

# Quantitative characterisation of extended-release tablets with quetiapine using NIR-chemometric methods

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## ABSTRACT

This study aims to develop and validate NIR-chemometric methods for quantifying the API (quetiapine) and two excipients in extended-release tablets without sample preparation.

The calibration samples were prepared following an experimental design with three variables (quetiapine, HPMC and microcrystalline cellulose) and five levels (concentration 80-90-100-110-120% of API). The validation set included three concentration levels (90-100-110%).

The best calibration algorithms have used the same pre-treatment method (SNV), and different factors: 7 PLS factors ( $R^2$  -0,966 and RMSEP-6,84) for quetiapine, 8 PLS factors ( $R^2$ -0,927 and RMSEP 6,84) for HPMC and 3 PLS factors ( $R^2$ -0,983 and RMSEP-7,26) for microcrystalline cellulose. The methods were fully validated according to the ICH guidance using these calibration models. Regarding the trueness of the methods, the recovery was between 98.51 and 99.43 for quetiapine, between 98.61 and 100.85 for HPMC, and between 100.61 and 101.78 for microcrystalline cellulose. According to data obtained, the accuracy profile was  $\pm 5$  for quetiapine and HPMC, and  $\pm 6$  for microcrystalline cellulose. Linearity profile was also in establish intervals at accuracy and the  $R^2$  value was 0.983 for quetiapine, 0.948 for HPMC and 0.997 for microcrystalline cellulose.

In conclusion, the developed NIR-chemometric methods have suitable reproducibility, accuracy, linearity and can be used for quantitative characterisation of extended-release tablets with quetiapine, with any sample preparation

**Keywords:** caffeic acid, tea, antioxidant potential

## INTRODUCTION

In August 2002, FDA initiated PAT Guidance for Industry, named "a framework for innovative pharmaceutical development, manufacturing and quality assurance" [1]. By implementing this new concept, the analytical procedures will be more effective by reducing time and increasing the final products' quality [2,3].

In recent years, the application of Near Infrared (NIR) spectroscopy as a Process Analytical Technology (PAT) tool and monitoring technique within the pharmaceutical industry has been overgrown. NIR spectroscopy can be used for raw material testing, product quality control and process monitoring. The growing pharmaceutical interest in NIR is probably a direct result of its advantages of being simple, fast,

and non-destructive and enabling the analysis of complex matrices without the need to manipulate samples [4]. NIR spectra are rich in chemical and physical information when is used in conjunction with appropriate chemometric. The primary step to develop a NIR assay method is the calibration procedure for model development. Once calibration is successful set and favourable predictions are expected, they must be validated in order to be accepted for routine use in the pharmaceutical industry [5,6].

In hydrophile matrix extended-release formulation, the ratio of the matrix-forming polymer plays a significant role in matrix swelling and erosion and, consequently, in the API kinetic release. Inadequate mixing or segregation problems may conduct to manufacture tablets with different content in HPMC/tablets, which may have a consequence on the reproducibility of kinetic release profile [4,7,8]. So, to have a method accessible to evaluate the content uniformity of HPMC in the hydrophilic matrix extended-release formulation is beneficial in current quality control [9]. The NIR spectroscopy in combination with chemometric may provide this tool, on intact tablets, and without any sample preparation [4,10].

This study aimed to develop and validate a NIR-chemometric method for directly and simultaneously quantification of one API (quetiapine) and two excipients (hydroxypropyl methylcellulose and microcrystalline cellulose) in extended-release tablets without any sample preparation.

## MATERIALS AND METHODS

### Materials

Quetiapine fumarate, the active pharmaceutical ingredient (API) was supplied by PharmaZell – India. Two diluents, lactose monohydrate (Tabletose 80 from Meggle – Germany) and microcrystalline cellulose - CMC (Avicel PH-102, from Chemo Pharma – Austria), were used in the formulation. During wet granulation, a 10% solution of polyvinylpyrrolidone (Kollidon 30 produced by BASF – Germany) was used as binder. Also, two matrix-forming excipients, based on hydroxypropyl methylcellulose HPMC, were used: Methocel K 100 M and Methocel K 100 LV (supplied by Colorcon – UK). Extra-granular excipients were, besides Avicel PH-102, colloidal silicon dioxide –

Aerosil 200 (Rohm Pharma Polymers, Germany), and magnesium stearate (Union Derivan S.A, Spain). All excipients were pharmaceutical grade.

### Extended-release tablets manufacturing

Extended-release tablets (hydrophilic type matrix) with quetiapine were prepared through wet granulation following the following protocol. Powders were weighted and sieved. Quetiapine fumarate, lactose monohydrate and microcrystalline cellulose were granulated in an Aeromatic Fielder AG fluidised bed processor (Aeromatic, Switzerland) using a water solution of polyvinylpyrrolidone 10% (m/m) as a binder. After granulation, a wet calibration was performed, and granules were dried for 24 hours in an oven. The next step was dry calibration was performed to break up crowds. The powders blend for tableting was obtained by mixing the granules with the rest of the excipients in an Erweka LK5 laboratory kneading equipment (Erweka, Germany). At the end, tablets were obtained using Korsch EK-0 tablet press (Korsch, Germany) equipped with a set of 12 mm punch and die. The tablet press was adjusted to obtain tablets with an average weight of 640 mg. Those tablets contain 230.26 mg quetiapine fumarate (corresponding to 200 mg quetiapine) were considered the 100% target formula (corresponding to level 3 in experimental design).

### Calibration and validation protocol

For validation purposes three fully independent batches (levels 2-3-4 and four replicated for each level) were manufactured daily, on three different days, resulting 36 batches for the validation set (Table 1).

TABLE 1. Protocol of calibration and validation samples

		Serie 1		Serie 2		Serie3	
		C	V	C	V	C	V
Levels		DoE	0	DoE	0	DoE	0
1.	80%		4		4		4
2.	90%		4		4		4
3.	100%		4		4		4
4.	110%		4		4		4
5.	120%		0		0		0

**TABLE 2. Composition of calibration and validation samples**

Concentration Level	1 80%	2 90%	3 100%	4 110%	5 120%
<b>Tablets composition (mg/tablet)</b>					
Quetiapine fumarate	184.21	207.23	230.26	253.28	276.31
Lactose monohydrate	14.14	15.91	17.68	19.45	21.21
Microcrystalline cellulose (intra granular)	39.25	44.15	49.06	53.96	58.87
Kollidon 30	4.53	5.09	5.66	6.22	6.79
Microcrystalline cellulose (extra granular)	209.08	156.42	103.75	51.09	0.00
HPMC 100M	17.92	20.16	22.4	24.64	26.88
HPMC 100LV	161.28	181.44	201.6	221.76	241.92
Aerosil 200	3.20	3.20	3.20	3.20	3.20
Magnesium stearate	6.40	6.40	6.40	6.40	6.40
Tablet weight	640.00	640.00	640.00	640.00	641.58

### Experimental design and calibration and validation samples composition

The qualitative and quantitative composition of calibration and validation samples is presented in Table 2.

For the calibration set, in order to develop NIR-chemometric methods for extended-release tablets with quetiapine characteristics prediction, an orthogonal experimental design, build in Modde 12.0 software (Umetrics, Sweden), with three variables (quetiapine quantity - X1, HPMC quantity – X2, microcrystalline cellulose quantity – X3) and five levels (80% - 90% - 100% - 110% - 120%) was used. The advantage of using design of experiments is the study of a maximum numbers of factors by means of a minimum number of experiments. The amount of quetiapine and HPMC was varied between 80-120% of the targeted quantity in tablets composition and the quantity of microcrystalline cellulose (X3) was varied according to maintain a constant tablet weight of 640mg. Practically, the X1 levels (quetiapine quantity) was varied between 28.78% (m/m) and 43.07% (m/m), X2 levels (HPMC quantity) were varied between 28% (m/m) and 41.92% and X3 (microcrystalline cellulose quantity) were varied between 9.17% (m/m) and 38.8% (m/m). Colloidal silicon dioxide and magnesium stearate were kept

constant in all formulations, at a percentage of 0.5% (m/m) and 1% (m/m) respectively. According to this experimental design, the calibration set contained 27 different formulations (Table 3).

**TABLE 3. Experimental design matrix for calibration set**

Exp Name Run Order	X1	X2	X3	Exp Name Run Order	X1	X2	X3
N1	184	179	214	N15	276	224	50
N2	230	179	154	N16	184	227	166
N3	276	179	95	N17	230	227	106
N4	184	183	210	N18	276	227	47
N5	230	183	150	N19	184	240	153
N6	276	183	91	N20	230	240	93
N7	184	186	207	N21	276	240	34
N8	230	186	147	N22	184	244	149
N9	276	186	88	N23	230	244	89
N10	184	220	173	N24	276	244	30
N11	230	220	113	N25	184	247	146
N12	276	220	54	N26	230	247	86
N13	184	224	169	N27	276	247	27
N14	230	224	109				

X1 – quetiapine quantity (mg/tablet); X2 – HPMC quantity(mg/tablet); X3 - microcrystalline cellulose (mg/tablet)

### NIR spectra recording

The NIR spectra were recorded on intact tablets using an FT-NIR spectrometer Antaris II (Thermoelectron, USA) in transmittance configuration. This configuration allows directly recording NIR spectra; no prior sample preparation is needed. In this configuration, NIR passes through the tablet and is measured by an InGaAS (indium galliumarsenide) detector positioned on the tablet. In order to increase the reproducibility of measurement, a sample holder was used. Spectra acquisition was performed by OMNIC (Thermoelectron, USA) for 15 different tablets from all calibration and validation batches. For each sample, the recorded spectra were an average of 32 scans integrated over the range from 10000 to 4000 cm<sup>-1</sup>, with a resolution of 16 cm<sup>-1</sup>.

### NIR data processing

The development of the multivariate models was based on partial least squares regression – PLS. Both no processing and pre-processing methods were used single or combined. The following pre-processing methods, constant offset elimination (COE), straight-

line subtraction (SLS), standard normal variate (SNV), minimum, maximum normalisation (mMN), multiplicative scattering correction (MSC), first derivative (FD) and second derivative (SD), FD+SLS, FD+SNV and FD+MSC, were tested for development of calibration models.

A cross-validation approach based on the leave-one-out procedure was applied to determine the optimal number of PLS factors. The prediction capability of multivariate models was evaluated considering: a small number of PLS factors, closed to 1 value for determination coefficient ( $R^2$ ) and as small as possible values for root mean standard error of prediction (RMSEP) and Bias [11,12].

### NIR method validation

Models with the best prediction capability were subjected to full validation. Calculated validation parameters are recommended by the International Conference of Harmonization (ICH). The validation approach was based on the technique proposed by Hubert et al. [13-15] and was applied to validation batches (Table 2). The calculations were performed using Microsoft Excel 2007 (Microsoft Corporation, USA) and included trueness (relative bias and recovery), precision (repeatability and intermediate precision) and accuracy (absolute and relative tolerance limits).

## RESULTS AND DISCUSSION

### Spectral investigation and models selection

The NIR transmittance spectra of the tablets corresponding to the calibration set are presented in Figure 1.

Because a high background noise characterises it, a spectral region below 4000  $\text{cm}^{-1}$  was first eliminated from the analysis. In order to correlate spectral information with analytes concentration levels, several spectral ranges were used: 11000 – 8560  $\text{cm}^{-1}$  (for quetiapine) and 10000-7400  $\text{cm}^{-1}$ ; 7050-5600  $\text{cm}^{-1}$ ; 5100-4150  $\text{cm}^{-1}$  (for HPMC and microcrystalline cellulose) respectively.

### Model development and selection

Based on both un-processed and pre-processed spectra, a number of 11 multivariate models were build for each analyte (quetiapine, HPMC and microcrystalline cellulose).

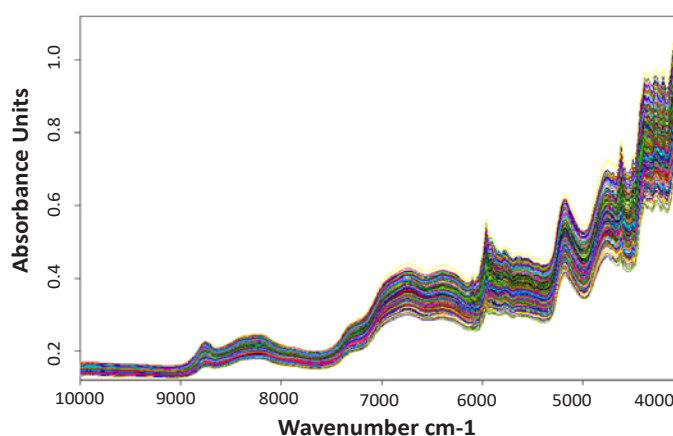


FIGURE 1. Transmittance spectrum of tablets recorded at a resolution of 16  $\text{cm}^{-1}$  for calibration set

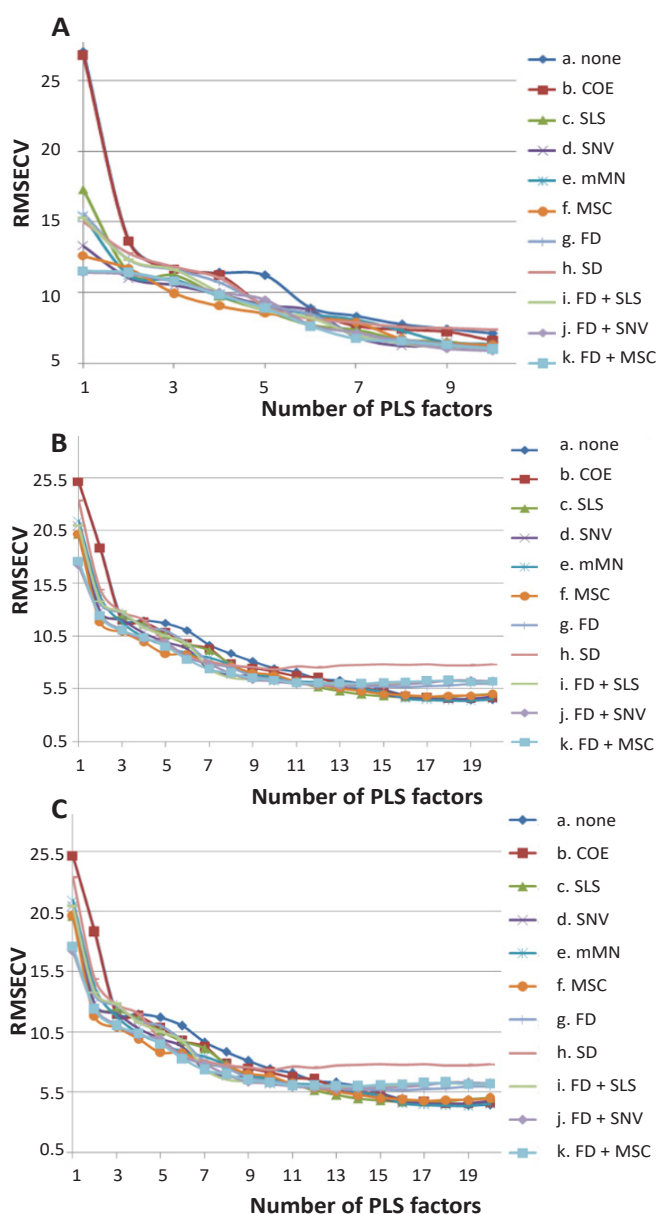


FIGURE 2. Plotting RMSEP vs. number of PLS factors for different proposed models for quetiapine (A), HPMC (B) and microcrystalline cellulose (C)

**TABLE 4.** Type of spectral pre-treatment, R2, spectral range selected, number of PLS factors, RMSEC and RMSEP of different models for prediction of quetiapine, HPMC and microcrystalline cellulose

<b>Quetiapine</b>											
<b>Model</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d*</b>	<b>e</b>	<b>f</b>	<b>g</b>	<b>h</b>	<b>i</b>	<b>j</b>	<b>k</b>
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	FS+SLS	FD+SNV	FD+MSC
Spectral range selected (cm <sup>-1</sup> )	11000-8560										
Number of PLS factors	8	5	6	7	9	8	7	7	9	9	7
R2	0.9572	0.9411	0.9574	0.9663	0.9697	0.9678	0.9650	0.9565	0.9736	0.9738	0.9673
RMSECV (%)	7.71	9.04	7.69	6.84	6.48	6.68	6.98	7.85	6.05	6.03	6.73
Bias (%)	0.0207	-0.017	0.038	-0.022	-0.014	-0.003	0.035	0.032	0.023	0.0184	0.0134
<b>HPMC</b>											
<b>Model</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d*</b>	<b>e</b>	<b>f</b>	<b>g</b>	<b>h</b>	<b>i</b>	<b>j</b>	<b>k</b>
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	FS+SLS	FD+SNV	FD+MSC
Spectral range selected (cm <sup>-1</sup> )	10000-7400; 7050-5600; 5100-4150										
Number of PLS factors	3	8	9	8	9	9	9	8	8	8	9
R2	0.7710	0.9053	0.9304	0.9278	0.9268	0.9239	0.9305	0.9079	0.9335	0.9253	0.9345
RMSECV (%)	12.2	7.84	6.72	6.84	6.89	70.2	6.71	7.73	6.57	6.96	6.52
Bias (%)	-0.007	-0.002	-0.023	0.006	0.012	-0.017	-0.217	-0.025	0.189	-0.018	-0.024
<b>Microcrystalline cellulose</b>											
<b>Model</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d*</b>	<b>e</b>	<b>f</b>	<b>g</b>	<b>h</b>	<b>i</b>	<b>j</b>	<b>k</b>
Pre-treatment	None	COE	SLS	SNV	mMN	MSC	FD	SD	FS+SLS	FD+SNV	FD+MSC
Spectral range selected (cm <sup>-1</sup> )	10000-7400; 7050-5600; 5100-4150										
Number of PLS factors	3	3	3	3	3	3	3	3	5	3	3
R2	0.9763	0.9761	0.9742	0.9830	0.9831	0.9850	0.9768	0.9806	0.9804	0.9827	0.9822
RMSECV (%)	8.56	8.59	8.93	7.26	7.22	6.81	8.48	7.75	7.94	7.32	7.44
Bias (%)	-0.005	-0.004	-0.169	0.009	-0.014	-0.003	0.002	0.009	0.019	-0.007	-0.0083

\* Model d was selected for validation for all three methods

The pre-treatment method, spectral range, number of PLS factors, RMSEP R2 and bias of the developed multivariate models are presented in Table 4. For each analyte, the model with the best predictive capacity was selected based on the lowest number of PLS factors, for that, the values of RMSEP were not significantly higher than the model with one more PLS factor. To see the variation of RMSEP with number PLS factors, the graphical plotting the value of RMSEP number vs. PLS factors is very useful. The results obtained on the models developed for quetiapine, HPMC and microcrystalline cellulose are presented in Figure 2.

#### API (quetiapine) content quantification

Several models were developed for quetiapine quantification in extended-release tablets, and such as, c. SLS, d. SNV, g. FD, j. FD + SNV, k. FD + MSC, seems to indicate good prediction (Table 4). Based on the decrease of RMSEP, the value of correlation coefficient  $R^2 = 0.9663$ , a number of 7 factors for the PLS model with pre-treatment of samples using the SNV method was selected as the model for quetiapine content quantification. At this model also has a shallow bias (0.0222), it is also observed that RMSEP values decrease sharply with the increasing number of PLS factors (Figure 2.). So, model d. SNV was selected for validation. Four independent batches at three

concentration levels (90-100-110%) were analysed in three different days for method validation. A total number of 36 samples were prepared and analysed for validation purposes. The results for validation of the method for quetiapine assay using the d. SNV model are presented in table 5, Figure 3A and Figure 4A. According to obtain the results, the best recovery (99.43%), the lowest bias coefficient (-0.566) and the best repeatability (0.91%) were found for the tablets with the highest quetiapine concentration (252mg / tablet). Instead, for the tablets with the smallest amount of quetiapine (204 mg /tablet), a bias coefficient of 1,486 and a recovery of 98.51% were obtained, also value very close to 100%. The method precision, that was evaluated as intra-day precision (repeatability) and inter-day precision (intermediate repeatability), has excellent value in all cases. A maximum RSD value of 1.5% was obtained at inter-day precision at the lowest concentration level of quetiapine. The linearity profile is obtained by plotting the predicted concentration in the validation samples

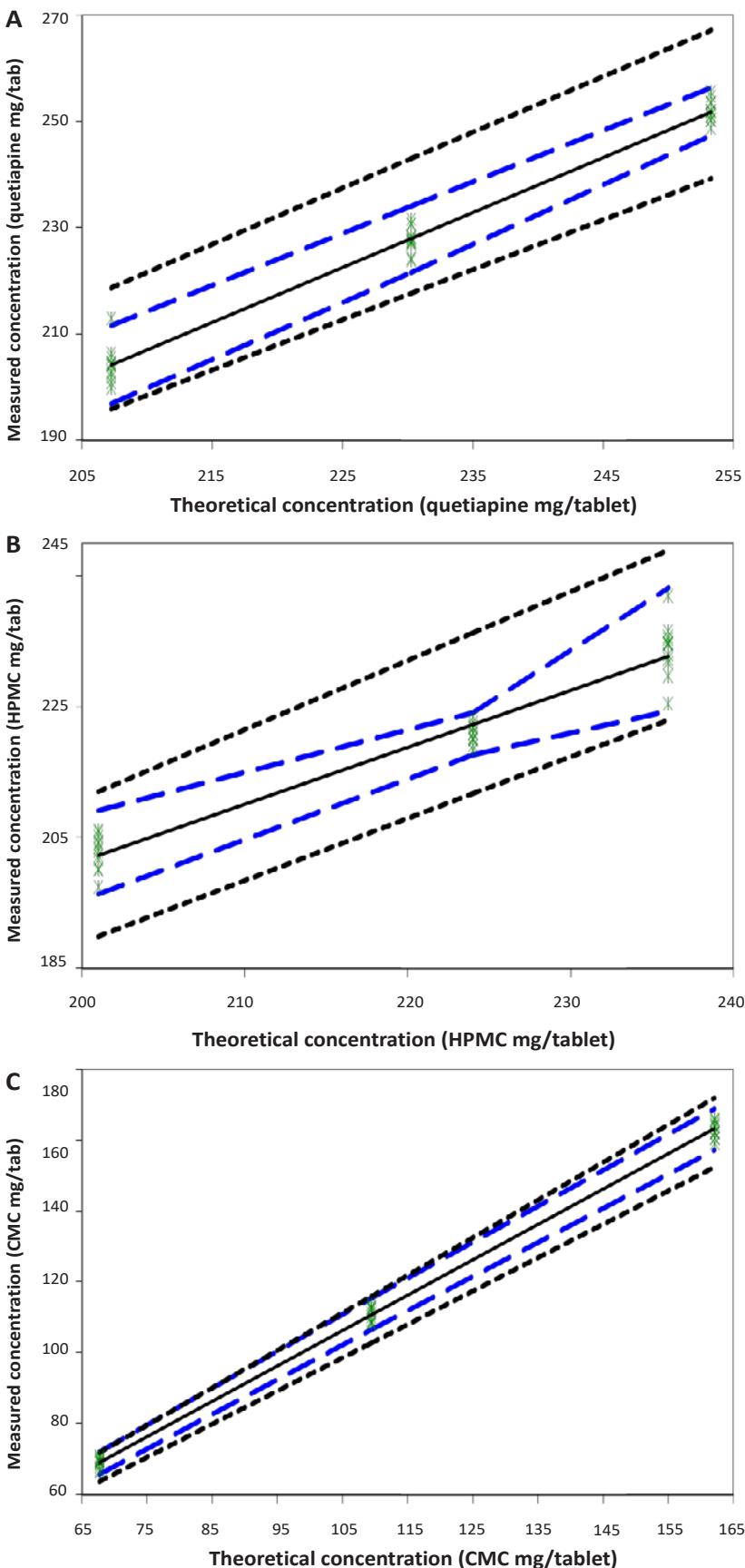
as a function of found (introduced) concentration in the samples when there were prepared [4,5,16]. In figure 3A, the plotline of the predicted quetiapine concentrations versus introduced concentrations shows an excellent linearity profile (an R2 close to 1). In terms of accuracy, relative tolerance limits were set at  $\pm 5\%$ , to make the method suitable for active substance quantification in pharmaceutical formulation. According to the graphical presentation of the accuracy profile, to have good accuracy, the  $\beta$ -expectation tolerance limits should not exceed the acceptance limits [4,15,16]. For quetiapine assay, the results obtained for accuracy profile were in the range of  $\pm 5\%$  at all three concentrations levels (Table 5 and Figure 4A), so the method is accurate for quetiapine quantification in extended-release tablets.

#### HPMC content quantification

HPMC was used in quetiapine extended-release formulation as matrix-forming polymer, and its quantification may be useful in routine quality control.

**TABLE 5. Validation results OF NIR – chemometric methods for assay of the quetiapine, HPMC (B) and CMC in extended-release tablets**

Quetiapine							
Concentration level (quetiapine)	Mean quetiapine content (mg/tablet)	Trueness		Precision		Accuracy	
		Relative bias (%)	Recovery(%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (mg/tablet)
207	204	-1.486	98.51	1.67	1.59	[-5.0, 2.1]	[196, 211]
230	228	-1.078	98.92	0.93	1.09	[-3.9, 1.7]	[221, 234]
253	252	-0.566	99.43	0.91	0.79	[-2.4, 1.2]	[247, 256]
HPMC							
Concentration level (HPMC)	Mean quetiapine content (mg/tablet)	Trueness		Precision		Accuracy	
		Relative bias (%)	Recovery(%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (mg/tablet)
201	203	0.85	100.85	1.23	1.31	[-2.3, 4.0]	[190, 209]
224	221	-1.39	98.61	0.69	0.64	[-2.8, 0.1]	[212, 224]
236	234	-0.96	99.04	1.67	1.72	[-5.0, 3.1]	[223, 243]
Microcrystalline cellulose							
Concentration level (Microcrystalline cellulose)	Mean quetiapine content (mg/tablet)	Trueness		Precision		Accuracy	
		Relative bias (%)	Recovery(%)	Repeatability (RSD %)	Intermediate precision (RSD %)	Relative tolerance limits (%)	Tolerance limits (mg/tablet)
68	68.9	1.78	101.78	1.84	1.94	[-2.8, 6.3]	[65.8, 72.0]
109	111.0	1.50	101.50	1.73	1.74	[-2.5, 5.5]	[106.6, 115.5]
162	163.1	0.61	100.61	1.28	1.46	[-3.0, 4.2]	[157.2, 168.9]

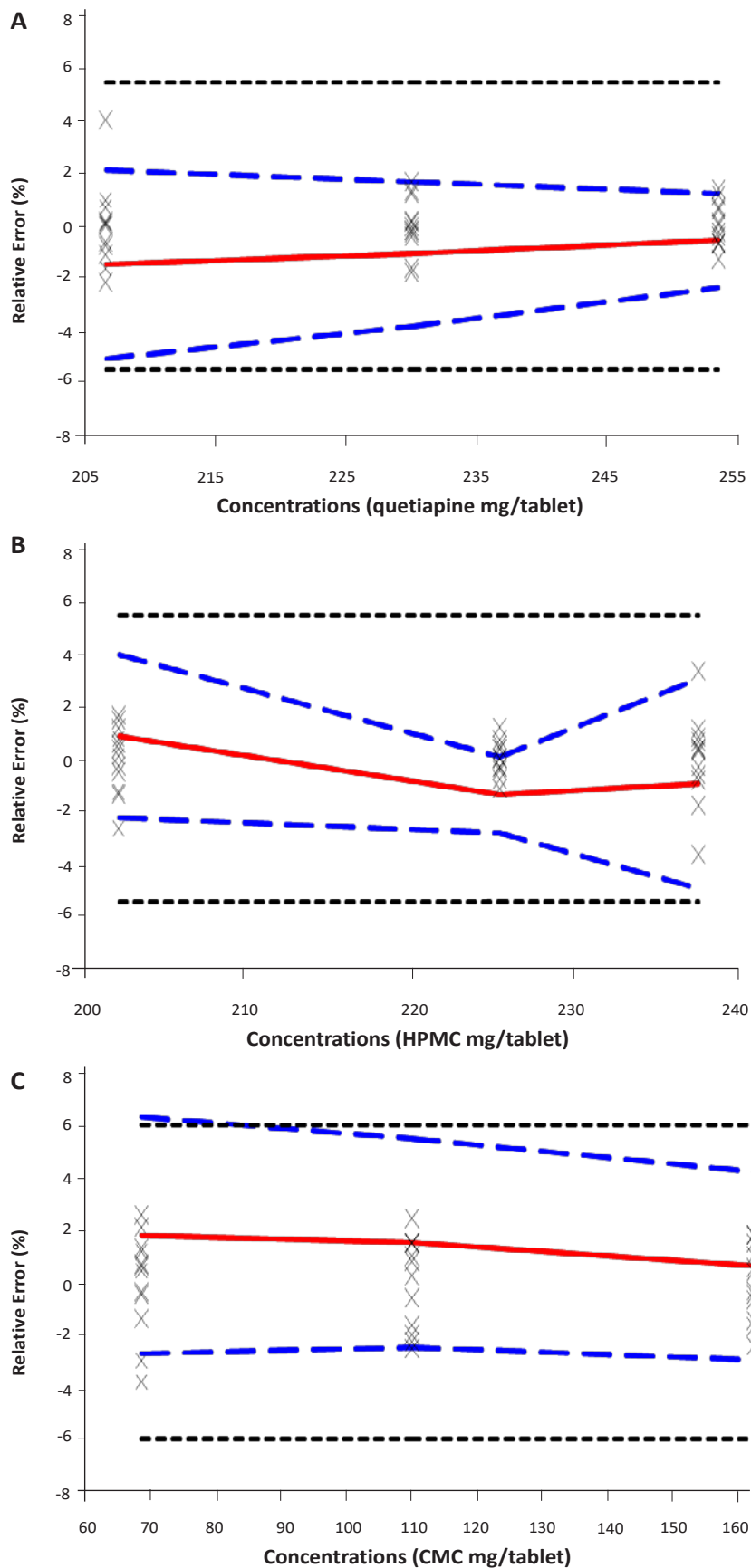


**FIGURE 3.** Linearity profile of NIR – chemometric methods for quetiapine (A), HPMC (B) and microcrystalline cellulose (C) quantification in extended-release tablets. The continuous line is the identity line  $y = x$ , dotted curves represent the acceptance limits set at  $\pm 5\%$  and dashed lines correspond to the accuracy profile

Eleven models were developed for HPMC quantification in extended-release tablets with quetiapine, and several (c. SLS, d. SNV, g. FD, i. FD + SLS, , J. FD + SNV, k. FD + MSC, seems to have a good prediction (Table 4). Based on the decrease of RMSEP, the value of correlation coefficient  $R^2 = 0.99278$ , a number of 8 PLS factors, the model with pre-treatment of samples using the SNV method (model d) was selected for HPMC quantification and tested in the validation step. Also, this model has a low bias (0.006), and its RMSEP values decrease slowly with the increasing number of PLS factors (Figure 2).

Figure 3B, 4B and Table 5 present the results for validation of the method for HPMC quantification in extended-release tablets using the d. SNV model. The best recovery (100.85%), the lowest bias coefficient (0.85) 0.91%) were found for the tablets with the lowest HPMC concentration (201 mg/tablet). The best precision (repeatability 0.69 and intermediate repeatability 0.64) was found for medium HPMC concentration (224 mg/tablet). A maximum RSD value of 1.72% was obtained for inter-day precision at the highest concentration level of HPMC. Figure 3B shows an excellent linearity profile for the HPMC quantification, plotting the predicted concentration vs. found (introduced) concentration of HPMC in the validation samples. The accuracy profile, graphically presented in figure 5B, show that the accuracy is very good, as the  $\beta$ -expectation tolerance limits do not exceed the acceptance limits, for the profile range of  $\pm 5\%$  at all concentrations levels.

Based on the obtain validation parameters (recovery, precision



**FIGURE 4.** Accuracy profile of the NIR-chemometric methods for quetiapine (A), HPMC (B) and microcrystalline cellulose (C) quantification in extended-release tablets. The dotted curves are the acceptance limits set at  $\pm 5\%$ , dashed lines are the  $\beta$ -expectation tolerance limits ( $\beta=95\%$ ) and the plain line is the relative bias

and accuracy) for HPMC quantification using model d (SNV pre-treatment and 8 PLS factors), it can be concluded that the NIR-chemometric method can be used for matrix-forming polymer assay in extended-release tablets with quetiapine.

#### Microcrystalline cellulose content quantification

For microcrystalline cellulose quantification in extended-release tablets with quetiapine, eleven models were developed (Table 4). Several of them (c. SLS, d. SNV, e. mMN, i. MSC, , J. FD + SNV, k. FD + MSC), seems to have a good prediction capacity. Based on RMSEP decrease Figure 2.), SNV method as pre-treatment with a number of 3 PLS factors, (model d) was selected to be tested in the validation step for microcrystalline cellulose quantification. This model also has an excellent correlation coefficient ( $R^2 = 0.9830$ ) and a low bias (0.0069). The validation results of the method for microcrystalline cellulose quantification in extended-release tablets using the d. SNV model are presented Figure 3C, 4C and Table 5. The best recovery (100.61%), the lowest bias coefficient (0.61) was found for the tablets with the highest microcrystalline cellulose concentration (163.1 mg/tablet). The best precision (repeatability 1.28 and intermediate repeatability 1.46) was found was also front for the highest concentration of microcrystalline cellulose. A maximum RSD value of 1.94% was obtained for inter-day precision at the lowest concentration level of microcrystalline cellulose. Figure 3C shows an excellent linearity profile for the microcrystalline cellulose. quantification, plotting the predicted concentration vs.



found concentration of microcrystalline cellulose in the validation samples. The accuracy profile, graphically presented in figure 5C, show that the accuracy is acceptable, as the  $\beta$ -expectation tolerance limits do not exceed the acceptance limits, for profile range of  $\pm 6\%$  at all concentrations levels. Based on the obtain validation parameters (recovery, precision and accuracy) for microcrystalline cellulose quantification using model d (SNV pre-treatment and 3 PLS factors), it can be concluded that the NIR-chemometric method can be used for microcrystalline cellulose assay in extended-release tablets with quetiapine.

## CONCLUSIONS

Different calibration models were developed for quantitative characterisation of quetiapine extended-

release tablets using NIR-chemometric technique. A validation procedure was followed using the best calibration models for each analyte of interest (API, HPMC used as matrix-forming polymer and microcrystalline cellulose). The method was fully validated according to ICH guidance. The results demonstrate the developed NIR-chemometric method is suitable for directly and simultaneously quantification of quetiapine, HPMC and microcrystalline cellulose in extended-release tablets. The method is reproducible, has good linearity and excellent accuracy profile, and may be used for routine analysis of the three analytes in tablets.

In conclusion, the NIR spectrometry associated with chemometry can provide suitable tools for the chemical characterisation of extended-release tablets with quetiapine without any sample preparation.

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