Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 303 (2023) 123268

Contents lists available at ScienceDirect

Spectrochimica Acta Part A:
Molecular and Biomolecular Spectroscopy

journal homepage: www.journals.elsevier.com/spectrochimica-acta-part-a-molecular-and-biomolecular-spectroscopy

Quantification of ciprofloxacin in pharmaceutical products from various brands using FT-NIR: A comparative investigation of PLS and MCR-ALS

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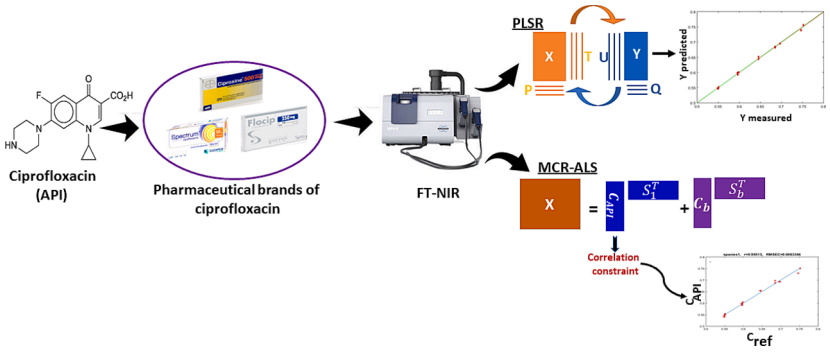
HIGHLIGHTS

- PLS vs. MCR-ALS for ciprofloxacin quantitation by FT-NIR in various cases.
- In the same matrix, both methods demonstrated good quantitation with low errors.
- PLS struggled with varying matrix compositions, while MCR-ALS excelled.
- PLS showed errors in quantitating ciprofloxacin with new excipients.
- MCR-ALS achieved accurate quantitation across all samples.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Ciprofloxacin
FT-NIR
Matrix effect
PLS
MCR-ALS

ABSTRACT

This study aims to quantify ciprofloxacin in commercial tablets with varying excipient compositions using Fourier Transform Near-Infrared Spectroscopy (FT-NIR) and chemometric models: Partial Least Squares (PLS) and Multivariate Curve Resolution - Alternating Least Squares (MCR-ALS).

Matrix variation, arising from differences in excipient compositions among the tablets, can impact quantification accuracy. We discuss this phenomenon, emphasizing potential issues introduced by varying certain excipients and its importance in reliable ciprofloxacin quantification.

We evaluated the performance of PLS and MCR-ALS models independently on two sets of tablets, each containing the same drug substance but different excipients. The statistical results revealed promising results with PLS prediction error of 0.38% w/w of the first set and 0.47% w/w of the second set, while MCR-ALS achieved prediction errors of 0.67% w/w of the first set and 1.76% w/w of the second set.

To address the challenge of matrix variation, we developed single models for PLS and MCR-ALS using a dataset combining both first and second sets. The PLS single model demonstrated a prediction error of 4.3% w/w and a relative error of 6.41% w/w, while the MCR-ALS single model showed a prediction error of 1.88% w/w and a relative error of 1.29% w/w.

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https://doi.org/10.1016/j.saa.2023.123268
Received 15 May 2023; Received in revised form 27 July 2023; Accepted 15 August 2023
Available online 16 August 2023

We then assessed the performance of the single PLS and MCR-ALS models developed based on the combination of the first and the second set in quantifying ciprofloxacin in various commercial tablet brands containing new excipients. The PLS model achieved a prediction error ranging between 6.2% w/w and 8.39% w/w, with relative errors varied between 8.53% w/w and 12.82% w/w. On the other hand, the MCR-ALS model had a prediction error between 1.11% w/w and 2.66% w/w, and the relative errors ranging from 0.8% to 1.74% w/w.

1. Introduction

The Association of chemometric techniques to spectroscopic methods has shown its efficiency in the pharmaceutical applications [1]. These applications vary according to the purpose whether quantitative, qualitative, or unveiling the degradation process of the active pharmaceutical ingredient (API) and reveal its multiple solid-state transitions [2,3]. Vibrational spectroscopy techniques are characterized by several advantages such as non-destructivity, simplicity and rapidity of use such as near infrared spectroscopy [4–6]. However, several challenges limit vibrational spectroscopy techniques to be applied as in case of the presence of high overlapped absorption spectra [7]. The application of multivariate calibration methods, based on the mathematical elaboration of a high number of variables, can allow to overcome the spectral overlap of API or excipients and permit their rapid qualitative and quantitative analysis [8]. Furthermore, the chemometric tools agree with the requirements of the green analytical chemistry. This area concerns the role of the analyst in developing laboratory practices more environmentally friendly, by minimizing the use of chemicals, energy use, waste and recycle.

Among of chemometric approaches that are used with vibrational spectroscopy for API quantitation in a mixture are PLS regression and MCR-ALS [9,10]. Each of these two approaches works in a different way, PLS regression aims to correlate spectral information with a dependent variable such as pharmaceutical tablet content [11]. Thus, a model is built to predict the property of interest from new sample spectra. MCR is a curve resolution method that decomposes the data matrix into its pure response profiles and their relative concentrations. MCR works in an iterative way (Alternating Least Squares–ALS) to achieve the best data decomposition. The ALS algorithm allows for several types of constraints (e.g. non-negativity in concentration/ spectral profile, correlation) to improve and reach chemical reasonable MCR solutions [12].

For the same API, the pharmaceutical product can be manufactured by many pharmaceutical companies; thus, the excipients used can vary in the different formulations [13,14]. Even though the target analyte to be analyzed with spectroscopic techniques is the same, the developed model for a specific formulation may be used only for the quantitative purpose of samples with the same composition. This constraint is due to the analysis by spectroscopic techniques usually applied on the whole matrix and the chemometric processing is applied in the spectral data [15,16].

This work focused on performing two distinct chemometric approaches. MCR-ALS with correlation constraint and PLS regression for the quantitative analysis of ciprofloxacin in different tablets. These samples composed of three sets. The first and second sets are a ternary mixture with different excipients. The third set was composed of different brands of ciprofloxacin pharmaceutical products, that were manufactured by different pharmaceutical companies. To test the ability of chemometric approaches to carry out the quantitation of ciprofloxacin in a sample with different excipients, both of first and second sets were merged and single models were developed by each chemometric approach. Both PLS and MCR-ALS models that are developed based on the merged sets, were used to quantitate ciprofloxacin in different brands of pharmaceutical products in a third set.

2. Material and methods

2.1. Sample preparation

Two sets of 16 mixtures were prepared based on a mixture design, each set consist of a quaternary mixture. Both of sets composed with the same target drug substance of ciprofloxacin (TCI-Chemicals, Belgium), but with different excipients. Microcrystalline cellulose (Sigma-Aldrich, Belgium) and monohydrate lactose (Sigma-Aldrich, Belgium) are excipients of the first set, whereas povidone (Sigma-Aldrich, Belgium) and starch (Sigma-Aldrich, Belgium) are the main excipients of the second set. while stearate of magnesium (TCI-Chemicals, Belgium) is the common excipient of both sets as it is shown in Table 1. Each compound was varied at five levels depend on the ratio of ciprofloxacin that is existed in the pharmaceutical formulations: ciprofloxacin varied in the range 55–75% (w/w), while all excipients varied between 10 and 30% (w/w) range except content of magnesium stearate was kept unchanged at 5% (w/w). all mixtures range with total weight of 200 mg.

Each mixture was weighted and then were mixed using pestle and mortar to ensure the homogeneity. Each sample was pressed in a Specac hydraulic press under 5 ton/cm^2 for 1 min to form a ciprofloxacin tablet with a diameter of 10 mm.

Besides of two sets, a set of ciprofloxacin commercial tablets, that contain 500 mg of ciprofloxacin, consists of three brands of pharmaceutical samples. These samples were acquired from local drugstore. Each brand has different excipient as illustrated in Table 2. Each commercial tablet of ciprofloxacin was grinded and homogenized using the pestle and mortar. A weight of 200 mg of the homogenized powder was transferred to form a tablet with 10 mm of diameter using Specac hydraulic press.

2.2. Instrumentation

The samples were analyzed with a Fourier transform near infrared multipurpose analyzer spectrophotometer (MPA, Bruker Optics, Billerica, MA, USA). The spectra were collected with the Opus software V6.5 (Bruker Optics). Each spectrum was the average of 32 scans and the resolution was set at 8 cm^{-1} over the spectral range from 12,500 to

Table 1A
Amount of ciprofloxacin in first set.

	Ciprofloxacin % w/w	MCC % w/w	Lactose % w/w	Mg st % w/w
1	75%	10%	10%	5%
2	75%	10%	10%	5%
3	65%	10%	20%	5%
4	66%	19%	10%	5%
5	70%	15%	10%	5%
6	66%	11%	17%	6%
7	60%	25%	10%	5%
8	60%	10%	25%	5%
9	55%	25%	15%	5%
10	55%	15%	25%	5%
11	55%	30%	10%	5%
12	55%	10%	30%	5%
13	60%	18%	17%	5%
14	60%	17%	18%	5%
15	70%	12%	13%	5%
16	70%	13%	12%	5%

*MCC: microcrystalline cellulose, Mg st: magnesium stearate.

Table 1B
Amount of ciprofloxacin in the second set.

	Ciprofloxacin % w/w	Povidone% w/w	Starch % w/w	Mg st % w/w
1	75%	10%	10%	5%
2	75%	10%	10%	5%
3	65%	10%	20%	5%
4	66%	19%	10%	5%
5	70%	15%	10%	5%
6	66%	11%	17%	6%
7	60%	25%	10%	5%
8	60%	10%	25%	5%
9	55%	25%	15%	5%
10	55%	15%	25%	5%
11	55%	30%	10%	5%
12	55%	10%	30%	5%
13	60%	18%	17%	5%
14	60%	17%	18%	5%
15	70%	12%	13%	5%
16	70%	13%	12%	5%

Table 2
Different commercial tablets.

	Name of pharmaceutical product	Number of tablets	manufacturer	Excipients
Brand-I	Spectrum- 500	5 tablets	Cooper pharma	Croscarmellose; microcrystalline cellulose; Povidone; magnesium stearate; Colloidal silica
Brand-II	ciproxine-500 mg	5 tablets	BAYER	Sodium starch glycolate; povidone; microcrystalline cellulose; magnesium stearate
Brand-III	Fleocip-250 mg	5 tablets	Sothema	microcrystalline cellulose; povidone; magnesium stearate; Corn starch

4000 cm^{-1}. (Fig. 1).

2.3. Data analysis and software

Before applying whether PLS or MCR-ALS, preprocessing of the spectra was the first step to be carried out on the NIR spectra. The aim of this initial step is to reduce the instrumental and physical artefacts, such as noise and light scattering, that are not related to the chemical behavior of the analyzed mixtures. The performance of different preprocessing techniques, including 1st and 2nd derivatives, Standard Normale variate (SNV) and multiplicative Signal Correction (MSC), were investigated individually and in combination. Among of the preprocessing techniques, SNV and 1st derivative proved to be the most efficient in correcting the NIR spectra, based on the lowest predictive error obtained of PLS regression and MCR-ALS models. Fig. 2 demonstrate the original spectral data, providing a basis for comparison with the preprocessed spectra in Fig. 3. The latter figure offers a direct visual comparison between the raw and preprocessed spectra using different techniques: SNV and 1st derivative.

Each of two datasets was split into a calibration and validation sets using Kennard-stone algorithm. The same calibration and test set were used to develop models of PLS regression and MCR-ALS.

To carry out the quantitation of ciprofloxacin using MCR-ALS, singular value decomposition (SVD) was the first step used to determine the number of components based on the differences between eigenvalues and prior knowledge about one or more compound that exist in the mixture. Then, the initial estimation was carried out using the purest variable approach to estimate the spectral profile of each compound (S^T) and their profile concentration (ciprofloxacin and excipients for each set). To acquire chemically and physically meaningful solutions of both C and S^T, the optimization was carried out by iterative ALS procedure. This procedure includes several constraints that were applied on the developed MCR-models to minimize the impact of rotational ambiguity problem and thus obtain a unique solution. In this sense, the constraint of non-negativity was used only on the concentration profile, whereas the same constraint was not applied to the spectral profile since the spectra were preprocessed. The correlation constraint, with the objective of performing quantitative analysis, was also used. By the application of this last constraint, it was possible to predict the concentration values in unknown samples as the concentration of a specific component, in this case, it was ciprofloxacin that was correlated with its reference concentration value. In this sense, a MCR calibration model is developed and used to predict the concentration of component of ciprofloxacin.

Both of MCR-ALS and PLS models were evaluated using root mean

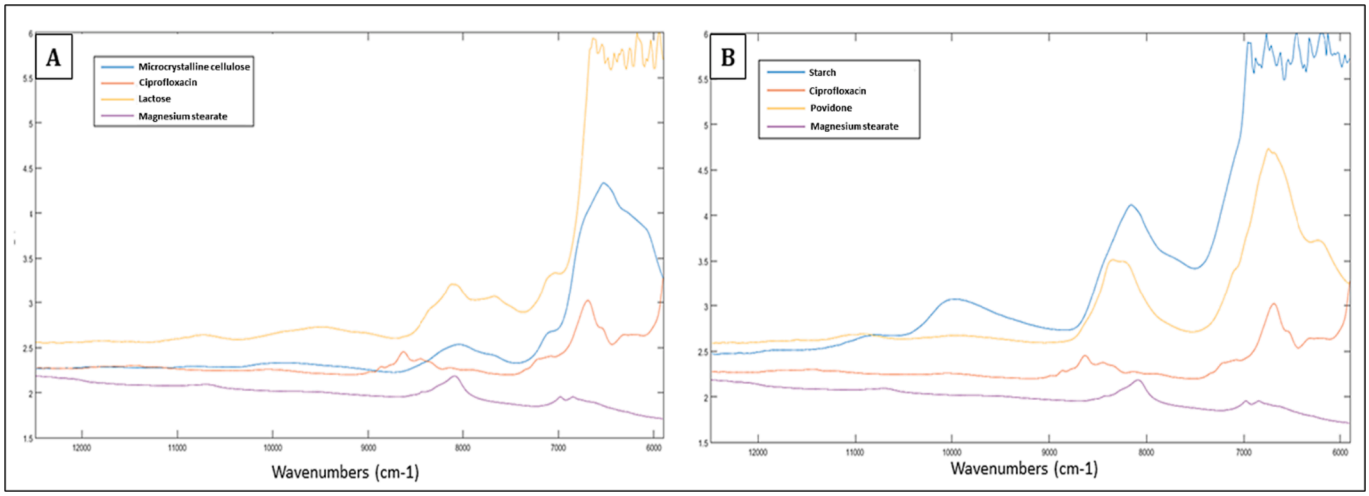

Fig. 1. Composition spectra of each set. (a): set-1; (B): set-2.

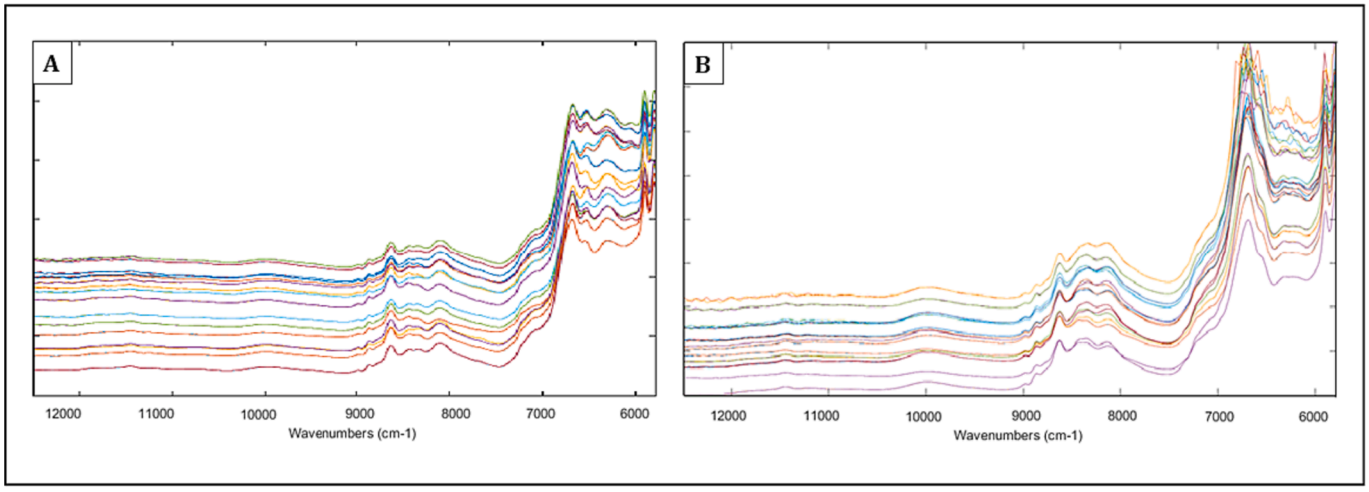

Fig. 2. Mixture spectra of each set. (a): set-1; (B): set-2.

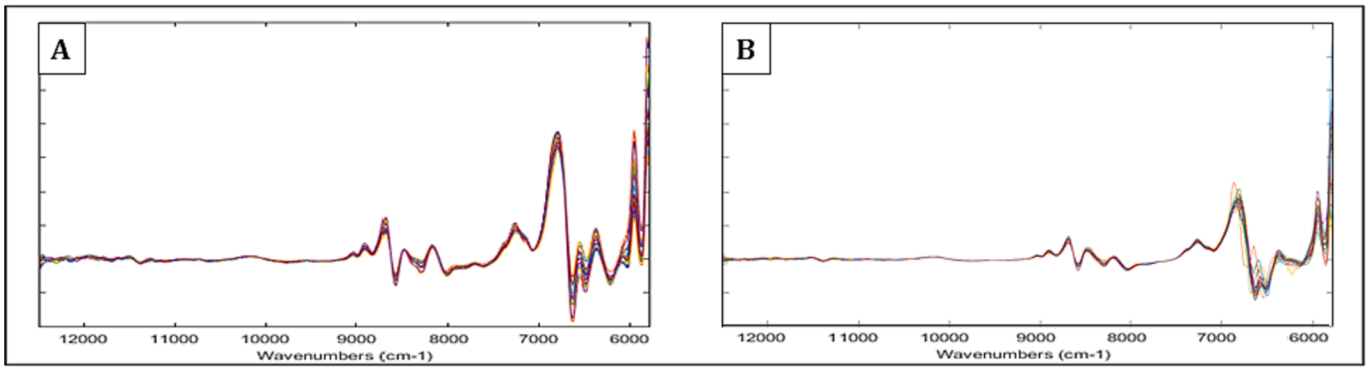

Fig. 3. Preprocessed mixture spectra. (A): set-1; (B): set-2.

square error of prediction (RMSEP), determination coefficient (R_p^2) and relative percentage error in concentration (RE). RMSEP were calculated according to the following equations:

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(c_i - \hat{c}_i)^2}{n}} \quad (1)$$

$$RE(\%) = \sqrt{\frac{\sum_{i=1}^{n}(c_i - \hat{c}_i)^2}{\sum_{i=1}^{n} c_i^2}} \times 100 \quad (2)$$

where, n is the number of samples, c_i is the experimental measurement for prediction samples, and $\hat{c}_i$ is the obtained value that correspond to validation.

The PLS modelling was performed using the PLS Toolbox V8.2.1 (Eigenvector Research INC, USA) running on Matlab version R2018b (MathWorks, USA) while the MCR-ALS modeling was performed trough an interface graphical user [17].

3. Results and discussion

3.1. NIR spectra of each set components

Fig. 1 shows the raw NIR spectra of compounds that form tablets of each set, where spectral feature of all compounds including the target analyte are identifiable. Whereas Fig. 1A and Fig. 1B shows spectra of each compound of the first and second set respectively, Fig. 2 represents NIR spectra of ciprofloxacin in mixtures. Regarding NIR spectra of ciprofloxacin in each mixture in Fig. 2A and Fig. 2B, it can be seen that the profile of NIR mixture spectra of the first set is different from the second one. Although the NIR spectra was recorded from 12,500 to 4000 cm^{-1}, the quantitative analysis whether by PLS or MCR-ALS was limited to 9792 cm^{-1}-7360 cm^{-1} in order to remove the high absorbance that were noticed at the end of spectra of some excipients of microcrystalline cellulose and starch that lead to a noisy region that have an impact on the developed model if it has been included. Then the preprocessed techniques were applied on the selected region as it is shown in Fig. 3.

3.2. Quantitative analysis of ciprofloxacin

Ciprofloxacin is the target analyte that was used in this study for quantitation, where two cases were considered as illustrated in Fig. 4. Regarding to the first case, the quantitative analysis was carried out on each set independently to evaluate the quantitation by PLS and MCR-ALS without considering matrix effect. Whereas the second case, the quantitation by PLS and MCR-ALS on the merged set based on gathering the first and second set was performed considering the matrix effect. The developed models in the second case were applied and tested on different brands of ciprofloxacin commercial tablets.

3.2.1. Quantitative analysis without considering matrix effect (first case)

The concentration of ciprofloxacin was performed in mixtures of each set independently using two different multivariate regression techniques PLS and MCR-ALS, applied to the NIR spectra. While the optimal latent variables of PLS, which used to develop the model, was obtained based on a leave-one-out cross validation, the model of MCR was based on the ALS optimization that includes constraints of non-

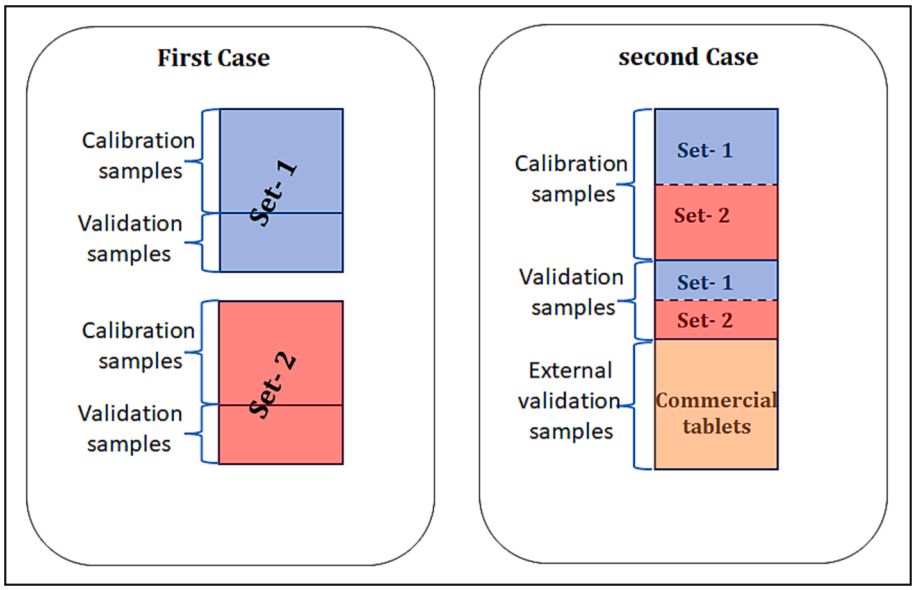

Fig. 4. Schematic representation of each situation.

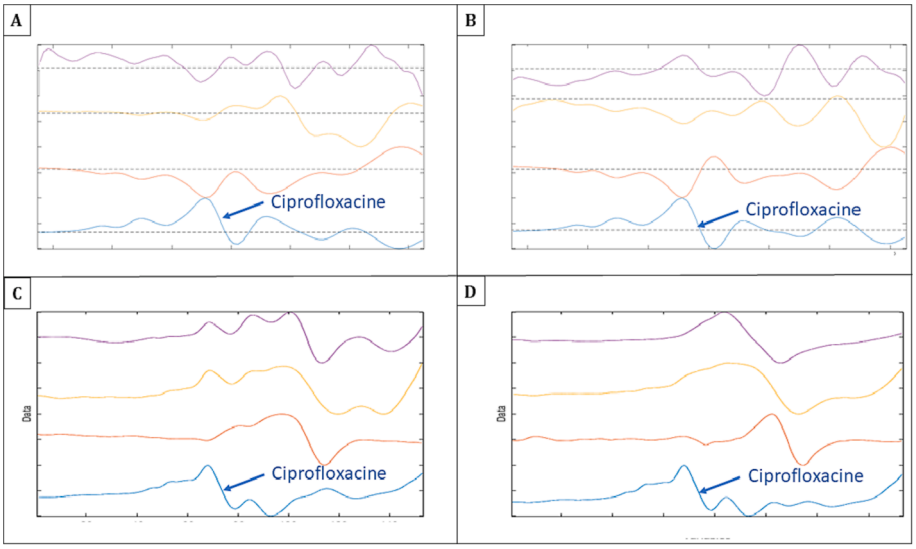

Fig. 5. Loadings (PLS) and recovered spectra (MCR-ALS). (A and C): loadings and recovered spectra of set-1; (C and D): loadings (PLS) and recovered spectra (MCR-ALS) of set-2.

negativity and correlation. The last cited constraint is responsible on performing the quantitative analysis by MCR. Regarding to Fig. 5A and Fig. 5C which shows the four loadings obtained by PLS in first and second set respectively, the first loading represents clearly the obtained preprocessed spectrum of ciprofloxacin. Whereas Fig. 5B and Fig. 5D correspond to spectra profiles obtained by MCR-ALS, which the main curve obtained by MCR was recognized to be the preprocessed spectrum of ciprofloxacin in both sets.

Fig. 6 shows the reference vs predicted concentration values plot for the developed models that shows clearly well distribution of predicted values around the line whether for PLS or MCR- ALS in both sets.

These obtained results are summarized in the Table 3. According to these results, both MCR-ALS and PLS models are able to predict the concentration values of unknown samples in the same matrix. However, in this case of quantifying ciprofloxacin in each set independently, PLS has lower RMSEP and RE compared to MCR-ALS.

3.2.2. Quantitative analysis of ciprofloxacin considering matrix effect (second case)

A single model of PLS and MCR-ALS was developed on a merged set of both first and second sets, where the matrix effect was caused by variation in excipients from one mixture to another. The PLS regression model was developed based on six latent variables determined by cross validation of leave-one-out, while for MCR-ALS, six principal components were determined based on singular value decomposition (SVD).

Table 3 summarizes the obtained results for validation of the merged set using PLS and MCR-ALS. It is observed that the PLS model developed on the merged set exhibits higher RMSEP and RE values compared to the PLS models developed on each set independently in section 3.2.1. On the other hand, the MCR-ALS models demonstrate consistently low errors for both the merged set and each set individually, indicating the model's robustness in handling variation in matrix composition. These results highlight the impact of matrix composition variation on the predictive accuracy of PLS models and underscore the ability of MCR-ALS to handle spectral differences arising from excipients not present in the merged

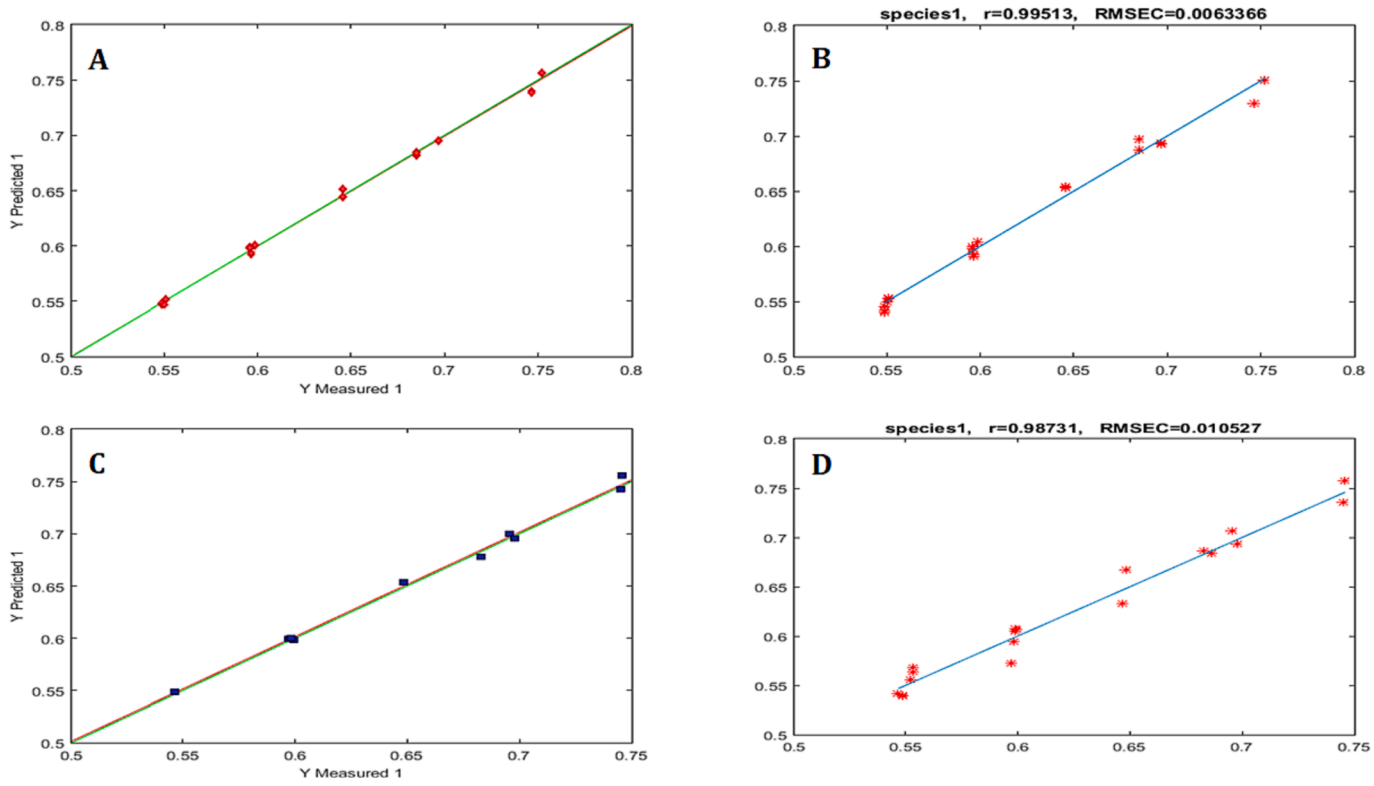

Fig. 6. Plots of reference values vs predicted values for PLS and MCR for set-1 (A and B) and set-2 (C and D).

Table 3
Results of PLS and MCR-ALS models for each set and merged set.

	PLS				MCR-ALS			
	LV	R^2p %	RMSEP	RE %	PCs	R^2p %	RMSEP	RE%
Set-1	4	99.7	0.38	0.54	4	99.27	0.67	1.15
Set-2	4	99.79	0.47	0.68	4	94.59	1.76	1.98
Merged set	6	85.55	4.3	6.41	6	95.39	1.88	1.29

set.

3.2.3. *Quantitative analysis of ciprofloxacin in different brands of pharmaceutical products*

The PLS and MCR-ALS models developed on the merged set, were employed to predict the ciprofloxacin content in commercial tablets from different manufacturers, each containing different excipients not included in the merged set.

Table 4 presents the performance of PLS and MCR-ALS for the commercial samples. The results indicate that the variation in matrix composition of commercial tablets leads to increased error in the PLS model. Specifically, the commercial tablets of Spectrum 500 mg show the highest relative error (RE) and prediction error (RMSEP) compared to other brands due to the presence of excipients (croscarmellose and colloidal silica) not found in the samples of the merged set. In contrast, the MCR-ALS model shows consistently low errors for all brands, regardless of the excipients' composition, validating its ability to handle spectral differences arising from the absence or presence of excipients in the pharmaceutical products.

Table 4
Results of the application of PLS and MCR-ALS models on the commercial tablets.

	Name of pharmaceutical product	PLS		MCR-ALS	
		RE %	RMSEP	RE %	RMSEP
Brand- I	Spectrum- 500	12.82	8.39	2.66	1.74
Brand- II	ciproxine-500 mg	9.78	6.38	2.54	1.65
Brand- III	Flocip-250 mg	8.53	6.20	1.11	0.80

4. Conclusion

A comparison between PLS and MCR-ALS were investigated to quantify ciprofloxacin using FT-NIR in different cases. Initially, quantitation was evaluated in the same matrix, followed by assessment in a varied matrix composition and finally in different brands of pharmaceutical products manufactured by different pharmaceutical companies.

In the first case, the obtained results demonstrated the ability of both chemometric tools to quantify ciprofloxacin in the same matrix with low errors, showcasing their first order advantage. However, In case of quantitation of ciprofloxacin in a dataset with varying matrix compositions. PLS model exhibited limitations, resulting in increased errors compared to the first case. On the other hand, the MCR-ALS model maintained low error even when the matrix composition was changed from one sample to another. This highlighted the MCR-ALS's ability to deal with matrix effects and predict the content of ciprofloxacin in different matrix composition, thanks to its second-order advantage.

Finally, the quantitation of ciprofloxacin in different brands of

commercial tablets revealed that the error of the PLS model kept arising especially in samples with new excipients. Conversely, the MCR-ALS enabled the accurate quantitation of ciprofloxacin in all commercial samples, regardless of the pharmaceutical sample's composition, thanks to its ability to resolve the spectra of mixture components.

CRediT authorship contribution statement

M. Alaoui Mansouri: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **M. Kharbach:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **M. El Maouardi:** Visualization, Resources. **I. Barra:** Visualization, Writing – review & editing. **A. Bouklouze:** Conceptualization, Supervision, Visualization, Project administration, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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