https://doi.org/10.31925/farmacia.2025.2.18 **ORIGINAL ARTICLE**

DEVELOPMENT OF HIGH-THROUGHPUT NIR-CHEMOMETRIC METHODS FOR THE CHARACTERISATION OF POWDER BLENDS FOR TABLETTING AND EXTENDED-RELEASE TABLETS WITH KETOPROFEN

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Abstract

This study aimed to develop and validate NIR-chemometric methods for direct quantification of ketoprofen and lactose in powder blends for tabletting, respectively, ketoprofen, lactose, and the kinetics of release from extended-release inert matrix tablets. Calibration samples were prepared using an experimental design with two variables and five levels, including 26 formulations. The *in vitro* release was carried out in phosphate buffer (pH = 7.4), utilising a dissolution testing device equipped with baskets at 100 rpm. The calibration algorithm for ketoprofen was obtained using as pre-treatment method FD+MSC (PLS = 7, RMSECV = 1.46) for powder blends, respectively SNV (PLS = 10, RMSECV = 3.94) for tablets in the 10000 - 6098 cm^{-1}; 5454 - 4596 cm^{-1} spectral ranges. In the case of lactose, the calibration algorithm was obtained using the pre-treatment method SLS (PLS = 7, RMSECV = 1.79) for powder blends, respectively FD+SNV (PLS = 4, RMSECV = 6.45) for tablets, in the 10000 - 4200 cm^{-1} spectral range. For kinetic release characterization, the Higuchi equation parameters were determined and correlated with the tablets' NIR spectra to develop a chemometric method to estimate the kinetic release directly. According to the experimental data, the calibration algorithms were validated with satisfactory accuracy, reproducibility and linearity.

Rezumat

Scopul acestui studiu a fost dezvoltarea și validarea metodelor NIR-chemometrice pentru cuantificarea directă a ketoprofenului și lactozei în amestecurile de pulberi pentru comprimate, respectiv ketoprofen, lactoză și cinetica eliberării din comprimatele cu matrice inertă cu eliberare prelungită. Probele de calibrare au fost pregătite conform unui design experimental cu 2 variabile și cinci niveluri, incluzând 26 de formulări. Cedarea *in vitro* a fost realizată în tampon fosfat (pH = 7,4), folosind un dispozitiv de testare a dizolvării echipat cu coșuri, la 100 rpm. Algoritmul de calibrare pentru ketoprofen a fost obținut folosind ca metodă de pretratare FD+MSC (PLS = 7, RMSECV = 1,46) pentru amestecurile de pulberi, respectiv SNV (PLS = 10, RMSECV = 3,94) pentru comprimate în intervalele spectrale 10000 - 6098 cm^{-1}; 5454 - 4596 cm^{-1}. În cazul lactozei, algoritmul de calibrare a fost obținut folosind ca metodă de pretratare SLS (PLS = 7, RMSECV = 1,79) pentru amestecurile de pulberi, respectiv FD+SNV (PLS = 4, RMSECV = 6,45) pentru tablete, în intervalul spectral 10000 - 4200 cm^{-1}. Pentru caracterizarea cineticii eliberării au fost determinați parametrii ecuației Higuchi și corelați cu spectrele NIR ale comprimatelor, pentru a dezvolta o metodă NIR-chemometrică pentru estimarea directă a cineticii eliberării. Conform datelor experimentale obținute, algoritmii de calibrare au permis validarea metodelor cu acuratețe, reproductibilitate și linearitate satisfăcătoare.

Keywords: ketoprofen, extended-release tablets, NIR spectroscopy, *in vitro* release

Introduction

Process Analytical Technology (PAT) is a concept introduced by the United States FDA that implies the design and control of pharmaceutical processes through real-time measurements of critical process parameters that could affect quality assurance. According to PAT, quality is/or should be built into pharmaceutical products and is only possible through the understanding and control of manufacturing processes [1].

NIR spectroscopy represents a powerful analytical tool that can fulfil the objectives of PAT and has been successfully applied in different domains, like powder blending [2-9], lyophilisation [10-12], granulation process [13, 14], tableting [15], film coating [16],

quantification of API and excipients [17-19] and even characterization of tablet physical properties [20, 21]. NIR spectroscopy is a vibrational spectroscopic method known for its high throughput and non-destructive nature. The technique has a low absorption coefficient, which allows an increased penetration, a characteristic that can be considered an analytical advantage, offering the possibility to analyse strongly absorbing samples or those that can disperse light. Throughout an analysis, the samples are irradiated with light of 700 - 2500 nm, characteristic of this spectral region, when an increase occurs in the molecule's vibrational state by the absorption of energy [22].

Through pre-processing methods, it is possible to amplify the relevant data contained in the spectra and reduce the irrelevant data, allowing the correlation with the physicochemical properties of the analysed samples without prior sample pre-treatment or separation [3].

This study aimed to develop and validate a NIR-chemometric method for quantifying ketoprofen and lactose from powder blends for tabletting and extended-release matrix tablets. Such a method, which doesn't require any sample pre-treatment, offers the possibility of real-time monitoring of powder blending and the analysis of the final product. Another objective was to develop a NIR-chemometric method for the direct estimation of the kinetic release of ketoprofen. Predicting the release of API from the tablet is advantageous and time-saving, as there would be no need to go through 24-hour-long dissolution tests characteristic of prolonged-release tablets.

The novelty of this work is represented by the new approach used to evaluate the drug dissolution rate by choosing an appropriate model that describes the kinetics of release from the prolonged-release tablet and correlating the equation parameter with the NIR spectra of the tablets.

Materials and Methods

Materials

The active pharmaceutical ingredient (API) ketoprofen was purchased from SIMS (Italy). Lactose monohydrate (grade GranuLac® 200, average particle size 50 μm, and Tablettose® 80, average particle size 170 μm) was supplied by Meggle (Germany), microcrystalline cellulose (grade VIVAPUR® 101, average particle size, 65 μm) by JRS Pharma (Germany). Polyvinyl-pyrrolidone k25 (grade Kollidon® 25, particle size distributions, max. 40%, < 50 μm) and co-processed excipient of polyvinyl acetate with povidone (Kollidon® SR, average particle size, 64 μm) were kindly gifted by BASF (Germany). Silicone dioxide (grade AEROSIL® 200 Pharma) and magnesium stearate (Kemilub® EM-F) were purchased from Evonik (Germany) and Union Derivan (Spain), respectively.

Apparatus

NIR spectrophotometer-Antaris (Thermo Electron, SUA), dissolution tester PT7 (PharmaTech, Germany), UV-VIS spectrophotometer (Analytic Jenna, Germany), Erweka Oscillating granulator (Germany), Erweka LK5 blender (Germany), Korsch EK0 eccentric tablet press.

Software

The software used for data analysis were OMNIC software (Thermo Scientific, USA), Opus Quant 2 (Bruker Optics, Germany), Microsoft Office Excel 2010 (Microsoft, USA) and Sigma Plot 11.0 (Systat Software, USA).

Methods

Preparation of powder blends and tablets for NIR calibration

Developing a quantitative NIRS method implies having an appropriate calibration set that includes any source of variability that could appear in the composition of the analysed sample. The calibration samples for powder blends and tablets were prepared using an experimental design with two variables (2 substances) and five levels (80% - 120%). The composition of tablets is presented in Table I.

Table I

Quantitative and qualitative composition of powder blends/tablets and levels of variation of the experimental variables (mg/tablets)

Substance/Levels of variation	80%	90%	100%	110%	120%
Ketoprofen	160	180	200.00	220	240.00
Kolidon RS	86.00	96.75	107.50	118.25	129.00
Lactose DC	130.03	93.34	56.65	19.96	0.00
PVP k25	7.52	8.46	9.40	10.34	11.28
Lactose monohydrate	10.00	11.25	12.50	13.75	15.00
Microcrystalline cellulose	30.00	33.75	37.50	41.25	29.00
Aerosil	2.15	2.15	2.15	2.15	2.15
Magnesium stearate	4.30	4.30	4.30	4.30	4.30
	430	**430**	**430**	**430**	**430**

Ketoprofen, microcrystalline cellulose, and lactose monohydrate were homogenised using an Erweka LK5 blender. The homogenous mix was transferred in an Erweka kneader granulator and processed by wet granulation using a 10% aqueous solution of PVP k25. The granules were passed through a 1.200 μm sieve and dried in an oven at 40ºC. Dry calibration was done with a 1.200 μm sieve to split the

agglomerates, ensuring the homogenous distribution of the size of the granules.

The resulting granules were homogenised with Lactose DC, Kolidon SR, and Aerosil for the appropriate time. Further, magnesium stearate was added, and the mixing continued.

The tablets for the calibration set were prepared by tableting the corresponding powder blends with a Korsch EK0 eccentric tablet press, equipped with punches and die of Ø 10 mm. The compression force was set between 20 - 25 kN, in order to obtain tablets with a hardness of 12 - 16 kgf.

In-vitro dissolution studies

The *in vitro* dissolution studies were realised using a PharmaTest PTWS100 dissolution testing device equipped with baskets. The dissolution study was carried out in phosphate buffer (pH 7.4) at a stirring rate of 100 rpm. Sampling was done at 1, 2, 3, 4, 6, 8, 10 and 24 hours, with every taken volume being replaced with the equivalent volume of dissolution medium. The dissolution profiles were obtained by quantifying the released API using a UV-VIS spectrophotometric method (Analytic Jenna, Germany) at the wavelength of 258 nm.

NIR analysis of the powder blends and tablets

NIR spectra for powder blends were recorded using an FT-NIRS, Antaris (Thermo Scientific, USA) in the Reflectance sampling configuration. Each spectrum was acquired *via* OMNIC software by integrating 32 scans taken over a wave between 4.000 cm^{-1} to 10.000 cm^{-1} with 8 cm^{-1} resolution. In the case of tablets, the NIR spectra were recorded using an FT-NIRS, Antaris (Thermo Scientific, USA) in the Reflectance sampling configuration. Each spectrum was acquired via OPUS software by integrating 32 scans taken over a wave between 4,000 cm^{-1} and 10,000 cm^{-1} with 8 cm^{-1} resolution. Both devices are equipped with an InGaAs (indium gallium arsenide) detector, combining measurement speed and a large spectral domain appropriate for this study [23].

NIR spectra processing

Multivariate regression methods are used to correlate the information between two matrices, for example, the quantity of API/excipients and NIR spectra.

The obtained spectra were analysed by PLS regression associated with different pre-treatment methods or their combination being applied on the whole spectra or to specific regions, using the OPUS Quant software package (Bruker Optics, Germany). The pre-treatment methods used to develop the calibration model were: constant offset elimination (COE), straight line subtraction (SLS), min-max normalization (MMN), multiplicative scatter correction (MSC), first derivative (FD), second derivative (SD) and the combination of them (FD+SLS, FD+SLS, FD+MSC). The model's predictive ability was evaluated according to the following criteria: low root mean square error of cross-validation (RMSECV), a high value of R^2, a low number of PLS factors, and a low Bias.

Method validation

For the validation of a method to be consistent with the regulatory guidelines such as EMA or FDA and with the suggestions of the International Conference of Harmonization (ICH), specific parameters must be determined: accuracy, precision, linearity, and range of applicability. The validation protocol was built using the strategy proposed by Hubert *et al*. [23-26] and other reviews on NIR methods validation [27, 28].

After obtaining an adequate calibration model, the method was validated using a set of independent formulations corresponding to 80% - 100% - 120% (N7, N13, N19), prepared by the same procedure.

Results and Discussion

Development of NIR-chemometric method for the quantification of ketoprofen and lactose from powder blends

The calibration model for powder blends was built by recording the spectra of three samples corresponding to each formulation from a total of 27. Overall, 81 spectra were recorded and analysed (Figure 1).

The model development consisted of applying a particular spectral pre-treatment method or its combination on different spectra regions that contain strong absorption bands of the substance for the model being built.

To obtain a valid PLS chemometric calibration, it is essential to ensure the correct number of PLS factors and the proper pre-treatment method. Every spectral pre-treatment method chosen has the lowest number of PLS factors and whose RMSECV (root mean square error of cross-validation) is not significantly higher than the RMSECV of the model with one more factor. Also, the squared correlation coefficient (R2) was determined to characterise the model's predictive ability. The optimal number of PLS factors was determined with the cross-validation procedure.

The results obtained during the development of the calibration models for ketoprofen and lactose assay from powder blends with and without pre-processing methods are presented in Table II.

In the case of ketoprofen, R^2 can be used to differentiate the models from each other, and a noticeable difference can be observed between no pre-processing and applying a pre-processing method. Also, the number of PLS factors and RMSECV must be considered, given the differences between different models.

The calibration algorithm for ketoprofen in powder blends was best used as pre-treatment method FD+MSC (PLS = 7, RMSECV = 1.46) in the 10000 - 7147 cm^{-1}; 6904 - 5619 cm^{-1}; 5303 - 4497 cm^{-1}; 4300 - 3999 cm^{-1} spectral ranges (Figure 1b).

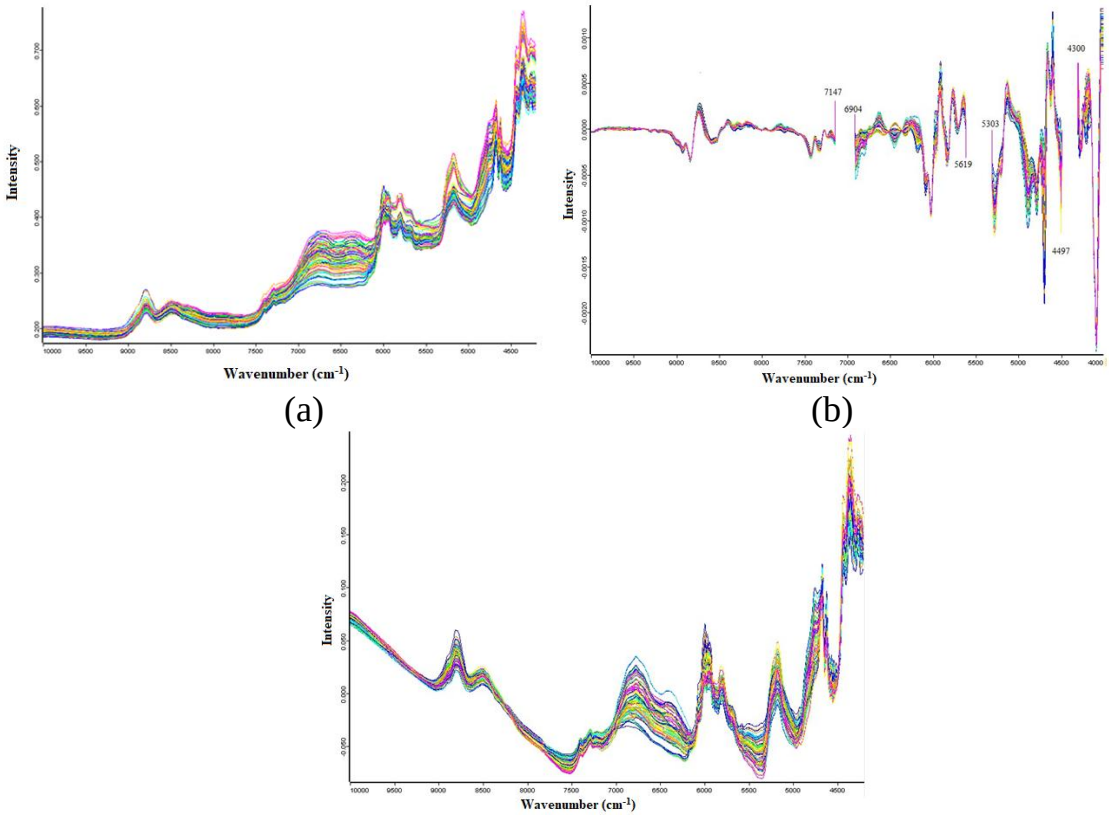

Figure 1.

NIR spectra of powder blends for tableting without pre-processing (a), pre-processed using FD+MSC for ketoprofen (b) and pre-processed using SLS for lactose assay (c)

Table II

Statistical parameters and number of PLS factors for different models proposed for ketoprofen and lactose assay in powder blends, with and without pre-processed spectra

Ketoprofen											
Model	a	b	c	d	e	f	g	h	i	j	k
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	FS+SLS	FD+SNV	**FD+MSC**
Spectral range (cm^{-1})	10000 - 7147; 6904 - 5619; 5303 - 4497; 4300 - 3999										
Number of PLS factors	9	9	8	9	8	13	8	6	8	9	**7**
R^2	89.79	92.11	92.07	93.3	93.64	95.85	93.9	92.65	93.65	95.08	**94.67**
RMSECV	2.03	1.78	1.79	1.64	1.6	1.29	1.57	1.72	1.6	1.41	**1.46**
Lactose											
Model	a	b	c	d	e	f	g	h	i	j	k
Pre-treatment	None	COE	**SLS**	SNV	mMN	MSC	FD	SD	FS+SLS	FD+SNV	FD+ MSC
Spectral range (cm^{-1})	10000 - 4200										
Number of PLS factors	9	8	**7**	8	9	7	7	3	4	4	3
R^2	94.63	94.67	**94.93**	95	92.69	94.74	95.38	94.2	93.2	94.26	93.24
RMSECV	1.84	1.83	**1.79**	1.77	2.15	1.82	1.71	1.91	2.07	1.9	2.06

None – no pre-processing; COE – Constant Offset Elimination; SLS – Slight Line Subtraction; SNV – Standard Normal Variate; mMN – Minim Maxim Normalization; MSC – Multiplicative Scattering Correction; FD – First Derivative; SD – Second Derivative

For lactose, the values of R^2 and RMSECV vary in a smaller domain compared to ketoprofen, giving close values between methods, even compared to no pre-treatment.

In the case of lactose, the calibration algorithm was obtained using as pre-treatment method SLS (PLS = 7, RMSECV = 1.79) in the 10000 - 4200 cm^{-1} spectral range (Figure 1c).

Validation of NIR-chemometric method for the quantification of ketoprofen and lactose from powder blends

The validation protocol included determining the method's trueness, precision, and accuracy. The method's trueness was evaluated by calculating the recovery and the relative bias. Bias represents the difference between the mean of measurement results

and the accepted reference value, while the recovery is expressed as the percentage of the amount of the analytical parameter detected reported to the amount included in the sample. The method's precision was estimated by calculating the repeatability and the intermediate precision. Table III shows the validation criteria of the NIR-chemometric methods.

Table III

Validation results of NIR-chemometric methods for quantification of ketoprofen and lactose in powder blends

Ketoprofen (FD+MSC)						
Concentration level (% ketoprofen)	**Trueness**		**Precision**		**Accuracy**	
	Relative bias (%)	Recovery (%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (%)
41.536	1.6523	101.652	2.1557	2.0752	[-3.058, 6.362]	[39.579, 43.492]
44.652	0.3146	100.315	1.2435	1.2101	[-2.439, 3.068]	[43.421, 45.881]
52.157	1.9426	101.943	0.9813	2.1591	[-5.836, 9.721]	[48.099, 56.214]
Lactose (SLS)						
Concentration level (% lactose)	**Trueness**		**Precision**		**Accuracy**	
	Relative bias (%)	Recovery (%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (%)
24.162	-0.6486	99.351	2.8299	3.0834	[-8.039, 6.742]	[22.376, 25.948]
16.705	3.8847	103.885	2.2221	1.9590	[-0.505, 8.275]	[15.971, 17.738]
7.881	0.5248	100.525	4.4542	4.4760	[-9.740, 10.790]	[7.0721, 8.6902]

The ketoprofen assay for powder blends (FD+MSC) showed good recovery for every concentration, all close to 100%. The highest concentration of ketoprofen (52.157%) shows the highest repeatability (0.981), a property that is adversely affected by the decrease in concentration.

The lactose assay for powder blends with SLS pre-processing showed good recovery for all concentrations and a small relative bias in the case of the lowest and highest concentrations. The lowest lactose content (7.871) showed the best recovery (100.525) and the lowest relative bias, but the highest value of repeatability (4.4542).

Figure 2 shows the linearity and accuracy profiles of the prediction models with the acceptance limits set to ± 10%, marked by the dotted line. The linearity profiles were obtained by plotting the measured concentrations of the external validation samples according to the theoretical concentrations. The accuracy profiles were represented by plotting the relative error according to the concentrations.

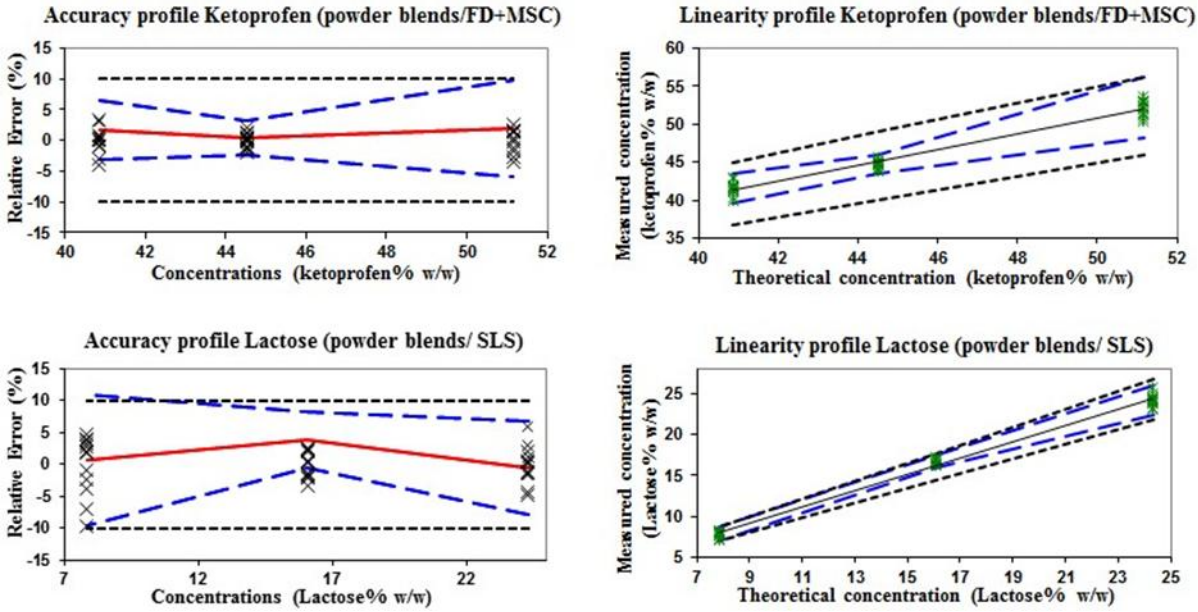

Figure 2.

The accuracy (left) and linearity profiles (right) obtained for the NIR chemometric methods developed for quantification of ketoprofen and lactose in powder blends

As seen in Figure 2, the ß-expectation tolerance limits for ketoprofen are fully included within the ± 10% acceptance limits and have the largest relative tolerance limits between -5.836 and 9.721.

The lowest concentration of lactose in the case of tablets the obtained (-9.740; 10.79) tolerance limits exceed the imposed limits.

Development of NIR-chemometric method for the quantification of ketoprofen and lactose from extended-release inert matrix tablets

The calibration model for tablets was built by recording fifteen spectra of each formulation from a total of 27. Four hundred five spectra were recorded (Figure 3a) and processed using PLS regression models with various pre-treatment methods or combinations.

The results obtained during the development of the calibration models for ketoprofen and lactose assay from extended-release inert matrix tablets with and without pre-processing methods are presented in Table IV.

Table IV

Statistical parameters and number of PLS factors for different models proposed for ketoprofen and lactose assay in extended-release inert matrix tablets, with and without pre-processed spectra

Ketoprofen											
Model	a	b	c	d	e	f	g	h	i	j	k
Pre-treatment	None	COE	SLS	**SNV**	mMN	MSC	FD	SD	FS+ SLS	FD+ SNV	FD+ MSC
Spectral range (cm^{-1})	10000 - 6098; 5454 - 4596										
Number of PLS factors	14	14	14	**10**	12	13	12	10	11	11	12
R^2	97.63	96.82	98.11	**97.89**	97.56	98.06	98.23	96.24	97.94	98.05	98.15
RMSECV	4.18	4.8	3.74	**3.94**	4.24	3.78	3.61	5.26	3.9	3.79	3.7
Lactose											
Model	a	b	c	d	e	f	g	h	i	j	k
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	FS+ SLS	**FD+ SNV**	FD+ MSC
Spectral range (cm^{-1})	10000 - 4200										
Number of PLS factors	3	3	3	3	3	3	3	4	4	**4**	4
R^2	94.71	94.75	94.82	95.65	95.4	95.64	94.45	94.72	94.79	**96.08**	94.78
RMSECV	7.49	7.46	7.41	6.79	7.25	6.8	7.68	7.48	7.43	**6.45**	7.44

None – no pre-processing; COE – Constant Offset Elimination; SLS – Slight Line Subtraction; SNV – Standard Normal Variate; mMN – Minim Maxim Normalization; MSC – Multiplicative Scattering Correction; FD – First Derivative; SD – Second Derivative

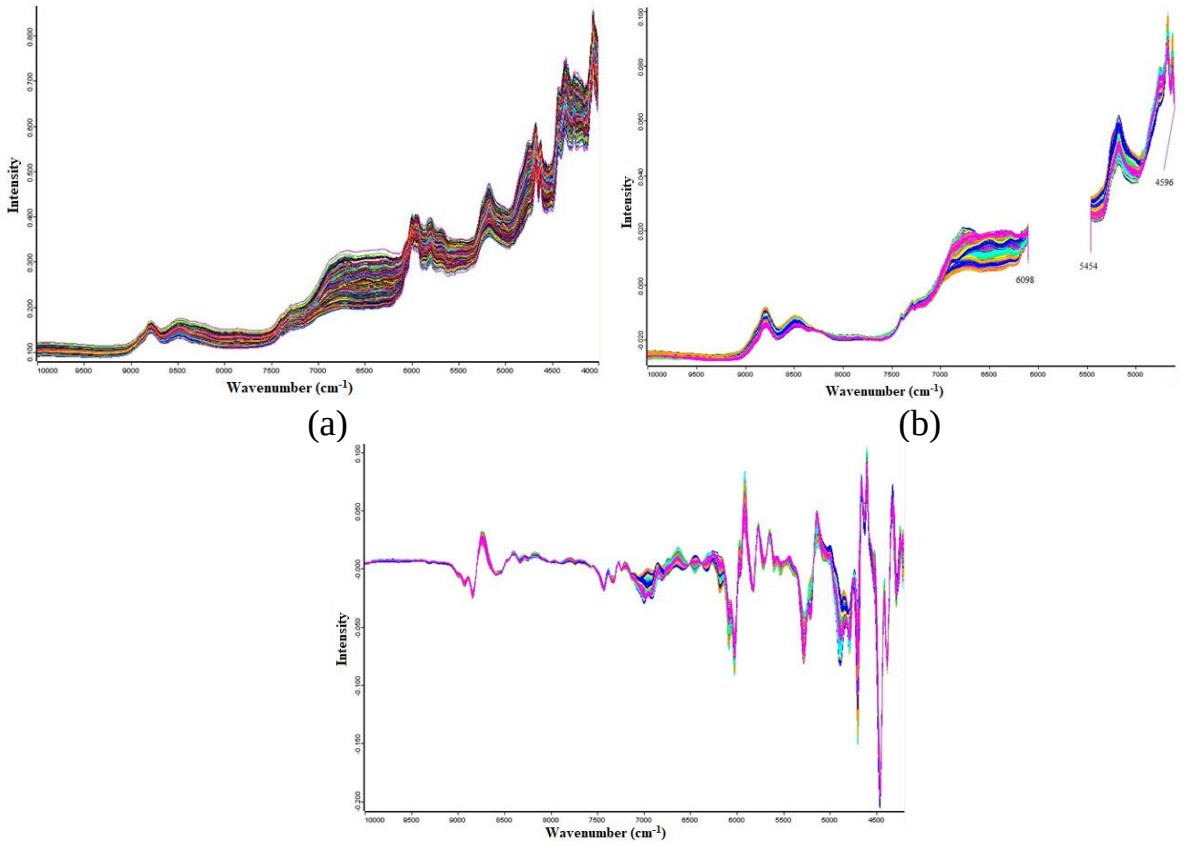

Figure 3.

NIR spectra of the calibration set tablets without pre-processing (a), pre-processed using SNV for ketoprofen assay (b) and pre-processed using FD+SNV for lactose assay

The calibration algorithm for ketoprofen in extended-release inert matrix tablets was best using as pre-treatment method SNV (PLS = 10, RMSECV = 3.94) in the 10000 - 6098cm^{-1}; 5454 - 4596cm^{-1} spectral ranges. The NIR spectra of tablets pre-processed by SNV used for ketoprofen assay are shown in Figure 3b.

In the case of lactose, the calibration algorithm was obtained using as pre-treatment method FD+SNV (PLS = 4, RMSECV = 6.45) in the 10000 - 4200 cm^{-1} spectral range. The NIR spectra of tablets pre-processed by FD+SNV used for lactose assay are shown in Figure 3c.

Validation of NIR-chemometric method for the quantification of ketoprofen and lactose from extended-release inert matrix tablets

For the validation of the method, three levels of concentration corresponding to 90%, 100% and 110% were selected, known as formulations 7, 13 and 19. The tablets were prepared using the same method on three different days, and each day, a number of 40 spectra were acquired for each formulation. Table V shows the validation criteria of the NIR-chemometric methods.

Table V

Validation results of NIR-chemometric methods for quantification of ketoprofen and lactose in powder blends

Ketoprofen (SNV)						
Concentration level (mg/ tablet)	**Trueness**		**Precision**		**Accuracy**	
	Relative bias (%)	Recovery (%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (mg/ tablet)
174.47	-3.072	96.93	0.64	0.99	[-6.132, -0.011]	[169.131, 179.810]
193.52	-3.242	96.76	1.08	1.21	[-6.207, -0.276]	[187.776, 199.255]
219.32	-0.311	99.69	1.08	1.20	[-3.262, 2.640]	[212.842, 225.788]
Lactose (FD+SNV)						
Concentration level mg/ tablet)	**Trueness**		**Precision**		**Accuracy**	
	Relative bias (%)	Recovery (%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (mg/ tablet)
94.53	1.277	101.28	1.99	1.72	[-2.618, 5.172]	[90.849, 98.214]
56.94	0.507	100.51	3.91	3.70	[-7.860, 8.874]	[52.172, 61.701]
19.55	-2.032	97.97	4.14	3.64	[-10.180, 6.117]	[17.961, 21.147]

The ketoprofen assay for tablets with SNV pre-processing showed good recovery for all concentration levels, above 96.5%. The best recovery (99.69%), lowest relative bias (-0.31%), and the smallest relative tolerance limits (-3.262; 2.640) were obtained at the highest content of ketoprofen (219.32).

The lactose assay for tablets with FD+SNV pre-processing showed its best result in the case of the intermediate concentration level: relative bias of 0.507, recovery of 100.51, repeatability of 3.91, and with the relative tolerance limits situated between -7.860 and 8.874.

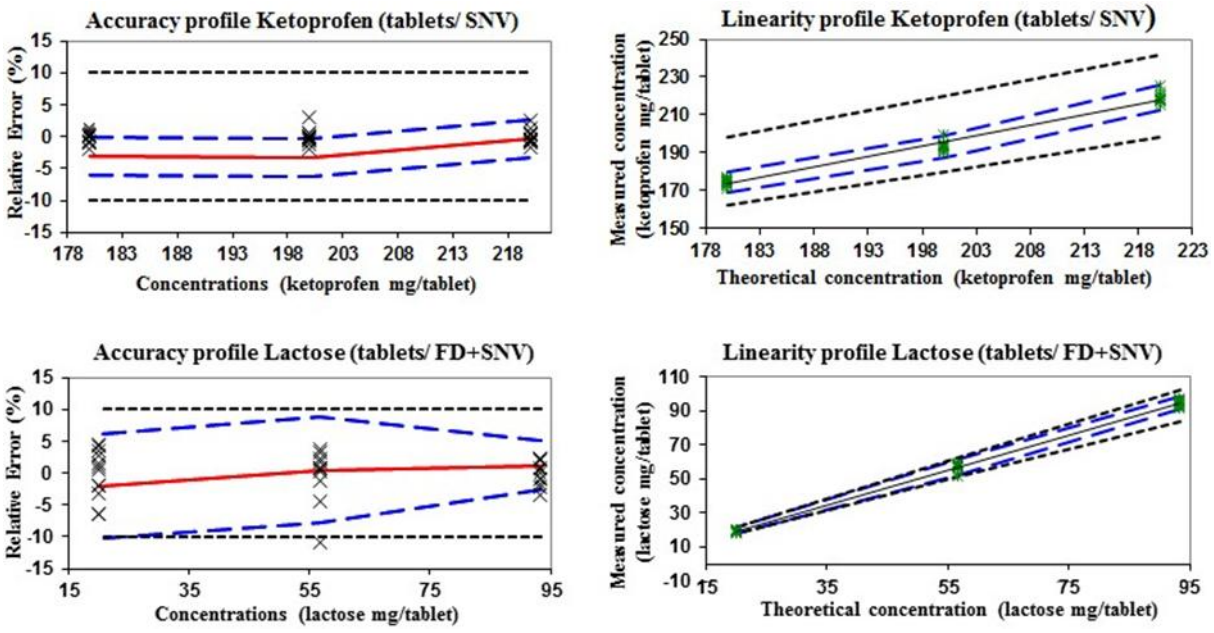

Figure 4.

The accuracy (left) and linearity profiles (right) obtained for the NIR chemometric methods of quantification of ketoprofen and lactose in tablets

Figure 4 shows the linearity and accuracy profiles of the prediction models with the acceptance limits set to ± 10%. The linearity profiles were obtained by plotting the measured concentrations of the external validation samples according to theoretical concentrations. The accuracy profiles were represented by plotting the relative error according to the concentrations.

As seen in Figure 4, the ß-expectation tolerance limits for ketoprofen and lactose are fully included in the imposed limits except for the lowest lactose concentration. At the lowest lactose content, the method can't perform with the imposed accuracy and precision. The problem can be solved by selecting a narrower concentration interval, maintaining the accuracy and the risk at the same values, or increasing the imposed acceptance limits of ± 10%.

Development of NIR-chemometric method for direct estimation of kinetic release parameters from extended-release inert matrix tablets

Another objective of our study was to develop a NIR-chemometric method for directly estimating kinetic release parameters from extended-release inert matrix tablets with ketoprofen using the Higuchi model.

The Higuchi model is characteristic of plane matrices, and it assumes that the initial concentration of the active pharmaceutical ingredient in the matrix is higher than its solubility. It also states that the size of the particles is less small than the dimension of the system pores. Throughout the dissolution process that takes place in sink conditions, the matrix gets soaked in the dissolution medium, but its erosion is insignificant [29]. This kinetic release model has been used to describe the release of API from extended-release matrix tablets containing soluble substances, so its use is justified [30].

The dissolution studies have been carried out in phosphate buffer (pH = 7.4) at 100 rpm stirring rate on six tablets of each formulation from 27 formulations. The average dissolution profile of each formulation can be seen in Figure 5.

The obtained kinetic release parameters, along with the Akaike information criterion (AIC) and the correlation factor (R) for each formulation using different models, such as Higuchi, Peppas, Baker, and Lonsdale can be observed in Table VI.

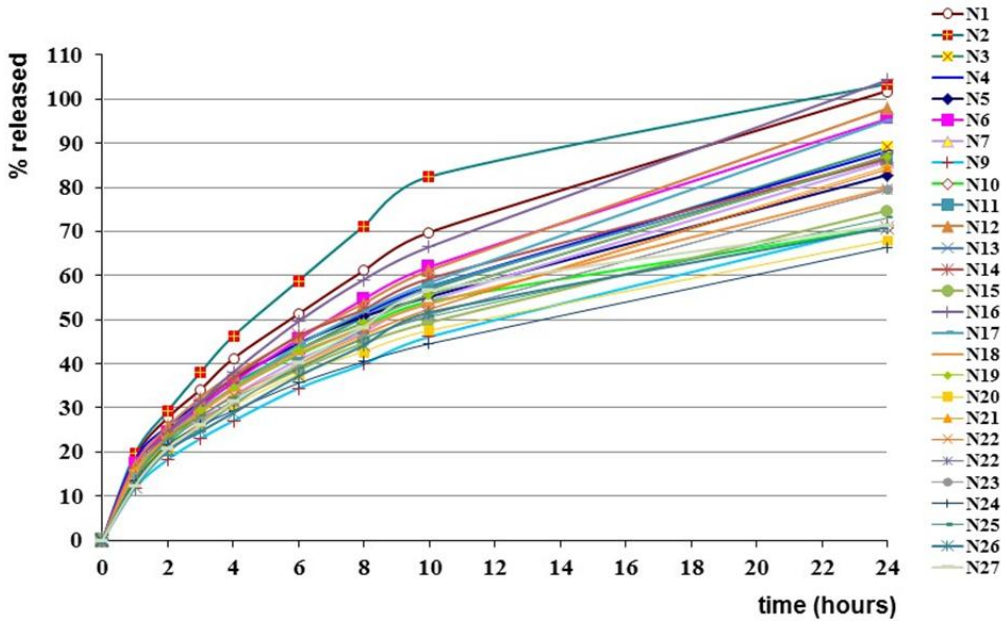

Figure 5.
The average dissolution profile of the extended release tablet formulations

Table VI
Kinetic release parameters along with AIC and the correlation factor (R) obtained for each formulation using different models

	Higuchi			Peppas				Baker and Lonsdale		
	R	AIC	$K_{Higuchi}$	R	AIC	K	n	R	AIC	K
N1	0.998	27.02	21.01	0.998	30.31	20.420	0.512	0.979	47.67	0.0111
N2	0.985	44.11	22.98	0.986	47.45	24.643	0.470	0.977	49.45	0.0144
N3	0.999	8.42	17.95	1.000	-8.43	17.339	0.515	0.986	41.82	0.0075
N4	0.999	-3.21	18.11	1.000	-12.00	18.390	0.494	0.990	38.77	0.0078
N5	0.998	22.09	17.44	0.999	19.81	18.573	0.473	0.995	32.58	0.0072
N6	0.998	27.43	19.08	0.999	21.52	17.359	0.540	0.977	47.10	0.0087
N7	0.998	23.80	17.01	1.000	-12.31	15.422	0.541	0.982	43.37	0.0066

	Higuchi			Peppas				Baker and Lonsdale		
	R	**AIC**	**$K_{Higuchi}$**	**R**	**AIC**	**K**	**n**	**R**	**AIC**	**K**
N8	0.998	26.22	20.01	0.998	29.48	19.440	0.512	0.982	45.70	0.0099
N9	0.997	23.15	14.23	1.000	14.02	12.834	0.543	0.987	38.21	0.0043
N10	0.987	36.58	15.89	0.991	37.32	18.078	0.445	0.994	32.01	0.0058
N11	0.993	35.03	17.02	0.998	29.48	14.370	0.571	0.974	47.10	0.0065
N12	0.998	24.87	19.36	1.000	3.07	17.647	0.539	0.977	47.54	0.0090
N13	0.999	18.04	17.53	1.000	12.52	16.568	0.524	0.985	42.05	0.0071
N14	0.998	24.82	18.11	0.998	28.58	18.412	0.493	0.990	38.86	0.0078
N15	0.999	15.87	15.44	0.999	19.78	15.464	0.500	0.993	33.37	0.0053
N16	0.994	35.92	20.53	0.999	28.25	17.579	0.565	0.966	52.05	0.0102
N17	0.995	32.42	18.50	1.000	7.78	15.807	0.566	0.972	48.66	0.0080
N18	0.999	17.50	16.68	0.999	19.16	17.263	0.486	0.994	33.23	0.0064
N19	0.999	18.04	17.53	1.000	12.52	16.568	0.524	0.985	42.05	0.0071
N20	0.996	25.16	14.61	0.999	21.18	16.098	0.459	0.999	18.42	0.0047
N21	0.997	26.52	16.60	1.000	-0.28	14.692	0.551	0.980	43.83	0.0062
N22	0.998	22.37	16.70	1.000	16.39	15.435	0.533	0.984	41.99	0.0063
N23	0.999	11.50	16.08	1.000	9.18	15.506	0.515	0.990	37.72	0.0058
N24	0.997	21.85	14.06	0.999	16.56	15.324	0.463	0.999	19.32	0.0043
N25	0.997	24.80	15.56	0.998	24.60	16.720	0.470	0.997	26.87	0.0055
N26	0.995	29.53	14.97	0.995	33.53	14.911	0.502	0.990	36.08	0.0049
N27	0.986	37.59	15.76	0.987	41.16	16.644	0.477	0.987	38.90	0.0056

In the process of building a calibration model, the spectra were correlated with the k Higuchi constants of each formulation and pre-processed using different models (Table VII). The most suitable model with a number of PLS factors of 10, a correlation factor (R^2) of 93.6, and a root mean square error of cross-validation of 0.966, was obtained using FD+SLS as pre-treatment model.

Table VII

Statistical parameters and number of PLS factors for different models proposed for kinetic parameter prediction of extended release tablets with ketoprofen

k Higuchi											
Model	a	b	c	d	e	f	g	h	i	j	k
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	**FD+SLS**	FD+SNV	FD+MSC
Spectral range(cm^{-1})	10000 - 4200										
Number of PLS factors	11	12	14	13	11	12	9	10	**10**	10	10
R^2	91.06	93.47	93.86	92.71	91.69	92.84	92.73	90.64	**93.6**	90.36	90.36
RMSECV	1.02	0.978	0.971	0.993	1.01	0.991	0.993	1.003	**0.996**	1.04	1.04

None – no pre-processing; COE – Constant Offset Elimination; SLS – Slight Line Subtraction; SNV – Standard Normal Variate; mMN – Minim Maxim Normalization; MSC – Multiplicative Scattering Correction; FD – First Derivative; SD – Second Derivative

The NIR spectra of tablets pre-processed by FD+SLS used for the kinetic parameter estimation assay are shown in Figure 6.

The kinetic release parameter estimated by developed model for the control samples, along with the reference method results, are shown in Table VIII. As presented in Table VIII similar results were obtained by both NIR-chemometric and dissolution method used as reference. No statistical difference was found between the two means at 95% confidence limit. Recovery was between 92.30% and 111.06% and was calculated by comparing NIR predicted results with reference method results.

Table VIII

Kinetic release parameter estimated for ketoprofen extended-release control samples using reference and NIR-chemometric method

	V7			V13			V19		
	Reference*	**NIR**	**Recovery**	**Reference***	**NIR**	**Recovery**	**Reference***	**NIR**	**Recovery**
P1	17.01	17.92	105.31	17.53	16.80	95.87	17.83	16.64	93.37
P2	17.01	18.45	108.46	17.53	17.03	97.15	17.83	17.53	98.33
P3	17.01	18.89	111.06	17.53	17.83	101.74	17.83	16.45	92.30
Mean				17.45	17.51	100.40			
SD				0.356	0.842				
t_{exp}					0.3966				
P (type 1 error)					0.6986				

*dissolution method

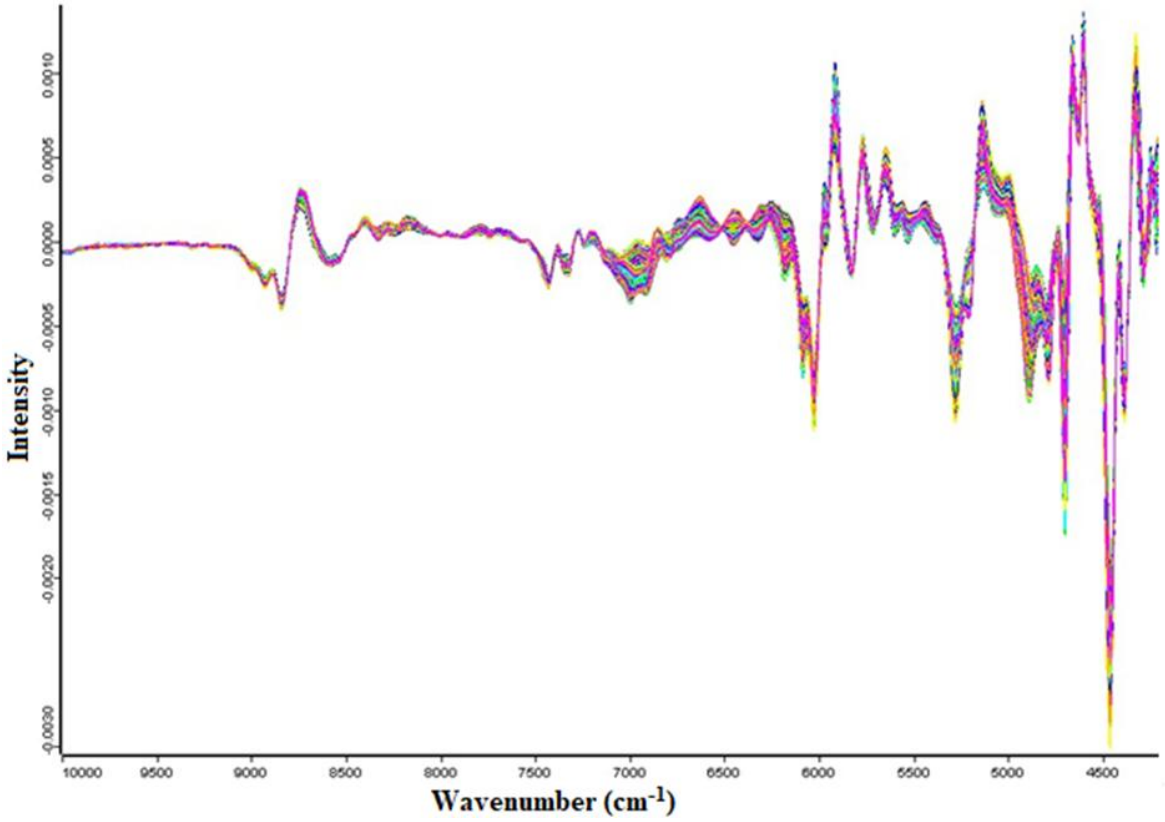

Figure 6.
NIR spectra of tablets pre-processed by FD+SLS used for the kinetic parameter estimation assay

The prediction of drug dissolution rates from tablets is an application that has been exploited in other articles but from a different point of view. Zannikos *et al.* correlated the dissolution rates of carbamazepine tablets with NIR spectra following high exposure to humidity. Other authors have predicted the drug dissolution profiles of tablets with a rate-controlling film coat from whole NIR spectra [3]. This approach is based on the dependence of the film coat thickness and uniformity on dissolution rates and, of course, on the NIR spectra. Tabasi *et al*. [31] have successfully applied NIR spectroscopy to predict dissolution profiles of sustained-release matrix tablets by differentiating the concentration of Eudragit NE 30D used as a granulation binder from each formulation.

In this study, we have successfully applied a different method of estimating the dissolution rate of the API from tablets by correlating the k Higuchi constants of each formulation with their corresponding NIR spectra. The estimated constant can determine the fraction of the active pharmaceutical ingredient released at a given time using the formula $Q = k_H t^{1/2}$.

Conclusions

This study successfully implements NIR-chemometric methods to characterize both powder blends for tableting and matrix extended-release tablets in terms of concentration levels of active pharmaceutical ingredient (ketoprofen) and lactose with satisfactory accuracy and precision. It also shows a new approach to estimate the kinetic release of the drug by correlating kinetic release parameters with NIR spectra of tablets.

NIR-spectroscopy is a method that can be applied to monitor properties of both intermediate and final products, ensuring the necessary quality attributes through different phases of a technological process, fulfilling at the same time the objectives of PAT.

The obtained results in this work show the possibility to predict both chemical properties (active content, ketoprofen) and pharmaceutical properties (*in vitro* release profile) directly, without any sample preparation, from the same NIR transmission spectrum of ketoprofen tablets. Such quick methods can be used for on-line, in-line, or at-line manufacturing process monitoring, so the next step is to implement those methods on an industrial manufacturing line as PAT sensors to achieve the goals of PAT. Implementation on an industrial manufacturing line can be done on ketoprofen tablets or extended-release tablets with other active pharmaceutical ingredients.

Conflict of interest

The authors declare no conflict of interest.

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