

QUANTIFICATION OF MELOXICAM AND EXCIPIENTS ON INTACT TABLETS BY NEAR INFRARED SPECTROMETRY AND CHEMOMETRY

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Abstract

The purpose of the present work was to develop a Near Infra Red (NIR) – chemometric method for the quantitation of a pharmaceutical active ingredient and excipients in tablets which is readily applicable to tablet testing. Tablets containing meloxicam as an active pharmaceutical ingredient (API) and tableting excipients at various concentrations were prepared by direct compression. An experimental design approach was used in generating a 5-level (% w/w) calibration sample set that included 28 samples. Their NIR spectra were measured by transmittance technique. High-performance liquid chromatography (HPLC) was used as a reference method for the meloxicam assay. Calibration models were generated by partial least-squares (PLS) and principal component regression (PCR) method followed by leave-one-out cross-validations. These calibration models with or without spectral pretreatment were used to predict the drug and excipients content in the tablets made for model validation. The result showed that Standard Normal Variate (SNV) spectral pretreatment with PLS calibration method is suitable for the quantitative analysis of meloxicam API and two excipients (isomalt and microcrystalline cellulose) in tablet formulation.

Rezumat

Scopul acestei lucrări experimentale a fost dezvoltarea unei metode NIR-chemometrice pentru cuantificarea substanței medicamentoase și a excipienților din comprimate. Comprimatele conținând meloxicam ca substanță activă și excipienți în diferite concentrații au fost preparate prin comprimare directă. Pentru calibrare s-au folosit 28 de probe, realizate conform unui plan experimental cu 5 niveluri. Spectrele NIR au fost măsurate în transmitanță. Ca metodă de referință s-a folosit o metodă HPLC pentru determinarea meloxicamului. Calibrarea s-a realizat utilizând metoda celor mai mici pătrate (PLS) și analiza comprimatelor principale (PCR) pe spectre cu sau fără pretratament. Rezultatele obținute au arătat că calibrarea prin metoda celor mai mici pătrate (PLS) pe spectre pretratate prin metoda (Normalizare Standard Variată) SNV este potrivită pentru cuantificarea substanței active (meloxicam) și a doi excipienți (izomalt și celuloză microcristalină) din comprimate.

Keywords: near infrared spectroscopy, chemometrics, experimental design, meloxicam

Introduction

Recently, the concept of process analytical technology (PAT) was introduced in the Food and Drug Administration's (FDA) Guidance for Industry [1,2]. As a PAT tool, near-infrared (NIR) spectroscopy is extensively used to monitor such CQAs as moisture content in the granules and crystal form of a drug during the granulating-drying process [3,4], compact hardness during the roller compaction process [5], blend uniformity during the powder blending process [6,7], tablet hardness during the tableting process [8] and film quantitation during the film coating process [9,10] because of its rapid and non-destructive process. NIR spectroscopic analysis of tablets is non-destructive and measures the absorption of irradiated light onto the tablet [2]. Additionally, chemometrics provides an ideal method of extracting quantitative information from samples through NIR spectra of multicomponent samples [11]. NIR spectroscopy can be used for tablet content uniformity testing and can be applied derivatively to monitor the drug content in each tablet during the tableting process [12,13].

The aim of this research study was the simultaneous quantitation of a pharmaceutical active ingredient and the excipients in tablets containing meloxicam, microcrystalline cellulose, isomalt, sodium starch glycolate and magnesium stearate.

Materials and methods

Materials

Meloxicam (Uquifa, Spain), isomalt (BENEO-Palatinit GmbH, Germany), microcrystalline cellulose (JRS Pharma, Germany), sodium starch glycolate (JRS Pharma, Germany), silicon dioxide - Aerosil (RohmPharma Polymers, Germany), magnesium stearate (Union Derivan, Spain).

Tablet preparation

Tablets containing meloxicam as an active pharmaceutical ingredient with a concentration in the range of 15mg/tablet, isomalt, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate were prepared by direct compression. The formulation is summarized in Table I.

Table I.
Tablets preparation formula (qualitative and quantitative).

	mg / tablet	%	Batch size (g)
Meloxicam	15.00	6.25	9.83
Isomalt	111.80	46.58	69.87
Microcrystalline Cellulose PH 102	100	41.67	62.25
Sodium starch glycolate	12	5.00	7.50
Magnesium stearate	1.2	0.50	0.75
	240.00		150.00

In detail, meloxicam, isomalt, microcrystalline cellulose, and sodium starch glycolate were mixed using a planetary mixer (PRS type, Erweka, Germany) for 5 min. The amount of microcrystalline cellulose was adjusted to give a final weight for each tablet of approximately 240 mg, as shown in Table I. Subsequently, magnesium stearate was added, and the mixture, was stirred in a plastic bag to make tableting powders. A total of 240 mg of this tableting powder was filled in a die ($\varnothing=9\text{mm}$) and then compressed using an eccentric tablet press (Korsch, Germany). The number of samples included three for each calibration batch and five for each prediction batch.

Near infrared (NIR) spectroscopic analysis

The prepared tablet samples were analyzed using an MPA NIR analyzer (Bruker Optics, Germany). The MPA NIR analyzer is specifically designed to analyze tablets using the transmittance NIR spectroscopic technique. The light transmitted through the tablets is then measured using a sensitive InGaAs (indium gallium arsenide) detector positioned immediately above the tablet. A sample cup for tablet that closely fits the contour of the tablets and has an aperture ($\varnothing 12.0\text{mm}$) beneath the tablet, is used as a sample holder in order to avoid producing an undesired mixed-mode, i.e. combined transmittance and reflectance, spectrum due to stray light or light leakage. The sample cup also ensures consistent sample presentation to the instrument, and this minimizes a significant source of the measurement variability. One side of each tablet sample was scanned three times. Each transmittance spectrum was recorded using OPUS software by integrating 32 scans taken from 12500 to 5800 cm^{-1} at 16cm^{-1} resolution. A reference (ambient air) spectrum was obtained previously, in order to compute each tablet's transmittance spectrum.

HPLC analysis

A reference HPLC analysis was performed on validation samples for meloxicam. After determining the average mass of the sample tablets, they were pulverized. Accurately weighed samples of the obtained tablet

powders were extracted with 5 mL methanol in an ultrasonic bath for 10 minutes and the obtained suspension was centrifuged for 5 minutes at 5000 rpm. Aliquots of the clear supernatants were diluted with the mobile phase in 5 mL volumetric flasks. The obtained solutions (sample volume 20 μ L) were then analyzed by HPLC (Shimadzu, Japan) with UV-detection. Data recording and processing was done using Lcsolution v.1.22SP1 (LabSolutions, Shimadzu) software. Separation was carried out at 30°C on a Nucleosil 100-5 C18 analytical column (80 x 4.6 mm i.d., 5 μ m particle size), with a mobile phase containing acetate buffer (50 mM, pH 5.0) – methanol (65:35, v/v) at a flow rate of 0.8 mL min⁻¹. Detection was performed at 366 nm. Under the given chromatographic conditions the retention time of meloxicam was 6.9 minutes. The active pharmaceutical ingredient (API) content of the tablets was determined using the linear regression of standard meloxicam in the range of 5 – 40 μ g mL⁻¹.

Data processing

The spectral pretreatments tested aimed to construct the calibration models included the first and second derivative, and the standard normal variate (SNV). First and second spectral derivatives were obtained by applying the Savitzky–Golay algorithm to 11 moving window points and a second-order polynomial [11].

The ability and the efficiency of calibration were studied by estimating the standard variation of chemometric calibrations in the case of the investigated mixtures. The root mean square error of prediction (RMSECV) was calculated using the following formula:

$$\text{RMSECV} = \sqrt{\frac{\text{PRESS}}{n}}$$

$$\text{PRESS} = \sum (Y_{\text{pred}} - Y_{\text{true}})^2$$

where, Y_{true} = true concentration of the drug

Y_{pred} = predicted concentration of the drug.

n = number of training samples

Software

Partial least squares regression (PLS) and principal component regression (PCR) analysis were performed using SIMCA P 11 software package (Umetrics Sweden). The software permits to validate the models by

full cross-validation. In this procedure, iterative calibrations were performed removing in turn each standard from the training set and then predicting the excluded sample with that calibration. The calibration set (Table II), containing the five component mixtures in a suitable combination, was built using a D-optimal experimental design, developed in Modde 6.0 Software (Umetrics Sweden) [2,9,14].

Table II
Composition of calibration set (D - Optimal Experimental Design)

Exp Name	Run Order	X ₁	X ₂	X ₃	X ₄	X ₅	Exp Name	Run Order	X ₁	X ₂	X ₃	X ₄	X ₅
N1	24	7.50	37.27	48.63	6.00	0.600	N15	21	7.50	52.64	33.33	6.00	0.533
N2	11	5.00	55.90	34.50	4.00	0.600	N16	4	7.50	53.90	33.33	4.67	0.600
N3	6	7.50	54.77	33.33	4.00	0.400	N17	10	7.50	37.27	50.00	4.76	0.467
N4	13	5.00	55.27	33.33	6.00	0.400	N18	22	6.67	38.73	50.00	4.00	0.600
N5	19	7.50	52.77	33.33	6.00	0.400	N19	25	6.30	55.90	33.33	4.00	0.467
N6	9	5.00	40.60	50.00	4.00	0.400	N20	17	7.11	37.27	49.22	6.00	0.400
N7	14	7.50	38.10	50.00	4.00	0.400	N21	16	5.44	38.16	50.00	6.00	0.400
N8	1	5.00	45.57	44.83	4.00	0.600	N22	7	5.83	54.24	33.33	6.00	0.600
N9	12	5.00	49.51	38.89	6.00	0.600	N23	3	6.20	37.27	50.00	6.00	0.533
N10	18	5.00	38.53	50.00	6.00	0.467	N24	2	6.27	46.64	41.68	5.02	0.400
N11	5	5.00	55.90	34.24	4.46	0.400	N25	27	6.25	46.59	41.67	5.00	0.500
N12	26	5.00	39.07	50.00	5.33	0.600	N26	8	6.25	46.59	41.67	5.00	0.500
N13	20	5.00	55.90	33.33	5.24	0.533	N27	23	6.25	46.59	41.67	5.00	0.500
N14	15	7.50	49.01	38.89	4.00	0.600	N28	28	5.00	38.53	50.00	6.00	0.467

X₁ - Meloxicam; X₂ - Isomalt; X₃ - Microcrystalline Cellulose; X₄ - Sodium starch glycolate; X₅ - Magnesium stearate

Results and discussion

The development of a model consisted in checking different spectral pretreatments, as well as its combination with different spectral ranges. Both the whole spectral range and specific spectral regions containing strong bands for the five analytes, and the SNV and first and second-derivative spectral treatments, were tested aiming to design the calibration models. Once the calibration model was defined, its predictive ability was tested using the sample set used during its development.

The near infrared spectra of several tablets of the meloxicam formulation are shown in Figure 1a. In the region below 7460 cm⁻¹ the amount of radiation reaching the detector is low and the detector signal becomes noisy. This observation has been made in other studies involving transmission NIRS, with the consequence that calibration models for transmission have been developed with the higher frequency part of the spectrum [15, 16, 17].

Figure 1 shows spectra for tablets at 4 nominal concentrations for meloxicam (at 5.0%, 5.8%, 6.6% 7.55% m/m, Figure 1, b) and 3 nominal concentrations for isomalt (at 5.0%, 49.01%, 6.6%, 53.90% m/m, Figure 1, c) and microcrystalline cellulose (at 37.27%, 44.83%, 50.00% m/m, Figure 1, d) respectively. This initial evaluation showed significant differences in the absorption bands of the different strengths in a spectral area where meloxicam and excipients absorb.

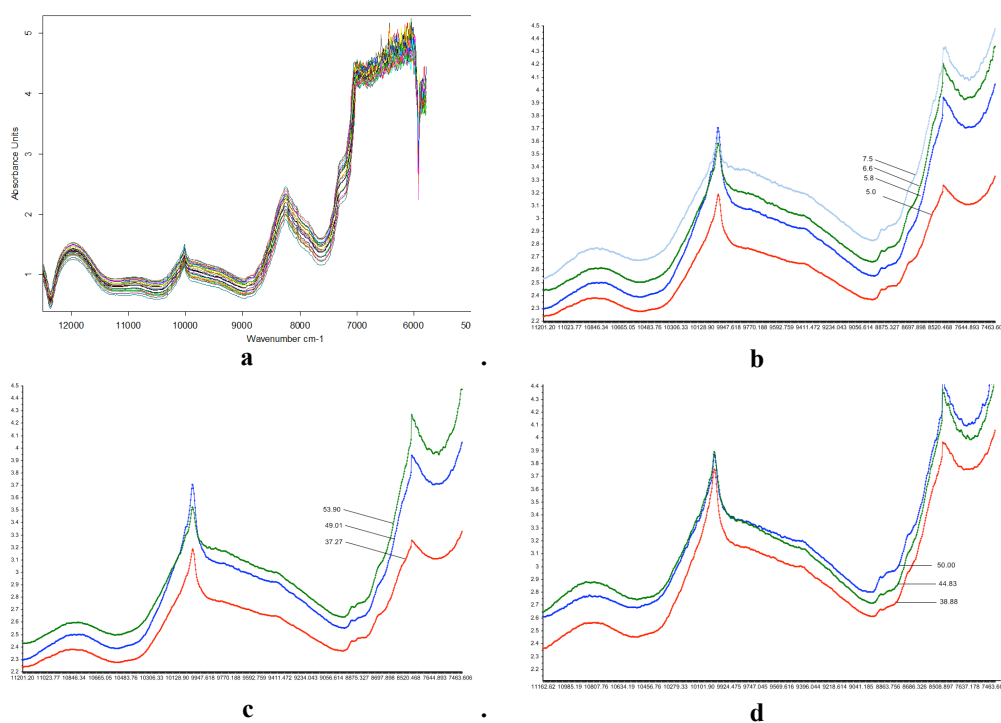


Figure 1.

Absorption NIR spectra of meloxicam (at 5.0%, 5.8%, 6.6% 7.55% m/m - b), isomalt (at 5.0%, 49.01%, 6.6%, 53.90% m/m -c) and microcrystalline cellulose (at 37.27%, 44.83%, 50.00% m/m - d) for tablets with a resolution of 16 cm^{-1}

Multivariate calibration

Mathematical models based on multivariate calibration were then applied to analyze these drugs. To improve the analysis for these compounds, two chemometric approaches based on PLS and PCR calibration were evaluated.

An appropriate choice of the number of factors (principal components) is necessary for PCR and PLS calibrations. The number of

factors should account as much as possible for the experimental data without resulting in over fitting. Various criteria have been developed to select the optimum number [18, 19,]. Cross-validation methods leaving out one sample at a time was employed [20]. The predicted concentrations were compared with the known concentrations of the compounds in each calibration sample.

The RMSECV was used as a diagnostic test for examining the errors in the predicted concentrations. It indicates both precision and accuracy of predictions. It was recalculated upon addition of each new factor to the PLS and PCR models. The evaluation of the predictive abilities of the models was performed by plotting the actual known concentrations against the predicted concentrations. Satisfactory correlation coefficient (r) values between actual and predicted concentrations are obtained for the studied components in the training set by PLS and PCR optimized models indicating good predictive abilities of the models. The RMSECV obtained by optimizing the calibration matrix of the absorption spectra for the PLS and PCR methods are shown in Table III - VI, indicating good accuracy and precision..

Table III
RMSECV and statistical parameter values for simultaneous
determination of meloxicam and excipients without data pretreatment

	Method		Slope	Offset	r	RMSECV	Bias
MELOXICAM	PCR	Calibration	0.96474	0.03962	0.96473	0.0259	0.00945
		Validation	0.95351	0.04651	0.96103	0.0270	-0.00012
	PLS	Calibration	0.99433	0.02169	0.99433	0.1915	0.00264
		Validation	0.98817	0.02578	0.98470	0.2176	-0.00341
ISOMALT	PCR	Calibration	0.94761	0.37716	0.93762	0.2041	0.00004
		Validation	0.93589	0.43408	0.93242	0.2247	0.03284
	PLS	Calibration	0.97551	0.25107	0.97555	0.1165	-0.00014
		Validation	0.96563	0.29525	0.96288	0.1857	0.00537
MICROCRYSTALLINE CELLULOSE	PCR	Calibration	0.96135	0.29178	0.96134	0.1842	0.00002
		Validation	0.95365	0.32317	0.94926	0.2011	-0.01348
	PLS	Calibration	0.98292	0.20012	0.98298	0.1525	0.00033
		Validation	0.97533	0.23217	0.97211	0.1705	-0.00203
SODIUM STARCH GLYCOLATE	PCR	Calibration	0.26208	3.79605	0.2621	0.7166	0.00223
		Validation	0.21432	4.03542	0.1716	0.7648	-0.00633
	PLS	Calibration	0.28233	3.69187	0.2923	0.7067	0.00002
		Validation	0.23708	3.91910	0.2093	0.7477	-0.00558
MAGNESIUM STEARATE	PCR	Calibration	0.12241	0.43318	0.1233	0.0759	-0.00001
		Validation	0.04664	0.47051	0.0123	0.0822	-0.00007
	PLS	Calibration	0.05232	0.46778	0.0522	0.0789	-0.00002
		Validation	0.00506	0.49602	0.0043	0.0836	-0.00008

Table IV
RMSECV and statistical parameter values for simultaneous determination of meloxicam and excipients after Standard Normal Variate (SNV) pretreatment

	Method		Slope	Offset	r	RMSECV	Bias
MELOXICAM	PCR	Calibration	0.97091	0.03593	0.97089	0.02466	-0.00005
		Validation	0.95574	0.04574	0.95463	0.02819	0.00582
	PLS	Calibration	0.99838	0.01923	0.99836	0.01804	-0.00005
		Validation	0.98808	0.02527	0.98814	0.02092	0.00034
ISOMALT	PCR	Calibration	0.98155	0.22177	0.98153	0.15659	0.00012
		Validation	0.97387	0.25931	0.97892	0.16312	0.02377
	PLS	Calibration	0.98651	0.19907	0.98648	0.14838	-0.00032
		Validation	0.97848	0.23824	0.97822	0.16316	0.02426
MICROCRYSTALLINE CELLULOSE	PCR	Calibration	0.99129	0.16452	0.99127	0.1383	0.00043
		Validation	0.98354	0.19535	0.98790	0.1459	-0.02122
	PLS	Calibration	0.99691	0.14066	0.99691	0.1279	0.00453
		Validation	0.96051	0.16600	0.99060	0.1406	-0.01827
SODIUM STARCH GLYCOLATE	PCR	Calibration	0.29224	3.64092	0.2922	0.70182	0.00223
		Validation	0.24597	3.87571	0.2076	0.74887	-0.00633
	PLS	Calibration	0.27826	3.71281	0.2782	0.70872	0.00002
		Validation	0.23387	3.93570	0.1988	0.75272	-0.00558
MAGNESIUM STEARATE	PCR	Calibration	0.09228	0.48805	0.0922	0.07724	-0.00001
		Validation	0.04111	0.47315	0.0138	0.08153	-0.00016
	PLS	Calibration	0.10315	0.44269	0.1031	0.07677	0.00009
		Validation	0.04554	0.47096	0.0602	0.08147	0.00016

Table V
RMSECV and statistical parameter values for simultaneous determination of meloxicam and excipients after 1st derivative pretreatment

	Method		Slope	Offset	r	RMSECV	Bias
MELOXICAM	PCR	Calibration	0.98891	0.01293	0.98891	0.0066	-0.00005
		Validation	0.94574	0.03474	0.94574	0.02319	0.00582
	PLS	Calibration	0.98538	0.04523	0.98538	0.00104	-0.00005
		Validation	0.98086	0.02527	0.98086	0.02392	0.00034
ISOMALT	PCR	Calibration	0.93355	0.22347	0.93355	0.23459	0.00012
		Validation	0.93875	0.12331	0.93875	0.23412	0.02377
	PLS	Calibration	0.95551	0.09907	0.95551	0.14243	-0.00032
		Validation	0.94548	0.23424	0.94548	0.13416	0.02426
MICROCRYSTALLINE CELLULOSE	PCR	Calibration	0.94529	0.12342	0.94529	0.14328	0.00043
		Validation	0.98854	0.14325	0.98854	0.14238	-0.02122
	PLS	Calibration	0.96791	0.15436	0.96791	0.14325	0.00453
		Validation	0.96581	0.12300	0.96581	0.13235	-0.01827
SODIUM STARCH GLYCOLATE	PCR	Calibration	0.29324	3.56792	0.29324	0.23332	0.00223
		Validation	0.21297	3.8658	0.21297	0.74232	-0.00633
	PLS	Calibration	0.24526	3.71281	0.24526	0.72332	0.00002
		Validation	0.22347	3.93470	0.22347	0.45454	-0.00558
MAGNESIUM STEARATE	PCR	Calibration	0.12328	0.45405	0.12328	0.33433	-0.00001
		Validation	0.12211	0.73315	0.12211	0.10345	-0.00016
	PLS	Calibration	0.15123	0.44269	0.15123	0.06553	0.00009
		Validation	0.09874	0.34596	0.09874	0.03434	0.00016

Table VI

RMSECV and statistical parameter values for simultaneous determination of meloxicam and excipients after 2nd derivative pretreatment

	Method		Slope	Offset	r	RMSECV	Bias
MELOXICAM	PCR	Calibration	0.98455	0.03434	0.98455	0.03443	-0.00005
		Validation	0.95224	0.03435	0.95224	0.04545	0.00582
	PLS	Calibration	0.97436	0.01223	0.97436	0.02232	-0.00005
		Validation	0.98346	0.02545	0.98346	0.04545	0.00034
ISOMALT	PCR	Calibration	0.98645	0.24555	0.98645	0.3234	0.00012
		Validation	0.97865	0.25655	0.97865	0.13434	0.02377
	PLS	Calibration	0.98343	0.18789	0.98343	0.13433	-0.00032
		Validation	0.97344	0.22343	0.97344	0.15454	0.02426
MICROCRYSTALLINE CELLULOSE	PCR	Calibration	0.99567	0.17543	0.99567	0.13423	0.00043
		Validation	0.98545	0.19333	0.98545	0.15654	-0.02122
	PLS	Calibration	0.99876	0.14565	0.99876	0.15655	0.00453
		Validation	0.97898	0.16454	0.97898	0.14452	-0.01827
SODIUM STARCH GLYCOLATE	PCR	Calibration	0.25653	3.64332	0.25653	0.73433	0.00223
		Validation	0.22444	3.84333	0.22444	0.67644	-0.00633
	PLS	Calibration	0.26333	3.45543	0.26333	0.67676	0.00002
		Validation	0.21223	3.86343	0.21223	0.76676	-0.00558
MAGNESIUM STEARATE	PCR	Calibration	0.19248	0.96538	0.19248	0.07445	-0.00001
		Validation	0.43411	1.33444	0.43411	0.08232	-0.00016
	PLS	Calibration	0.31543	0.48876	0.31543	0.07334	0.00009
		Validation	0.29090	0.49565	0.29090	0.08234	0.00016

In the application of PCR and PLS algorithm, it is generally known that the spectral pretreatment methods and the number of PCR/PLS factors are critical parameters. The optimum number of components was selected by following the criterion of Haaland and Thomas [13]. The selected model is that with the smallest number of factors such that RMSECV for that model is not significantly greater than RMSECV from the model with one or more additional factors. Figure 2 shows RMSECV plotted as a function of PCR and PLS factors for determining meloxicam, isomalt and microcrystalline cellulose content with the different spectral preprocessing methods. As seen from Figure 2, SNV spectral pretreatment method is obviously superior to others, and for every spectral preprocessing method, RMSECV decreases dramatically with the initial factors. However, it gradually decreases as more PCR or PLS factors “are removed”. According to the RMSECV decrease and its correlation coefficient a number of 4 factors were found to be optimum for using methods PLS with SNV pretreatment for meloxicam, 5 factors for isomalt and 6 factors for microcrystalline cellulose, respectively (Figure 2, and tables III-VI).

The low concentrations of some excipients made it difficult to build their models; according to the obtained results this was particularly the case of sodium starch glycolate (5%) and magnesium stearate (0.5%).

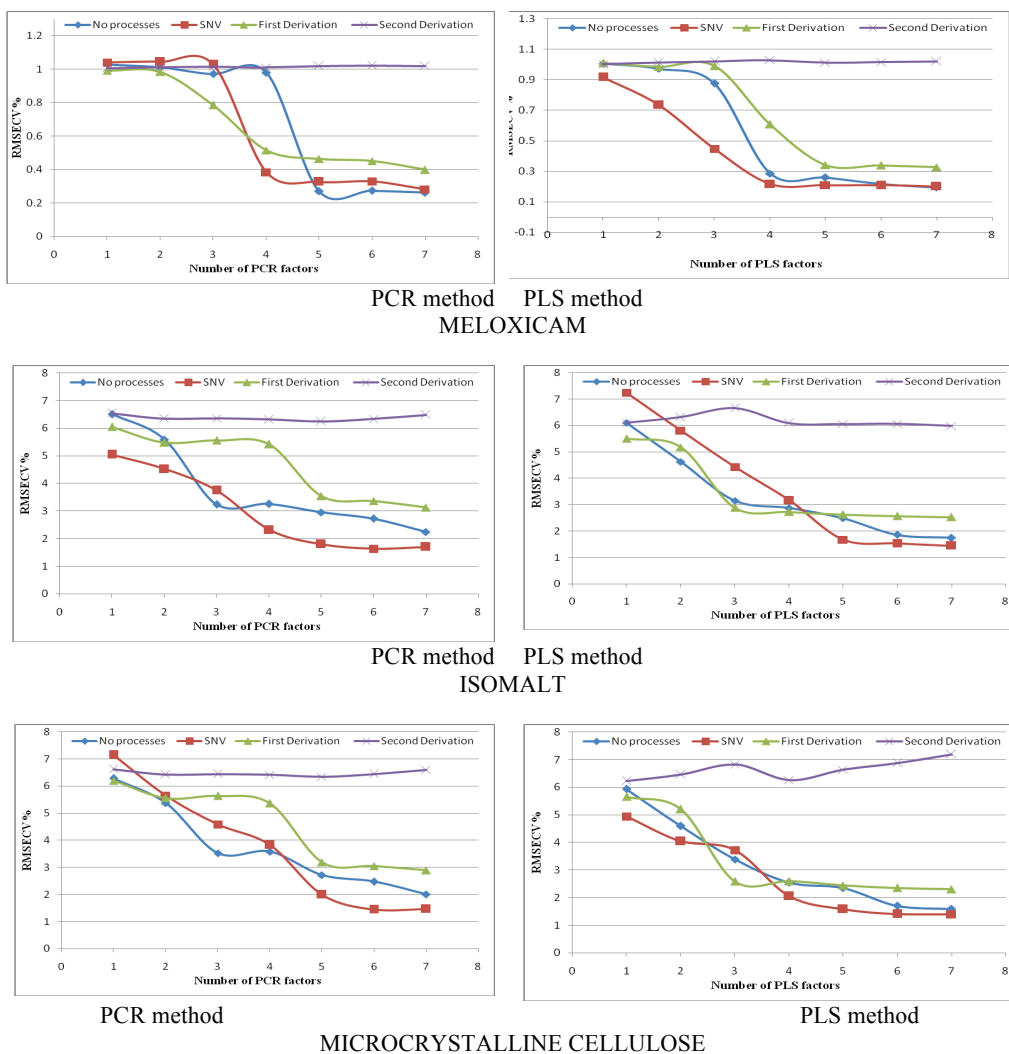


Figure 2.
Plotting RMSECV in function of number of components

Results on control samples

Quantitative analysis of meloxicam, the main component in tablets, on six control samples was performed by the chemometric method and a reference HPLC method. The results for the predictive ability and those obtained by the HPLC assay for the control samples were listed in Table VII.

The data arrays of the control samples obtained by applying the chemometric methods were compared with the ones obtained using the

HPLC reference method. Considering a confidence level of 95%, the obtained probability of Type 1 error showed no statistically significant difference among the means obtained for the three arrays of predictive and reference data. Therefore a good similarity was considered between the results from the proposed NIR chemometric and HPLC reference method.

Table VII
Results obtained for meloxicam on control samples using the proposed and reference HPLC methods

Control samples	Taken (%, w/w)	NT - PLS		SNV - PLS		HPLC	
		Found (%, w/w)	Recovery (%)	Found (%, w/w)	Recovery (%)	Found (%, w/w)	Recovery (%)
P1	7.11	6.884	96.82	6.930	97.47	6.817	95.88
P2	5.44	5.506	101.21	5.567	102.34	5.442	99.98
P3	5.83	5.982	102.61	6.067	104.08	5.697	97.66
P4	6.19	6.084	98.29	5.866	94.77	6.415	103.52
P5	6.26	6.063	96.85	5.997	95.81	5.870	93.67
P6	6.25	6.014	96.22	5.964	95.44	5.647	90.35
Mean	6.1800	6.0888		6.0652		5.9813	
SD	0.5561	0.4449		0.4584		0.5258	
t_{exp}		0.3135		0.3902		0.6358	
P (type 1 error)		0.7603		0.70450		0.5391	

Conclusions

Different calibration methods are evaluated for the nondestructive quantitative analysis of one API (meloxicam) and four excipients (isomalt, microcrystalline cellulose, sodium starch glycolate and magnesium stearate) in pharmaceutical tablet formulation. From the pretreated spectra method, the Standard Normal Variate (SNV) spectra have the smallest RMSECV and the best R, thus the best results. Calibration samples can be prepared by weighing, mixing and tableting the appropriate powders in small amounts in the laboratory. Suitably designed calibration sample sets may allow the calibration model to account for variability caused by the varied amounts of each of the components in the blend.

For API (meloxicam) and two other excipients (isomalt and microcrystalline cellulose) it is feasible to obtain quantitative information by processing NIR spectra of the tablets with different multivariate calibration models. For the API, assay results on six control samples obtained by applying the chemometric method were compared with the results obtained using the HPLC reference method. A good similarity between the results from the proposed NIR chemometric and HPLC reference method was observed. The calibration sample designs presented in this study appear to

be very non-effective for the determination of two minor components at 5% (sodium starch glycolate) and 0.5% (magnesium stearate).

In conclusion, NIR method is suitable for the quantitative analysis of meloxicam and two other excipients (isomalt and microcrystalline cellulose) in tablet formulation.

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References

1. Food, Drug Administration, Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, FDA CDR 2004, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf>
2. Ito M., Suzuki T., Yada S., Kusai A., Nakagami H., Yonemochi E., Terada K., Development of a method for the determination of caffeine anhydrate in various designed intact tablets by near-infrared spectroscopy: A comparison between reflectance and transmittance technique, *Journal of Pharmaceutical and Biomedical Analysis* 2008, 47, 819–827
3. Davis T.D., Peck G.E., Stowell J.G., Morris K.R., Byrn S.R., Modeling and monitoring of polymorphic transformations during the drying phase of wet granulation *Pharm. Res.* 2004, 21(5), 860–866.
4. Findlay W.P., Peck G.R., Morris K.R., Determination of fluidized bed granulation end point using near-infrared spectroscopy and phenomenological analysis, *J. Pharm. Sci.*, 2005, 94(3), 604–612.
5. Gupta, G.E. Peck, R.W. Miller, K.R. Morris, Real-time near-infrared monitoring of content uniformity, moisture content, compact density, tensile strength, and young's modulus of roller compacted powder blends, *J. Pharm. Sci.* 2005, 94 (7), 1589–1597.
6. El-Hagrasy A.S., Drennen J.K., A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending. Part III: Quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics, *J. Pharm. Sci.*, 2006, 95, (2) 422–434.
7. Li W., Johnson M.C., Bruce R., Ulrich S., Rasmussen H., Worosila G.D., Mass-balanced blend uniformity analysis of pharmaceutical powders by at-line near-infrared spectroscopy with a fiber-optic probe, *Int. J. Pharm.*, 2006, 326, 182–185.
8. El-Hagrasy A.S., Chang S.Y., Kiang S., Evaluation of risk and benefit in the implementation of near-infrared spectroscopy for monitoring of lubricant mixing, *Pharm. Dev. Technol.*, 2006, 11, 303–312.
9. Perez-Ramos J.D., Findlay W.P., Peck G., Morris K.R., Quantitative analysis of film coating in a pan coater based on in-line sensor measurements, *AAPS PharmSciTech*, 2005, 6 (1), E127–E136.
10. Gendrin C., Roggo Y., Collet C., Content uniformity of pharmaceutical solid dosage forms by near infrared hyperspectral imaging: A feasibility study, *Talanta* 2007, 73, 733–741.
11. Otsuka M., Mouri Y., Matsuda Y. Chemometric Evaluation of Pharmaceutical Properties of Antipyrine Granules by Near-Infrared Spectroscopy. *AAPS PharmSciTech*. 2003; 4(3): article 47.

12. M. Blanco, M. Alcalá, J.M. González, E. Torras, A process analytical technology approach based on near infrared spectroscopy: Tablet hardness, content uniformity, and dissolution test measurements of intact tablets, *J. Pharm. Sci.* 2006, 95 (10) 2137–2144.
13. Meza C.P., Santos M.A., Romanach R.J., Quantitation of Drug Content in a Low Dosage Formulation by Transmission Near Infrared Spectroscopy, *AAPS PharmSciTech* 2006, 7 (1), Article 29, E1–E9.
14. Popa L. Ghica M., Moisesescu St., Taguchi method in the formulation and optimization of dosage forms, *Farmacia*, 2004, 52, 9-16
15. Xiaobo Z., Jiewen Z., Povey M.J.W., Holmes M., Hanpin M., Variables selection methods in near-infrared spectroscopy, *Analytica Chimica Acta* 667 (2010) 14–32.
16. Ramirez J.L., Bellamy M.K., Romanach R.J., A novel method for analyzing thick tablets by near infrared spectroscopy. *AAPS PharmSciTech*. 2001, 2(3), Article 11, 1-10.
17. Gottfries J., Depui H., Fransson M., et al. Vibrational spectrometry for the assessment of active substance in metoprolol tablets: a comparison between transmission and diffuse reflectance near infrared spectrometry, *J Pharm Biomed Anal.*, 1996, 14,1495-1503.
18. Eriksson L., Johansson E., Kettaneh-Wold N., Trygg J., Wikström C., Wold S., Multi- and megavariate data analysis part I, Basic principles and applications, Second revised and enlarged edition, *Umetrics Academy*, Umea, 2006.
19. Martens H., Naes T., *Multivariate Calibration*, Wiley, Chichester, 1989.
20. Espinosa-Mansilla A., Salinas F., De Orbe Paya I., Simultaneous determination of sulfadiazine, doxycycline, furaltadone and trimethoprim by partial least squares multivariate calibration, *Anal. Chim. Acta* 1995, 313, 103–112.

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