QUANTITATIVE CHARACTERIZATION OF SUSTAINED RELEASE TABLETS WITH DICLOFENAC SODIUM BY MEANS OF NEAR-INFRARED SPECTROSCOPY AND CHEMOMETRY

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Abstract

A NIR-chemometric method for direct quantitative determination of diclofenac sodium and two major excipients (matrix-forming excipient and diluent) in sustained release, inert matrix type tablets was developed. The 26 tablet batches were prepared according to an experimental design. The NIR spectra of samples were recorded in the transmittance mode and the spectral ranges were selected using Principal Component Analysis (PCA), scores plot and loadings plot. Multiple pre-processing methods were tested and 6 multivariate models for quantitative determination were developed based on partial least squares (PLS) methodology for each substance. The models with the best prediction capability were fully validated in accordance with the current guidelines and regulations. Validation results showed that the methods have good precision, trueness and accuracy. The tolerance limits were $\pm 10\%$ for diclofenac sodium assay and $\pm 5\%$ for Kollidon® SR and lactose DC (direct compressible), respectively.

Rezumat

S-a dezvoltat și validat o metodă NIR-chemometrică de determinare cantitativă directă a diclofenacului sodic și a doi excipienți (formatorul de matriță și diluantul) din comprimate cu cedare susținută de tip matriță inertă. Au fost preparate 26 de loturi de comprimate în acord cu un plan experimental. S-au înregistrat și prelucrat spectrele NIR ale comprimatelor în modul transmitanță. Zonele spectrale au fost alese folosind analiza componentelor principale (PCA), reprezentarea grafică a scorurilor și ponderilor. S-au testat mai multe metode de pretratament spectral și s-au dezvoltat 6 modele multivariate de determinare cantitativă pentru fiecare substanță analizată, bazate pe metoda celor mai mici pătrate parțiale (PLS). Metodele cu cea mai bună capacitate de predicție au fost validate complet în acord cu ghidurile și reglementările în vigoare. Rezultatele validării au demonstrat faptul că metodele au o bună precizie, exactitate și acuratețe. Limitele de toleranță au fost $\pm 10\%$ pentru dozarea diclofenacului sodic și $\pm 5\%$ pentru dozarea Kollidon® SR și respectiv lactoză DC (direct compresibilă).

Keywords: chemometrics, near infrared spectroscopy, diclofenac sodium assay, DoE

Introduction

Diclofenac sodium [2-(2-((2,6-dichlorophenyl)amino)-phenyl)acetic acid sodium salt], is a nonsteroidal anti-inflammatory drug (NSAID) that has been used for more than 50 years. Diclofenac is an inhibitor of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Diclofenac has a higher affinity for COX-2 inhibition comparing with COX-1 inhibition [22], acting at plasma concentration of 1.6 $\mu\text{mol/L}$ [2]. Diclofenac sodium is used for its' anti-inflammatory action and for its' analgesic and antipyretic effects, in the treatment of acute gout, headache and migraine, musculoskeletal injuries and pain, osteoarthritis, post-operative pain and rheumatoid arthritis [6, 7, 9, 41, 47]. Diclofenac sodium is completely absorbed from the gastrointestinal tract when administrated orally. A

maximum plasma level is reached in about 4 hours from ingestion [2, 47, 53]. When used in large doses, diclofenac sodium exhibits a high incidence side effects, mainly gastrointestinal disturbances (gastric bleeding, ulceration), due to its relative high acidity (pK_a is approximately equal to pK_a of acetic acid) [2, 47]. In order to avoid gastrointestinal side effects and to increase patient compliance, gastroresistant, modified release tablets with diclofenac are used [21]. Many papers describing quantitative determination of diclofenac sodium in pharmaceutical dosage forms (tablets, capsules, ampoules, suppositories, ointments, gels) and biological fluids (whole blood, plasma, serum, urine) were published: HPLC [5, 8, 14, 50, 54, 57], HPTLC [4, 17, 36, 57, 63], spectrophotometry [11, 17, 24, 33, 44], GC-MS [10, 32], spectrofluorimetry [13, 16, 45], CE [15, 31], voltammetry [3, 40],

potentiometry [34, 35]. Few papers described IR, NIR and Raman spectroscopic methods for quantification of diclofenac in pharmaceuticals [38, 39, 62].

Kollidon® SR is widely used for the manufacturing of sustained release matrix preparation of tablets and granules [12], due to its excellent properties (flowability, compressibility, dissolution profile of matrix tablets based on Kollidon® SR, independent from pH of media) [25, 37, 42, 48, 49, 51, 56].

NIR is a powerful tool of Process Analytical Technology (PAT) used for easy and rapid pharmaceutical processes monitoring [18-20, 23, 30] and non-destructive chemical and physical characterization of pharmaceutical finished products [58, 59, 61] and intermediate products [46, 55, 60]. Nowadays, NIR spectroscopy is frequently applied for the identification and quality testing of raw materials, in-line monitoring of process steps like granulation or drying by water content quantification or in-line monitoring of powder blending or powder tableting by API quantification, as well as for process troubleshooting [43]. In order to be used in pharmaceutical industry the NIRs methods require validation procedure in accordance with the ICH requirements, regardless of the area of use, in order to prove its suitability [58-61].

Sustained release tablets matrix type represents one of the systems most widely used for controlling of drug release in oral solid dosage form formulation and the mechanisms involved in drug release from these matrix systems are complex and depend on many factors. The main factors that affect the release of drugs are related to matrix forming polymer, type, particle size or ratio, the presence of other excipients as filler or the technological factors as the homogeneity of powder/granules blend for tableting or compression force. In the same time, at industrial scale manufacturing, the reproducible drug release profile from sustained release matrix tablets is related with the possibility to prepare tablets with same composition (constant ratio between API – matrix forming polymer – filler). This is a challenge in condition when the powder have segregation tendency [42, 48, 49, 51, 56].

If some of these factors may be monitored by a strict control of raw materials (polymer forming type or particle size) or by using instrumented tableting press (compression force), others (as the homogeneity of powder/granules blend for tableting or the chemical composition of each tablet) need the development of special methods. In the same time, in-line/at-line quantitative characterization of finite dosage forms may be integrated into Real Time Release Testing as part of a Control Strategy for batch release.

Establishing a control strategy, including in process controls and monitoring, is a phase of Quality by Design (QbD) development approach [1, 52].

So, the aim of this paper was the development and validation of a NIR-chemometric method for direct and simultaneous quantification of API (diclofenac sodium), matrix forming polymer (Kollidon® SR) and filler (lactose DC) in sustained release matrix tablets.

Materials and Methods

Materials

Diclofenac sodium was supplied by Aarti Drugs Ltd. - India. As diluents the following excipients were used: – microcrystalline cellulose (Avicel PH-102) from Chemo Pharma – Austria and directly compressible lactose (lactose DC) (SuperTab 14 SD) from DMV-Frontera Excipients – Germany. In the wet granulation step, polyvinylpyrrolidone (Kollidon 30), from BASF – Germany, was used as binder (as 10% solution). Kollidon® SR from BASF-Germany was chosen as matrix-forming excipient. Other extra granular excipients were: hydrophilic fumed silica (Aerosil 200) from Degussa AG – Germany and magnesium stearate from Merck – Germany.

Experimental design

In order to develop NIR-chemometric methods for the quantitative characterization of the sustained release inert matrix tablets, an experimental design with two factors (diclofenac sodium and Kollidon® SR) and five levels (80% - 90% - 100% - 110% - 120%) was used (Table I). The Modde 11.0 package from Umetrics (Sweden) was used.

Table I
Experimental design factors and levels

Factor	Symbol	Levels				
		-2	-1	0	1	2
		80%	90%	100%	110%	120%
Diclofenac sodium (mg/tablet)	X ₁	80	90	100	110	120
Kollidon® SR (mg/tablet)	X ₂	98	110.25	122.5	134.75	147

A total of 26 formulations were developed with diclofenac sodium ranging from 80 to 120 mg/tablet and Kollidon® SR ranging from 98 to 147 mg/tablet (Table II). Aerosil 200 and magnesium stearate were used in a constant percent of 1.75% and 3.5%, respectively, in all 26 formulations. All 26 formulations consisted of tablets with a total weight of 350 mg.

Multiple batches were manufactured in order to perform calibration (15) and validation (36) of NIR-chemometrics methods in order to ensure representative samples for every formulation, every level of concentration and to simulate routine analysis (Table III).

Table II

Experimental design matrix

Sample	Run order	X ₁	X ₂
N1	23	80	98
N2	26	90	98
N3	7	100	98
N4	24	110	98
N5	9	120	98
N6	1	80	110.25
N7	17	90	110.25
N8	8	100	110.25
N9	10	110	110.25
N10	14	120	110.25
N11	19	80	122.5
N12	18	90	122.5
N13	13	100	122.5
N14	4	110	122.5
N15	25	120	122.5
N16	20	80	134.75
N17	5	90	134.75
N18	6	100	134.75
N19	21	110	134.75
N20	22	120	134.75
N21	11	80	147
N22	16	90	147
N23	2	100	147
N24	3	110	147
N25	12	120	147
N26	15	100	122.5

Tablets preparation

All powders were weighed on the balance with three decimal places (Sartorius, Germany) and passed through an 800 µm sieve. The mixture of diclofenac sodium and microcrystalline cellulose was granulated in an Aeromatic Fielder AG fluidized bed granulator (Aeromatic, Switzerland) using polyvinylpyrrolidone (10%) as binder. The granules were mixed with lactose, Kollidon® SR, Aerosil and magnesium stearate in a Mixer Y5, Y-shaped mixing vessel (Erweka, Germany). The tablets were obtained using an eccentric tablet press Korsch EK-0 (Korsch, Germany) equipped with a 9 mm die, with flat punch.

NIR spectra recording

NIR spectra were recorded by means of an MPA FT-NIRS analyser (Brucker Optics, Germany) in Transmittance Sampling Mode. Each transmittance spectrum of intact tablets was acquired via OMNIC software by integrating 20 scans over a wavenumber in the interval 5000 cm⁻¹ to 12000 cm⁻¹, with a resolution of 7.7 cm⁻¹. No further preliminary operations were necessary due to the sample holder that reduces variability.

NIR spectra processing

Calibration models were developed (based on partial least squares regression – PLS) considering various spectral ranges and different pre-processing modes (single or in combinations) for spectra: first derivative (FD), second derivative (SD), multiplicative scattering correction (MSC) and standard normal variate (SNV). The Simca 14.0 package from Sartorius Stedim (Sweden) was used for the development of prediction models. Prediction capability of multivariate calibration models was evaluated considering the following approach: a small number of PLS factors, a high value of determination coefficient (R²) and as small as possible values for RMSECV (root mean standard error of cross-validation) and for RMSEP (root mean standard error of prediction).

Methods validation

Best prediction capability, calibration models for each analyte were considered candidates for validation. The validation was performed by evaluating trueness (relative bias and recovery), precision (repeatability and intermediate precision), and accuracy (absolute and relative tolerance limits). The Microsoft Excel 2007 software, from Microsoft Corporation (USA), was used for the calculation of validation related parameters and to generate accuracy and linearity profiles. The validation strategy was based on the technique developed by Hubert *et al.* [26-29] and was applied on validation series (Table III). The 90%, 100% and 110% levels were considered calibration series and were manufactured in three different days. A total of 40 spectra were recorded every day for each series.

Table III

Calibration and validation protocols matrix

Levels		Series 1		Series 2		Series 3	
		Calibration	Validation	Calibration	Validation	Calibration	Validation
-2	80%	1	0	1	0	1	0
-1	90%	1	4	1	4	1	4
0	100%	1	4	1	4	1	4
1	110%	1	4	1	4	1	4
2	120%	1	0	1	0	1	0

Results and Discussion*Spectral range selection*

The NIR spectra for calibration samples are presented in Figure 1.

After the visual inspection of spectra, it was concluded that the spectral region between 5790 and 7175 cm⁻¹ is characterized by noise and was eliminated from the analysis. The spectral region between 7200 and 9000 cm⁻¹ presents differences between absorption

bands and was used in order to build multivariate calibration models.

Spectra were evaluated by means of Principal Component Analysis (PCA) after pre-processing with MSC and

SNV methods, in order to choose the spectral regions for the multivariate regression models and number of Principal Components (PC) and their role in explaining system variability.

Figure 1.
NIR spectra of calibration samples

Development of calibration models

The NIR spectrum of pure diclofenac sodium presents an absorption peak at 8780 cm^{-1} (Figure 2). Considering loading plot of the first PC (Figure 3), the spectral region from 7313.18 and 8894.61 cm^{-1} was chosen for the multivariate regression model for diclofenac

sodium. The score plot for diclofenac sodium (Figure 4) splits, very well, the samples into groups, depending on the concentration. The statistical parameters for PLS models built for quantification of diclofenac sodium are summarized in Table IV.

Figure 2.
NIR spectrum of pure diclofenac sodium

Figure 3.
Loading plot (first PC) of pure diclofenac sodium

Figure 4.
Score plot for diclofenac sodium

Table IV

Statistical parameters of PLS models for diclofenac sodium

Diclofenac sodium						
Model	A	B	C	D	E	F
Pre-processing	SD+MSC	SD+SNV	FD+SNV	FD+MSC	MSC	SNV
Spectral range	7313.18 - 8894.61 cm ⁻¹				7205.18 - 12489.5 cm ⁻¹	
PLS factors number	4	5	5	5	6	6
R ²	0.805	0.82	0.920	0.845	0.84	0.845
RMSECV	6.225	5.963	4.194	5.583	5.773	5.706
RMSEP	4.906	4.774	4.619	4.859	4.972	5.208

As shown in Table IV, the developed multivariate calibration models are quite similar. No considerable improvement of the prediction ability was obtained by enlarging spectral range (models E and F). Model C (with 5 factors) was chosen as a possible candidate for

the method validation since it has the best prediction capability (RMSEP = 4.619).

The NIR spectrum of pure Kollidon® SR is presented in Figure 5.

Figure 5.
NIR spectrum of pure Kollidon® SR

Figure 6.
Loading plot (second PC) of pure Kollidon® SR

Figure 7.
Score plot for Kollidon® SR

Considering the loading plot of the second PC (Figure 6), spectral region from 7260.31 and 8948.16 cm^{-1} was chosen for multivariate regression model for Kollidon® SR. The peak from 8780 cm^{-1} (Figure 6) is not generated by Kollidon® SR as it doesn't appear in pure substance spectrum (Figure 5), but the negative peak from 8500 cm^{-1} is generated by Kollidon® SR. The score plot for Kollidon® SR (Figure 7) splits, very well, the samples into groups, as a function of concentration, so

the second PC explains the variation of the concentration for the matrix-forming excipient.

The statistical parameters for PLS models built for quantification of Kollidon® SR are summarized in Table V.

As shown in Table V the developed multivariate calibration models are quite similar. Model G (with 2 factors) was chosen as a possible candidate for method validation since it has the best prediction capability ($\text{RMSEP} = 3.367$).

Table V

Statistical parameters of PLS models for Kollidon® SR

Kollidon® SR						
Model	G	H	I	J	K	L
Pre-processing	SD+MSC	SD+SNV	FD+SNV	FD+MSC	MSC	SNV
Spectral range	7260.31 – 8948.16 cm^{-1}					
PLS factors number	2	2	2	2	2	2
R^2	0.932	0.933	0.937	0.937	0.932	0.933
RMSECV	4.436	4.442	4.27	4.27	4.442	4.416
RMSEP	3.367	3.417	3.484	3.427	3.769	3.813

Figure 8.
NIR spectrum of pure Lactose DC

Figure 9.
Score plot for Lactose DC

The NIR spectrum of pure lactose DC is presented in Figure 8. Considering the loading plot of the first PC (Figure 9) the negative peak in the spectral range 7428 - 8339 cm^{-1} is not generated by diclofenac sodium or Kollidon® SR since neither absorbs there. The negative peak from 7500 cm^{-1} (Figure 3) is generated by lactose DC.

Considering the loading plot of the first PC (Figure 3), the spectral region from 7259.18 to 9951.47 cm^{-1}

was chosen for the multivariate regression model for lactose DC.

The score plot for Lactose DC (Figure 9) splits, very well, samples into groups, as a function of the concentration, so the first PC explains the variation of the concentration of this excipient. The statistical parameters for PLS models built for the quantification of lactose DC are summarized in Table VI.

Table VI

Statistical parameters of PLS models for Lactose DC

Lactose DC						
Model	M	N	O	P	Q	R
Pre-processing	SD+MSC	SD+SNV	FD+SNV	FD+MSC	MSC	SNV
Spectral range	7259.18 - 9951.47 cm^{-1}				7205 - 10005 cm^{-1}	
PLS factors number	2	2	2	2	2	3
R²	0.96	0.96	0.964	0.965	0.967	0.968
RMSECV	4.875	4.883	4.602	4.594	4.415	4.385
RMSEP	4.399	4.311	3.569	3.641	3.694	3.237

As shown in Table VI, the developed multivariate calibration models are quite similar. Model R (with 3 factors) was chosen as a possible candidate for the method validation since it has the best prediction capability (RMSEP = 3.237).

NIR-chemometric methods validation

Validation criteria for the considered models (C, G and R) are presented in Table VII.

For diclofenac sodium, recoveries above 99% for all concentration levels were obtained. The best recovery (100.31%) and relative bias (0.306%) were obtained for the intermediate concentration level (100%). Best precision and accuracy parameters were obtained for

the upper concentration level (110%): repeatability 1.81%, intermediate precision 1.64%, quite small relative tolerance limits [-4.467 – 2.953%]. The relative tolerance limits did not exceed $\pm 5\%$ for all concentration levels. In case of Kollidon® SR, recoveries above 99% for all concentration levels were obtained. The best recovery (99.88%) and relative bias (-0.122%) were obtained for the low concentration level (90%). Best precision and accuracy parameters were obtained for the low concentration level (90%): repeatability 0.65%, intermediate precision 0.57%, quite small relative tolerance limits [-1.423 – 1.179%]. The relative tolerance limits did not exceed $\pm 5\%$ for all concentration levels.

Table VII

Validation criteria for the multivariate models C, G and R

Diclofenac sodium – model C (FD+SNV)				
Concentration (mg/tablet)		90	100	110
Trueness	Relative bias (%)	1.494	0.306	-0.757
	Recovery (%)	101.49	100.31	99.24
Precision	Repeatability (RSD %)	2.27	2.46	1.81
	Intermediate precision (RSD %)	2.01	2.18	1.64
Accuracy	Relative tolerance limits (%)	[-3.012, 5.999]	[-4.578, 5.191]	[-4.467, 2.953]
	Tolerance limits (mg/tablet)	[87.22, 95.46]	[95.40, 105.20]	[105.11, 113.21]
Kollidon® SR – model G (SD+MSC)				
Concentration (mg/tablet)		110.25	122.50	134.75
Trueness	Relative bias (%)	-0.122	0.338	1.115
	Recovery (%)	99.88	100.34	101.12
Precision	Repeatability (RSD %)	0.65	0.77	0.91
	Intermediate precision (RSD %)	0.57	0.70	0.89
Accuracy	Relative tolerance limits (%)	[-1.423, 1.179]	[-1.235, 1.910]	[-0.917, 3.148]
	Tolerance limits (mg/tablet)	[108.68, 111.54]	[120.98, 124.84]	[133.48, 139.02]
Lactose DC - model R (SNV)				
Concentration (mg/tablet)		122	97.25	72.50
Trueness	Relative bias (%)	-1.845	-0.221	0.567
	Recovery (%)	98.15	99.79	100.57
Precision	Repeatability (RSD %)	1.16	1.67	2.21
	Intermediate precision (RSD %)	1.03	1.49	1.94
Accuracy	Relative tolerance limits (%)	[-4.170, 0.478]	[-3.576, 3.154]	[-3.773, 4.907]
	Tolerance limits (mg/tablet)	[116.96, 122.53]	[93.778, 100.31]	[69.746, 76.075]

For lactose DC, recoveries above 98% for all levels of concentration were obtained. The best recovery (99.79%) and relative bias (-0.221%) were obtained for the intermediate concentration level (100%). Best precision and accuracy parameters were obtained for the upper concentration level (110%): repeatability 1.16%, intermediate precision 1.03%, quite small relative tolerance limits [-4.170 – 0.478%]. The relative tolerance limits did not exceed $\pm 5\%$ for all concentration levels. Accuracy profiles for the models C (diclofenac sodium), G (Kollidon® SR) and R (lactose DC) are presented in Figure 10.

Figure 10.

Accuracy profiles for diclofenac sodium, Kollidon® SR and lactose DC

The relative bias is represented as a plain red line, tolerance limits (β expectation = 95%) are presented as dashed blue line and the dotted black lines are the acceptance limits ($\pm 10\%$ for diclofenac sodium and $\pm 5\%$ for Kollidon® SR and lactose DC). All tolerance

limits, for all substances and all concentration levels, tolerance limits were within the acceptance limits, proving that the developed methods are able to quantify at all levels the studied analytes with a good accuracy. The linearity profiles for the models C (diclofenac sodium), G (Kollidon® SR) and R (lactose DC) are presented in Figure 11. In Figure 11, identity line $y = x$ is represented as a plain black line, tolerance limits are presented as dashed blue line and the dotted black lines are the acceptance limits ($\pm 10\%$ for diclofenac sodium and $\pm 5\%$ for Kollidon® SR and lactose DC). For all substances, the tolerance limits are within the acceptance limits.

Figure 11.

Linearity profiles for diclofenac sodium, Kollidon® SR and lactose DC

Corroborating the information presented in Table VII and Figures 10 and 11, we concluded that the developed models are linear and have satisfactory

precision and accuracy and are suitable for direct and simultaneous assay of diclofenac sodium, Kollidon® SR and lactose DC from sustained release, inert-matrix tablets.

Conclusions

A NIR-chemometric method was developed for direct quantification of diclofenac sodium and two major excipients: the matrix-forming excipient – Kollidon® SR and lactose (diluent).

The 26 formulations (inert-matrix type tablets) were prepared and analysed using a NIR-chemometric method in order to perform direct, simultaneous, fast and non-invasive quantitative determination of the active pharmaceutical ingredient (diclofenac sodium), the matrix-forming excipient (Kollidon® SR) and the diluent excipient (lactose DC). No sample preparation was necessary, in comparison with the classical methods that involve wet sample preparation (that sometimes require the use of toxic solvents and are time consuming). Different pre-processing methods for spectra were applied and the best spectral ranges were selected based on a multivariate approach (PCA, scores plot and loadings plot). Six NIR-chemometric methods were developed (using the PLS model) for each analyte. More predictive models were fully validated following the latest regulatory guidance and techniques. The validation results showed that developed methods are linear and have sufficient precision and accuracy in order to quantify diclofenac sodium, Kollidon® SR and lactose DC from sustained release, inert-matrix type, tablets with concentrations within the validated interval.

The developed and validated methods can be used routinely for monitoring of manufacturing process of diclofenac sustained release tablets, in a QbD and PAT regulated environment.

Conflict of interest

The authors declare no conflict of interest.

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