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DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF CINNARIZINE AND DOMPERIDONE MALEATE IN PURE AND TABLET DOSAGE FORM

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ABSTRACT

The method for the simultaneous estimation of Cinnarizine and Domperidone maleate from tablet dosage form has been developed, based on simultaneous equation method at two selected wavelength 254nm and 284nm respectively, and also absorbance ratio method at two selected wavelengths 274.0nm (Iso-absorptive point) and 254.0nm (λ_{max} of cinnarizine). The linearity was obtained in the concentration range of 5-20µg/ml and 5-20µg/ml for cinnarizine and Domperidone maleate respectively. These methods are simple, accurate and results of analysis have been validated statistically and by recovery studies.

INTRODUCTION: Domperidone maleate (DOM) is chemically 5-Chloro-1-[1-[3-(2-oxo-1, 3-dihydrobenz imidazol-1-yl)propyl]-4-piperidyl]-1, 3-dihydrobenz imidazol-2-one maleate. Its gastroprokinetic properties are related to its peripheral dopamine receptor blocking properties. It facilitates gastric emptying and decreases small bowel transit time. Antiemetic property is related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It is used for the symptomatic management of upper GI motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis; prevention of GI symptoms associated with use of dopamine-agonist anti-Parkinson agents.

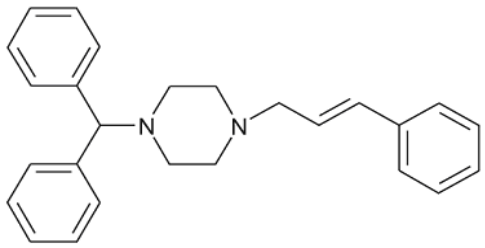
Cinnarizine (CIN) is chemically (E)-1-(diphenyl methyl)-4-(3-phenylprop-2-enyl) piperazine. Cinnarizine has antihistamine properties blocking the histamine H_1 receptors. It also shows weak antimuscarinic and local anaesthetic activity. Cinnarizine is sedative calcium antagonist, inhibiting influx of calcium intracellularly. Cinnarizine inhibits contractions of vascular smooth muscle cells by blocking calcium channels.

It is official in the Indian Pharmacopoeia. Literature survey reveals, HPLC and HPTLC methods have also been reported for estimation of DOM in Pharmaceutical dosage forms and also there are various methods such as UV spectrophotometry for DOM [9-11].

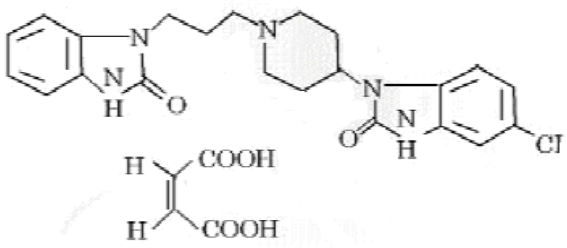
Extensive literature survey reveals, none of the method is available that is based on estimation of Cinnarizine and Domperidone maleate simultaneously by absorption ratio UV-spectrophotometric method.

Aim of the present work was to develop simple, precise, accurate and economical spectrophotometric methods for simultaneous determination of binary drug formulation.

The proposed method was optimized and validated in accordance with International Conference on Harmonization (ICH) guidelines [12].



CINNARIZINE



DOMPERIDONE MALEATE

EXPERIMENTAL:

Instrumentation: A double-beam Jasco UV- 2075; UV Visible spectrophotometer, spectral bandwidth of 2nm,wavelength accuracy ±0.5nm and a pair of 1-cm matched quartz cells was used to measure absorbance of the resulting solution.

Materials: Standard samples of cinnarizine and Domperidone maleate were taken. Combined dose Cinnarizine and Domperidone tablets (STUGIL, 20mg Cinnarizine and 15mg Domperidone; manufactured by Janssen-Cilag Pharmaceutical Pvt. Ltd.) were taken.

Solvent: Hydrochloric acid selected as solvent for developing spectral characteristics of the drug. The selection was made after assessing the solubility of both the drugs in different solvents.

Preparation of Standard Stock Solutions: Cinnarizine and Domperidone (10mg each) were accurately weighed and dissolved separately in100ml of methanol to give stock (100µg/ml) [2]. From the standard stock solution, 1ml each of CIN and DOM was taken in 10ml volumetric flask. Volume was made up to mark with methanol. Aliquot portion was appropriately diluted with 0.1 N HCl to get final concentration of 5-20µg/ml (CIN) and 5-20 µg/ml (DOM) prepared respectively to give final concentrations and scanned between 200-400nm [3].

METHOD:

Application of the Proposed Method for the determination of CIN and DOM in Tablet Dosage Form:

1) **Simultaneous Equation Method:** Twenty tablets were weighed and average weight was calculated[3-6]. The tablets were crushed into fine powder. Tablet powder equivalent to 10mg of CIN was transferred to 100ml volumetric flask and ultra sonicated for 10min .The volume was made upto the mark with HCl. The resulting solution was then filtered through a Whatmann filter paper (No. 41).

   Aliquot portion was appropriately diluted with HCl to get final concentration of 20µg/ml. The concentration of both CIN and DOM were determined by measuring absorbance of sample at 254.0nm, 284.0nm in spectrum mode (**fig. 1**) and values were substituted in respective formulae to obtain the concentration.

$C_x = A_2ay_1 - A_1ay_2 / ax_2\, ay_1 - ax_1\, ay_2$

$C_Y = A_1ax_2 - A_2ax_1 / ax_2\, ay_1 - ax_1\, ay_2$

Where,

C_x = Concentration of CIN,

Cy = Concentration of DOM;

A1 = Absorbance of mixture at 254nm;

A2 = Absorbance of mixture at 284nm;

ax1= Absorptivity of CIN at 254nm;

ax2 = Absorptivity of CIN at 284nm;

ay1 = Absorptivity DOM at 254nm;

ay2 = Absorptivity of DOM at 284nm

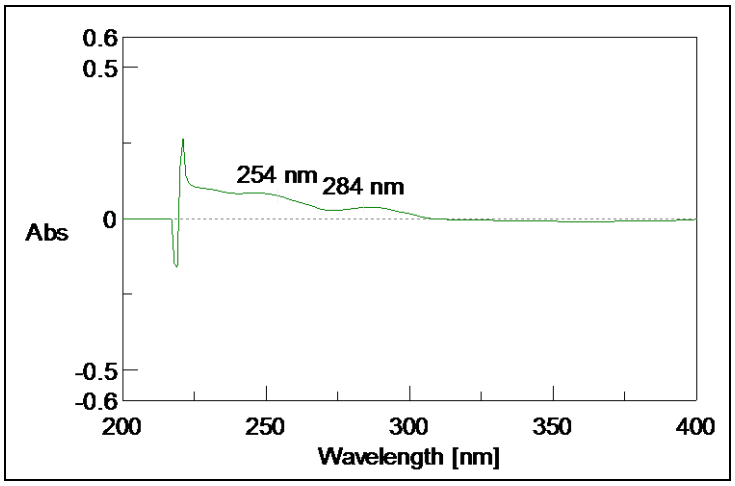


FIG 1: SIMULTANEOUS SPECTRA FOR CIN AND DOM IN THE RANGE 200-400nm

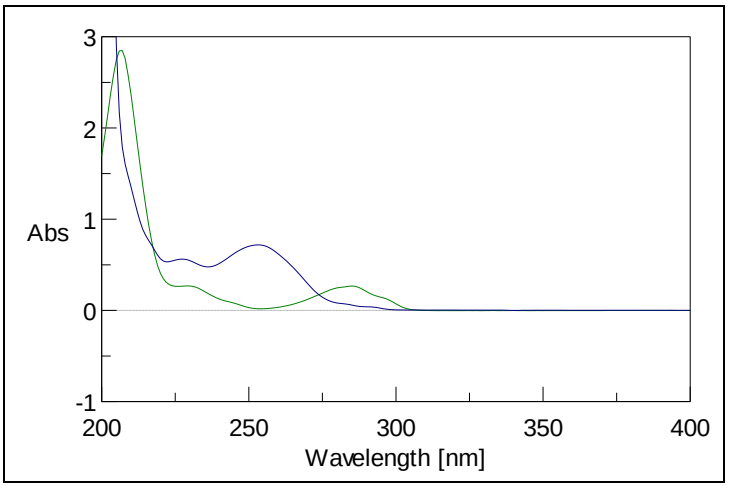


FIG. 2: OVERLAIN OR ABSORBANCE SPECTRA FOR CIN AND DOM IN THE RANGE 200-400nm

2) **Absorbance Ratio Method**: In the absorbance ratio method, from the over lay spectra of drugs (**fig. 2**), wavelengths274.0nm (Iso-absorptive point) and 254.0nm (λ_{max} of cinnarizine) were selected for analysis. The calibration curves for cinnarizine and domperidone were plotted in the concentration range of 5-20µg/ml and 5-20µg/ml at both the wavelengths respectively. The absorptivities values were determined for both the drugs at both the wavelengths (fig. 2). From the following set of equations the concentration of each component in sample was calculated,

$Cx=Qm-Qy/Qx-Qy \ .A_1/ax_1$ …… (1) and;

$Cy=Qm-Qx/Qy-Qx \ .A_1/ay_1$ ……(2)

Where

Cx= concentration of Cinnarizine

Cy= concentration of Domperidone,

A_1= absorbance of sample at wavelength 254.0nm,

ax_1= absorptivity of cinnarizine at 254.0nm,

ay_1=absorptivity of domperidone at 284.0nm,

Qm= ratio of absorbance of sample solution at 274.0nmand 254.0nm,

Qx= ratio of absorptivities of cinnarizine at 274.0nm and 254.0nm and

Qy= ratio of absorptivities of domperidone at274.0nm and 284.0nm.

VALIDATION PARAMETER

Linearity [7]**:** The linearity was obtained in the concentration range of 5-20µg/ml and 5-20µg/ml for cinnarizine and domperidone respectively in both methods which obeys Beer-Lambert's law. The results of the same are shown in **fig. 3 and fig. 4.**

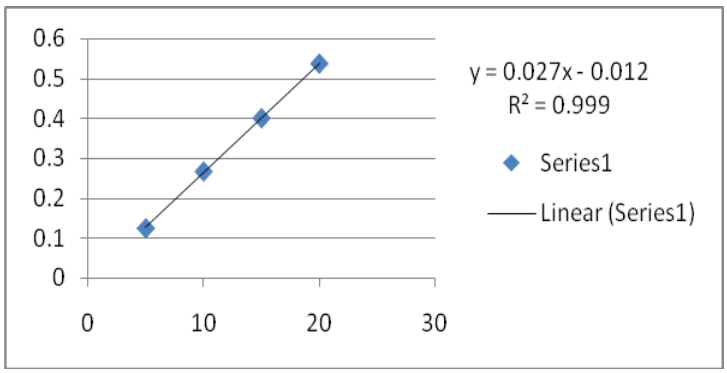


FIG. 3: LINEARITY OF CINNARIZINE

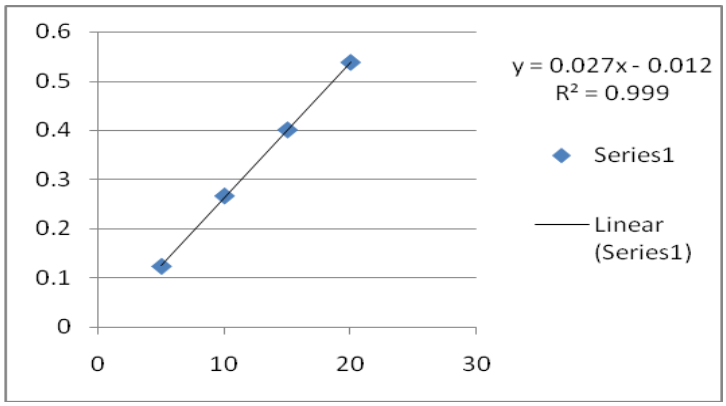


FIG. 4: LINEARITY OF DOMPERIDONE

Accuracy [8]**:** To ascertain the accuracy of the proposed methods, recovery studies were carried out by standard addition method at **Table 1 and Table 2**.

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The LOD and LOQ by proposed methods were determined using calibration standards. LOD and LOQ were calculated as 3.3s/S and 10s/S, respectively, where S is the slope of the calibration curve and s is the standard deviation of response. The results of the same are shown in **Table 1 and Table 2**.

Results of Analysis of Tablet Formulation:

TABLE 1: SIMULTANEOUS EQUATION METHOD

Drug	Label Claim (µg/ml)	Amount Taken (mg/tab)	Amount Found(mg)	% Recovery	S.D	S.E.	C.V.	LOD (µg/ml)	LOQ (µg/ml)
			9.93	99.3					
CIN	20mg/tab	10	9.81	98.1	0.916	0.529	0.931	0.015	0.070
			9.75	97.5					
			7.43	99.06					
DOM	15mg/tab	7.5	7.40	98.66	0.202	0.116	0.204	0.009	0.074
			7.41	98.80					

S.D: Standard Deviation**, S.E:** Standard Error**, C.V.:** Coefficient Variation

TABLE 2: ABSORBANCE RATIO METHOD

Drug	Label Claim (µg/ml)	Amount Taken (mg/tab)	Amount Found(mg)	% Recovery	S.D.	S.E	C.V.	LOD (µg/ml)	LOQ (µg/ml)
			9.81	98.1					
ATN	20mg/tab	10	9.74	97.4	1.014	0.581	1.031	0.123	0.375
			99.4	99.4					
			7.35	98					
IND	15mg/tab	7.5	7.30	97.33	1.017	0.588	1.036	0.124	0.377
			7.45	99.33					

S.D: Standard Deviation**, S.E:** Standard Error**, C.V.:** Coefficient Variation

RESULTS AND DISCUSSION: From the proposed research, it was found that cinnarizine and Domperidone obeys linearity within the concentration range 5-20µg/ml and 5-20µg/ml respectively. Percentage label claim for CIN and DOM in tablet, by simultaneous equation and absorption ratio methods was found in the range of 97.5% to 99.4% and 97.33% to 99.33% respectively. For Coefficient of variation (CV) were calculated, which was found to be less than 2% indicating the both method has good reproducibility.

Accuracy of proposed methods was ascertained by recovery studies and results are expressed as %recovery. Percent recovery for CIN and DOM by simultaneous equation and absorption ratio method was found in range of 97.5% to 99.4% and 97.33% to 99.33% respectively, values of standard deviation, standard error and coefficient of variation for both method were in range of 0.202 to 0.916 and 1.014 to 1.017; 0.116 to 0.529 and 0.581 to 0.588; 0.204 to 0.931 and 1.031 to 1.036 respectively indicating the accuracy of proposed method.

CONCLUSION: Based on the results obtained, it is found that the proposed methods are accurate, precise, reproducible and economical and can be employed for routine quality control of cinnarizine and domperidone maleate in combined dose tablet formulation.

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