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Research Article

VALIDATED SPECTROPHOTOMETRIC METHODS FOR THE ESTIMATION OF CINNARIZINE IN BINARY MIXTURE WITH PARACETAMOL IN BULK AND TABLETS

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ABSTRACT

Objectives: The aim of this work was to develop and validate new, simple, accurate, and selective spectrophotometric methods (derivative and derivative ratio spectrophotometric methods) for the determination of these drugs. These methods can be used as analytical tools in routine examination in quality control laboratories.

Methods: The first method was derivative method in which the first derivative method (^{1}D) for determination of PCM and the second derivative method (^{2}D) for determination of CIN. The second method was the first derivative ratio spectrophotometric method (^{1}DD) for determination of CIN and PCM.

Results: In first method, the first derivative spectrum (^{1}D) of PCM where PCM was determined by measuring the amplitude of the valley at 235 nm while CIN showed zero crossing spectrum, and the second derivative spectrum (^{2}D) of CIN where CIN was determined by measuring the amplitude of the peak at 287.5 nm while PCM showed a zero value. In the second method, the first derivative ratio spectrophotometry (^{1}DD) for CIN and PCM determination, where the amplitude at 290 and 291 nm, was selected for the determination of CIN and PCM, respectively.

Conclusions: The developed methods were applied for the determination of the cited drugs in tablets containing binary drug mixture. The methods are simple and precise and can be used for routine analysis of the labeled drugs in combined dosage forms in quality control laboratories.

Keywords: Cinnarizine, Derivative, Derivative ratio, Paracetamol, Spectrophotometry, Validation.

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INTRODUCTION

Cinnarizine (CIN) (Fig. 1a), [1-(diphenyl methyl)-3-(4-phenylprop-2-enyl)-piperazine] is a piperazine derivative that has antihistaminic (H1 blocker), calcium channel blocker, and sedative activity. CIN is used for the treatment of vertigo, nausea caused by Meniere's disease and motion sickness. In addition, it is used in the various peripheral and cerebral vascular disorders management [1,2]. It is commonly used in combination with other drugs for prophylaxis of vertigo [1,3].

Paracetamol (PCM) (Fig. 1b) is chemically designated as N-[4-hydroxyphenyl] acetamide. PCM has antipyretic and analgesic effects and can be used for treatment of mild-to-moderate pain as headaches, fever, and other minor pains and aches. It is also used as a main constituent in several cold medications in combination with nonsteroidal anti-inflammatory drugs [1,4]. PCM acts mainly by inhibition of prostaglandin synthesis in the central nervous system. Such combination is highly effective as each drug potentiates the other in boosting brain oxygen supply.

Literature review revealed that several analytical methods were reported for the spectrophotometric determination of CIN in pharmaceutical preparations and biological fluids. These methods include spectrophotometric [5-19], and spectroflorometric [20-22], voltammetry [23], high-performance liquid chromatography (HPLC) [9,24-41], high-performance thin-layer chromatography (HPTLC) [9,41-45], and capillary electrophoresis [46]. Other methods were developed to determination of CIN in combination with PCM which include spectrophotometry [47], high-performance liquid chromatography (HPLC) and high- performance thin layer chromatography, (HPTLC)[48,49]. However, there is only one UV spectrophotometric method for the determination of CIN in combination with PCM [47]. The aim of the present work was to develop and validate new, selective, accurate, and precise spectrophotometric methods for determination of CIN in binary mixture with PCM in bulk powder and in their pharmaceutical dosage form without the previous separation.

MATERIALS AND METHODS

Materials and reagents

PCM and CIN pure standards were supplied by Quality Control Laboratory-Ministry of Health- Sana'a, Yemen, with certified purities of 99.97%, and 99.95%, respectively. The pharmaceutical dosage form was purchased from the Egyptian local market. Cinnarizine® tablets were manufactured by Arab Drug Company Cairo. A.R.E, Batch No. 310363, each tablet was claimed to contain 20 mg CIN. Paracetamol® tablets were manufactured by (Misr Company for Pharmaceuticals, Batch No. 119026), each tablet was claimed to contain 500 mg PCM. Methanol (analytical grade, Daejung Chemicals & Metals, Co., Ltd. Korea) was purchased. Distilled water was purchased from Otsuka Pharmaceuticals (Cairo, Egypt).

Instrumentation

Jenway 6800 Ultraviolet/Visible recording spectrophotometer, U.K. connected to an IBM compatible computer with 1 cm quartz cell and supported with Jenway Flight Deck software. Ultrasonic processor (Soniclean 120T, Thebarton SA, Australia) was used.

Preparation of stock and working standard solutions

Stock solutions

Standard stock solutions of CIN and PCM were separately prepared by accurately transferring 10 mg of each CIN and PCM into two separate

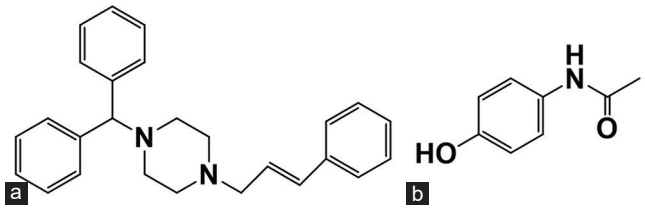

Fig. 1: Chemical structures of (a) cinnarizine and (b) paracetamol

100 ml volumetric flasks then dissolving in methanol to prepare standard stock solutions of concentration (1 mg/ml).

Working solutions

Two aliquots (10 ml) from CIN and PCM standard stock solutions (1 mg/ml) were further diluted to 100 ml with methanol to obtain 100 µg/ml of CIN and PCM as working solutions.

Laboratory prepared mixtures

Different aliquots of CIN and PCM working solution containing 60–220 µg and 54–102 µg of PCM and CIN, respectively, for ^{1}D and ^{2}D method and 50–200 µg and 50–150 µg of CIN and PCM, respectively, for ^{1}DD method were introduced into two series of 10 ml volumetric flasks.

Sample preparation

Ten tablets Cinnarizine® and ten paracetamol® tablets were weighed, ground and mixed well. An accurately weighed amount of the powdered tablets equivalent to 10 mg CIN and 250 mg PCM was transferred into a 100 ml volumetric flask. A 50 ml aliquot of methanol was added; the mixture was sonicated for 15 min, cooled and completed to volume with the same solvent. Filtration of the obtained sample stock solution was carried out to obtain sample working solution (100 µg/ml CIN and 2500 µg/ml PCM).

General procedure and linearity

First and second derivative spectrophotometric methods

Different aliquots of CIN and PCM working solution containing 40–240 µg of CIN and PCM were introduced into a series of 10 ml volumetric flasks and each flask was completed to volume with methanol. First derivative spectra of PCM were recorded against methanol as blank, using the following instrumental parameters (scaling factor = 1 and wavelength range 200–400 nm). The amplitudes of the valleys at 235 nm were measured and used for construction of the calibration curve. Second derivative spectra of CIN were recorded against methanol as blank, using the same above instrumental parameters. The amplitude of the peak at 287.5 nm was measured and used for construction of the calibration curve.

First derivative ratio spectrophotometric method

Different aliquots of CIN and PCM working solution containing (50–300 µg and 25–150 µg) of CIN and PCM were introduced into a series of 10 ml volumetric flasks and each flask was completed to volume with methanol. The zero-order spectra were recorded against methanol as blank using the following instrumental parameters for CIN (scaling factor = 100 and wavelength range 200–400 nm) and for PCM (scaling factor = 1 and wavelength range 200–400 nm) and stored in the computer. The stored spectra of CIN were divided by the spectrum of selected concentration of PCM (4 µg/ml) to obtain the ratio spectra. Then, the first derivatives of the ratio spectra were obtained using the following instrumental parameters (scaling factor=100 and smoothing factor=50), the amplitudes at 290.0 nm were measured and used for construction of the calibration curve. The stored spectra of PCM were divided by the spectrum of selected concentration of CIN (4 µg/ml) to obtain the ratio spectra. Then, the first derivatives of the ratio spectra were obtained using the following instrumental parameters (scaling factor=1 and smoothing factor=50), the amplitudes at 291.0 nm were measured and used for construction of the calibration curve.

Analysis of laboratory prepared mixtures

The same procedures mentioned under linearity were applied for the determination of CIN and PCM in the laboratory prepared mixtures. The concentrations of CIN and PCM were calculated from the computed regression equations.

Analysis of pharmaceutical formulation

To estimate the cited drug in mixed Cinnarizine® and paracetamol® tablets, different aliquots were introduced into a series of 10 ml volumetric flasks and each flask was completed to volume with methanol to prepare solutions equivalent to 0.2–0.84 µg/ml of CIN and to 5–21 µg/ml of PCM for first and second derivative method and to 0.16–0.48 µg/ml of CIN and to 4–12 µg/ml of PCM for first derivative ratio method. The same procedures mentioned under linearity were followed. The validity of the methods was evaluated by applying the standard addition technique.

RESULTS AND DISCUSSION

The ultimate goal of the present work was to develop and validate new, accurate, selective, and precise spectrophotometric methods (first and second derivative and first derivative ratio methods) for the determination of CIN and PCM in binary mixture without previous separation.

Methods development

By scanning CIN and PCM solution (10 µg/ml) in methanol, over the wavelength range (200–400 nm), a severe overlapping was revealed in their zero-order spectra, Fig. 2.

Derivatization solved such overlap, the first derivative spectrum of PCM in methanol shows a valley at 235.0 nm, where CIN exhibits a zero crossing which could be used for the estimation of PCM, Fig. 3 and the second derivative spectrum of CIN in methanol shows a peak at 287.5 nm, where PCM exhibits a zero value which could be used for the estimation of CIN, Fig. 4 For the ^{1}DD, the factors affecting the shape of the ratio spectrum such as the divisor concentration and smoothing factor were investigated.

Different concentrations of CIN for PCM and PCM for CIN (3, 4, 5, and 6 µg/ml) were tried as divisor, a concentration of CIN and also PCM (4 µg/ml) was selected as divisors for each other while the smoothing factor 50 was found to be appropriate. The first derivative ratio spectrum of CIN in methanol shows a peak at 290.0 nm which could be used for its determination, as showed in Fig. 5 and the first derivative ratio spectrum of PCM in methanol shows a valley at 291.0 nm which could be used for its determination, as showed in Fig. 6.

Methods validation

Methods validation was achieved in accordance with International Conference on Harmonization guidelines [50].

Linearity

Linear relationships were obtained over the concentration ranges of 4–24 µg/ml for CIN and PCM (^{1}D and ^{2}D method) and 5–30 µg/ml for CIN and 2.5–15.0 µg/ml for PCM for ^{1}DD methods. The regression equations were computed and validation data are summarized in Tables 1 and 2.

Accuracy

The accuracy of the developed methods was established by analyzing pure samples of the cited drugs. The accuracy was expressed as % recovery by calculation of concentration from regression equations (Tables 1 and 2). In addition, accuracy was further tested by applying the standard addition technique on mixed Cinnarizine® and Paracetamol® tablets. Good recoveries were obtained, revealing

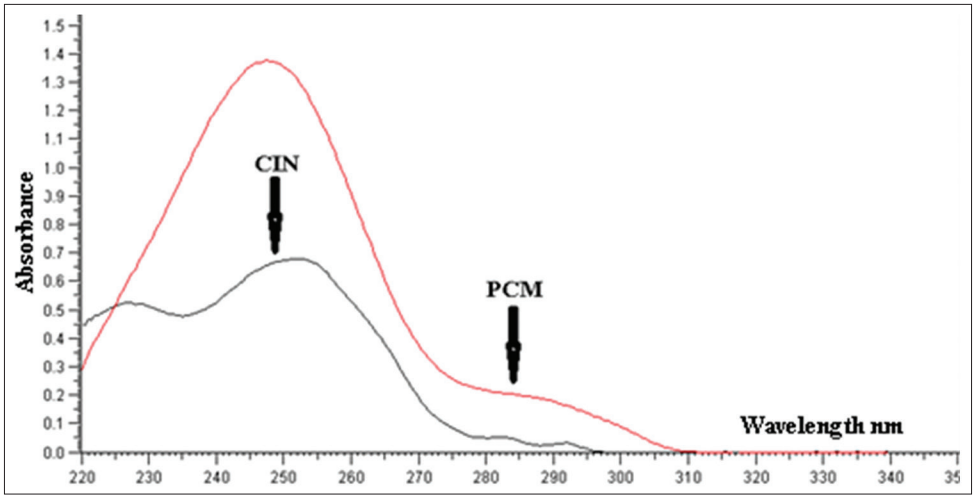

Fig. 2: Zero-order absorption spectra of PCM (8 µg/ml) and CIN (8 µg/ml) in methanol

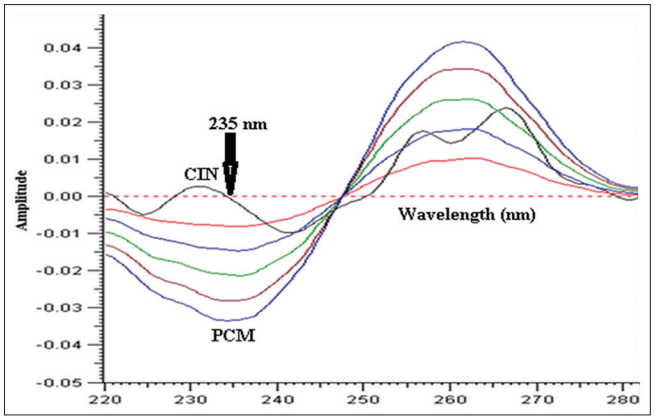

Fig. 3: First derivative spectra of PCM (4–24 µg/ml) and CIN (8 µg/ml) in methanol

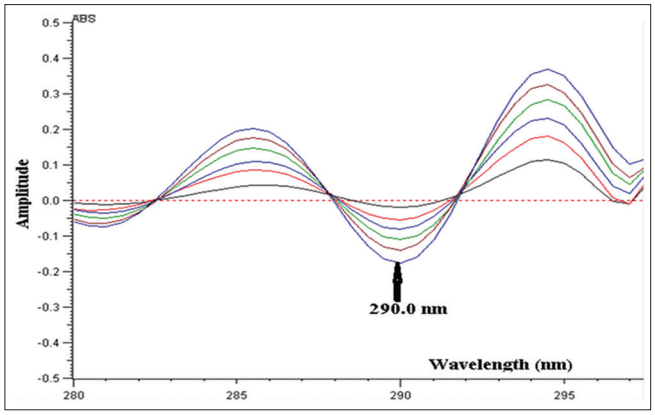

Fig. 5: The first derivative ratio spectra (^{1}DD) of different concentrations of CIN working solution (5–30 µg/ml) in methanol (divisor: 4 µg/ml PCM) at 290.0 nm

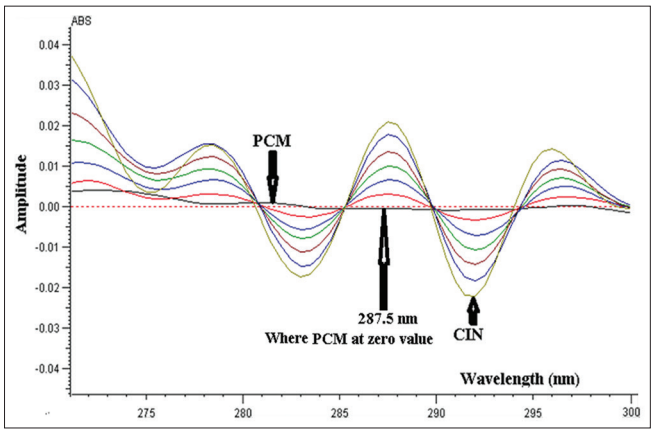

Fig. 4: Second derivative spectra of CIN (4–24 µg/ml) and PCM (8 µg/ml) in methanol

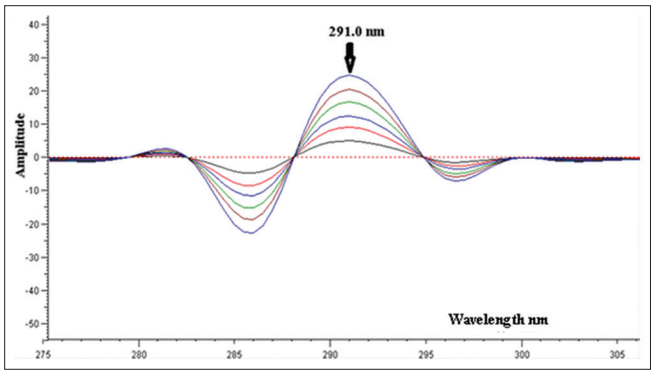

Fig. 6: The first derivative ratio spectra (^{1}DD) of different concentrations of PCM working solution (2.5–15.0 µg/ml) in methanol (divisor: 4 µg/ml CIN) at 291.0 nm

no interference from excipients and good accuracy of the proposed methods, Tables 1 and 2.

Precision

The analytical methods precision provided a satisfactory intraday and interday study. In intraday, the same three concentrations for two drugs (6, 12, and 22 µg/ml) for first derivative (^{1}D) for paracetamol (PCM) and second derivative (^{2}D) for cinnarizine (CIN). Furthermore, three concentrations of CIN (6, 12, and 22 µg/ml) and three concentrations of PCM (4, 9, and 14 µg/ml) for ^{1}DD were analyzed 3 times during the same day using the developed methods. For intermediate precision, the developed methods were repeated on 3 successive days for the analysis of the previously mentioned drug concentrations. The obtained results and RSD %

values were satisfactory indicating good precision of the developed methods, Tables 1 and 2.

Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ were calculated based on standard deviation (SD) of the response and slope, where LOQ = 10×SD/slope and LOD=3.3×SD/slope. The low value of LOD and LOQ confirm the high sensitivity of the developed methods, Tables 1 and 2.

Statistical analysis

All results obtained from the proposed methods were statistically compared with those obtained from reported RP-HPLC method [9], and spectrophotometric method [51]. The student t-test and F ratio test were applied; the obtained values of t and F were less than the tabulated ones, confirming that the difference between the developed and reported methods is insignificant in terms of accuracy and precision, Table 3.

Table 1: Validation parameters and results obtained by the first derivative and second derivative spectrophotometric methods for the determination of CIN and PCM

Item	The proposed first derivative spectrophotometric method (PCM)	The proposed second derivative spectrophotometric method (CIN)
Solvent used	Methanol	Methanol
λ_{max} of measurement	235.0 nm	287.5 nm
Linearity range	4–24 µg/ml	4–24 µg/ml
LOD (µg/ml)	0.499	0.407
LOQ (µg/ml)	1.508	1.233
Regression equation	Amp 235.0 nm=0.015 C_{PCM} - 0.0009	Amp 287.5 nm=0.0071 C_{CIN} - 0.008
Regression coefficient (r^2)	0.9994	0.9999
Standard error of estimation	0.00295	0.00057
Standard deviation of slope S_b	0.00017	0.00034
Standard deviation of intercept S_a	0.00274	0.00053
Confidence limit of the slope	0.015±0.0005	0.0071±0.0001
Confidence limit of the intercept	0.0009±0.0067	0.0079±0.0015
Intraday precision*		
RSD%	0.469-0.787	0.636-1.274
Interday precision**		
RSD%	1.132-1.723	1.401-1.723
Results		
Recovery % in drug substance	100.13±0.458	100.73±0.833
Recovery % in laboratory prepared mixtures	100.48±0.503	100.66±0746
Recovery % in (Cinnarizine® & Paracetamol®) dosage form	100.58±0.533	100.84±0.972
Recovery % of drug added	99.18±1.113	99.59±1.381

*The intraday (n=3), average of three concentrations (6, 12, and 22 µg/ml) of PCM and CIN products repeated 3 times in the same days. **The interday (n=3), average of three concentrations (6, 12, and 22 µg/ml) of PCM and CIN products repeated 3 times in three successive days

Table 2: Validation parameters and results obtained by the first derivative ratio spectrophotometric methods for the determination of CIN and PCM

Item	The proposed first derivative ratio spectrophotometric method	
	CIN	PCM
Solvent used	Methanol	Methanol
λ_{max} of measurement	290 nm	291 nm
Linearity range	5–30 µg/ml	2.5–15 µg/ml
LOD (µg/ml)	0.655	0.324
LOQ (µg/ml)	1.985	0.981
Regression equation	Amp 290.0 nm=0.0063 C_{CIN} - 0.0104	Amp 291.0 nm=1.9281 C_{PCM} - 0.6922
Regression coefficient (r^2)	0.9994	0.9997
Standard error of estimation	0.00163	0.16780
Standard deviation of slope S_b	0.00008	0.15621
Standard deviation of intercept S_a	0.00152	0.01604
Confidence limit of the slope	0.0063±0.00021	1.9281±0.0445
Confidence limit of the intercept	0.0104±0.00421	0.6922±0.4337
Intraday precision*		
RSD%	0.443-1.306	0.142-0.645
Inter-day precision**		
RSD%	0.775-1.828	0.682-1.773
Results		
Recovery % in drug substance	100.01±0.572	99.24± 0.991
Recovery % in laboratory prepared mixture	100.52±0.642	101.11±0.777
Recovery % in (Cinnarizine® & Paracetamol®) dosage form	100.53±1.187	100.96±0.855
Recovery % of drug added	100.63±0.643	100.12±1.241

*The intraday (n=3), average of three concentrations (6, 12, and 22 µg/ml) of CIN and (4, 9, 14) of PCM products repeated 3 times in the same days. **The interday (n=3), average of three concentrations (6, 12, and 22 µg/ml) of CIN and (4, 9, and 14) of PCM products repeated 3 times in three successive days

Table 3: Tests of significance for the developed first derivative, second derivative, and first derivative ratio spectrophotometric methods for the determination of CIN and PCM

Statistical term	CIN			PCM		
	Reference method**	Second derivative spectrophotometric method	First derivative ratio spectrophotometric method	Reference method***	First derivative spectrophotometric method	First derivative ratio spectrophotometric method
Mean	100.48	100.73	100.01	100.11	100.13	99.24
±SD	0.536	0.833	0.572	0.76	0.458	0.991
±SE	0.24	0.373	0.256	0.34	0.205	0.443
RSD%	0.534	0.827	0.572	0.759	0.458	0.999
N	5	5	5	5	5	5
V	0.288	0.695	0.327	0.577	0.21	0.982
t(2.306)*		0.558	1.342		0.055	1.547
F(6.388)*		2.416	1.135		2.746	1.702

SD: Standard deviation, SE: Standard error, RSD: Relative standard deviation. *Figures in parentheses are the theoretical t and F values at (p=0.05). **Metwally *et al*. RP-HPLC method [9]. *** USP 2016: Spectrophotometric method [51]

CONCLUSION

The developed spectrophotometric methods for the estimation of CIN and PCM in combination are selective, sensitive, accurate, and precise. The methods were validated and successfully applied for the determination of the cited drugs in pharmaceutical formulation. They can be used for the routine analysis of these drugs in quality control laboratories.

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AUTHORS' CONTRIBUTIONS

The correspondent author conceived the idea and developed the theory and performed the calculations of the presented work. All authors participated in conducting experiments, discussing the results, and contributing to the last manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest of publishing this article.

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