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SIMULATANEOUS SPECTROPHOTOMETRIC DETERMINATION OF ETORICOXIB AND PARACETAMOL IN TABLETS BY CHEMOMETRIC METHODS

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ABSTRACT

Simultaneous spectrophotometric determination of Etoricoxib and Paracetamol was performed by partial least-squares (PLS) and principal component regression (PCR) methods do not require any priori graphical treatment of the overlapping spectra of two drugs in the mixture. The absorbance values in the UV-Vis spectra were measured for the 101 wavelength points (from 210-310) in the spectral region 200–400 nm considering the intervals of 1 nm. The calibration range was found to be 0.5-2.5 µg/ml for Etoricoxib, 4-20 µg/ml for Paracetamol with a correlation coefficient of 0.9999(PLS), 0.9997(PCR) for Etoricoxib and 0.9999(PLS), 0.9999(PCR) for Paracetamol. The validation of the multivariate methods was realized by analyzing the synthetic mixtures of Etoricoxib and Paracetamol. The numerical calculations were performed with the 'Unscrambler 10.1 X' software. The chemometrics analysis methods were satisfactorily applied to the simultaneous determination of Etoricoxib and Paracetamol in the pharmaceutical formulation.

KEYWORDS: Paracetamol, Chemometrics, Etoricoxib, spectrophotometry, partial least square, principal component regression.

INTRODUCTION

Etoricoxib (ETOR) Etoricoxib chemically 5–chloro-2-(6-methylpyridin-3-yl) 3-(4-methyl sulfonyl phenyl) pyridine, Paracetamol (PARA) chemically is a 4-hydoxy acetanilide having analgesic and antipyretic activity. From the literature survey it was found that UV,[1-9] derivative spectrophotometry,[10] Chemometrics[11-15] with other combinations, HPLC[16-22] and HPTLC[23-27] and are available for the determination of Etoricoxib and Paracetamol alone and combined dosage form with other drugs but there are no methods available for the simultaneous estimation of Etoricoxib and Paracetamol in combined dosage form by chemometrics. So there is a need for a method capable of simultaneous estimation of Etoricoxib and Paracetamol in pharmaceuticals by chemometric methods.

The aim of this paper is to investigate the ability of PLS and PCR methods to quantify binary mixture of ETOR and PARA with overlapping spectra and to apply the optimized models in pharmaceutical preparations. The proposed methods are simple, sensitive and reproducible method for the simultaneous estimation of Etoricoxib and Paracetamol from combined dosage form.

In recent years, multivariate calibrations, such as classical least-squares (CLS), inverse least-squares (ILS), principal component regression (PCR) and partial least-squares (PLS) are started to apply to the analysis of the analytical data obtained in all the instrumentations[28,29] The same methods and their algorithms (NIPALS) have been applied to the simultaneous spectrophotometric determination of drugs in the pharmaceutical formulation containing two or more compounds with overlapping spectra. On the other hand the chemometric calibration methods as those enumerated above have been used extensively in quantitative spectral analysis to get selective information from unselective data. The main advantages of these techniques are the following a higher speed of processing data concerning the values of concentrations and absorbance of compounds with strongly overlapping spectra, the errors of calibration model are minimized by measuring the absorbance values at many points in the wavelength range. Analytical methods using multivariate calibrations and their applications include the spectrophotometric, chromatographic and electrochemical for determinations of analytes in the mixtures.

MATERIALS AND METHODS

Instruments and software

Digitized UV/VIS absorbency spectra were collected using a UV-visible spectrometer 2300 Tech comp with 1 cm quartz cells. The data acquisition was made with UV solutions software at a scan rate of 1000 nm min−1 and the slit width of 2 nm. The UV spectra of mixtures were recorded over the wavelength 210–310 nm with one data point per nm. All spectral measurements were performed using blank solution as a reference. Partial least squares regression, and principal component regression were used for chemometric analysis of data. For all calculations Unscrambler for windows (Version 10.1 X) was used.

Pharmaceutical tablet formulations

A commercial pharmaceutical formulation (NUCOXIA-P) capsule containing 60 mg of ETOR and 500 mg of PARA was analyzed by the proposed chemometric methods.

Standard solutions

Stock solutions of Etoricoxib and Paracetamol of 10 mg were prepared in 100 ml volumetric flasks with methanol. The training set containing 0.5-2.5µg/ml Etoricoxib and 4-20µg/ml Paracetamol working standard solutions were prepared by diluting the stock solutions for each drug according to its linear calibration range. Two sets of standard solutions were prepared, the calibration set contained 25 standard solutions and the prediction set contained 9 standard solutions. To a series of 10 ml volumetric flasks, aliquots of Etoricoxib and Paracetamol solutions, containing appropriate amount of these drugs in the range of calibrations, were added and then the solutions were diluted to 10 ml with methanol. UV spectra of the mixtures were recorded in the wavelength range 210–310 nm versus a solvent blank, and digitized absorbance was sampled at 1 nm intervals.

Sample preparations

Twenty tablets were taken and their average weight was determined. An amount of the powder equivalent to 15mg was weighed and dissolved in methanol in 100 ml calibrated flasks. 20ml of methanol was added and ultra sonicate for 5minutes and the volume was made up to100 ml with methanol and shake well. Then, the solution was filtered through what man filter paper No. 41 the filtrate was further diluted with methanol to get the sample solutions. Aliquots of these solutions were used in such a way that the concentration of each drug was obtained within the range of the calibration.

RESULTS AND DISCUSSIONS

The absorption spectra of ETOR and PARA solutions in methanol recorded between 210 – 310 nm. The two drugs show an overlap in their absorption shown in Fig.1.

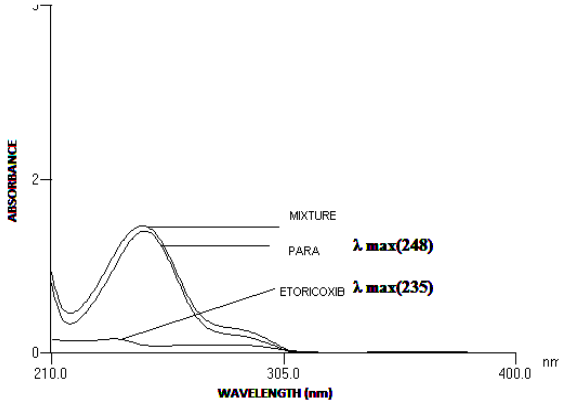


Fig 1: Overlaid Spectrum of Etoricoxib and Paracetamol.

Experimental design of sample sets

Calibration and test sets for two component systems were designed according to factorial principle five-level factorial design was used to produce a calibration set (Training step) of 25 samples. Calibration spectra are shown in Fig. 2.

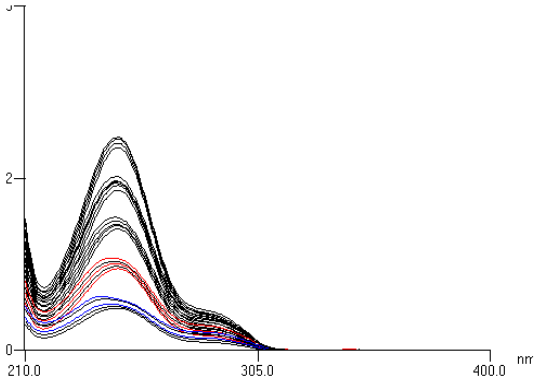


Fig. 2: Calibration Spectra of Etoricoxib and Paracetamol.

A three-level set was derived to produce a prediction set (Validation step) of nine samples. Prediction spectra are shown in Fig. 3.The compositions of the used calibration and Validation sets are summarized in Tables. 1 and 2 respectively

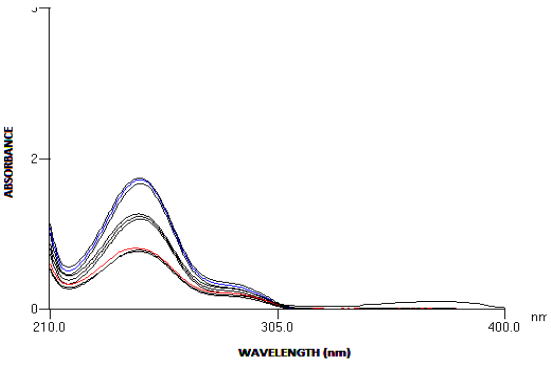


Fig. 3: Prediction Spectra of Etoricoxib and Paracetamol.

Table 1: Composition of calibration set for PLS and PCR methods.

S. No.	Etoricoxib			Paracetamol		
	Reference µg/ml	Predicted µg/ml		Reference µg/ml	Predicted µg/ml	
		PLS	PCR		PLS	PCR
1	0.5	0.48	0.48	4	4.01	4.01
2	0.5	0.49	0.49	8	7.99	7.99
3	0.5	0.51	0.51	12	11.97	11.97
4	0.5	0.5	0.5	16	16.01	16.01
5	0.5	0.499	0.499	20	19.99	19.99
6	1.00	0.999	0.999	4	3.99	3.99
7	1.00	1.01	1.01	8	8.01	8.01
8	1.00	0.98	0.98	12	11.99	11.99
9	1.00	1.02	1.02	16	16.02	16.02
10	1.00	1.00	1.00	20	20.01	20.01
11	1.5	1.49	1.49	4	3.98	3.98
12	1.5	1.5	1.5	8	7.99	7.99
13	1.5	1.48	1.48	12	12.01	12.01
14	1.5	1.47	1.47	16	15.99	15.99
15	1.5	1.49	1.49	20	11.98	11.98
16	2.0	1.99	1.99	4	4.02	4.02
17	2.0	1.98	1.98	8	8.02	8.02
18	2.0	1.97	1.97	12	12.02	12.02
19	2.0	2.01	2.01	16	16.00	16.00
20	2.0	2.04	2.04	20	11.96	11.96
21	2.5	2.51	2.51	4	3.97	3.97
22	2.5	2.49	2.49	8	8.00	8.00
23	2.5	2.50	2.50	12	12.03	12.03
24	2.5	2.48	2.48	16	16.04	16.04
25	2.5	2.49	2.49	20	20.03	20.03

Table 2: Composition of validation set for PLS and PCR methods.

S. No.	Etoricoxib			Paracetamol		
	Reference µg/ml	Predicted µg/ml		Reference µg/ml	Predicted µg/ml	
		PLS	PCR		PLS	PCR
1	0.75	0.76	0.76	6	6.07	6.05
2	0.75	0.75	0.75	10	6.07	6.05
3	0.75	0.74	0.74	14	6.06	6.05
4	1.25	1.25	1.25	6	9.97	9.95
5	1.25	1.24	1.24	10	9.96	9.95
6	1.25	1.23	1.23	14	9.95	9.95
7	1.75	1.76	1.76	6	14.05	14.03
8	1.75	1.75	1.75	10	14.04	14.03
9	1.75	1.74	1.74	14	14.03	14.03

Selection of optimum number of factors and the spectral region

The most commonly employed validation criterion is to divide the dataset into two subsets, a calibration set and a validation set. The calibration model is calculated using the calibration set. Then, the root mean square errors of calibration and validation, RMSEC – root mean square error of calibration and RMSECV – root mean square error of cross validation, are calculated using the calibration model under investigation to predict the samples in the calibration set and validation set, respectively.

For PCR and PLS methods, 25 calibration spectra were used for the selection of the optimum number of factors using the cross-validation with the leave-out-one technique. This allows modeling of the system with the optimum amount of information and avoidance of over-fitting or under-fitting. The cross-validation procedure consisted of systematically removing one of a group of training samples in turn and using only the remaining ones for the construction of latent variable factors and applied regression. The predicted concentrations were then compared with the actual ones for each of the calibration samples and the root mean square error of prediction (RMSEP) was calculated. The RMSEP was computed in the same manner each time, and then a new

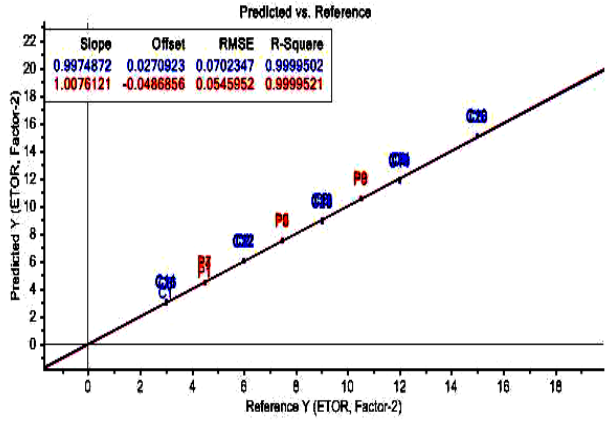
factor was added to the PCR and PLS models. The selected model was that with the smallest number of factors such that its RMSECV values were not significantly greater than that for the model, which yielded the minimum RMSECV. A plot of RMSECV values against the number of components indicates that the latent variable factor 3 was optimum for PCR and PLS models based on the RMSEC and RMSECV, respectively, for the estimation of the titled drugs. At the selected principal component of PCR and PLS, the concentrations of each sample were then predicted and compared with the known concentration and the RMSEP was calculated. The results are presented in Table. 3.

$$RMSECV = \sqrt{\sum_{i=y}^{N} \frac{(y_{ipred} - y_{iref})^2}{N}} \qquad RMSEC = \sqrt{\frac{(y - y_{pred})^i (y - y_{pred})}{m-1}}$$

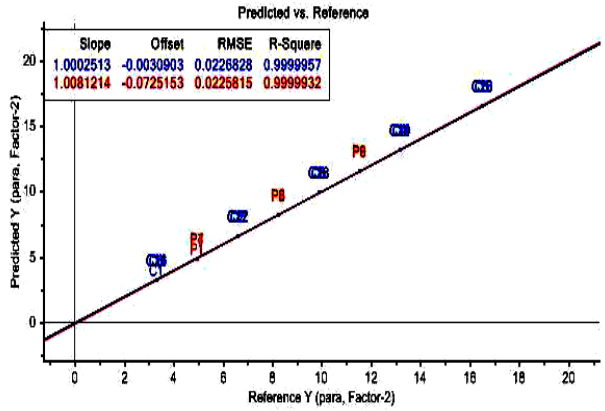
Table 3: Summary of statistics in PLS and PCR methods.

Drug	RMSEP		RMSEC		r^2		Intercept		Slope	
	PLS	PCR	PLS	PCR	PLS	PCR	PLS	PCR	PLS	PCR
Etor	0.054	0.056	0.07	0.068	0.9999	0.9997	0.02	0.002	0.9974	0.9997
Para	0.0225	0.0215	0.0226	0.0225	0.9999	0.9999	0.003	0.0002	1.000	0.9999

ETOR-Etoricoxib, Para- Paracetamol, RMSEP-Root mean square error of prediction, RMSEC-Root mean square error of calibration and r^2 - Correlation coefficient.



Graph 1: PLS Calibration and Prediction curves of Etoricoxib.



Graph 2: PLS Calibration and Prediction curves of Paracetamol.

Market Sample Analysis (Assay)

The proposed PLS and PCR methods were applied to the simultaneous determination of ETOR and PARA in commercial formulation. Determination of six replicates was made. Satisfactory results were obtained for each drug in good agreement with the label claims. Assay spectra are shown in Fig. 4. The results are presented in Table. 4.

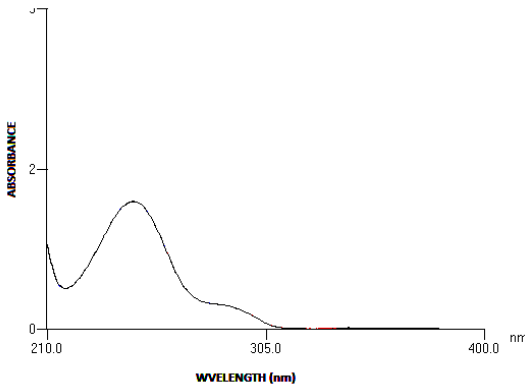


Fig.4

Table 4: Analysis of Tablet Formulation.

Formulation	Label claim	PLS mg/tab found*	PCR mg/tab found*
NUCOXIA-P	ETOR 60mg	60.43	60.43
	Para 500 mg	500.44	500.43

*Each value is a mean of six readings

Precision

The method was found to be precise with six sample preparations for the quantification of ETOR and PARA. The precision and intermediate precision variations were calculated in terms of relative standard deviation and the results were found to be less than 2.0% and the results are presented in Table. 5.

Table 5: Precision Data.

	System precision				Method precision			
	Etoricoxib		Paracetamol		Etoricoxib		Paracetamol	
	PLS (µg/ml)	PCR (µg/ml)	PLS (µg/ml)	PCR (µg/ml)	PLS% purity	PCR% purity	PLS % purity	PCR% purity
Mean	1.49	1.49	12.03	12.03	100.31	100.31	100.44	100.40
S.D	0.011	0.011	0.017	0.017	0.2165	0.2165	0.1626	0.1632
%RSD	0.78	0.78	0.14	0.14	0.21	0.21	0.1619	0.1626

n=6.

Recovery Studies

To check the validity of the proposed methods, recovery studies were carried out by addition of the standard to the pre-analyzed formulation. (Standard addition technique) Recovery spectra are shown in Fig. 5 and the results are presented in Table. 6.

Table 6: Recovery studies by PLS and PCR methods.

% OF		Etoricoxib		Paracetamol	
Target		PLS	PCR	PLS	PCR
80%	Mean	100.83	100.83	100.01	99.87
	S.D	0.83	0.83	0.33	0.33
	RSD	0.82	0.82	0.33	0.33
100%	Mean	99.77	99.77	99.87	99.83
	S.D	0.38	0.38	0.33	0.26
	RSD	0.38	0.38	0.33	0.26
120%	Mean	99.44	99.44	100.14	100.17
	S.D	0.55	0.55	0.25	0.25
	RSD	0.55	0.55	0.25	0.25

CONCLUSION

The most striking features of spectrophotometric method are its simplicity and rapidity without requiring time-consuming sample preparation. Chemometric calibration techniques in spectral analysis are widely used in quality control of drugs in mixtures and multi- component pharmaceutical formulations with overlapping spectra, as separation procedures in the drug determinations are not required. A comparative study of the use of PLS and PCR for the simultaneous spectrophotometric determination of Etoricoxib and Paracetamol has been accomplished.

High percentage of recovery shows that the methods are free from additional signals (interference) of the excipients used in the commercial formulation. Results also showed that the developed methods can be applied to a routine analysis, quality control of mixtures and commercial preparations containing these drugs.

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