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Simultaneous determination of valsartan, amlodipine besylate and hydrochlorothiazide in tablets by near infrared

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ABSTRACT

Interval partial least-squares calibration (*i*PLS) and synergical partial least-squares calibration (*si*PLS) methods in combination with near infrared spectroscopy coupled with integrating sphere (NIRA) have been developed for simultaneous determination of amlodipine (AML), valsartan (VAL) and hydrochlorothiazide (HCT) in raw material powder mixtures used for production commercial pharmaceutical product (tablets). Variable selection methods (*iPLS* and *si*PLS) were applied to select a spectral range that provided significant information and models with lower prediction errors. A near-infrared reflectance accessory (NIRA) was used for direct sample analysis. Spectral data were acquired between 10000 - 4000 cm^{-1} and divided into 32 intervals. A relative standard error of prediction of 1.27% for VAL, 1.92% for HCT and 5.19% for AML was obtained after selection of better intervals by *si*PLS. Results shown that variable selection methods associated to NIRA is a relatively simple, free solvent and non-destructive procedure that could be applied to the simultaneous determination of AML, VAL and HCT in tablets.

INTRODUCTION

In the field of pharmaceutical research, High-Performance Liquid Chromatography (HPLC) is a method-of-choice in bulk drugs and pharmaceutical dosage forms analysis. Although HPLC can be well established and recognized by regulatory agencies, have some disadvantages such as large consumption of solvents. "Green methods" as infrared spectroscopy has become an attractive alternative because they provide accurate results and a low sample preparation time. Near infrared using reflectance accessory (NIRA) has been extensively used in quality control of finished pharmaceuticals and monitoring processes in combination with multivariate regression methods as Partial Least Squares (PLS) (Roggo *et al.*, 2007; Alcalà *et al.*, 2008; Souza *et al.*, 2012; Pan *et al.*, 2014; Wood *et al.*, 2016).

Most recently applications have been published showing that spectral region selection using suitable algorithms such as interval partial least squares (*i*PLS) and synergical partial least squares (*si*PLS) can significantly improve the performance of PLS regression techniques (Xiaobo *et al.*, 2010; Shi *et al.*, 2012; Piantavini *et al.*, 2015; Silva, Flores and Parisotto, 2016). Moreover, spectral region selection containing relevant chemical information is especially important for spectra with strong band overlapping such as pharmaceutical formulations (containing active substance, impurities and excipients) (Silva *et al.*, 2009; Piantavini *et al.*, 2014). Recent papers in the literature describe assay methods for tablets containing triple combination of valsartan (VAL), hydrochlorothiazide (HCT) and amlodipine besylate (AML) by HPLC and ultraviolet spectroscopy (UV) (Shaalan *et al.*, 2013; Darwish *et al.*, 2014).

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However, only one paper can be founding reporting simultaneous determination of this pharmaceutical product involving multivariate calibration (Darwish *et al.*, 2013). Thus, the main objective of this work was to investigate the availability of NIRA spectroscopy associated to *i*PLS and *si*PLS algorithms for the obtained regression models. These models were used to predicting VAL, HCT and AML in powder mixtures and commercial tablets.

EXPERIMENTAL

Samples

VAL, HCT and AML bulk drugs commercially acquired were used to prepare synthetic samples. Thirty six formulations (synthetic samples) containing VAL (261 to 500 mg g^{-1} range), HCT (20 to 84 mg g^{-1} range), AML (11 to 50 mg g^{-1} range) and diluents magnesium stearate, talc and microcrystalline cellulose (2.5:5:92.5, respectively) were prepared in laboratory. Commercial tablets (Exforge HCT®, Novartis Pharma, Switzerland) labeled to contain 160 mg VAL, 12.5 mg HCT and 5 mg AML were purchased from a local drugstore. VAL, HCT, AML bulk drugs and commercial tablets were previously analyzed by HPLC (El-Gizawy, 2012).

NIR spectroscopy

All spectra were recorded from 10,000 cm^{-1} to 4,000 cm^{-1} using a Frontier Optica NIR spectrometer (Perkin Elmer, United States). The spectrophotometer was set to record an average spectrum from 16 scans at 4 cm^{-1} resolution. A near-infrared reflectance accessory – NIRA (Perkin Elmer, USA) was used for direct sample analysis.

Data processing and chemometrics

For PLS multivariate calibration models, the "PLS Toolbox" 2.0 (Eigenvector Technologies, Manson, USA) and MATLAB® software 7.10 (The Math Works, Natick, USA) were used. The spectral data were preprocessed with either multiplicative scatter correction (MSC), autoscalling (A), mean centering (MC), MC followed by MSC or A followed by MSC. Leave-one-out cross-validation procedure was applied in order to detect outliers and select the final PLS model. The calibration set was constructed with 26 synthetic samples and the prediction set was constructed using 10 synthetic samples (Kennard-Stone algorithm - MATLAB® 7.10, 2010). Real sample (Exforge HCT®, Novartis Pharma, Switzerland) was included in prediction set since it is unique pharmaceutical formulation available in market.

The full spectrum was divided into 8, 16 and 32 intervals and a combination of 2 or 3 subintervals was used for variable selection (*i*Toolbox for MATLAB®, USA). The optimum number of latent variables (LV) was chosen according to root mean square error of cross validation (RMSECV). The iPLS and *si*PLS routines generate graphical information indicating the RMSECV values used in each interval. In this case was selected the interval (or combined interval) than presented the minor RMSECV value. Resulting prediction models were validated based on LV used in the model, root mean square error of prediction (RMSEP), relative standard error of prediction (RSEP%), intercept, slope and correlation coefficient of calibration (r^2_{cal}) and validation (r^2_{val}). Root mean square error of calibration (RMSEC) and RMSEP were used to evaluate the prediction ability among different PLS models (F-test $_{\alpha= 0.5\%}$). The results obtained by proposed models were compared to the interval allowed by Brazilian Pharmacopoeia (90–110% declared value) considering each separate active substance since there is no monograph available for coformulated tablets studied (ANVISA, 2010).

RESULTS AND DISCUSSION

Full-spectrum PLS models

Full-spectrum PLS models of VAL, HCT and AML were obtained with five, four and seven LV, respectively (results shown in Table 1). MC followed by MSC preprocessing showed the lower RMSEP and RMSECV values for full spectrum PLS models of VAL, HCT and AML.

Valsartan PLS models

In Table 1 are shown selected intervals, LV, total number of variables (TV), RMSECV and RMSEP obtained to full-spectrum PLS, *i*PLS and *si*PLS models. Interval number 32 for *i*PLS model with spectrum subdivided into 32 intervals produced better result according to lower RMSECV value (using 4 LV and 188 TV). In general, *i*PLS models showed RMSEP values lower than those obtained with full-spectrum model. However, *overfitting* demonstrated that this algorithm was not able to produce adequate models for this data set. Synergical PLS was implemented to develop PLS models for all possible combinations (2 or 3 subintervals). The *si*PLS models obtained by full-spectrum division into 8 and 16 intervals showed high RMSEP values attributed to the commercial sample error (data not shown). These results clearly show that the representativity of the calibration set is essential to the success of a model (Ebrahimi-Najafabadi *et al.*, 2012). The achievement of low prediction errors on a prediction set is possible as a consequence of the fact that the calibration set be representative of pharmaceutical formulation (quantitative composition of synthetic samples very similar to the real sample). Nevertheless, spectral region selection using suitable algorithms can be reducing these prediction errors attributed to composition of calibration and prediction set.

The best results for *si*PLS models were obtained whit the full-spectrum divided into 32 intervals and combined 3 subintervals. In general way, the combination of intervals 21 and 30 by *si*PLS algorithm reduced RMSEP values [*si*PLS32(2) model]. Interval 19 inclusion [model *si*PLS32(3) with intervals numbers 19, 21 and 30] modified significantly the quality of model. This model showed no *overfitting* between RMSECV and RMSEP values, small prediction errors and reduced variable numbers (560 TV compared to 6000 TV used in full-spectrum model). The selected intervals included the regions of 6431-6617

cm^{-1} (interval 19), 6077-6243 cm^{-1} (interval 21) and 4374-4561 cm^{-1} (interval 30). Interval 19 corresponds to N-H stretch vibrations presented in VAL molecule, but absent in excipients/diluents of prediction set samples (real and synthetic samples). Indeed, the spectral region selected in this interval (interval 19) showed contain relevant information to model constructed. For the calibration set, the slope and correlation coefficient with values close to unit and the intercept with values close to zero were considered adequate (y = 0.999x - 0.05931; r^2_{cal} = 0.995). The *si*PLS32(3) model showed lower relative standard error of prediction (RSEP = 1.33%) and correlation coefficient close to unity (r^2_{val} = 0.996), suggesting that the method used is accurate.

Table 1: Results to iPLS and siPLS calibration models and full-spectrum PLS model for the VAL.

Model	TV[a]	Intervals	LV[b]	RMSECV, VAL (mg g^{-1})	RMSEP, VAL (mg g^{-1})
PLS	6000	All	5	4.84	44.66
iPLS8	750	3	3	10.11	19.29
iPLS16	375	15	4	7.87	37.60
iPLS32	188	32	4	6.94	19.65
siPLS8(2)	1500	6 and 8	4	4.94	48.38
siPLS8(3)	2250	3, 4 and 8	8	3.81	62.89
siPLS16(2)	750	8 and 15	5	4.42	58.13
siPLS16(3)	1125	5, 8 and 15	6	3.93	62.27
SiPLS32 (2)	375	21 and 30	4	12.72	22.52
siPLS32(3)*	560	19, 21 and 30	4	6.08	5.30

[a] TV: Total number of variables; [b] LV: latent variables; * selected model

Interval PLS plots and LV used for each constructed model, RMSECV values for each interval selected and the RMSECV values for the full-spectrum model (dotted line) are shown in Figure 1.

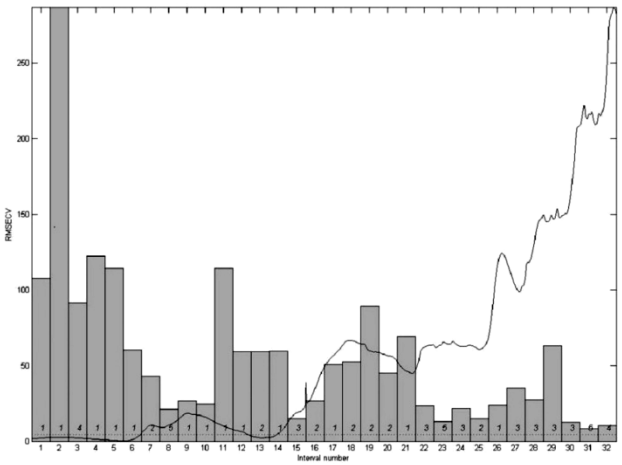

Fig. 1: Cross-validated prediction errors (RMSECV) values to full-spectrum model and interval models (bars) to VAL determination using PLS and *i*PLS algorithms (dotted line and numbers above interval numbers refer to full-spectrum RMSECV and latent variables using in each model, respectively).

Hydrochlorothiazide PLS models

In Table 2 are shown selected intervals, LV, TV, RMSECV and RMSEP obtained to full-spectrum PLS, *i*PLS and *si*PLS models. The developed model using the interval 30 for *i*PLS with 32 intervals [*i*PLS32 (30)] resulted in low RMSECV and RMSEP (when compared with the other iPLS models), as showed in Table 2. The selected interval included 4374-4561 cm^{-1} region that corresponds to N-H stretch vibrations. The siPLS32 (3) model showed lower RMSEP value when the intervals 19, 24 and 30 were combined. This way, it was possible to find a spectral region to HCT determination with reduced variable numbers (560 TV compared to 6000 TV used in full-spectrum model). For the calibration set, the slope and correlation coefficient with values close to unit and intercept with values close to zero were considered adequate (y = 0.994x + 0.2630; r^2_{cal} = 0.995). The *si*PLS32 (3) model showed lower relative standard error of prediction (RSEP = 1.30%) and correlation coefficient close to unity (r^2_{val} = 0.997).

Table 2: Results to iPLS and siPLS calibration models and full-spectrum PLS model for the HCT.

Model	TV[a]	Intervals	LV[b]	RMSECV, HCT (mg g^{-1})	RMSEP, HCT (mg g^{-1})
PLS	6000	All	4	1.90	2.33
iPLS8	750	8	4	1.53	7.18
iPLS16	375	15	4	3.72	4.91
iPLS32	188	30	5	1.19	1.66
siPLS8(2)	1500	5 and 6	5	1.55	7.85
siPLS8(3)	2250	5, 6 and 8	6	1.41	3.08
siPLS16(2)	750	10 and 15	7	1.20	5.41
siPLS16(3)	1125	10, 15 and 16	6	1.24	6.81
siPLS32(2)	375	19 and 31	3	1.48	4.22
siPLS32(3)*	560	19, 24 and 30	4	1.72	1.30

[a] TV: Total number of variables; [b] LV: latent variables; *selected model

Interval PLS plots and LV used for each constructed model, RMSECV values for each interval selected and the RMSECV values for the full-spectrum model (dotted line) are shown in Figure 2.

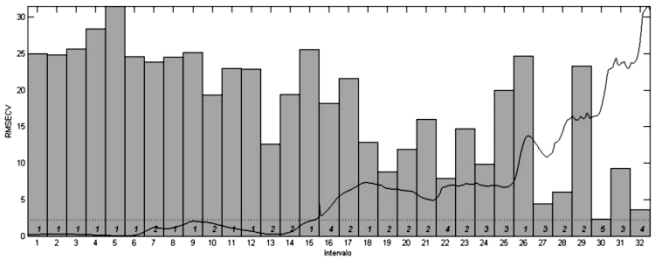

Fig. 2: Cross-validated prediction errors (RMSECV) values to full-spectrum model and interval models (bars) to HCT determination using PLS and *i*PLS algorithms (dotted line and numbers above interval numbers refer to full-spectrum RMSECV and latent variables using in each model, respectively).

Amlodipine besilate PLS models

In Table 3 are shown selected intervals, LV, TV, RMSECV and RMSEP obtained to full-spectrum PLS, *i*PLS and *si*PLS models. The full-spectrum divided into eight intervals produced minor RMSECV values for *i*PLS as much as *si*PLS. Interval PLS plots and LV used for each constructed model, RMSECV values for each interval selected and the RMSECV values for the full-spectrum model (dotted line) are shown in Figure 3.

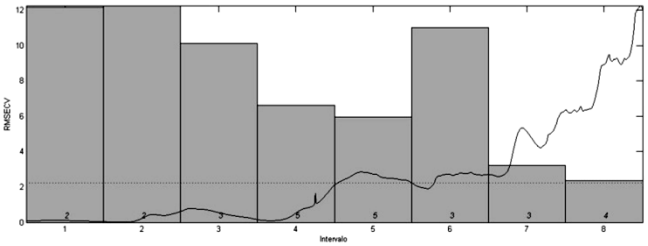

Fig. 3: Cross-validated prediction errors (RMSECV) values to full-spectrum model and interval models (bars) to AML determination using PLS and *i*PLS algorithms (dotted line and numbers above interval numbers refer to full-spectrum RMSECV and latent variables using in each model, respectively).

The siPLS8 (3) model showed lower RMSEP value when the intervals 5, 7 and 8 were combined. For this model, results showed good correlation between reference and predicted values (r^2_{val} = 0.985) and no overfitting. Selected intervals include N-H stretch vibrations presented in AML molecule, but absent in excipients/diluents of prediction set samples (real and synthetic samples).

Table 3: Results to iPLS and siPLS calibration models and full-spectrum PLS model for the AML.

Model	TV[a]	Intervals	LV[b]	RMSECV, AML (mg g^{-1})	RMSEP, AML (mg g^{-1})
PLS	6000	All	7	1.61	7.85
iPLS8	750	8	4	1.86	28.11
iPLS16	375	15	4	2.99	2.78
iPLS32	188	32	5	1.88	6.77
siPLS8(2)	1500	6 and 7	6	1.56	54.36
siPLS8(3)*	**2250**	**5, 7 and 8**	**8**	**1.50**	**1.51**
siPLS16(2)	750	11 and 15	6	1.17	6.46
siPLS16(3)	1125	7, 11 and 15	7	1.09	7.20
siPLS32(2)	375	29 and 32	5	1.93	3.34
siPLS32(3)	560	19, 29 and 30	4	2.90	1.99

[a] TV: Total number of variables; [b] LV: latent variables; * selected model.

For the calibration set, the slope and correlation coefficient with values close to unit and the intercept with values close to zero were considered adequate (y = 0.999x - 0.01862; r^2_{cal} = 0.990). The *si*PLS8(3) model showed lower relative standard error of prediction (RSEP = 5.33%) and correlation coefficient close to unity. The selection of 3 intervals for the spectrum divided into 8 (TV = 2250) was necessary to build a model with appropriate predictive ability for AML, unlike the other two pharmaceuticals (VAL and HCT) in which the spectrum had been divided into 32 intervals and 3 were selected (TV = 560). In this case, a larger spectral range allowed the construction model with adequate predictive capability. It is worth highlighting that the wavelengths selected for the AML model included those selected for VAL and HCT. However, the use of *si*PLS algorithm for quantification of AML not produced prediction errors in the same order of magnitude as for VAL and HCT.

CONCLUSION

Using *si*PLS algorithm associated with NIRA data it was possible to build models for fast, simultaneous, free solvent and non-destructive analysis of VAL, HCT and AML in tablets. The variable selection techniques produced models with better predictive capability compared to full-spectrum PLS models. Selection of intervals by synergy demonstrated to be most suitable for quantification of these analytes and to provide an overall perspective of the significant information in different spectral regions.

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CONFLICT OF INTERESTS

The authors' declare no conflict of interest.

REFERENCES

Alcalà M, León J, Ropero J, Blanco M, Romañach RJ. Analysis of low content drug tablets by transmission near infrared spectroscopy: Selection of calibration ranges according to multivariate detection and quantitation limits of PLS models. J Pharm Sci, 2008; 97(12): 5318–5327.

ANVISA. 2010. Farmacopeia Brasileira 5° edição. Brasília. Brasil.

Darwish HW, Hassan SA, Salem M Y, El-Zeany BA. Comparative study between derivative spectrophotometry and multivariate calibration as analytical tools applied for the simultaneous quantitation of Amlodipine, Valsartan and Hydrochlorothiazide. Spectrochim Acta A Mol Biomol Spectrosc, 2013; 113: 215–223.

Darwish H W, Hassan S A, Salem M Y, El-Zeany B A. Different approaches in Partial Least Squares and Artificial Neural Network models applied for the analysis of a ternary mixture of Amlodipine, Valsartan and Hydrochlorothiazide. Spectrochim Acta A Mol Biomol Spectrosc, 2014; 122: 744–750.

Ebrahimi-Najafabadi H, Leardi R, Oliveri P, Chiara Casolino M, Jalali-Heravi M, Lanteri S. Detection of addition of barley to coffee using near infrared spectroscopy and chemometric techniques. Talanta, 2012; 99:175–179.

El-Gizawy S M. Development and Validation of HPLC Method for Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma. Am J Analyt Chem, 2012; 3(6): 422–430.

Pan D, Crull G, Yin S, Grosso J. Low level drug product API form analysis – Avalide tablet NIR quantitative method development and robustness challenges. J Pharm Biomed Anal, 2014; 89: 268–275.

Piantavini M S, Pontes F L D, Cerqueira L B, Peralta-Zamora P G, Pontarolo R. Simultaneous spectrophotometric determination of pyrantel pamoate and febantel in pharmaceutical preparations using partial least-squares regression. J Anal Chem, 2014; 69(10): 948–952.

Piantavini M S, Pontes F L D, Weiss L X, Sena M M, Pontarolo R. Comparison between Ultraviolet and Infrared Spectroscopies for the Simultaneous Multivariate Determination of Pyrantel and Praziquantel. J Braz Chem Soc, 2015; 26(7): 1387–1395.

Roggo Y, Chalus P, Maurer L, Lema-Martinez C, Edmond A, Jent N. A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. J Pharm Biomed Anal, 2007; 44: 683–700.

Shaalan R A, Belal T S, El Yazbi F A, Elonsy S M. Validated stability-indicating HPLC-DAD method of analysis for the antihypertensive triple mixture of amlodipine besylate, valsartan and hydrochlorothiazide in their tablets. Arab J Chem, 2013; 10(1):S1381-S1394.

Shi J, Zou X, Zhao J, Mel H, Wang K, Wang X, Chen H. Determination of total flavonoids content in fresh Ginkgo biloba leaf with different colors using near infrared spectroscopy. Spectrochim Acta A Mol Biomol Spectrosc, 2012; 94: 271-276.

Silva F E B, Ferrão M F, Parisotto G, Müller E I, Flores E M M. Simultaneous determination of sulphamethoxazole and trimethoprim in powder mixtures by attenuated total reflection-Fourier transform infrared and multivariate calibration. J Pharm Biom Anal, 2009; 49(3): 800–805.

Silva F E B, Flores, É M M, Parisotto G. Green method by diffuse reflectance infrared spectroscopy and spectral region selection for the quantification of sulphamethoxazole and trimethoprim in pharmaceutical formulations. An Acad Bras Cien, 2016; 88:1–15.

Souza J A L, Albuquerque M M, Grangeiro S, Pimentel M F, de Santana D P, Simões S S. Quantification of captopril disulphide as a degradation product in captopril tablets using near infrared spectroscopy and chemometrics. Vib Spectrosc, 2012; 62:35–41

Wood C, Alwati A, Halsey S, Gough T, Brown E, Kelly A,Paradkar A. Near infra red spectroscopy as a multivariate process analytical tool for predicting pharmaceutical co-crystal concentration. J Pharm Biomed Anal, 2016; 129:172–181.

Xiaobo Z, Jiewen Z, Povey MJW, Holmes M, Hanpin M. Variables selection methods in near-infrared spectroscopy. Anal Chim Acta, 2010; 667(1): 14–32.

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