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DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD FOR SIMULTANEOUS ESTIMATION OF CINNARIZINE AND DIMENHYDRINATE IN TABLET DOSAGE FORM

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Keywords:

Cinnarizine, Dimenhydrinate, RP-HPLC method, Validation

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ABSTRACT: A simple, rapid and precise reverse phase high performance liquid chromatographic method has been developed for simultaneous estimation of Cinnarizine and Dimenhydrinate in Tablet Dosage Form. Chromatography was performed on a Phenomenex Partisil ODS C_{18} (250 X 4.6 mm) 5µm column using Acetonitrile: Water (90:10) as a mobile phase. The detection of the synthetic mixture was carried out at 265 nm with a flow rate of 0.7 ml/min. The retention times were 4.3 and 5.8 minutes for Cinnarizine and Dimenhydrinate, respectively. Proposed method was validated as per ICH guidelines for linearity, accuracy, precision; specificity and robustness for estimation of Cinnarizine and Dimenhydrinate in Tablet Dosage Form and results were found to be satisfactory. The linearity of the method was excellent over a concentration range 20-100µg/ml for Cinnarizine and 40-200µg/ml for Dimenhydrinate. The correlation coefficient was 0.996 and 0.992 for Cinnarizine and Dimenhydrinate, respectively. The limit of detection was 1.62µg/mL and 2.62µg/mL for Cinnarizine and Dimenhydrinate, respectively. The limit of quantitation was 4.93µg/mL and 7.95µg/ml for Cinnarizine and Dimenhydrinate, respectively. The relative standard deviation values for repeatability, intraday precision and interday precision studies were less than 2 % and % recovery was 98 % to 102 % for both drugs. So the proposed method was found to be suitable for the routine estimation of Cinnarizine and Dimenhydrinate in Tablet Dosage Form.

INTRODUCTION: Chemicaly, Cinnarizine is known as 1-(diphenylmethyl)- 4 - (3-phenylprop – 2 – en - 1-yl) piperazine **(Figure 1)**. It is a drug derivative of piperazine, and characterized as an antihistamine and a calcium channel blocker, it is also known to promote cerebral blood flow, and so is used to treat cerebral apoplexy post-trauma cerebral symptoms, and cerebral arteriosclerosis. However, it is more commonly prescribed for nausea and vomiting due to motion sickness or vertigo.

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Dimenhydrinate, 8-chloro-1, 3-dimethyl-2, 6-dioxo-2, 3, 6, 7 – tetra Cinnaro-1H-purin-7-ide; [2(diphenylmethoxy) ethyl] dimethylazanium is used in the management of nausea and vomiting in the postoperative patient controlled analgesia. 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.

The fixed low-dose combination is effective, clinically beneficial, and well tolerated in patients with vestibular vertigo of central and/or peripheral origin. Literature review revealed that several spectroscopic and chromatographic methods have been reported for estimation of Cinnarizine alone and in combination with other drugs also for

Dimenhydrinate alone. However, no method is reported for simultaneous estimation of these two drugs by HPLC in combined dosage form.

MATERIALS AND METHODS:

Chemicals and reagents:

The reference samples of Cinna, Dimen were provided by Meridian Medicare Ltd. Himachal Pradesh and Chiral drugs Pvt. Ltd. Surat, Gujarat. Tablet used for analysis was ISOLAZINE (Label claim: Cinna 20mg, Dimen 40 mg) is procured from the local market. Acetonitrile, methanol, and water used were of HPLC grade. Ortho phosphoric acid used is of Analytical grade.

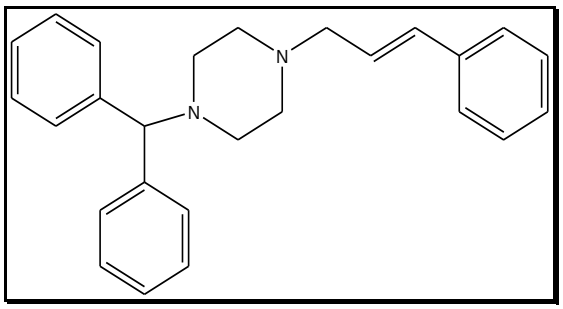
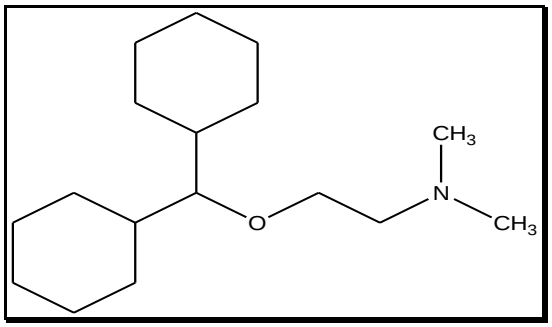


FIGURE 1: MOLECULAR STRUCTURE OF CINNARIZINE



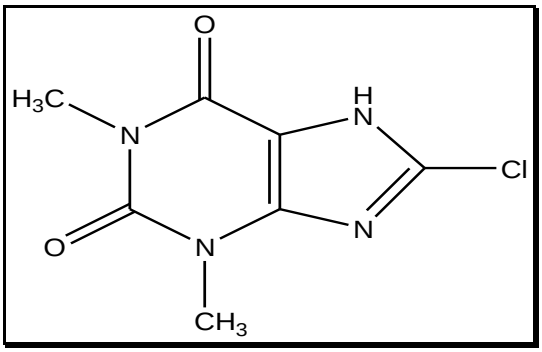


FIGURE 2: MOLECULAR STRUCTURE OF DIMENHYDRINATE

Instrument and chromatography condition:

The liquid chromatographic system consisted of Shimadzu, Pump (LC-10AT), fitted with UV-Visible detector (SPD-20A) with manual injector. The chromatogram was recorded using LC Solution software. HPLC separations were carried out on Phenomenex ODS C_{18} (250 × 4.6 mm) packed with 5 µ diameter particles. The mobile phase was a mixture of Acetonitrile and Water in the ratio of 90:10 v/v and pH adjusted to 2.4 using ortho phosphoric acid. pH of the aqueous phase was adjusted to 3 with orthophosphoric acid and filtered through 0.45µm membrane filter and degassed before use. The flow rate was 0.7 ml/ min. The detection wavelength was set at 265 nm. The injection volume was 20 µl.

Preparation of mobile phase:

Mixed a mixture of 900 ml of Acetonitrile (90%) and 100 ml water (10%) of HPLC grade, and degassed in ultrasonic water bath for 15 minutes, filtered through 0.45µm membrane filter then 2.4 pH is adjusted with OPA.

Diluent Preparation: Mobile phase is used as diluents.

Preparation of Standard Solution:

Stock solutions of standard drugs Cinna and Dimen were prepared by weighing accurately 20 mg of Cinna and 40 mg of Dimen into a 100 ml clean dry volumetric flask. About 70 ml of the mobile phase was added and sonicated to dissolve the drugs completely. The volume was made upto 100 ml with the mobile phase and filtered through 0.45 µm membrane filter. From the above prepared standard stock solution, 1 ml was taken to 10 ml volumetric flask and the volume was made up with the mobile phase to obtain a concentration of 20µg/ml and 40 µg/ml for Cinna and Dimen respectively.

Preparation of Sample Solution:

Twenty tablets of Vertizac were weighed and powdered. Powder weight equivalent to 20 mg of Cinna and 40 mg of Dimen was weighed and transferred into a 100 ml clean dry volumetric flask. About 70 ml of the mobile phase was added and sonicated to dissolve the drugs completely. The volume was made upto 100 ml with the mobile phase and filtered through 0.45 µm membrane filter. From the above prepared standard stock solution, 1 ml was taken to 10 ml volumetric flask and the volume was made up with the mobile phase

to obtain a concentration of 20µg/ml and 40µg/ml for Cinna and Dimen respectively.

Method Validation:

The proposed method was validated in compliance with ICH guidelines for linearity, accuracy, precision, specificity, robustness, and system suitability parameters by the following procedures.

Linearity:

Linearity of developed HPLC method was studied by obtaining calibration curves of Cinna, Dimen at six different concentration levels in triplicate ranging from 20-120 µg/ml for Cinna, and 40-240 µg/ml for Dimen. **Table 1** shows the linearity data of Cinna and Dimen. The linearity regression co-efficient (R2) values were found to be 0.996 and 0.992 for Cinna, Dimen each. Linearity equation obtained for Cinna, Dimen were y = 48024x – 76365, and y = 25282x – 81003 respectively. **Figure 3 and 4** shows calibration curves for Cinna, Dimen respectively. High level of correlation coefficient indicates good linearity.

TABLE 1: LINEARITY DATA OF CINNARIZINE, DIMENHYDRINATE

Cinnarizine		Dimenhydrinate	
Con. µg/ml	**Peak area**	**Con. µg/ml**	**Peak area**
20	297982	40	346137
40	1086682	80	1028370
60	1303486	120	2139540
80	3114097	160	3376873
100	4086682	200	4228370

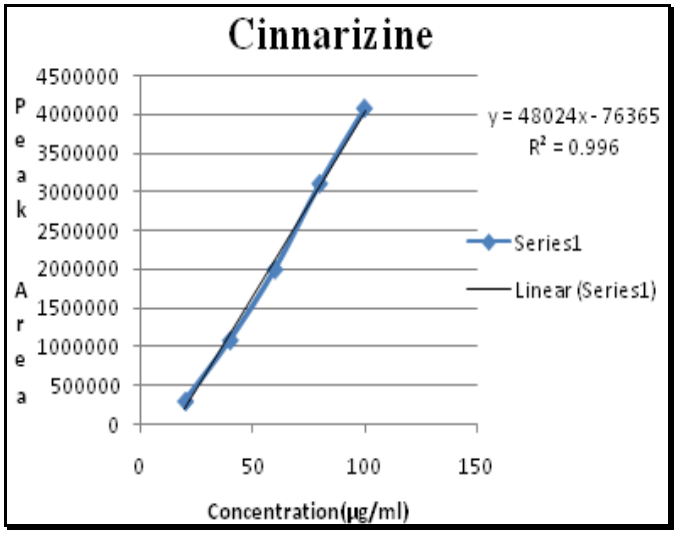


FIGURE 3: CALIBRATION CURVES FOR CINNA

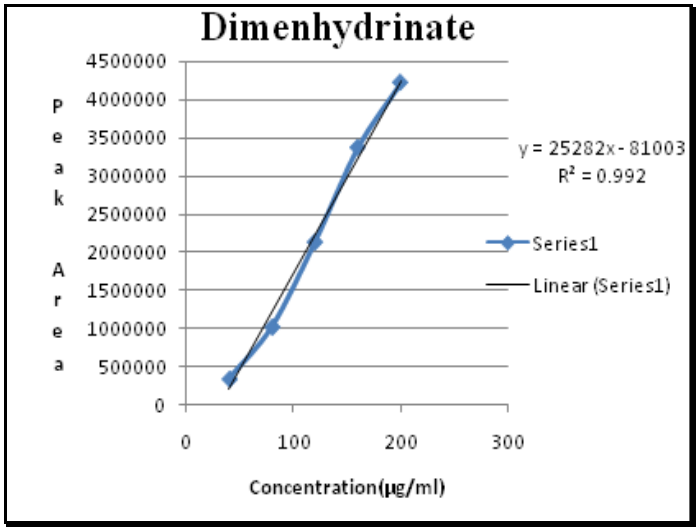


FIGURE 4: CALIBRATION CURVES FOR DIMEN

Accuracy:

The accuracy of the developed method was evaluated in triplicates by recovery studies at three different concentration levels of 50%, 100 %, and 150% for Cinna, Dimen respectively. Known amounts of standard drug concentrations were added to the sample and peak area was determined. The mean percentage recovery values are shown in **Table 2**. The mean recovery of the drugs was found to be in the range of 99- 101% indicating a high degree of accuracy for the developed method.

TABLE 2: ACCURACY RESULTS

Drug	Conc.	Amt. present	Amt. spiked	Conc. After spiking	% Mean Recovery
Cinna	50%	30µg/ml	15 µg/ml	45 µg/ml	98.33
	100%	30 µg/ml	30 µg/ml	60 µg/ml	99.85
	150%	30 µg/ml	45 µg/ml	75 µg/ml	99.97
Dimen	50%	60 µg/ml	30 µg/ml	90 µg/ml	99.63
	100%	60 µg/ml	60 µg/ml	120 µg/ml	99.91
	150%	60 µg/ml	90 µg/ml	150 µg/ml	99.88

Precision:

The precision at 20 % concentration of the assay method was evaluated by six replicate injections and measurement of peak areas by determining the % RSD of Cinna, Dimen. The calculated values of % RSD for Cinna and Dimen are mentioned in **Table 3**. The results indicated a high degree of repeatability.

TABLE 3: RESULTS FOR PRECISION

	Cinnarizine		Dimenhydrinate	
Injection	RT	Area	RT	Area
1	4.3	297982	5.8	3461378
2	4.2	295763	5.8	3452469
3	4.3	293991	5.9	3462378
4	4.3	296853	5.8	3441253
5	4.2	294692	5.8	3471457
Average		2958562		3457787
STD		208626.8		18224
%RSD		0.52		0.55

Specificity:

Chromatogram of only diluent was taken to check the interference of diluent with the peaks of Cinna and Dimen at the retention time of respective drugs. There was no peak detected at retention time of Cinna 4.3 min and Dimen 5.8 min. so, proposed method is specific in nature.

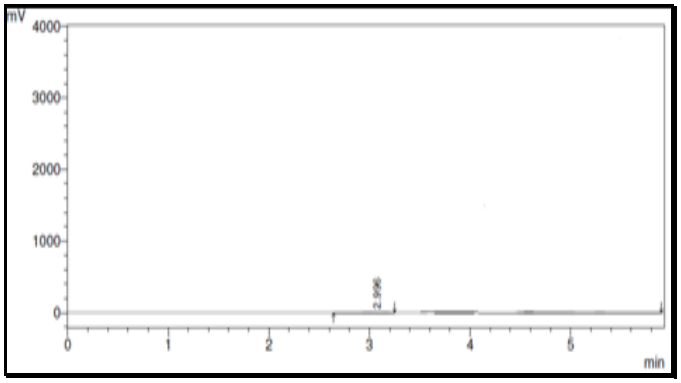


FIGURE 5: CHROMATOGRAM OF DILUENT

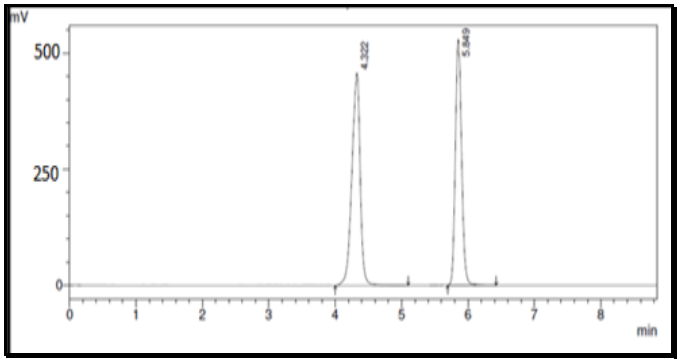


FIGURE 6: CHROMATOGRAM SHOWING PEAKS OF CINNARIZINE AND DIMENHYDRINATE

LOD and LOQ:

LOD and LOQ for Cinna, Dimen by this method were evaluated on the basis of signal-to-noise ratio method described in ICH guidelines. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit. A typical signal-to-noise ratio required for LOQ is 10:1.Using the proposed HPLC method, the LOD and LOQ values were calculated and are given in **Table 4**.

TABLE 4: LOD AND LOQ VALUES OF CINNA AND DIMEN

	Cinnarizine	Dimenhydrinate
LOD µg/ml		
LOQ µg/ml		

Robustness:

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in the optimized parameters were made in chromatographic conditions like of flow rate and wavelength. The effect of change in flow rate and wavelength of detection on retention time and tailing factor were examined. The values obtained are mentioned in **Table 5**. The method was found to be unaffected by the small changes like ± 0.2 ml/min in flow-rate of mobile phase and ± 2 nm in detection wavelength.

TABLE 5: RESULTS OF ROBUSTNESS BY VARIATIONS IN FLOW RATE AND WAVELENGTH

Parameters	**Value**	**Cinnarizine**		**Dimenhydrinate**	
		RT	**TF**	**RT**	**TF**
Flow rate	0.5ml/min	3.0	0.93	4.0	1.17
	1ml/min	5.0	0.99	5.8	1.18
Wavelength	260nm	3.2	1.0	4.0	1.2
	270nm	4.7	0.63	5.8	1.15

System suitability:

Six replicate of sample containing Cinna, Dimen were given to evaluate equipment, electronics, analytical operations and samples suitability. Parameters calculated for system suitability were %RSD of retention time and area, number of theoretical plates and Resolution. The results are given in **Table 6**.

TABLE 6: SYSTEM SUITABILITY RESULTS FOR CINNA AND DIMEN.

S. No	**Parameters**	**Cinnarizine**	**Dimenhydrinate**
1	**Theoretical plates**	5305.591	16463.92
2	**Tailing factor**	0.87	1.18
3	**Resolution**		7.27
4	**Relative retention time (min)**	4.3	5.8

RESULT AND DISCUSSION:

Optimized chromatography condition:

Chromatographic conditions were screened for mobile phase composition, mobile phase proportion, pH and flow rate Finally, mobile phase of Acetonitrile: Water (2.4 p^H) in the ratio of 90:10 v/v was optimized to give symmetric peak with short runtime at UV detection wavelength of 265 nm and flow rate at 0.7ml/min was found to be appropriate with adequate separation between the two drugs. Chromatogram of Cinna, Dimen at optimized chromatographic condition was recorded, the runtime was 4 min and the retention times of Cinna, Dimen were found to be 4.3 and 5.8 min as shown in **Figure 5, 6.**

Assay:

The proposed method was applied for the analysis of tablet sample of Vertizac and the results of the assay were obtained within the specification limit. From the peak area obtained for Cinna, Dimen, the amount of the drug in the sample was calculated and was found to be 99.64% for Cinna, and 99.01% for Dimen.

CONCLUSION: The proposed HPLC method was found to be economical, simple, sensitive, accurate, precise, specific and robust and can be used for the routine quality control analysis of Cinna, Dimen in bulk as well as in tablet formulation.

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