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Simultaneous Spectrophotometric Estimation of Cinnarizine and Domperidone maleate in Tablet Dosage Form.

Sohan S. Chitlange[1] *, Monesh B. Nikumbh[1], Ramesh D. Bhusal[1], Navin K. Khare[2]

Department of Quality Assurance Technique.

Center for Innovative Pharmaceutical Education, Research and Development.

[1] Padmashri Dr. D.Y. Patil Institute of Pharmaceutical sciences and Research.

Sant Tukaram Nagar, Pimpri, Pune-411018, Maharashtra, INDIA.

[2] Hindustan Antibiotics Ltd, Pimpri, Pune, Maharashtra, INDIA.

*E-Mail: sohanchitlange@rediffmail.com

Abstract: Two U.V. spectrophotometric methods for the simultaneous estimation of Cinnarizine (CINN) and Domperidone maleate (DOM) in tablet were developed in present work. The first method A is Vierodt's Method (Simultaneous Equation Method); the sampling wavelengths selected are 251 nm (λ_{max} for Cinnarizine) and 287 nm (λ_{max} for Domperidone maleate). The second; method B involves Multicomponent Mode of analysis; the sampling wavelengths selected are 251 nm (λ_{max} for Cinnarizine) and 287 nm (λ_{max} for Domperidone maleate) respectively. Both the methods were found linear between concentration ranges of 4-24 µg/ml and 3-18 µg/ml for Cinnarizine and Domperidone maleate respectively. The accuracy and precision of the methods were determined and validated stastically which showed no significant difference between the results obtained by these methods. The proposed methods are highly sensitive, precise and accurate and therefore can be used for its intended purpose.

Key Words: Cinnarizine, Domperidone maleate, Vierodt's Method (Simultaneous Equation Method) and Multicomponent Mode Method.

Introduction

Cinnarizine (CINN) is chemically, 1-benzhydryl-4-cinnamyl-piperazine.[1-3] which is mainly used for the control of nausea and vomiting due to motion sickness.[4] It acts by interfering with the signal transmission between vestibular apparatus of the inner ear and the vomiting centre of the hypothalamus. The disparity of signal processing between inner ear motion receptors and the visual senses is abolished, so that the confusion of brain whether the individual is moving or standing is reduced. Domperidone maleate (DOM) is chemically, 5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl] piperidin-4-yl] -1,3-dihydro-2H-benzimidazol-2-onehydrogen (Z)-butenedioate.[1-3] used in the treatment of nausea and vomiting. Domperidone is a first choice antiemetic in some countries. Domperidone blocks the action of dopamine. It has strong affinities for the D_2 and D_3 dopamine receptors. which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which, among others, regulates nausea and vomiting[4]. Domperidone alone or in combination with other drugs is reported to be estimated by U.V. spectrophotometry[9], RP-HPLC[11] ,where as to our knowledge not single method are reported for estimation of Cinnarizine and Domperidone maleate in combination therefore , in present work, a successful attempt has been made to estimate both drug simultaneously, The proposed method

were optimized and validated as per ICH guidelines[12].

Materials and methods

Instrumentation

A double-beam Shimadzu UV-Visible spectrophotometer, model 1700 was used with spectral bandwidth of 2 nm, wavelength accuracy ± 0.5 nm and pair of 1 cm matched quartz cell was used to measure absorbance of solution. A Denver electronic analytical balance was used for weighing the sample. An Equitron digital ultrasonic cleaner was used for sonicating the tablet sample solution.

Reagents and Chemicals

Pure Cinnarizine and Domperidone maleate were kindly gifted by Micro Lab, Bangalore, India. Commercial tablets (VERTIDOM, Geno pharmaceutical Ltd, Goa) containing Cinnarizine (20 mg) and Domperidone maleate (15 mg) were used for the study. Methanol were used of analytical grade (Merck, Mumbai, India)

Preparation of Standard Stock Solution

Standard stock solution containing CINN and DOM were prepared by accurately weighed quantity of Cinnarizine (10 mg) and Domperidone maleate (10 mg) were transferred to two separate 100 ml volumetric flask. Then diluted to the mark with methanol. (stock solution 100 µg/ml)

Method A

Vierodt's Method (Simultaneous Equation Method)

For the Vierodt's Method (Simultaneous Equation Method), for the selection of analytical wavelength, solution of Cinnarizine (12 µg/ml) and Domperidone (9 µg/ml) were prepared separately by appropriate dilution of standard stock solution (100 µg/ml) with methanol and scanned in the spectrum mode from 400-200 nm. Cinnarizine has λ_{max} of 251 nm, and Domperidone maleate has λ_{max} of 287 nm were selected as the two sampling wavelengths. Cinnarizine and Domperidone maleate exhibited linearity with absorbances in the range of 4-24 µg/ml and 3-18 µg/ml at their respective selected wavelengths and calibration curves were plotted. Co-efficient of correlation was found to be 0.999 and 0.998 for CINN and DOM respectively. Two simultaneous equations (in two variables C_1 and C_2) formed using absorptivity coefficient value.

$A_1 = (0.0550)\ C_1 + (0.0075)\ C_2$ ..... (i)

$A_2 = (0.0029)\ C_1 + (0.0232)\ C_2$ ..... (ii)

Where C_1 and C_2 are the concentrations of CINN and DOM measured in µg/ml, in sample solutions. A_1 and A_2 are the absorbance of mixture at selected wavelengths i.e. 251 nm and 287 nm.

By applying the Cramer's rule to equation (i) and (ii), the concentration of C_{CINN} and C_{DOM} can be obtained as follows,

$$C_{CINN} = \frac{\mathbf{A_2\ ay_1 - A_1\ ay_2}}{\mathbf{ax_2\ ay_1 - ax_1\ ay_2}} \quad \text{Eq. (iii)}$$

$$C_{DOM} = \frac{\mathbf{A_1\ ax_2 - A_2\ ax_1}}{\mathbf{ax_2\ ay_1 - ax_1\ ay_2}} \quad \text{Eq.(iv)}$$

ax_1 and ax_2 are absorptivities of CINN at λ_1 and λ_2 and ay_1 and ay_2 are absorptivities of DOM at λ_1 and λ_2 respectively.

Method B

Multicomponent Mode Method

For the analysis of CINN and DOM by multicomponent method, the multicomponent

mode of the UV visible spectrophotometer was used. In this method six mixed standard solution with concentration of Cinnarizine and Domperidone maleate in the ratio of 12:9 µg/ml were prepared in methanol. All the standard solution were scanned over the range of 400-200 nm at the selected sampling wavelengths. For multicomponent method of analysis using two working wavelengths 251 nm and 287 nm selected as wavelengths for CINN and DOM respectively. The data from these scans was used to determine the concentrations of two drugs in tablet sample solutions.

Assay of tablet Formulation by method A and B.

For estimation of drugs in the commercial formulations, twenty tablets were weighed and average weigh was calculated. The tablets were crushed to obtained fine powder. Powder equivalent to 10 mg of CINN and 7.5 mg DOM was transferred in to 100 ml volumetric flask and dissolved in 50 ml methanol and sonicated for 15 min and the volume was then made up to the mark with methanol. The resulting solution was then filtered through Whatmann filter paper No.41 and diluted further to get approximate concentration of 12 µg/ml of CINN and 9 µg/ml of DOM. In method A, the concentration of both Cinnarizine and Domperidone maleate were determined by measuring absorbance of sample solutions at 251 nm (λ_{max} for Cinnarizine) and 287 nm (λ_{max} for Domperidone maleate). The concentrations of each drug in sample solutions were calculated using equations (iii) and (iv) for the Vierodt's Method (Simultaneous Equation Method). For method B, the same tablet solutions were subjected to analysis in multicomponent mode of instrument, the concentration of both Cinnarizine and Domperidone maleate determined by analysis of spectral data of sample solution with reference to mixed standard at 251 nm(λ_{max} for Cinnarizine) and 287 nm(λ_{max} for Domperidone maleate). Result of tablet analysis are shown in (Table.1)

Validation

The proposed methods were validated as per ICH guidelines. [12]

Linearity

The linearity of measurement was evaluated by analysing different concentration of the standard solution of Cinnarizine and Domperidone maleate. For both the method Beer-Lambert's concentration range was found to be 4-24 µg/ml and 3-18 µg/ml for Cinnarizine and Domperidone maleate respectively.

Precision

The reproducibility of proposed method were determined by performing tablet assay at different time interval on same day (Intra-day) and on different days (Inter-day) assay precision.

Accuracy

The accuracy of the proposed methods was determined by standard addition method performing recovery studies at three different levels (80%, 100% and 120%) of the test concentration. The result of recovery studies were satisfactory and are presented in (table.3)

Results and Discussion

For both methods linearity was observed in concentration range of 4-24 µg/ml and 3-18 µg/ml for Cinnarizine and Domperidone maleate respectively. Commercial formulations containing Cinnarizine and Domperidone maleate were analyzed by the proposed methods. The proposed methods were validated as per ICH guidelines for

linearity, repeatability, intermediate precision (inter-day and intra-day precision studies) as shown in (Table.1). Six replicate analysis of formulation were carried out and mean assay value was found to be in the range of 100 to 100.45% shown in (Table.2). The accuracy of proposed method was determined by recovery studies. Pure Cinnarizine and Domperidone maleate was added to the tablet powder at three levels viz 80, 100, 120% three replicate analysis were carried out at each level. The mean % recoveries of CINN and DOM were found to be in the range of 99.44% and 101.02 % for both methods shown in (Table.3).

Conclusion

Two simple U.V. spectrophotometric methods Vierodt's Method (Simultaneous Equation Method) and Multicomponent Mode Method were developed for simultaneous analysis of CINN and DOM. The standard deviation, RSD calculated for the methods are low, indicating high degree of precision of the methods. The % recovery performed show the high degree of accuracy of the proposed methods.

Hence, it can be concluded that the developed spectrophotometric methods are simple, rapid, precise, accurate and selective can be employed for the routine estimation of Cinnarizine and Domperidone maleate in marketed formulation. Both the method were validated as per ICH guidelines.

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Parameters	CINN		DOM	
	Method-A	Method-B	Method-A	Method-B
Working wavelengths	251 nm	251 nm	287 nm	287 nm
Beer-Lamberts Law range (µg/ml)	4-24	4-24	3-18	3-18
Precision*				
Interday (%RSD)	0.1501	0.2456	0.1760	0.2004
Intraday (%RSD)	0.0564	0.1623	0.2322	0.2119
Regression Values:				
I. Slope	0.056	0.051	0.022	0.013
II. Correlation Coefficient (r^2)	0.999	0.998	0.998	0.998

Table 1: Optical Characteristics and Validation Data of CINN and DOM.

* average of Six estimations.

Method A – Vierodt's Method (Simultaneous Equation Method)

Method B – Multicomponent Mode Method.

Method	Component	Labeled Drug (mg)	Amount obtained (mg)	% Amount Found	S.D.*	% R.S.D.*
A	CINN	20	20.08	100.45	0.1949	1.59
	DOM	15	15.02	100.16	0.1673	1.85
B	CINN	20	20.00	100.02	0.0681	0.56
	DOM	15	15.00	100.00	0.0466	0.51

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Table 2: Statistical Validation Data of Tablet Formulation

Results of Commercial Sample Analysis

* average of Six estimations.

S.D.* = Standard deviation, n= 6, RSD= Relative standard deviation.

Table 3: Statistical Validation of Recovery Studies

Level of % Recovery	Component	Method A		Method B	
		Recovery*	±S.D.	Recovery*	±S.D.
80	CINN	100.46	0.5907	100.37	0.8270
	DOM	100.24	0.2264	100.61	0.2954
100	CINN	100.16	0.1880	100.41	0.4989
	DOM	100.33	0.6698	99.44	0.3139
120	CINN	100.75	0.5002	99.62	0.4244
	DOM	100.50	0.3356	101.02	0.3009

* average of three estimations at each level of recovery.

The % drug obtained and % recovery value are mean of three determinations.

S.D.* = Standard deviation, n = 3, RSD = Relative standard deviation.

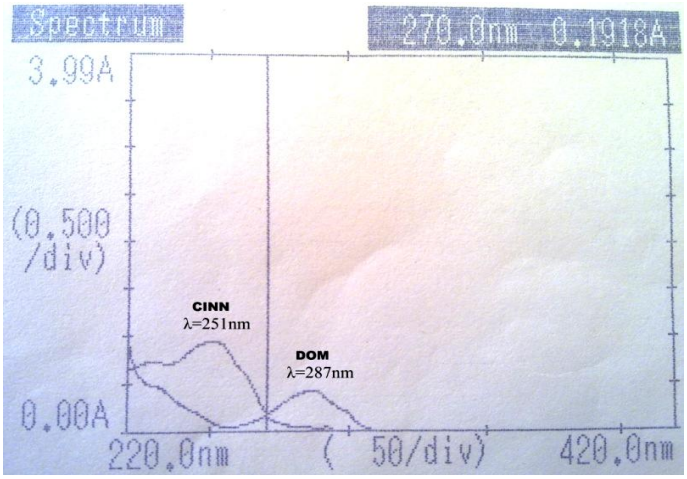

Fig.1: Overlain Spectra of CINN and DOM in Vierodt's Method (Simultaneous Equation Method).