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Q-Absorbance Ratio Spectrophotometric Method for the Simultaneous Estimation of Cinnarizine and Dimenhydrinate in their Combined Dosage Form

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ABSTRACT:

The present manuscript describes simple, sensitive, rapid, accurate, precise and economical Q-absorbance ratio method for the simultaneous determination of Cinnarizine and Dimenhydrinate in combined dosage form. Absorbance ratio method uses the ratio of absorbances at two selected wavelengths, one which is an isoabsorptive point and other being the λ-max of one of the two components. Cinnarizine and Dimenhydrinate show an isoabsorptive point at 267 nm in methanol. The second wavelength used is 252 nm, which is the λ-max of Cinnarizine in methanol. The linearity was obtained in the concentration range of 2-20 µg/ml for Cinnarizine and Dimenhydrinate. The concentrations of the drugs were determined by using ratio of absorbances at isoabsorptive point and at the λ-max of Cinnarizine. The method was successfully applied to pharmaceutical dosage form because no interference. The results of analysis have been validated statistically and by recovery studies.

KEY WORDS Cinnarizine, Dimenhydrinate, absorbance ratio method, isoabsorptive point, validation, simultaneous.

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INTRODUCTION:

Cinnarizine (CINNA) is chemically (1-(diphenylmethyl)-4-(3-phenylprop-2-en-1-yl) piperazine) (Maryadele et al., 2006) (Figure 1) is a well known Calcium channel blocker and anti allergic drug (sweetman et al., 2007). It is official in IP, BP and EP. IP (Indian Pharmacopoeia., 2010) BP (British Pharmacopoeia., 2010) and EP (European Pharmacopoeia) describe Potentiometric Titration [1] and Liquid Chromatography [3] method for its estimation. Literature survey reveals colorimetry, Potentiometry titration[4](Saad S.M.Hassan et al 2005) and Simple Spectrophotometry[7] (Abdine Het al 2001) methods for determination of CINNA in pharmaceutical dosage forms as well as in biological fluids. Literature survey also reveals RP-HPLC [8] (A.P Argekar et al., 1996) and HPTLC [12] (Mohamed A.F Elmosallamy et al, 2002) methods for determination of CINNA with other drugs in combination. Dimenhydrinate (DIMEN) is chemically 8-chloro-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-7-id[2(diphenylmethoxy)ethyl]dimethylazanium (Maryadele et al., 2006) (Figure 2) is a Antiemetics , Histamine H1 Antagonists Atal CK et al., 1985). Dimenhydrinate is official in BP, USP and EP. BP (British Pharmacopoeia., 2010), USP (United State Pharmacopoeia., 2005) and (European Pharmacopoeia) describe Potentiometric Titration [3] and liquid chromatography [2] method for its estimation. Literature survey reveals HPLC [14] (Ding L, Yang L et al., 2006), UV Spectrophotometry[15] (Kar A, Aniuha GI et al., 2007) and Liquid Chromatography-Electrospray Tandem Mass Spectrometry[17] (Tavares V, Macedo CC et al ,2008) method for the determination of DIMEN. Literature survey also reveals HPLC[19] (Doge U, Eger K et al., 2005) method for determination of DIMEN with other drugs in combination.The combination of these two drugs is not official in any pharmacopoeia; hence no official method is available for the simultaneous estimation of CINNA and DIMEN in their combined dosage forms. Literature survey does not reveal any simple Spectrophotometric method for simultaneous

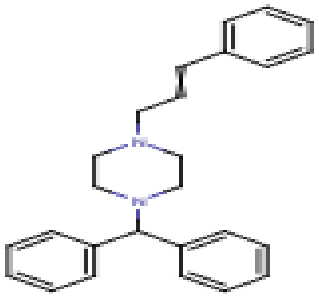


Figure 1: Structure of Cinnarizine

Figure 2: Structure of Dimenhydrinate

estimation of CINNA and DIMEN in combined dosage forms. The present communication describes simple, sensitive, rapid, accurate, precise and cost effective spectrophotometric method based on Q-absorbance ratio spectrophotometric method for simultaneous estimation of both drugs in their combined

MATERIALS & METHODS

Materials

A Shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe system software. A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the study. CINNA and DIMEN bulk powder was kindly gifted by Torrent Research Center, Ghandhinagar, Gujarat, India.. Methanol (AR Grade, S. D. Fine Chemicals Ltd., Mumbai, India) were used in the study.

Methods

Preparation of Standard Solutions

A 10 mg of standard CINNA and DIMEN were weighed and transferred to 100 ml separate volumetric flasks and dissolved in methanol. The flasks were shaken and volumes were made up to mark with methanol to give a solution containing 100µg/ml each of CINNA and DIMEN.

Methodology

Absorbance ratio method uses the ratio of absorbances at two selected wavelengths, one which is an isoabsorptive point and other being the λ-max of one of the two components. From the overlay spectra of two drugs, it is evident that CINNA and DIMEN show an isoabsorptive point at 267 nm. The second wavelength used is 252 nm, which is the λ-max of CINNA. Working standard solutions having concentration 2, 4, 8, 12, 16 and 20 µg/ml for CINNA and DIMEN were prepared in methanol and the absorbances at 267 nm (isoabsorptive point) and 252 nm (λ-max of CINNA) were measured and absorptivity coefficients were calculated using calibration curve.

The concentration of two drugs in the mixture can be calculated using following equations.

$$CX = [(QM - QY) / (QX - QY)] \times A_1/ax_1 \ldots\ldots\ldots \quad (1)$$

$$CY = [(QM - QX) / (QY - QX)] \times A_1/ay_1 \ldots\ldots\ldots \quad (2)$$

Where, A_1 and A_2 are absorbances of mixture at 252 nm and 267 nm; ax1 and ay1 are absorptivities of CINNA and DIMEN at 252 nm; ax2 and ay2 are absorptivities of CINNA and DIMEN respectively at 267 nm; $QM = A_2 / A_1$, $QX = ax_2 / ax_1$ and $QY = ay_2 / ay_1$.

Validation of the proposed method

The proposed method was validated according to the International Conference on Harmonization (ICH) guideline.

Linearity (calibration curve)

The calibration curves were plotted over a concentration range of 2-20 µg/ml for CINNA and DIMEN. Appropriate aliquots from the standard stock solutions of CINNA and DIMEN were used to prepare two different sets of dilutions: Series A, and B as follows. Series A consisted of different concentration of CINNA (2-20 µg/ml). Aliquot from the stock solution of CINNA (100 µg/ml) was pipette out in to a series of 10 ml volumetric flask and diluted with methanol to get final concentration in range of 2-20 µg/ml (0.2, 0.4, 0.8, 1.2, 1.6, and 2.0ml). Series B consisted of varying concentrations of DIMEN (2-20 µg/ml). Appropriate volume of the stock solution of DIMEN (100 µg/ml) was transferred into a series of 10 ml volumetric flask and the volume was adjusted to the mark with methanol to get final concentration in range of 2-20 µg/ml (0.2, 0.4, 0.8, 1.2, 1.6 and 2.0 ml). The absorbances of solution were then measured at 252 nm and 267 nm. The calibration curves were constructed by plotting absorbances versus concentration and the regression equations were calculated.

Method precision (repeatability)

The precision of the instrument was checked by repeated scanning and measurement of absorbance of solutions (*n* = 6)

for CINNA and DIMEN (12 µg/ml for both drugs) without changing the parameter of the proposed spectrophotometry method.

Intermediate precision (reproducibility)

The intraday and interday precision of the proposed method was determined by analyzing the corresponding responses 3 times on the same day and on 3 different days over a period of 1 week for 3 different concentrations of standard solutions of CINNA and DIMEN (4, 8 and 12 µg/ml). The result was reported in terms of relative standard deviation (% RSD).

Accuracy (recovery study)

The accuracy of the method was determined by calculating the recoveries of CINNA and DIMEN by the standard addition method. Known amounts of standard solutions of CINNA and DIMEN were at added at 50, 100 and 150 % level to prequantified sample solutions of CINNA and DIMEN (6µg/ml for CINNA and 6µg/ml for DIMEN). The amounts of CINNA and DIMEN were estimated by applying obtained values to the respective regression line equations.

Limit of detection and limit of quantification

The limit of detection (LOD) and the limit of quantification (LOQ) of the drug were derived by

Calculating the signal-to-noise ratio (S/N, i.e., 3.3 for LOD and 10 for LOQ) using the following equations designated by International Conference on Harmonization (ICH) guidelines.

$LOD = 3.3 \times \sigma/S$ ..... (3)

$LOQ = 10 \times \sigma/S$ ..... (4)

Where, σ = the standard deviation of the response and

S = slope of the calibration curve.

Analysis of drugs in sample

The absorbances of the sample solution i.e. A_1 and A_2 were recorded at 252 nm (λ-max of CINNA) and 267nm (isoabsorptive point) respectively, and ratios of absorbance were calculated, i.e. A2/A1. Relative concentration of two drugs in the sample was calculated using above equation (1) and (2). The analysis procedure was repeated three times with synthetic mixture.

RESULTS AND DISCUSSION

In absorbance ratio method (Q-analysis), the primary requirement for developing a method for analysis is that the entire spectra should follow the Beer's law at all the wavelength (Beckett et al., 1997), which was fulfilled in case of both these drugs. The two wavelengths were used for the analysis of the drugs were 252 nm (λ-max of CINNA) and 267 nm (isoabsorptive point) at which the calibration curves were prepared for both the drugs. The overlain UV absorption

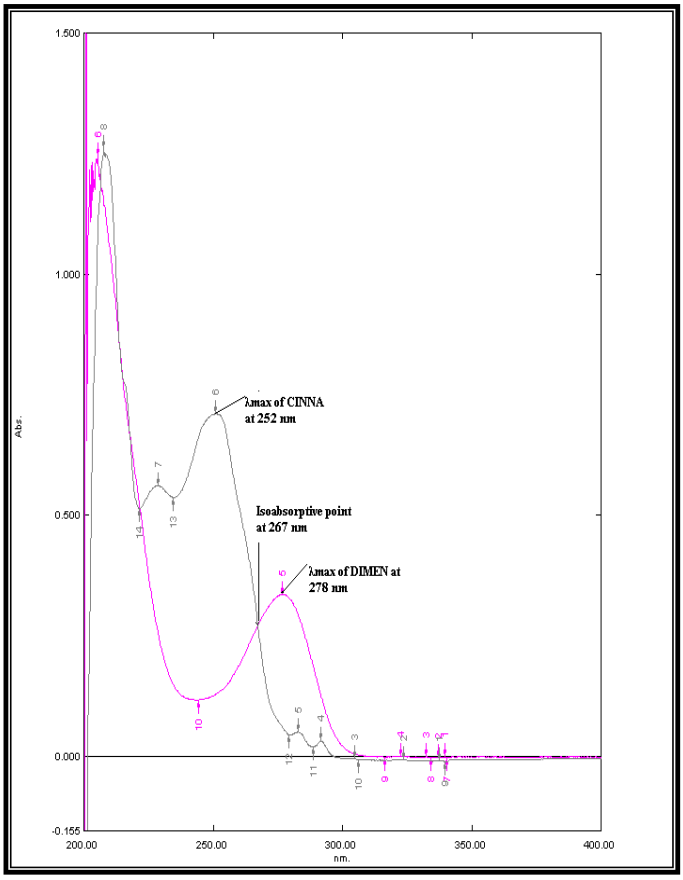
Table 1: Regression Analysis Data and Summary of Validation Parameters for CINNA and DIMEN by Q-Absorbance Spectrophotometric Method

Parameters	CINNA	DIMEN	CINNA & DIMEN
Wavelength (nm)	252	278	267
Beer's law limit (µg /ml)	2-20	2-20	2-20
Regression equation (y = a + bc)	Y=0.0585X+ 0.035	Y=0.0117X+ 0.001	Y= 0.0232X- 0.0011
Slope (b) Intercept (a)	0.0585 0.0359	0.0117 0.001	0.0232 0.0011
Correlation coefficient (r^2)	0.9983	0.9983	0.9994
LOD[a] (µg/ml)	0.275	0.608	0.627
LOQ[b] (µg /ml)	0.835	1.804	1.958
Repeatability (% RSD[c], n =6)	0.3246	1.0479	1.00597
Precision (%RSD, n = 3) Interday Intraday	 0.59-1.35 0.25-1.23	 1.15-1.73 0.64-1.38	 0.75-1.98 0.5-1.47
Accuracy ± S.D[d]. (%Recovery, n= 5)	98.84 ± 0.54	98.52 ± 0.42	99.24 ± 0.46

[a]LOD = Limit of detection, [b]LOQ = Limit of quantification, [c]RSD = Relative standard deviation, [d]S. D. = Standard deviation

Table 2: Recovery Data of CINNA and DIMEN by Spectrophotometric Method

Drug	Amount taken (µg/ml)	Amount added (%)	%Recovery ± S. D. (n=5)	
			At 252 nm	At 267 nm
CINNA	6	50	98.36 ± 0.19	99.53 ± 0.77
	6	100	98.93 ± 0.56	99.29 ± 0.41
	6	150	99.23 ± 0.87	98.91 ± 0.22
DIMEN	6	50	98.01 ± 0.50	99.53 ± 0.77
	6	100	98.90 ± 0.55	99.29 ± 0.41
	6	150	98.67 ± 0.21	98.1 ± 0.22



Figgure 3: Overlain absorption spectra of Cinnarizine (252 nm) and Dimenhydrinate (278 nm) showing isoabsorptive point (267 nm) in methanol

Table 3: Analysis of CINNA and DIMEN by Spectrophotometric Method

Mixture	Label Claim (mg)		Amount Found (mg)		% Label Claim ± S.D. (n=6)	
	CINNA	DIMEN	CINNA	DIMEN	CINNA	DIMEN
I	20	40	19.9	40.14	99.92 ± 0.44	101.40 ± 0.52

spectra of CINNA (252 nm) and DIMEN (278 nm) showing isoabsorptive point (267 nm) in methanol is shown in **Figure 3.** The validation parameters were studied at all the wavelengths for the proposed method. Accuracy was determined by calculating the recovery and the mean was determined (**Table 2**). The method was successfully used to determine the amounts of CINNA and DIMEN present in the synthetic mixture. The results obtained were in good agreement with the corresponding labeled amount (**Table 3**). Precision was calculated as repeatability and intra and inter day variations (% RSD) for both the drugs. Optical characteristics and summary of validation parameters for method is given in Table 1. By observing the validation parameters, the method was found to be simple, sensitive, accurate and precise. Hence the method can be employed for the routine analysis of these two drugs in combined dosage form.

CONCLUSION

The proposed spectrophotometric method was found to be simple, sensitive, accurate and precise for determination of CINNA and DIMEN in synthetic mixture. The method utilizes easily available and cheap solvent for analysis of CINNA and DIMEN hence the method was also economic for estimation of CINNA and DIMEN from synthetic mixture. The common excipients and other additives are usually present in the synthetic mixture do not interfere in the analysis of CINNA and DIMEN in method, hence it can be conveniently adopted for routine quality control analysis of the drugs in combined pharmaceutical formulation.

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