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Quantification of cinnarizine and dimenhydrinate in tablet dosage form by simultaneous equation spectrophotometric method

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Abstract

Simple, accurate, precise, reproducible, requiring no prior separation and economical procedures for simultaneous estimation of Cinnarizine(CNZ) and Dimenhydrinate(DMH) in tablet dosage form have been developed. Method employs formation and solving of simultaneous equation using 250 nm and 277 nm as two analytical wavelengths for both drugs in methanol. CNZ and DMH at their respective λ_{max} 250 nm and 277 nm shows linearity in a concentration range of 2-12 µg /ml and 10-35 µg /ml. Recovery studies for CNZ 98.9-100.75% and 96.16-100.69% for DMH in case of simultaneous equation method confirming the accuracy of the proposed method. The proposed method is recommended for routine analysis since it is rapid, simple, accurate and also sensitive and specific.

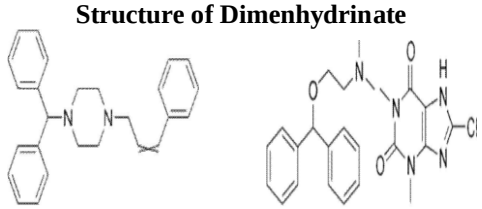
Keywords: Cinnarizine, Dimenhydrinate, Validation

1. Introduction

(Cinnarizine (CNZ) is a white powder. Chemically it is (E)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl) piperazine[1,2] (Fig. 1: A). It is antihistaminic agent and calcium channel blocker. It has calcium-channel blocking activity selective for arterial smooth muscles. It also has some antihistamine activity. Cinnarizine acts as a sedative. It also improves microcirculation by reducing ischemia-induced blood viscosity. Dimenhydrinate (DMH) is white crystalline odourless powder. Chemically, it is 8-chloro-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-7-ide; [2-(diphenylmethoxy)ethyl]dimethylazanium[1,2] (Fig. 1: B). It is very soluble in alcohol and practically insoluble in ether[3]. It is antiemetic agent and antihistaminic agents. The mechanism by which some antihistamines exert their antiemetic, anti–motion sickness, and antivertigo effects is not precisely known but may be related to their central anticholinergic actions. They diminish vestibular stimulation and depress labyrinthine function. An action on the medullary chemoreceptive trigger zone may also be involved in the antiemetic effect. Dimenhydrinate is a competitive antagonist at the histamine H1 receptor, which is widely distributed in the human brain. Dimenhydrinate's anti-emetic effect is probably due to H1 antagonism in the vestibular system in the brain[1].

The combination of Cinnarizine and Dimenhydrinate is indicated as antivertigo agents[4]. DMH and CNZ are official in British Pharmacopeia and Indian Pharmacopeia respectively. Many methods have been reported in literature for determination of CNZ individually and with other drugs in combination.[5-8] and for dimenhydrinate individually and with other drugs[9-11] However there is no UV spectrophotometric method reported for the simultaneous equation method of CNZ and DMH in pharmaceutical preparations in literature survey. The objective of the present work is to develop and validate new analytical methods for simultaneous determination of CNZ and DMH in tablet dosage form.

Figure 1: (A) Structure of Cinnarizine (B) Structure of Dimenhydrinate



(A) (B)

2. Experimental

2.1 Materials and Methods

A double-beam Shimadzu UV-Visible spectrophotometer 1700 (Pharma spec) was used with wavelength accuracy of ± 0.5 nm and a pair of 1-cm matched quartz cells, was used to measure absorbance of the resulting solution. All weighing were done on electronic balance (Model Shimadzu BL-220H). All statistical calculations were carried out using Microsoft Excel 2007 analytical tool.

Analytically pure CNZ and DMH were procured as gift sample from Kamud Pharmaceuticals Ltd. and Ajanta Pharmaceutical Pvt. Ltd., (Bombay, India). Methanol (E. Merck, Mumbai, India) analytical grade was used as diluents. Tablet formulation (VERTIZAC, Ajanta Pharmaceutical Pvt. Ltd) containing labelled amount of 20 mg of Cinnarizine and 40 mg of Dimenhydrinate were purchased from local market.

2.2 Preparation of solutions

Accurately weighed 10mg of CNZ and DMH standards were transferred to separate 10ml volumetric flask and dissolved in 10 ml Methanol.

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The flasks were shaken and volume was made up to the mark with Methanol to give solutions containing 1000 µg/ml CNZ and 1000 µg/ml DMH respectively.

2.3 Methodology

Selection of analytical wavelengths was done by taking pure samples of CNZ and DMH which were separately dissolved in methanol to give two solutions of 10 µg/ml, respectively. They were scanned in the wavelength range of 200–400 nm. From the overlain spectra (Figure 2), wavelengths 250 and 277nm were selected for the formation of simultaneous equations. For constructing a calibration curves, two series of different concentrations in range of 2-12 μg/mL for CNZ and 10-35 μg/mL for DMH were prepared from stock solutions. The calibration curves were plotted at 250 and 277 nm. The absorptivities (A1%, 1 cm) of both the drugs at both the wavelengths were determined. These calculated values were the mean of five independent determinations. Concentrations in the sample were obtained by using following equations-

$$C_x = \frac{A_1\, ay_2 - A_2\, ay_1}{ax_1 ay_2 - ax_2 ay_1} \quad \text{..... Eq. (i)}$$

$$C_y = \frac{A_1\, ax_2 - A_2\, ax_1}{ay_1 ax_2 - ay_2 ax_1} \quad \text{.....Eq. (ii)}$$

Where, A_1 and A_2 are absorbance of mixture at 250nm and 277 nm respectively,

ax_1 and ax_2 are absorptivities of CNZ at λ1 and λ2 respectively

ay_1 and ay_2 are absorptivities of DMH at λ_1 and λ_2 respectively.

C_x and C_y are concentrations of CNZ and DMH respectively.

2.4 Method Validation

The proposed method was validated according to International Conference on Harmonization (ICH) guidelines[12].

2.4.1 Linearity and range

Developed analytical method shows linearity response over the range of 2-12 µg/ml for CNZ and 10-35 µg/ml for DMH at 250nm and 277nm respectively.

2.4.2 Precision

The intra-day and inter-day precision study of the proposed simultaneous equation spectrophotometric method was carried by estimating responses three times on the same day and on three different days (first, second, third day) for three different concentrations of CNZ (2, 6, 10 µg/ ml) and DMH (20, 25, 30 µg/ ml) and the results reported in terms of percentage relative standard deviation (%RSD).

2.4.3 Accuracy

The accuracy of the method was determined by calculating recoveries of CNZ and DMH by method of standard additions. Known amount of CNZ (50%, 100% and 150%) and DMH (50%, 100% and 150%) were added to a pre quantified sample solutions and the amount of CNZ and DMH were estimated by measuring response at the appropriate wavelengths. The recovery was verified by estimation of drugs in triplicate preparations at each specified concentration levels.

2.4.4 LOD and LOQ

Calibration curve was repeated for 5 times and the standard deviation (SD) of the intercepts was calculated. Then LOD and LOQ were measured as follows

$LOD = 3.3 \times \sigma/S$

$LOQ = 10 \times \sigma/S$

Where, σ = the standard deviation of the y - intercept

S = slope of the calibration curve.

2.5 Solution stability

Solution stability of the method was studied by observing the stability of both the drug solutions at 25 ± 2°C for 24 h.

2.6 Analysis of marketed formulation

The pharmaceutical dosage form used in this study was VERTIZAC tablets with a content of 20mg CNZ and 40mg DMH as per tablet. Twenty tablets of brand VERTIZAC tablets were weighed and finely powdered. Accurately weighed tablet powder equivalent to 20 mg of cinnarizine and 40mg of Dimenhydrinate taken in 10ml volumetric flask. Few ml of methanol was added and sonicated for 5 min. The volume was made upto the mark with methanol. Aliquot portion of this solution was further diluted to achieve final concentration of 10µg/ml for CNZ and 20µg/ml DMH. The absorbances were noted at respective wavelengths. The concentration of each drug in tablet formulation was determined using above methods.

3. Result and Discussion

A simultaneous equation spectrophotometric method was successfully developed for determination of CNZ and DMH from their combined dosage form.

The proposed simultaneous equation method shows good linearity in the concentration range of 2-12 µg/ml of CNZ and 10-35 µg/ml of DMH with correlation co-efficient 0.995 for CNZ and 0.998 for DMH, respectively. (Table 2)

The % RSD values for CNZ and DMH were found to be 0.54 % and 0.38 %, respectively. The low values of relative standard deviation (less than 2 %) indicate that the proposed method is repeatable. The % RSD values for intraday study was found to be 0.52 - 0.65 % and 0.11 - 0.39 % for CNZ and DMH, respectively. The % RSD values for interday study was found to be 0.63 - 0.73 % and 0.10 - 0.58 % for CNZ and DMH, respectively. The low RSD value indicates that the proposed method is precise (Table 3 - 4). The detection limit of CNZ and DMH were 0.06 and 0.55 µg/ml, while quantitation limit of CNZ and DMH were 0.206 and 1.680 µg/ml, respectively. The

above data shows that a nanogram quantity of both the drugs can be accurately and precisely determined. The validation parameters are summarized in Table 1.

The accuracy of the method was determined by calculating recoveries of CNZ and DMH by method of standard additions. The % recoveries were found to be 98.9 % – 100.75% for CNZ and 96.16 % - 100.69 % for DMH (Table 5). The results of recovery studies indicate that the proposed method is accurate.

The proposed validated method was successfully applied to determine CNZ and DMH in tablet dosage form. The results obtained for CNZ and DMH were comparable with the corresponding labelled amounts (Table 6). No interference of the excipients with the absorbance of interest appeared; hence the proposed method is applicable for the routine simultaneous estimation of CNZ and DMH in pharmaceutical dosage forms.

Table 1: Summary of validation parameters

Parameters	CNZ	DMH
Limit of Detection	0.06	0.55
Limit of Quantitation	0.206	1.680
Accuracy (%)	98.9-100.75	96.16-100.69
Precision		
Intraday (n = 3)	0.52 - 0.65 %	0.11 - 0.39 %
Interday (n = 3)	0.63 - 0.73 %	0.10 -0.58 %
Repeatability (RSD, n = 6)	0.531 %	0.424 %
Solvent suitability	Suitable for 24 hrs.	Suitable for 24 hrs.

Table 2: Statistical data of CNZ and DMH

Parameters	CNZ at 250nm	DMH at 277nm
Linear range	2 – 12 µg/ml	10-15 µg/ml
Slope	0.022	0.019
Intercept	0.046	0.037
Standard deviation of intercept	0.00044	0.00324
Standard deviation of slope	0.0009	0.0004
Regression Coefficient (r2)	0.995	0.998

Table 3: Determination of Precision for CNZ

CNZ	Conc. (µg/ml)	Intraday Mean ± SD (n =3)	% RSD	Interday Mean ± SD (n =3)	% RSD
At250nm	2	0.088±0.000577	0.653	0.088±0.00557	0.651
	6	0.190±0.001	0.523	0.182±0.00114	0.636
	10	0.284±0.00173	0.610	0.310±0.00577	0.737
At277nm	2	0.03067±0.00058	1.882	0.03067 ± 0.00058	1.882
	6	0.03633±0.00058	1.589	0.03667±0.00058	1.574
	10	0.04367±0.00058	1.322	0.04767±0.00058	1.211

Table 4: Determination of precision for DMH

DMH	Conc. (µg/ml)	Intraday Mean ± SD (n =3)	% RSD	Interday Mean ± SD (n =3)	% RSD
At250nm	20	0.2832±0.00283	1.01	0.306±0.00371	1.34
	25	0.339±0.00084	0.23	0.4075±0.0018	0.372
	30	0.453±0.00261	0.386	0.486±0.0074	0.51
At277nm	20	0.442±0.001732	0.391	0.45±0.00264	0.587
	25	0.5233±0.000577	0.110	0.5286±0.00057	0.109
	30	0.6336±0.00208	0.328	0.6397±0.00173	0.271

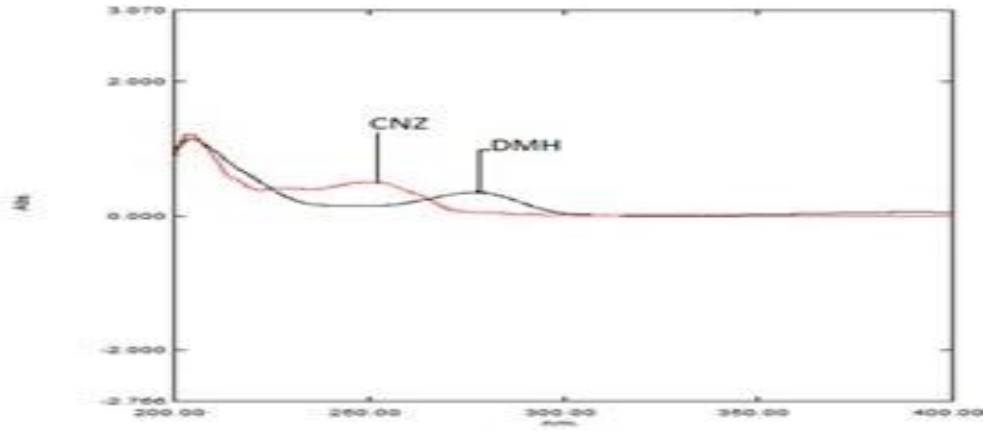
Table 5: Determination of accuracy

% Level	Amount of drug added (µg/ml)		Recovered amount of drug (µg/ml)		% Recovery	
	CNZ (µg/ml)	DMH (µg/ml)	CNZ (µg/ml)	DMH (µg/ml)	CNZ	DMH
50	6	15	5.914	15.06	98.74±0.28	100.38±0.17
100	8	20	8.070	20.06	100.75±0.088	100.69±0.22
150	10	25	9.89	24.04	98.9±0.26	96.16±0.30

Table 6: Assay Results of Marketed Formulation

Formulation	Actual concentration (µg/ml)		Amount obtained (µg/ml)		% CNZ	% DMH
	CNZ	DMH	CNZ	DMH		
Tablet	20.0	40.0	19.75	39.78	98.75%	99.45%

Figure 2: Overlain spectrum of CNZ and DMH in Methanol of 10ppm



4. Conclusions

Sensitive, precise and accurate simultaneous UV spectroscopic method was developed and validated. The proposed method is accurate, precise, reproducible, and economical and can be successfully used for routine analysis of simultaneous estimation of CNZ and DMH. The method was validated as per ICH guidelines in terms of linearity, accuracy, precision, limits of detection (LOD) and quantification (LOQ), and robustness. The proposed method can be used for quality control assay of CNZ and DMH in their pharmaceutical dosage form.

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