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Simultaneous determination of domperidone maleate and cinnarizine in a binary mixture using derivative ratio spectrophotometry and classical least squares calibration

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Abstract

This work is concerned with the simultaneous determination of domperidone maleate (DOM) and cinnarizine (CINN) in a binary mixture form without previous separation by two different methods. The first method is the application of derivative ratio spectrophotometry where the linearity range was 2.5–30 μg/ml, 2.5–25 μg/ml for DOM and CINN, respectively, and percentage recoveries were 100.26 ± 1.308 and 99.86 ± 0.939 for DOM and CINN, respectively, in their laboratory prepared mixtures. The second method depends on the application of classical least squares (CLS) calibration model. Two training sets were constructed and the best model was used for the prediction of the concentrations of both drugs. The proposed procedures were successfully applied for the simultaneous determination of both drugs in laboratory prepared mixtures and in commercial tablet preparations. The validity of the proposed methods was assessed by applying the standard addition technique where the percentage recovery of the added standard was found to be 99.83 ± 1.861 and 98.38 ± 0.871 for DOM and CINN, respectively, using the derivative ratio method and 99.53 ± 0.916 and 99.39 ± 0.599 for DOM and CINN, respectively, using the CLS method. The proposed procedures are rapid, simple, require no preliminary separation steps and can, therefore, be used routine analysis of both drugs in quality control laboratories.

Keywords: Domperidone maleate; Cinnarizine; Binary mixture; Derivative ratio spectrophotometry; Classical least squares

1. Introduction

Domperidone maleate (DOM) is a dopamine antagonist used as an antiemetic for the short term treatment of nausea and vomiting of various etiologies [1]. Cinnarizine (CINN) is a piperazine derivative with histamine H_1-receptor and calcium channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Meniers disease and other vestibular disorders. It is also used for the prevention and treatment of motion sickness [1].

Both drugs are formulated in a binary mixture for the treatment of motion sickness.

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DOM was determined by several methods including colorimetric methods [2,3], spectrophotometric methods [4,5], high-performance thin-layer chromatography [6,7], high-performance liquid chromatography [8–10] and titrimetric methods [11]. CINN was determined spectrophotometrically [12–18] or by using HPTLC [7], HPLC [10,19–24], ion selective electrodes [13,25], GC [26,27], titrimetry[11,28], or voltammetry [25,29].

Only two methods were reported for the simultaneous determination of DOM and CINN, the first one is a reversed phase ion pair HPLC method [10]. The second one is a HPTLC method [7].

The aim of this paper was to demonstrate the capability of derivative ratio spectrophotometry and classical least squares (CLS) for the simultaneous analysis of both drugs in mixture form without the need of preliminary separation steps.

2. Experimental

2.1. Apparatus

A dual-beam Shimadzu UV–visible spectrophotometer 1601PC connected to an IBM compatible computer. The software was UVPC personal spectroscopy software version 3.7 (Shimadzu).

The absorption spectra of the reference and test solutions were carried out in a 1 cm quartz cells over the range of 220–320 nm. The data was then exported into MICROSOFT EXCEL program. The chemometric calculations were done with MATLAB 5.3 program.

2.2. Reagents and chemicals

- Methanol of spectroscopic grade (Merck) was used as a solvent.
- DOM and CINN powders were kindly supplied by Minapharm pharmaceutical company and their percentage purity was found to be 100.61 ± 0.481 and 99.32 ± 0.940, respectively, according to the B.P. method 2000 [11].
- Touristil tablets batch numbers 99972 and 99815 were purchased from the Egyptian market. Each tablet is claimed to contain 19.1 mg DOM (equivalent to 15 mg domperidone base) and 20 mg CINN.

2.3. Standard stock and working solutions

1. DOM stock solution: 1 mg/ml in methanol.
2. DOM working solution: 0.05 mg/ml in methanol, prepared by transferring 2.5 ml from stock DOM to a measuring flask 50 ml and completing to volume with methanol.
3. CINN stock solution: 1 mg/ml in methanol.
4. CINN working solution: 0.05 mg/ml in methanol, prepared by transferring 2.5 ml from stock DOM to a measuring flask 50 ml and completing to volume with methanol.

2.4. Prepared mixtures

In measuring flasks 10 ml, aliquot volumes of DOM and CINN from their corresponding working solutions (0.05 mg/ml) were transferred accurately to prepare mixtures containing different ratios of the two drugs as shown in table [1].

2.5. Procedures

2.5.1. Derivative ratio spectrophotometry

2.5.1.1. Spectral characteristics of DOM and CINN. Aliquot portions equivalent to 100 μg/ml DOM and CINN were transferred separately into two 10 ml volumetric flasks and the volume was completed with methanol. The zero order absorption spectra of both solutions were recorded (Fig. 1).

2.5.1.2. Linearity. Aliquot portions (0.5, 1, 2, 3, 4, 5 and 6 ml) from DOM working solution 0.05 mg/ml were transferred accurately to measuring flasks 10 ml then the volume was completed with methanol. Similarly, aliquot portions (0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 ml) from CINN working solution 0.05 mg/ml were transferred accurately to measuring flasks 10 ml then the volume was completed with methanol.

The spectra of the prepared standard solutions were recorded from 200 to 320 nm and stored in the computer. For the determination of DOM, the stored spectra of DOM were divided (amplitude at each wavelength) by the spectrum of 2.5 μg/ml standard CINN, then the first derivatives of the ratio spectra were obtained with $\Delta\lambda = 4$ nm (Fig. 2). The amplitude of the first derivative peak at 304 nm ($^1DD_{304}$) was used to calculate the content of DOM. For the determination of

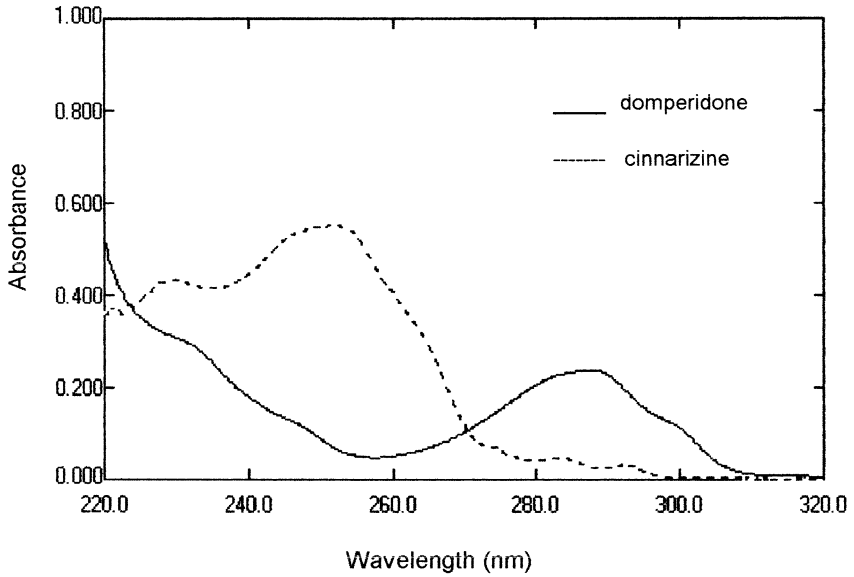

Fig. 1. Absorption spectra of domperidone and CINN. Concentration of each is 10 μg/ml.

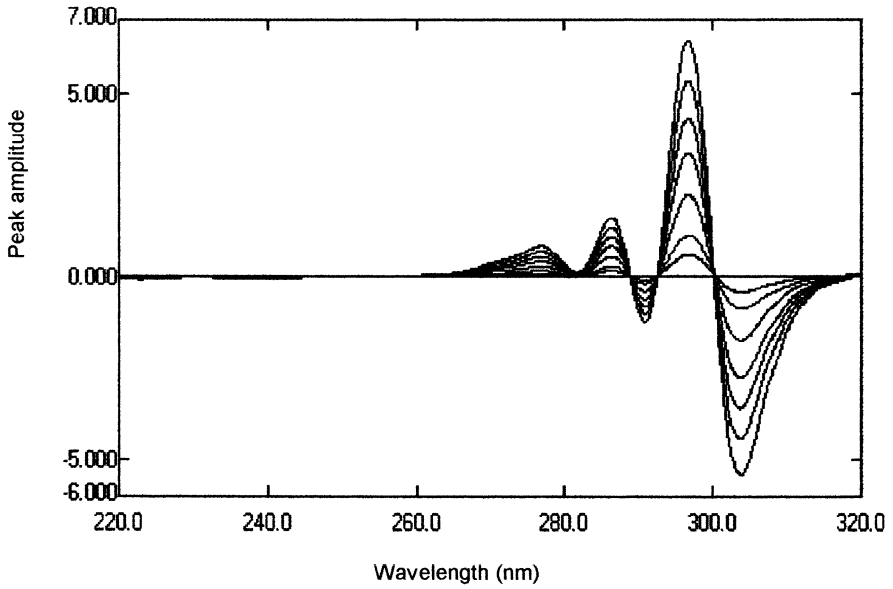

Fig. 2. First derivative ratio spectra of domperidone (2.5–30 μg/ml) in methanol. Divisor is 2.5 μg/ml CINN.

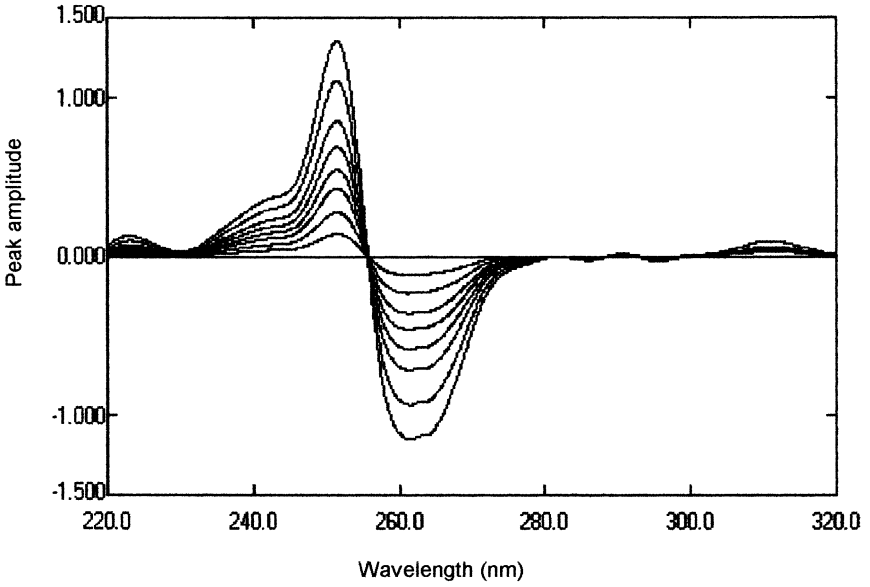

Fig. 3. First derivative ratio spectra of CINN (2.5–25 μg/ml) in methanol. Divisor is 2.5 μg/ml domperidone.

CINN, the stored spectra of CINN were divided (amplitude at each wavelength) by the spectrum of 2.5 μg/ml standard DOM, then the first derivative of the ratio spectra were obtained with $\Delta\lambda = 4$ nm (Fig. 3). The amplitude of the first derivative peak at 264 nm ($^1DD_{264}$) was used to calculate the content of CINN.

2.5.1.3. Application of the proposed procedure for the simultaneous determination of the two drugs in laboratory prepared mixtures. The spectra of the prepared solutions (Table 1) were recorded and stored, then divided by the spectrum of 2.5 μg/ml CINN then from the peak amplitude at ($^1DD_{304}$) the concentration of DOM in the mixtures was obtained by substituting in regression equation Eq. (1). To determine CINN in the mixtures, the stored spectra were divided by the spectrum of 2.5 μg/ml DOM then the peak amplitude at ($^1DD_{264}$) was obtained and the concentration of CINN was calculated by substituting in regression equation Eq. (2). Results obtained are shown in Table 1.

2.5.1.4. Application of the proposed procedure for the simultaneous determination of DOM and CINN in Touristil tablets. Ten tablets were accurately weighed and powdered. An amount of the powder equivalent to 9.55 mg DOM and 10 mg CINN was transferred to a measuring flask of 100 ml and completed to volume with methanol. The solution was stirred for 10 min using a magnetic stirrer then filtered. One ml of the filtrate was transferred accurately to a measuring flask of 10

Table 1
Determination of DOM and CINN in laboratory prepared mixtures by the proposed derivative ratio spectrophotometric method

Concentration (μm/ml)		Recovery (%)	
Domperidone	CINN	Domperidone	CINN
10.00	5.00	98.56	99.00
10.00	7.50	101.84	99.40
7.50	10.00	100.07	98.60
5.00	10.00	100.91	100.57
10.00	15.00	101.95	101.48
10.00	10.00	99.98	100.73
15.00	5.00	99.87	100.00
10.00	20.00	100.97	99.85
20.00	10.00	98.20	99.09
Mean		100.26	99.86
S.D[a]		1.308	0.939

[a] Standard deviation.

Table 2
Determination of domperidone and CINN in Touristil tablets by the proposed procedures

BN	Derivative ratio spectrophotometry		CLS	
	Recovery (%) + S.D.[a]		Recovery (%) + S.D.	
	Domperidone	CINN	Domperidone	Clnnarizine
99972	99.72 ± 0.851	99.47 ± 0.813	99.51 ± 2.32	100.48 ± 0.781
99815	100.41 ± 1.270	100.45 ± 1.257	99.90 ± 0.52	100.06 ± 0.730

[a] Standard deviation.

ml and completed to volume with methanol. Complete as before starting from "The spectra of the prepared solutions were recorded and stored in the computer…". Results obtained are shown in Table 2.

2.5.2. Classical least squares

2.5.2.1. Construction of the training sets. Two training sets for the CLS were constructed by diluting different volumes of DOM and CINN working solutions (0.05 mg/ml) into 10 ml measuring flasks and completing to volume with methanol to reach the concentrations listed in Tables 3 and 4. The first training set (A1) contains pure samples of DOM and CINN separately (Table 3), while the second training set (A2) was constructed with different mixtures of DOM and CINN Table 4. The zero order absorbance spectra were measured and stored in the computer. To estimate the CLS models for both training sets A1 and A2, the computer was fed with the absorbance and concentration matrices, then calculations were carried out and two models M1 and M2 were obtained for both training sets A1 and A2, respectively.

2.5.2.2. Construction of the validation set. Different mixtures of the two drugs were prepared by diluting different volumes of DOM and CINN working solutions (0.05 mg/ml) in 10 ml measuring flasks and diluting to volume with methanol (Table 5). The suggested models were then applied to these mixtures to predict the concentration of both drugs. Results obtained are summarized in Table 5.

2.5.2.3. Application of the proposed procedures for the simultaneous determination of DOM and CINN in Touristil tablets. Proceed exactly as under Section 2.5.1 up to '1 ml of the filtrate was transferred to a measuring flask 10 ml and completed to volume with methanol'. The spectrum of this prepared solution was recorded, then the developed multivariate model (M_2) was applied for the calculation of DOM and CINN concentrations. Results obtained are shown in Table 2.

Table 3
The concentrations of domperidone and CINN in training set A_1

Sample number	Concentration (μg/ml)	
	Domperidone	CINN
1	0.00	2.50
2	0.00	5.00
3	0.00	10.00
4	0.00	15.00
5	0.00	20.00
6	0.00	25.00
7	0.00	7.50
8	0.00	12.50
9	2.50	0.00
10	5.00	0.00
11	10.00	0.00
12	15.00	0.00
13	20.00	0.00
14	25.00	0.00
15	30.00	0.00

Table 4
The concentrations of domperidone and CINN in training set A_2

Sample number	Concentration (μg/ml)	
	Domperidone	CINN
1	10.00	5.00
2	5.00	10.00
3	10.00	7.50
4	7.50	10.00
5	10.00	10.00
6	10.00	20.00
7	20.00	10.00
8	5.00	15.00
9	15.00	5.00
10	10.00	0.00

3. Results and discussion

The use of the 'zero-crossing' method in derivative spectrophotometry for resolving a mixture with overlapped spectra produces some loss of accuracy and sensitivity. This problem is due to the fact that measurements are carried at a very critical wavelength, the localization of which is sometimes difficult and any small change in its location may produce some error. Derivative ratio spectrophotometry permits the determination of components in mixtures at wavelengths corresponding to a maximum or minimum. The values at these points sometimes permit better sensitivity and better accuracy. Derivative ratio spectrophotometry was applied for the determination of binary mixtures [30,31]. This method was then extended for the determination of ternary mixtures [32,33].

The main instrumental parameters that affect the shape of the derivative ratio spectra are the wavelength scanning speed, the concentration of the standard solution used as a divisor, the wavelength increment over which the derivative is obtained ($\Delta\lambda$) and the smoothing function [32]. The effect of wavelength scanning speed was studied and it was found that at high speed noisy spectra were obtained and at low scanning speed, the noise decreased but a longer time was needed for the measurements, so medium scanning speed was chosen to carry out our measurements. The concentration of the divisor was also studied and it was found that using the 2.5 μg/ml spectrum of both drugs as a divisor gave the best compromise in terms of sensitivity, repeatability and signal to noise ratio while upon dividing by 20 μg/ml, lower sensitivity was obtained as the range of linearity started from 5 μg/ml for both drugs.

For the determination of DOM measurements were done at 296 and 304 nm, but the peak at 296 nm gave very low results for DOM in the laboratory prepared mixtures, so all calculations were done using the peak amplitude at $^1D_{304}$ nm. Simi-

Table 5
The results obtained for the analysis of the mixtures of the validation set using the proposed CLS models

Sample number	Concentration (μg/ml)		Recovery (%)			
	Domperidone	CINN	Model M_1		Model M_2	
			Domperidone	CINN	Domperione	CINN
1	10.00	5.00	107.97	102.82	100.50	99.50
2	5.00	10.00	109.13	99.93	101.90	100.63
3	20.00	10.00	101.48	98.37	98.90	98.45
4	10.00	20.00	109.52	102.02	102.12	99.95
5	20.00	15.00	105.13	101.26	100.95	100.95
6	5.00	15.00	107.01	99.91	100.14	99.15
Mean			106.71	100.72	100.75	99.77
RMSEP[a]			0.61	0.18	0.13	0.09
S.D.			3.010	1.624	1.192	0.935

[a] Root Mean Square Error of Prediction.

Table 6
Statistical analysis of the results obtained by the proposed derivative ratio spectrophotometric method and the official method [a] for the analysis of DOM and CINN in pure powder form

	Derivative ratio spectrophotometry		Official method[a]	
	Domperidone	CINN	Domperidone	CINN
Mean	99.99	100.06	100.61	99.31
S.D.	1.064	0.931	0.481	0.940
Variance	1.132	0.867	0.231	0.884
n	7	8	4	4
F test	4.90 (8.94)	1.02 (4.35)		
Student's test	1.688 (2.262)	1.262 (2.228)		

The figures in parenthesis are the corresponding tabulated values at $P = 0.05$.
[a] The B.P 2000 method [11].

larly, for the determination of CINN, the peak at 264 nm showed better sensitivity and was chosen, therefore, chosen for the determination of CINN.

The linearity between the peak amplitudes at the selected wavelengths and the corresponding concentrations of the two drugs was studied. A linear relationship was obtained in the range 2.5–30 μg/ml for DOM and from 2.5 to 25 μg/ml for CINN. The regression equations were computed and found to be:

$$^1DD_{304} = 0.4371C - 0.0925 \quad r = 0.9999 \qquad (1)$$

$$^1DD_{264} = 0.2536C - 0.0075 \quad r = 0.9998 \qquad (2)$$

for DOM and CINN, respectively, where C is the concentration of the drugs in μg/ml, r is the correlation coefficient.

The proposed method was successfully applied for the determination of the two drugs in their pure powdered form with mean recoveries 99.99 ± 1.064 and 100.06 ± 0.931 for DOM and CINN, respectively, and this proves the accuracy and reasonable precision of the proposed method.

The accuracy of the proposed method was further verified by comparing the results of analysis of pure DOM and CINN obtained by the proposed method and those obtained by the official method for both drugs [11]. Statistical analysis shows that the calculated t and F values are less than the tabulated ones indicating that there is no significant difference between the accuracy and precision of our proposed method and those of the official method (Table 6).

The selectivity of the proposed procedure was also assessed by the analysis of laboratory prepared mixtures containing different ratios of the two drugs, where satisfactory results were obtained over the calibration range as shown in Table 1.

The reproducibility of the proposed procedure was evaluated using five identical samples containing 10 μg/ml DOM and 10 μg/ml CINN. The relative standard deviations were found to be 0.383 and 0.641% for DOM and CINN, respectively (Table 7).

The proposed procedure was also applied for the determination of DOM and CINN in Touristil tablets (Table 2). Applying the standard addition technique further assessed the validity of the proposed procedure (Table 8).

Table 7
Reproducibility of the results obtained for the analysis of DOM and CINN by the suggested derivative ratio method

	Peak amplitude of 10 μg/ml domperidone at 304 nm	Peak amplitude of 10 μg/ml CINN at 264 nm
1	4.221	2.473
2	4.231	2.493
3	4.199	2.51
4	4.243	2.5
5	4.226	2.513
Average	4.224	2.4978
S.D.[a]	0.016	0.016
R.S.D.[b]	0.383	0.640

[a] Standard deviation.
[b] Relative standard deviation (%).

Table 8
Results of the application of the standard addition technique for the determination of domperidone and CINN by the proposed derivative ratio spectrophotometric method and CLS method (model M_2)

BN	Derivative ratio spectrophotometry				CLS			
	Standard added (μg/ml)		Recovery % of added		Standard added (μg/ml)		Recovery % of added	
	Domperidone	CINN	Domperidone	CINN	Domperidone	CINN	Domperidone	CINN
999712	5.00	5.00	98.78	100.12	2.50	2.50	100.78	99.33
	10.00	10.00	101.90	99.36	5.00	5.00	99.65	98.78
	15.00	15.00	100.06	97.70	10.00	10.00	98.87	100.21
	20.00	20.00	97.54	98.07	15.00	15.00	98.82	99.22
Mean			99.83	98.38			99.53	99.39
S.D.			1.861	0.871			0.916	0.599

[a] Standard deviation.

Chemometrics is another technique that is gaining wide application for the resolution of drug mixtures. Therefore, CLS was applied for the simultaneous determination of DOM and CINN.

To produce a calibration using the CLS, we started with a training set consisting of a concentration matrix, **C**, and an absorbance matrix **R**, for known calibration samples [the calibration samples can either be the pure components separately (training set A_1) or mixtures of known concentrations of the constituents (A_2)].

Both DOM and CINN in the validation samples are reasonably distributed and span a wide range of concentration for both drugs (Table 5).

Upon examining the spectra, it was noticed that the region from 200 to 220 nm is noisy and so it was deleted.

The following diagnostic tools were used for validation of the proposed CLS models [34]:

3.1. Predicted versus known concentration plot (model and sample diagnostic)

The predicted concentrations of the validation samples were plotted against the known concentration values. This tool is used to determine whether the model accounts for the concentration variation in the validation set or not. Plots were expected to fall on a straight line with a slope of 1 and 0 intercept. The predicted versus known concentration plots of the prepared validation samples are shown in Figs. 4 and 5. It was noticed that both DOM and CINN in all samples lay on a straight line and the equations of these lines are

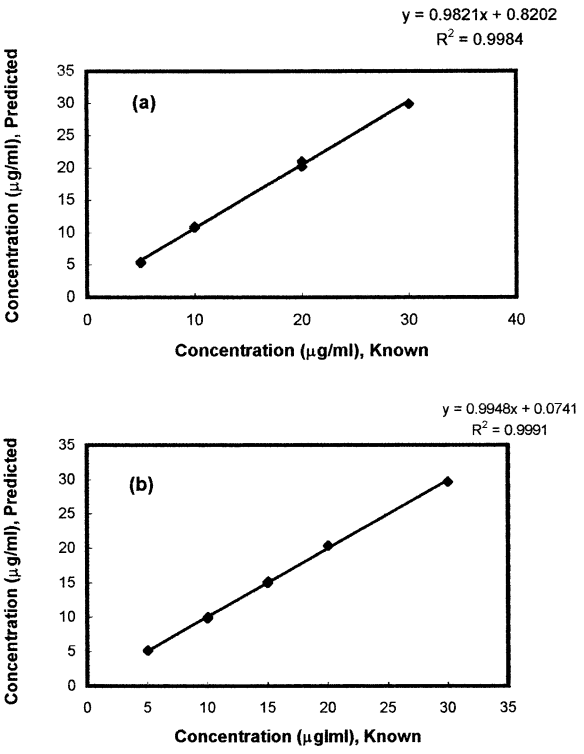

Fig. 4. Predicted concentrations vs. known concentrations for domperidone (a) and CINN (b) in the validation samples using CLS, model M_1.

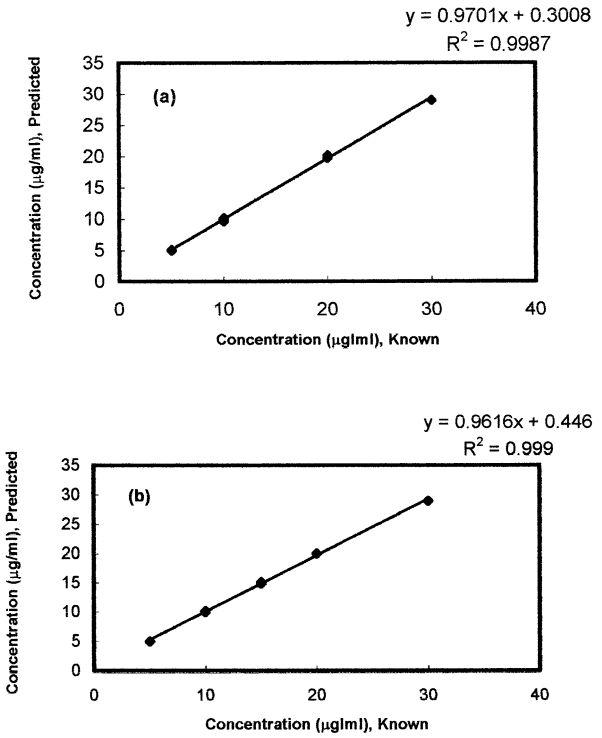

Fig. 5. Predicted concentrations vs. known concentrations for domperidone (a) and CINN (b) in the validation samples using CLS, model M_2.

shown on the graphs. It was also noticed that all plots have a slope of nearly 1 and an intercept close to 0 except for that of DOM using M_1 that has a big intercept indicating that the prediction ability of model M_2 is better than that of M_1 with respect to DOM. This was also noticed from the recovery percentage of DOM in table [5].

3.2. Concentration residuals versus actual concentration plot (model and sample diagnostic)

The difference between the known and the predicted concentration (residuals) were plotted against the actual concentrations for the validation samples. This tool is used to determine whether the model accounts for the concentration variation in the validation set and it also provides information about how well the method will predict future samples. For the suggested models, it was found that the residual values for model M_1 and M_2 (Figs. 6 and 7) show that the residuals for M_2 are more close to zero and more randomly distributed.

3.3. Root mean square error of prediction (RMSEP) (model diagnostic)

The RMSEP is another diagnostic for examining the errors in the predicted concentrations. While the statistical prediction error quantifies precision, RMSEP summarizes both precision and accuracy. RMSEP is calculated from the following equation

$$\mathrm{RMSEP} = \sqrt{\frac{\sum(c_i - c)2}{n}}$$

where c_i is the true concentration of the component of interest in the ith sample, c_i is the pre-

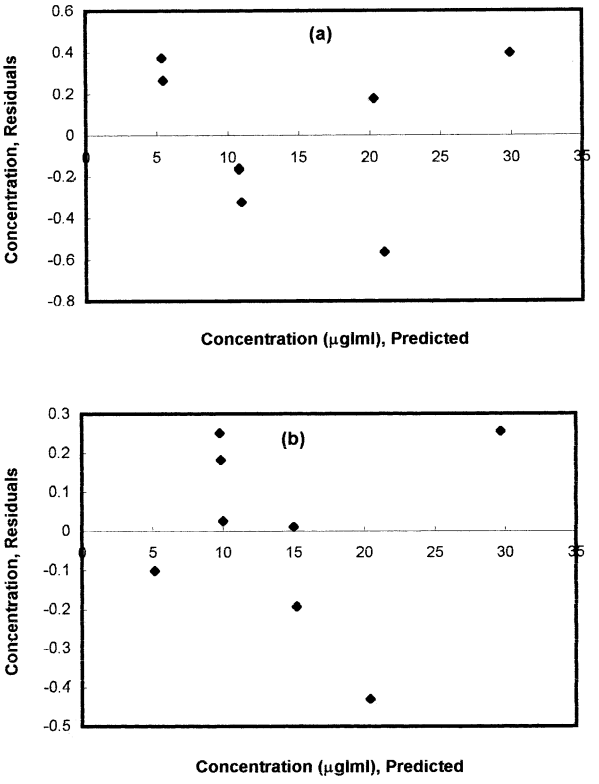

Fig. 6. Residual vs. predicted concentration plots for domperidone (a) and CINN (b) using CLS, model M_1.

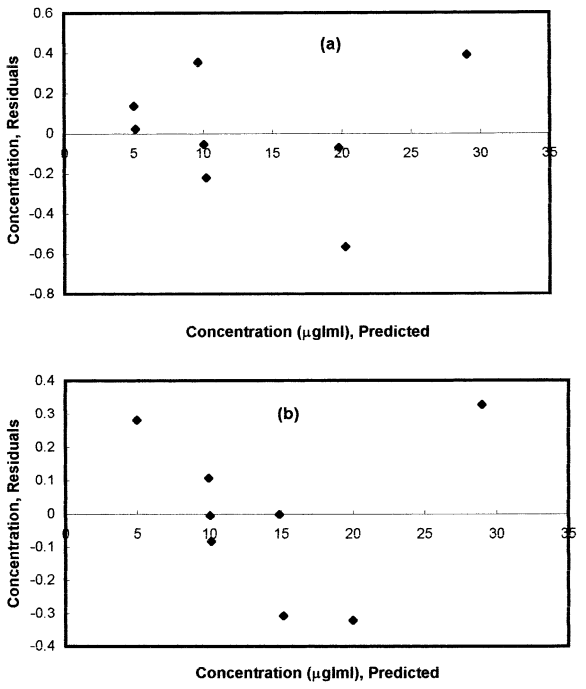

Fig. 7. Residual vs. predicted concentration plots for domperidone (a) and CINN (b) using CLS, model M_2.

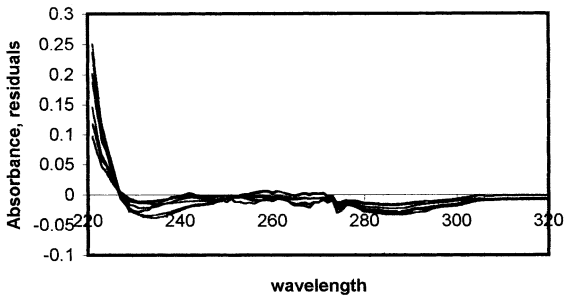

Fig. 8. Spectral residuals for the validation set using CLS model M_1.

dicted concentration and n is the number of samples.

The RMSEP summarizes the spread of the concentration errors into one number similar to a standard deviation and in the same units as the concentration values. The full range of concentration residuals should correspond to approximately 2–3 RMSEP units if there is no bias.

In model M_1 the RMSEP was found to be 0.61 and 0.18 for DOM and CINN, respectively, while for M_2 it is 0.13 and 0.09 for DOM and CINN, respectively, indicating that M_2 gives better results in terms of accuracy and precision, (Table 5).

3.4. Measurement residual plot (model, sample and variable diagnostic)

The residuals are the portion of the sample measurement that is not fit by the pure spectra. It is generated using the measured vector **r** (the measured spectrum of each sample), the estimated concentrations for the two components in each sample **c***, and the pure component matrix, **a**. First the estimated concentrations generated by using the model are multiplied by matrix **a**, then the resulting spectra are subtracted from the measured spectra. If the model is appropriate and **c*** is a good estimate of the true concentrations, the residuals will have random variation around a line of 0 intercept and slope corresponding to the instrumental noise. Model error is suspected if there is a pattern for a number of samples away from the ideal line.

The spectral residuals of the validation samples were plotted in Figs. 8 and 9. For model M_1, it was noticed that for all samples the residuals appear to be randomly distributed between $\pm$ 0.03 absorbance units which is within the expected instrumental noise but only up to 230 nm. In the range from 220 to 230 nm there is a positive structure for all samples and may be that is why there was a problem in the prediction ability of M_1. For model M_2, it was found that the spectral residuals for all samples were randomly dis-

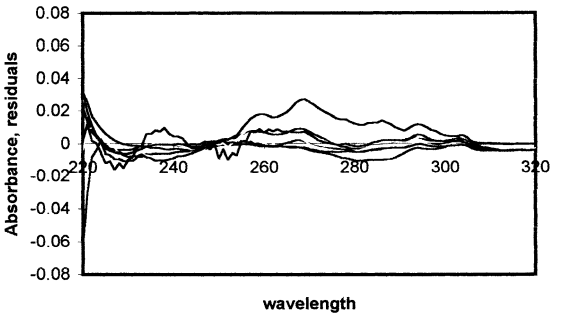

Fig. 9. Spectral residuals for the validation set using CLS model M_2.

Table 9
Summary of the validation diagnostic tools for CLS models M_1 and M_2

Item	Model M_1	Model M_2
Calibration design	15 pure component spectra	8 mixture spectra
Validation design	8 samples randomly varying in concentration	
Preprocessing	Due to the high noise, the region 200–220 nm was deleted leaving the region from 220 to 320 nm to be used in the model	
Variable range	101 wavelength	101 wavelength
Operating range(μg/ml)		
Domperidone	5–30	5–20
CINN	5–25	5–20
RMSEP[a]		
Domperidone	0.61	0.13
CINN	0.18	0.09
Expected error in prediction		
Domperidone	±1.03	±0.20
CINN	±0.40	±0.15

[a] Root mean square error of prediction.

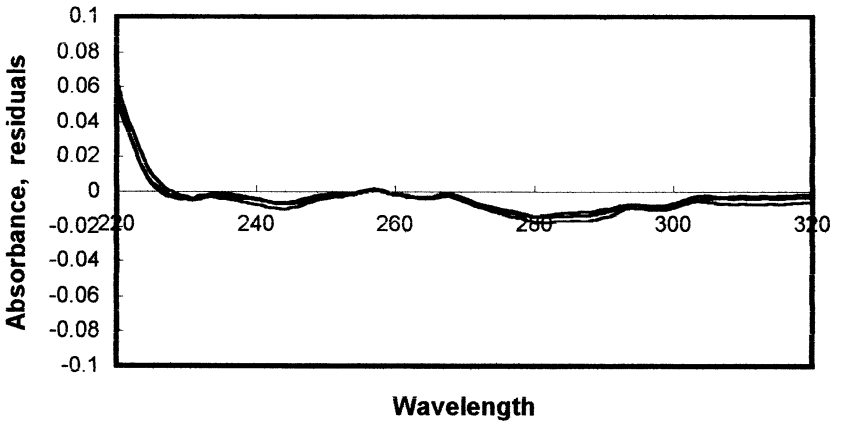

Fig. 10. Spectral residuals for tablets batch No. 999712 using CLS model M_2.

tributed between ±0.025, which is within the expected instrumental noise.

A summary of the validation diagnostic tools for models M_1 and M_2 is shown in Table 9.

This summary shows that M_2 has a better prediction ability than M_1 especially for DOM.

Due to its better prediction ability, model M_2 was then used for the prediction of the concentration of both DOM and CINN in their tablet form. Results obtained are shown in Table 2.

To validate the prediction the spectral residual versus wavelengths for the predicted samples were plotted (Figs. 10 and 11). From these plots, it was found that the residual values vary randomly around zero for all samples indicating that these residuals are the noise associated with measurements. It can also be noticed that there are no unusual features for any sample indicating that the prediction is doing well and there is no unusual behavior for any of the samples. The valid-

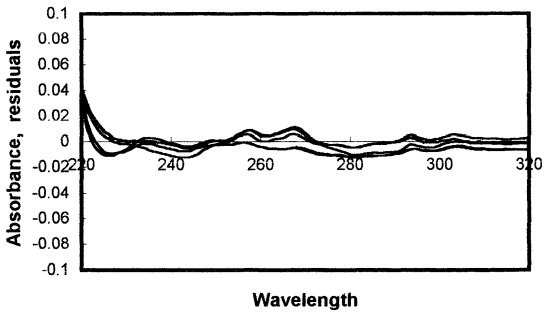

Fig. 11. Spectral residuals for Touristil tablets batch No. 99815 using CLS model M_2.

ity of the proposed CLS procedure for the analysis of Touristil tablets was further assessed by applying the standard addition technique Table 8.

4. Conclusion

The proposed derivative ratio and CLS methods can be used for the simultaneous determination of DOM and CINN either in their pure powder form or in their tablet preparation. The proposed methods are precise, accurate, and simple. Also, no separation step is required. They are rapid and do not require any expensive or sophisticated apparatus if compared with the chromatographic methods d [7,10]. So, the proposed methods can be used for the routine analysis of DOM and CINN.

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