value. The quality of the images, which depends on the spatial and also spectral resolution, could be a disadvantage when MCR-ALS is applied because

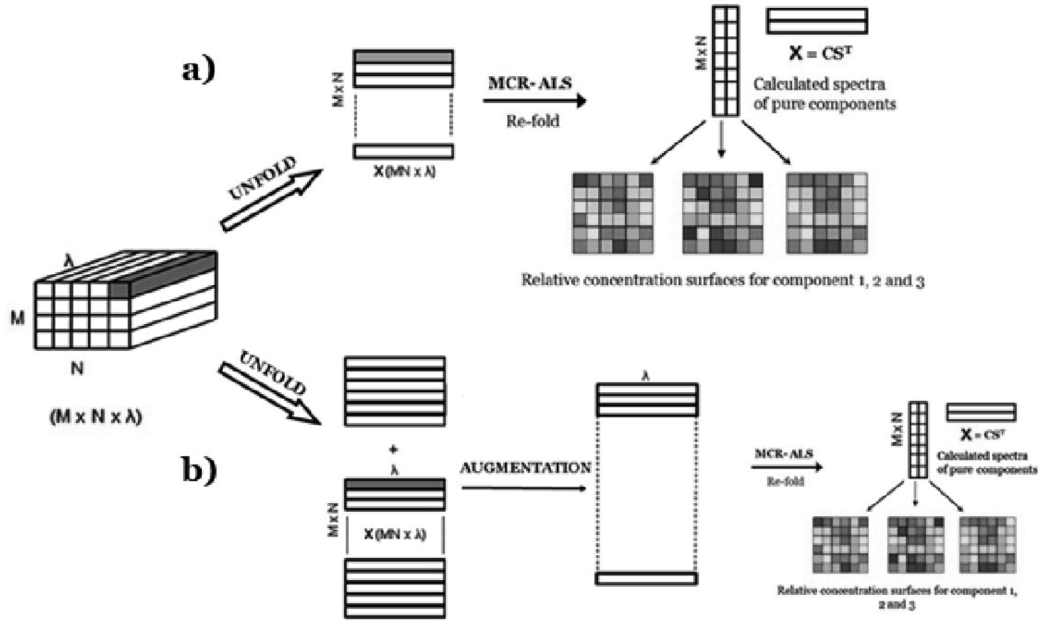

Figure 1. Scheme of the application of MCR-ALS a) and Augmented MCR-ALS b) to hyperspectral cube data.

there could be a lack of selectivity in the surface of the image. To overcome this problem an alternative has already been formulated concerning the augmentation of the original sample with images of the pure analytes. A scheme of the unfolding and augmentation is shown in Figure 1b.

Results and discussion

Different pre-treatments were tested with the images, and the combination of SNV and smoothing average with a window size of seven points provided the best results. Prior to the application of MCR-ALS, non-negativity of concentration profiles and closure were applied as constraints. Despite the fact that the tablets were constituted by a different number of components, closure constraint was applied. ASA and the excipients used in this study provided the highest spectral information, and were used to perform the MCR-ALS analysis, while the spectral contribution of minor excipients may be related to the residual matrix. The pure spectra of the main components were included as initial estimations to start the iterations. Augmented MCR-ALS was applied, adding 10 spectra for both pure analytes (ASA and the major excipient) to the unfolded matrix, in order to improve the decomposition.

A tablet hyperspectral image analysis

Table 1 also shows the quantitative results for the 10 brands of tablets obtained by applying augmented MCR-ALS.

Table 2. Results obtained for content uniformity (10 tablets) of 4 commercial brands.

Commercial Brand	Nominal concentration (%)	NIR-CI concentration (%)	Standard deviation	Acceptance value (limit A.V.=15, n=10)
Bayer 500	82.8	82.4	1.5	4.0
Adiro 100	73.1	72.6	2.5	6.5
Bioplak 250	72.9	72.7	2.7	6.7
Bioplak 125	71.4	67.8	2.2	8.7

The ASA concentration was similar to calculated values, confirming the integrity of the quantitative analysis. Good results were obtained for almost all of the samples, including samples with lower values of ASA content. Tablets with Manitol as the main significant excipient showed the poorest results for the determination of ASA content.

The concentration map and histogram of the local concentration for ASA and MCC of the Bayer 500 tablet [see Figure 2(a)] allow observation of the regular distribution with little heterogeneities for the ASA and the MCC in the surface, and with concentrations remaining close to a normal distribution in the histogram, which is the ideal situation. The same behaviour can be observed for the other samples (not shown in the figure), except for AAS 100 and AAS 500, in which the concentration range was not as narrow as for the others.

Ten tablets hyperspectral image analysis (Content uniformity test)

The hyperspectral image of 10 tablets was cropped and the area corresponding to each tablet selected. The background data around each tablet was suppressed, and a masking routine[3] been applied to unfold the tablet spectra without including the background. Then the MCR-ALS algorithm was applied to the unfolded spectra applying the same restrictions indicated before. This process was done for each image of the 10 tablets and the concentration calculated. The average values for each tablet brand are shown in Table 2.

The low spatial resolution of the hyperspectral camera and the deficient illumination of the sample of 10 tablets, are likely to be the origin of a deficient hyperspectral image (bad resolution in the tablets' corners). For this reason, in order to avoid poor ASA determinations, the central pixels of each tablet must be selected.

The results obtained for determination of the ASA in four different brands of tablets are shown in Table 2 (these values are the average value for 10 tablets from each brand).

The mean concentration for ASA in the surface of the tablets was similar to the calculated value, confirming the consistency of the content uniformity analysis for the 4 brands. Results of distribution of API [Figure 2(b)], in 10 tablets per image, could probably be improved with an instrument with better spectral/spatial resolution.

The histograms for ASA and MCC show values around the prediction values, and with a narrow variation, implying that the whole surface of the tablets contained a similar amount of ASA.

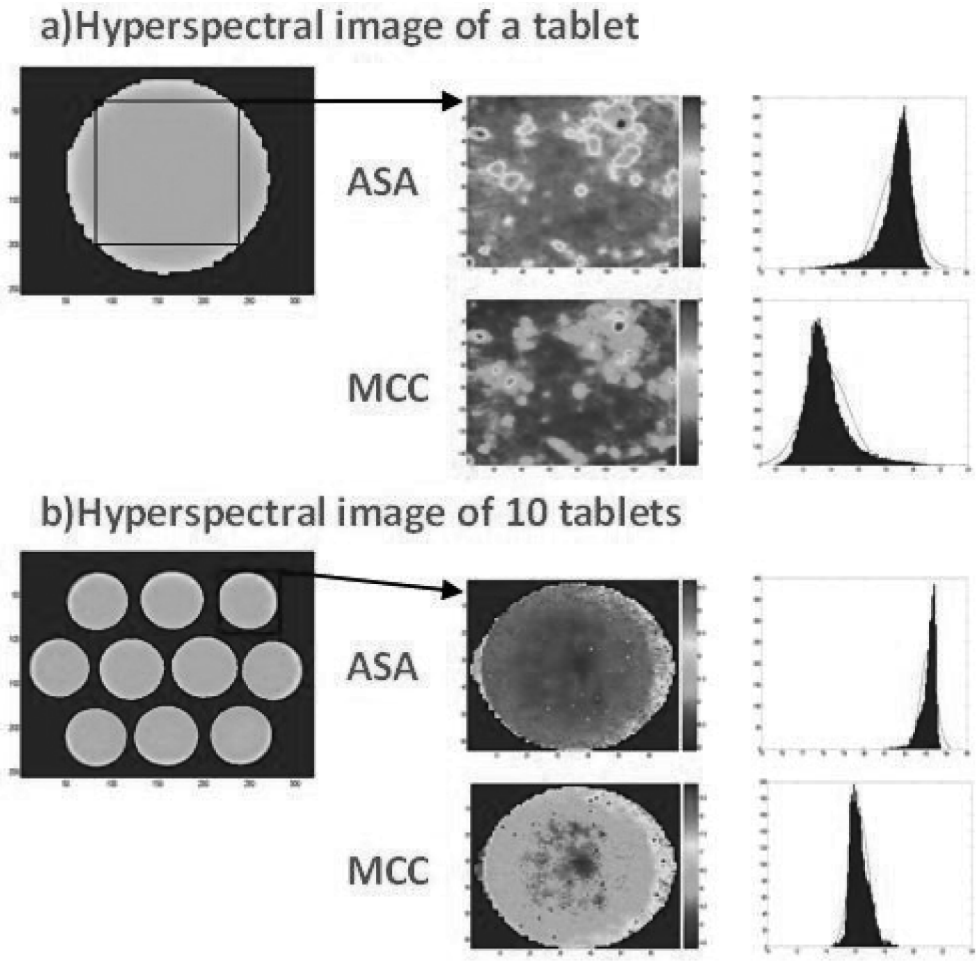

Figure 2. Concentration ASA and MCC maps and histograms calculate with MCR-ALS for an individual registered tablet a) and for 10 registered tablets b).

For content uniformity, the European Pharmacopoeia defines an acceptance value (AV) which is computed and compared with a limit for the acceptance range.[5]

$$AV = |M - X| + k \cdot s \tag{2}$$

where M is the reference value, X the mean value of the individual tablets, k is a constant ($k = 2.4$ for $n = 10$) and s the standard deviation. The requirement of content uniformity is fulfilled if the AV of the first 10 dosage units is less than or equal to *15.*

The results obtained for four brands are shown in Table 2; and indicate the fulfilment of the Pharmacopoeia requirements.

Conclusions

Intact commercial tablets were analysed by NIR-Chemical Imaging in order to determine the distribution of ASA, and the ASA concentrations for each tablet, using the MCR-ALS decomposition.

MCR-ALS is a powerful tool to quantify the use of hyper-spectral images. It allows the generation of concentration maps, with only the requirement of pure spectra, and without needing a calibration model with reference values. The tablet surface's concentration map allows establishing the API and the major excipient homogeneity of distribution.

A unique hyper-spectral image of 10 tablets allows assessment of content uniformity, according to the Pharmacopoeia rules, thereby saving time of analysis, with respect to conventional methods.

References

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