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Research Article

Significance and Applicability of QBD Approach in the UV-VIS Spectrophotometric Estimation of Cinnarizine and Dimenhydinate from the Combined Dosage Form

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ABSTRACT

Approach of Quality by design for the development of various pharmaceutical processes including analytical methods is a monumental and acceptable in the built of quality assurance. QbD approach was applied and analytical method-based UV-VIS spectrophotometry was developed for the simultaneous estimation of Cinnarizine (CIN) and Dimenhydrinate (DIM) from the combined formulations. Appropriately selected solvent 0.1 N HCl, was utilised and 253 nm 276 nm was the wavelength for absorbance measurement of CIN and DIM respectively. Effect of input variables on spectrum characteristics were studied for selection of critical parameters and developed method was validated as per ICH Q 2 R1 regulatory guidelines. Linearity of both the drugs was ascertained over the conc range 1-24 and 1-36 µg/ml for CIN and DIM respectively. The percentage of assay was found 101.91% and 98.34% for CIN and DIM respectively, data of accuracy was found 0.12664-0.33731 for CIN and 0.24901-0.72698 for DIM; and % RSD in precision study 0.28368 for CIN and 0.15131 for DIM was found and all statistical values were within the acceptable limit. The developed method is rigid, robust and efficient for the estimation of CIN and DIM, which are in 1:2 proportionate in the composition of dosage form. QbD was applied to build rigid robust method through risk assessment at early stage and defining the design space at the later stage.

Keywords: QbD, Cinnarizine, Dimenhydrinate, ICH, simultaneous equation, multicomponent method.

INTRODUCTION

Cinnarizine (CIN) chemically (ϵ) – 1-(diphenylmethyl) - 4- (3-phenylprop-2-enyl) piperazine [1, 2] is an antihistaminic, sedative and has calcium channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Meniere's disease and other vestibular disorders and for the prevention and treatment of motion sickness [3].

Literature survey revealed that various analytical methods have been reported for estimation of CIN along with DIM or other drugs such as chromatographic HPLC methods lonely [4], along with DIM [5-8], with domperidone [9-12], with paracetamol [13,14], bio-analytical methods HPLC [15], bioanalytical gas chromatography [16], LC-MS/MS [17], HPTLC methods [18-20], a lonely UV spectroscopic methods [21], along with DIM [22-27], along with domperidone [28,29], UV spectrophotometric method with other drugs [30,31] and review article of CIN [32].

Dimenhydrinate is Diphenhydramine 8-chlorotheophylline chemically [2-(diphenylmethoxy)-N, N-dimethylethanamine] (8-chloro-1, 3-dimethyl-3, 7-dihydro-1H-purine-2, 6-Dione) [1, 2], a monoethanolamine derivative, sedative antihistamine. It also has antimuscarinic and significant sedative effect; and mainly used as antiemetic in the prevention and treatment of motion sickness, also used symptomatic treatment of nausea and vertigo [3].

Also, various analytical methods have been reported for estimation of DIM such as chromatographic HPLC methods lonely[33], along with CIN chromatographic[34,35], bio-analytical methods HPLC[36], UV spectroscopic methods with CIN [37, 38], HPTLC along with CIN [39, 40].

Cinnarizine (CIN) and Dimenhydrinate (DIM) both these drugs are official in British Pharmacopoeia [41] and CIN is official in Indian Pharmacopoeia [2]. Chemical structure of both drugs is shown in (Figure 1).

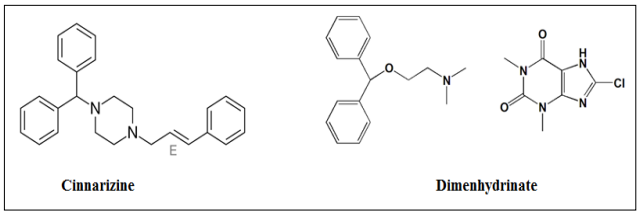

Figure 1: Chemical structure of Drug molecule

AQbD based analytical method can be beneficial in the development of suitable, robust, low cost and eco-friendly method which is applicable at any stage of the lifecycle of the product. Also, some regulatory guidelines have mentioned flexibility of changing analytical method without revalidation if the AQbD approach has been implemented during analytical method development [42].

The first stage of AQbD approach is to fix an analytical target profile (ATP) for the method. ATP defines the goal of the analytical method development process and it is the sign of method performance [43, 44]. For analytical method validation ICH Q2 (R1) [45-46] has given various method performance characteristics for an analytical method. Thus, a QbD based UV spectrophotometric was developed,

QbD approach was implemented with the study of the effect of method input variables on spectral shape, intensity of absorbance, and absorbance maxima λ_{max} and critical parameters were selected for the proposed method and method was validated as per ICH guidelines Q2 (R1) [47-48].

MATERIALS AND METHODS

Instrumentation

Analysis was performed with a Shimadzu Double beam UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was utilised for weighing and for degassing the solutions Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

Reagents and Chemicals

Pharmaceutically pure sample of CIN was procured from Yarrow chem products, Mumbai and DIM was procured from Medinex Lab Gujarat as a gift samples and the commercial formulation Cinzan plus containing Cinnarizine 20 mg and Dimenhydrinate 40 mg was procured from local market.

AQbD approach application in method development

For AQbD approach Ishikawa diagram was studied and shows the influence of input variable parameters on spectrophotometric analytical method performance. The applied input variable parameters are shown in figure 2.

Solvent selection

CIN is partially insoluble in water and freely soluble in alcohol, methylene chloride whereas DIM is slightly soluble in water, freely soluble in alcohol. Although the solubility of the procured drugs was studied in alcohol 90%, 0.1 N HCl and 0.1 N NaOH separately; and each solution with known conc of analyte were scanned in UV range of 215 nm to 400 nm against respective blank solution. Recorded spectra in each solvent were overlain with the help of instruments software and are shown in Figure 3. It was found that suitable solvent is 0.1 N HCl with respect to well absorbance, low cost, robust and precise in producing result.

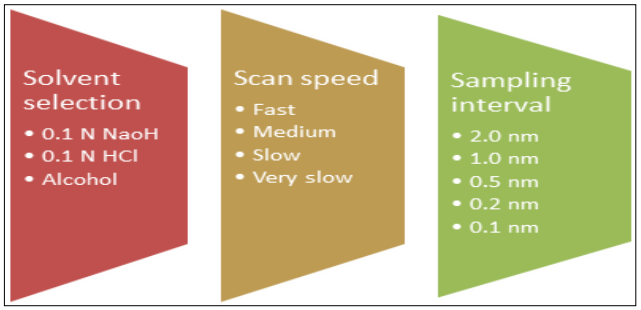

Figure 2: Diagram showing the input variable parameters applied to set spectrophotometric method performance characteristics

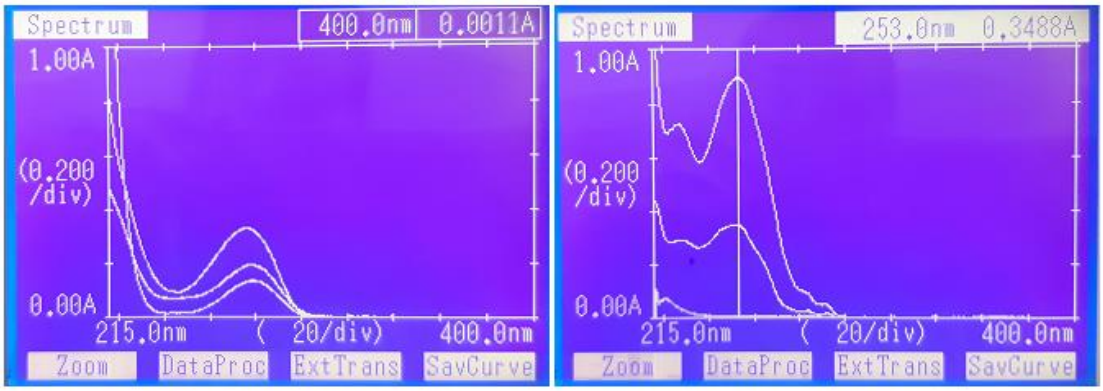

Figure 3: Overlain spectra of DIM and CIN in solvents

Preparation of stock solutions and standard solutions

10 mg each of drug CIN and DIM were separately and accurately weighed; and transferred into separate 25 ml volumetric flask. Dissolved into 0.1 N HCl and volume was made to 25 ml with solvent. Subsequent standard solution of each drug with conc 10µg/ml was prepared by diluting aliquot 0.5 ml of stock solution to 10 ml capacity volumetric flask.

Selection of wavelength and conc range

From UV spectra it was found that CIN has measurable absorbance at 253 nm and slight interference was observed by DIM; similarly DIM has maximum absorbance at 276 nm and less interference by CIN was accounted shown in (Figure 4). Chemometric method using simultaneous equation method was applied and which was reasonable remedy to overcome interference at each other's absorbance. From the nature of spectra working conc range 1 to 24 µg/ml for CIN and 1 to 36 µg/ml for DIM was selected in 0.1 N HCl. Also combined drug solution was prepared simulated to marketed formulation. Selected critical parameters based upon above discussed observations were listed in Table No 1 and by using these; method was validated as per ICH guidelines and by analysing marketed preparations.

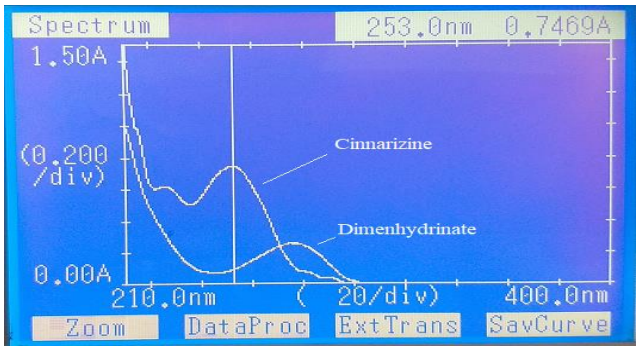

Figure 4: Overlain spectra of CIN and DIM in 0.1 N HCl

Experimental Method for estimation

From the overlain spectra it was found that many approaches of multicomponent analysis are applicable for estimation of both these drugs. Among of this simultaneous equation method and multicomponent method was selected for estimation of both these drugs from the combined dosage form.

Method-I: Simultaneous equation method

CIN was shown absorbance at (λ_{max}) 253 nm and DIM has maximum absorbance (λ_{max}) at 276 nm. The wavelength 253 and 276 nm was considered as 1 and 2 respectively. The equation A= abc was applied for x (CIN) and y (DIM) determination. On rearranging the 2 generated equations, the conc of x and y was calculated by following formula. Working standard solutions of CIN and DIM containing 10 µg /ml conc were separately prepared and used for the method.

$$Cx = \frac{A2\ .ay1 - \ A1.ay2}{ax2.ay1 - \ ax1.ay2}$$

$$Cy = \frac{A1\ .ax2 - \ A2.ax1}{ax2.ay1 - \ ax1.ay2}$$

Where CX and Cy = Conc of CIN and DIM in sample solution

A_1 and A_2 = absorbance of sample solution at 1 and 2 wavelength

ay_1 and ay_2 = absorptivity of DIM at 1 and 2 wavelength of standard solution

ax_1 and ax_2 = absorptivity of CIN at 1 and 2 wavelength of standard solution

Method-II: Multicomponent method

After the interpretation of spectra both drugs have less interference at another drugs λ_{max}, hence wavelength 253 nm and 276 nm selected. The characteristics of spectra was guided that the use of mixed standards was found appropriate than the use of pure standards. Mixed standards containing different proportions of both the drugs were rationally experimented keeping in view the conc of the drugs in the available formulations. Six mixed standards were selected for quantitative analysis shown in Table 1.

Table 1: Selected critical parameters for UV-VIS analytical method of CIN and DIM

Parameter	Selected variables for simultaneous equation method	
	CIN	DIM
Wavelength	253	276
Solvent	0.1 N HCl	0.1 N HCl
Scan speed	Fast	Fast
Sampling interval	0.5 nm	0.5 nm

Selected Mixed standard solutions for multicomponent method						
Standard No and conc of drug	1	2	3	4	5	6
Conc of CIN in µg/ml	0	4	8	12	16	20
Conc of DIM in µg/ml	20	16	12	8	4	0

Sample solutions were prepared in the CIN: DIM ratio of 1: 4, 2: 3, 3: 2, 4: 1 and sampling wavelength and conc.of each drug in the six mixed standards were provided to the instrument using multicomponent mode of the instrument. Subsequently all the mixed standards were scanned in the range of 400 to 210 nm. The instrument's multicomponent mode collected and computed spectral data from the mixed standards employing matrix equations; and used for quantitative analysis of the samples. The conc of each of the drug in the sample solutions were computed and printed out by the instrument.

Validation of the Method

Selected critical parameters should meet the performance characteristics of the analytical method so as to attain analytical target profile of the method. An ICH guideline Q2 R1 was applied to study methods performance with critical parameters in order to implement AQbD approach. The method was validated as per ICH guidelines

System suitability

System suitability is studied to demonstrate the suitability of the developed procedure under consideration for the analytical method. Six replicates of working standard solutions with conc 10 µg/ml each of CIN and DIM were prepared separately and absorbance was recorded, SD and % RSD of the response was calculated.

Linearity

The linearity of an analytical method is its ability to obtain response i.e. absorbance which is directly proportional to the conc of analyte. series of working standard solutions were prepared in conc. range of 1 -24 µg/ml for CIN and 1-36 µg/ml for DIM and scanned in 210 to 400 nm range in spectrum mode of the spectrophotometer, absorbance of the standard solutions were recorded at 253 for CIN and 276 nm for DIM in spectrum order. Microsoft office excel

software tool was used to obtain the standard regression curve and its analysis as slope, intercept, and correlation coefficient.

Assay of formulation

Assay was carried out by proposed methods and assay was validated by statistical parameters.

Estimation of formulations by simultaneous equation method

Twenty tablets were weighed, and powdered; tablet powder equivalent to 10 mg CIN and 20 mg DIM was weighed and transferred into 50 ml volumetric flask. Dissolved into 0.1 N HCl and volume was made to 50 ml with solvent. Solution was filtered through whatman filter paper and aliquots of solution were diluted to obtain tablet solution. Solution was scanned in the range of 210 to 400 nm to obtain absorbance of tablet solution at 253 and 276 nm in spectrum order. Obtained absorbance was utilised to estimate unknown conc of formulation; and results are statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Estimation of formulations by Multicomponent method

Above prepared tablet Solution was scanned in 210 to 400 nm range and conc of each of the drug component in the tablet solution was obtained in Multicomponent method. Obtained results are statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Accuracy and Precision

The accuracy of an analytical method expresses the closeness of an agreement between test result and true result. Accuracy study was performed by recovery study i.e. standard addition method; diluted standard solutions of CIN and DIM were prepared and standard solutions added in 80,100 and 120% proportionate to the tablet solution. Three replicates at each of these three levels were prepared and measured and % of conc, SD and RSD of replicates were calculated.

The precision study was carried out by performing assay of tablet six times; also the reproducibility in result was studied by interday and intraday precision.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of CIN and DIM by the proposed method were determined using calibration graph method and calculated as 3.3σ/s and 10 σ/s for LOD and LOQ respectively. σ is the standard deviation of calibration curve and s is the slope of regression line.

Robustness and Ruggedness

It is measure of capacity of analytical procedure to remain unaffected by small but deliberate variations in method parameter.

RESULTS AND DISCUSSION

Multicomponent formulations are beneficial due to greater patient acceptability, increased potency, multiple actions and fewer side effects and so getting significance [49]. Method development comprises numerous steps of which solvent selection, method for measurement selection are significant one. Uses of aqueous solvents, eco-friendly solvents like hydrotropic have got remarkable weightage due to low cost, readily available and environmentally sound. Drugs underlying analysis must have appreciable solubility in the selected solvent. Chemical structure of the drug and physico-chemical properties available in the literature guides about use of appropriate solvent in the method.

System Suitability

The absorbances of six replicates of standard solutions (10µg/ml) are reported in Table 2. The SD and % RSD was found for CIN and DIM and meets the system suitability requirements indicates method was suitable for analysis.

Table 2: System suitability study of CIN and DIM

Sr No	Conc in µg/ml	Absorbance of CIN	Absorbance of DIM
1	10 µg/ml	0.7751	0.3456
2	10 µg/ml	0.7723	0.3481
3	10 µg/ml	0.7693	0.3519
4	10 µg/ml	0.7761	0.3678
5	10 µg/ml	0.7825	0.3518
6	10 µg/ml	0.7811	0.3686
SD		0.46421	0.91488

Linearity

The calibration curve of both drugs was found to be linear in the conc range of 1-24 µg/ml for CIN and 1-36 µg/ml for DIM as shown in Figure 5. The regression equation of line and its parameters slope, r^2 value and intercept are tabulated in Table 3, which proved the linear relationship between conc and obtained response.

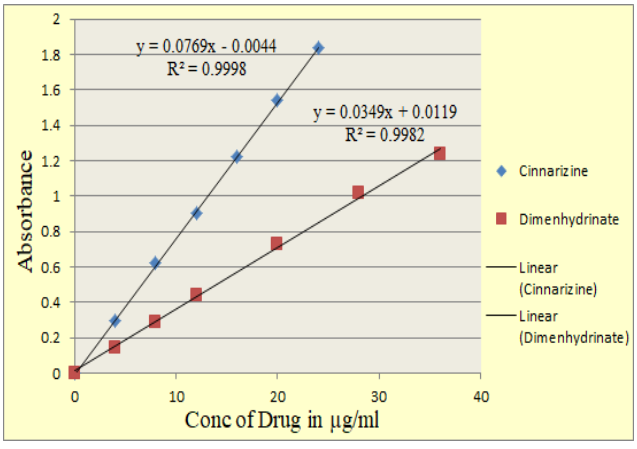

Figure 5: Calibration curve of CIN and DIM in 0.1 N HCl Solvent

Table 3: Parameters of regression equation obtained in Microsoft excel

Parameters	CIN	DIM
Detection wavelength	253	276
Beer's law limit (µg/ml)	1 – 24 µg/ml	1 – 36 µg/ml
Correlation coefficient (r^2)	0.9998	0.9998
Regression equation (y = mx + c)	Y = 0.0769 X - 0.0044	Y = 0.0349 X + 0.0119

Assay

The assay was carried out by both the methods. The overlain spectra obtained in method II was shown in Fig No 6, the spectra of formulation by method I and II was shown in Figure 6. The assay of formulation was carried out by proposed method and calculated % of nominal conc and RSD was found within acceptable limits are summarized in Table 4. The results indicated applicability of the method for estimation of formulation.

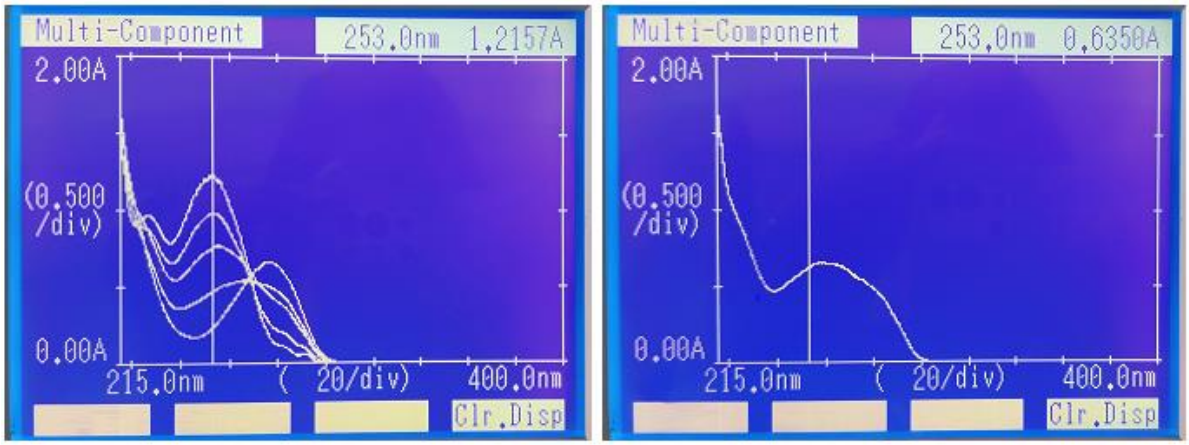

Figure 6: Overlain spectra of CIN and DIM in multicomponent mode and formulation spectra

Table 4: Results of assay of formulation by proposed method

Formulation	Drug	Label Claim (mg/Tablet; n=6)	Amount found/mg	Drug Content %	Std Deviation	% RSD
Method-I	CIN	20 mg	20.38	101.912 %	1.25384	1.34265
	DIM	40 mg	39.33	98.343 %	3.21128	3.26538
Method-II	CIN	20 mg	19.68	98.401%	0.20770	0.21097
	DIM	40 mg	40.145	100.362%	0.54616	0.54418

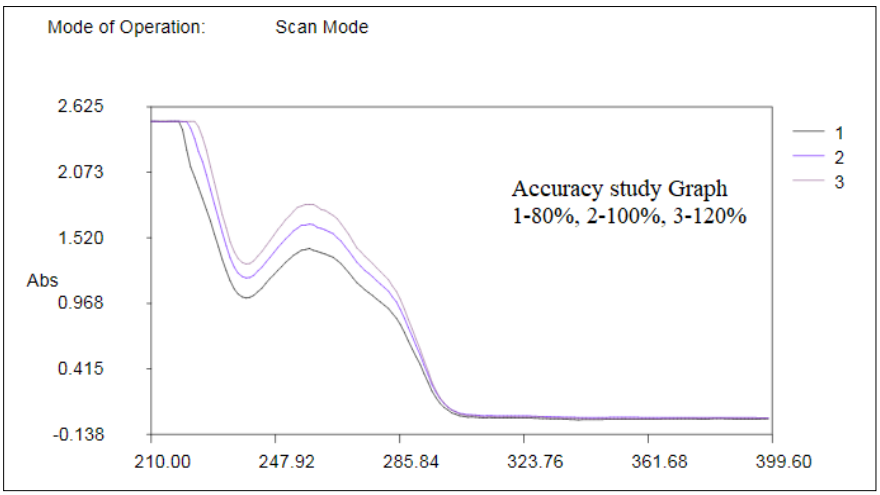

Figure 7: Overlaid Spectra of Accuracy study

Table 5: Results of accuracy, precision obtained in Method-I, Method-II and LOD, LOQ

Sr. No.	Parameter	Level of study	Drug Name	S.D.	RSD
1	Precision Method - I	Intraday Precision	CIN	0.28001	0.28368
			DIM	0.15182	0.15131
		Interday precision	CIN	0.51804	0.45556
			DIM	0.13097	0.14797
2	Accuracy study of CIN and DIM Method - I	80%	CIN	0.33721	0.26562
		100%		0.12664	0.10677
		120%		0.28121	0.25261
		80%	DIM	0.24901	0.20822
		100%		0.72698	0.55288
		120%		0.53305	0.40085
Results of accuracy and precision obtained in Method-II					
3	Precision Method -II	Intraday Precision	CIN	0.50025	0.50573
			DIM	0.45088	0.46014
		Interday precision	CIN	0.12688	0.12796
			DIM	0.42265	0.42112
4	Accuracy study of CIN and DIM Method – II	80%	CIN	0.21521	0.21281
		100%		0.53662	0.53181
		120%		0.69648	0.69032
		80%	DIM	0.22752	0.21951
		100%		0.14811	0.14562
		120%		0.15422	0.15362
5	**Parameters**	**CIN**		**DIM**	
	LOD mcg/ml	0.34867		0.89846	
	LOQ mcg/ml	1.05659		2.72261	
	Robustness ± 2 nm	(251 and 255) 0.52597-0.69864		(274 and 278) 0.11532-0.36831	

Accuracy and Precision

The study carried out at 3 levels shown in Figure 7 and results of accuracy are summarised in Table 5, the obtained results were within acceptable limit; and methods accuracy was justified by calculating % drug content.

The precision study was carried out by performing assay of solutions; further the reproducibility in result was studied by inter day and intraday precision. The values obtained SD and % RSD was shown methods precision and are summarised in Table 5.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of CIN and DIM by the proposed method were shown in Table No 5. The standard deviation of the calibration curve was obtained in Microsoft excel word and found within acceptable limit shown in Table No 5.

Robustness and Ruggedness

Robustness was studied and capacity of analytical procedure to measure analyte was remain unaffected by small but deliberate variations in method parameter. The analytical method was found rugged during development; similarity the result was produced by performing the analysis by different analyst.

CONCLUSION

Both the drugs were estimated from the combined formulation by simultaneous equation and multicomponent method. Both the validated methods are precise and accurate, shown results within acceptable limits; however multicomponent method is rapid, free from arithmetic calculations as compare to simultaneous equation method, hence normally could be accepted by analyst. Solvent utilised in the method is economical, common and free from any type of interference.

Thus, the validated method became economical, precise, accurate, robust and reproducible hence can be routinely used for simultaneous estimation of cinnarizine and dimenhydrinate from combined dosage form.

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