



Simultaneous Estimation of Paracetamol, Phenylephrine Hydrochloride and Triprolidine Hydrochloride by Second Order Derivative Spectroscopy

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A simple, sensitive and reproducible second order derivative UV spectrophotometric method was developed for simultaneous estimation of mixture of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in the tablet dosage form. The method utilizes second order derivative technique, which helps to isolate the individual peaks of the mixture drugs and overcome the problem of merging of mixture peaks with each other. For quantification of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride wavelength selected were 244, 276 and 297 nm, respectively. The method was linear over the concentration range of 5-40 µg/mL. Intra-day and inter-day precision were within acceptable range (percentage relative standard deviation 2.27 %). The percentage recovery was within the range between 97.22-99.43 %. The method was also found to be robust and rugged. The method stands validated as per ICH guidelines and hence, can be used for the routine quality control analysis of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in the tablet dosage form.

Keywords: Paracetamol, Phenylephrine, Triprolidine, Second order derivative.

INTRODUCTION

Paracetamol is one of the most important drugs used as antipyretic and analgesic [1]. It is chemically *N*-(4-hydroxyphenyl)acetamide. The exact mechanism of action of paracetamol is yet to be determined. There are evidences for a number of central mechanisms, including effects on prostaglandin production and on serotonergic, opioid, nitric oxide (NO) and cannabinoid pathways and it is likely that a combination of interrelated pathways are in fact involved [2].

Phenylephrine hydrochloride is an α_1 -selective agonist [3]; a direct-acting sympathomimetic amine chemically related to adrenaline and ephedrine with potent vasoconstrictor property [4]. It is chemically (1*R*)-1-(3-hydroxyphenyl)-2-(methylamino) ethanol hydrochloride. It is presented in many over the counter products for symptomatic relief of nasal and nasopharyngeal mucosal congestion [5].

Triprolidine hydrochloride is chemically 2-[(1*E*)-1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]pyridine mono-

chloride monohydrate. It is propylamine antihistamine with a rapid onset of action and long duration of action found in OTC cold and sinus preparations [6]. It provides effective, temporary relief of sneezing, watery and itchy eyes and runny nose due to hay fever and other upper respiratory allergies [7].

Several methods have been reported for analysis of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in bulk powder, formulations or in biological fluids present individually or in combined dosage forms. Some analytical methods for quantitative analysis of paracetamol are spectrophotometric [8-10], titrimetric [11,12], HPLC [13-15], HPTLC [16-18], voltametric [19,20] and chemometric [21,22]. Similarly, for phenylephrine hydrochloride spectrophotometric [22-24], titrimetric [25], colorimetric [26,27], voltametric [28,29], chromatographic [30-33] and chemometric [34,35] methods are reported. In the same way, for quantitative analysis of triprolidine hydrochloride also various spectrophotometric [36,37], voltametric [38] and chromatographic [39,40] methods are reported. It is revealed from the literature survey that there

is no single analytical method available for simultaneous analysis of these three drugs together in combination product. Thus, an attempt has been made to develop a new second order derivative spectroscopic method to simultaneously estimate paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in tablet dosage forms.

Derivative spectroscopy involves the conversion of a normal spectrum to its first, second or higher derivative spectrum. According to derivative spectroscopy the normal absorption spectrum is referred to as fundamental, zeroth or D₀ spectrum. The first, second, third and fourth order derivative spectra can be obtained directly from the zeroth order spectrum [41]. If a spectrum is expressed as absorbance (A) as a function of wavelength (λ), the derivative spectra is given as:

$$A = f(\lambda)$$

Second order derivative spectrum is obtained by derivatizing twice the spectra of zero order [42]. It is a plot of curvature of absorption spectrum against wavelength [43].

$$\frac{d^2A}{d\lambda^2} = f'(\lambda)$$

Derivative spectroscopy provides two major advantages of effective enhancement of resolution, which can be useful to separate two or more components with overlapping spectra and discrimination in favour of the sharpest features of a spectrum, used to eliminate interferences by broad band constituents responsible for excipients [44].

EXPERIMENTAL

Shimadzu UV-VIS spectrophotometer (UV 1800, Shimadzu, Japan) with fixed slit width 2 nm was used for absorbance measurements. UV Probe 2.34 software was used for analyzing and converting the spectrum to second order derivative spectrum. All weighing was done on digital electronic balance (Sartorius CP 225D, Germany). Paracetamol was purchased from Bharat chemicals, India. Phenylephrine hydrochloride and triprolidine hydrochloride were purchased from Divi's Laboratories Ltd, India, which was used as such without purification. Active-P tablets (labeled to contain paracetamol 500 mg, phenylephrine hydrochloride 10 mg and triprolidine hydrochloride 5 mg) from Alive Pharmaceuticals Pvt. Ltd, Nepal was purchased from the local pharmacy store. Methanol of spectroscopy grade was from Sd. Fine Chemicals Ltd., Mumbai, India. All other reagents used were of analytical grade.

Preparation of standard stock solution: In a 50 mL volumetric flask, 50 mg paracetamol was weighed and transferred, dissolved with 30 mL methanol and shaken for 10 min. The volume was made up with the same solvent. The standard stock solution of phenylephrine hydrochloride and triprolidine hydrochloride was also prepared in the similar manner.

Preparation of tablet stock solution: In a clean mortar and pestle, previously weighed 20 tablets were crushed and

powdered. The tablet powder containing 50 mg equivalent of paracetamol was weighed and transferred in a 50 mL volumetric flask. It was dissolved with 30 mL methanol by shaking it for 15 min. The volume was made up to the mark by methanol. The solution was filtered through a Whatmann filter paper No. 40 and kept in a closed volumetric flask.

Selection of wavelength: Various concentration of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride (10, 20, 25, 30, 40 $\mu\text{g}/\text{mL}$) were prepared by diluting standard stock solution using 0.1 M HCl. The individual solutions were scanned from 190-400 nm. These zero order spectra obtained were converted to second order derivative spectra ($\Delta = 10$), using UV probe software. In the second order derivative spectra, the wavelength where maximum amplitude was obtained for all the three drugs, paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride were recorded. These wavelengths were also checked for any interference from excipients absorption. The wavelength having no interference was selected for quantification purpose.

Linearity: From the standard stock solution of paracetamol, 10 mL was pipetted out in a 100 mL volumetric flask and the volume was made up to the mark with 0.1 M HCl. A series of solutions containing 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 mL were pipetted out from this solution and transferred to different 10 mL volumetric flasks, the volume was made up to the mark with 0.1 M HCl. The resulting solution contains 5-40 $\mu\text{g}/\text{mL}$ of paracetamol. The standard stock solution of phenylephrine hydrochloride and triprolidine hydrochloride was also diluted in the similar manner to get the concentration of 5-40 $\mu\text{g}/\text{mL}$ of phenylephrine hydrochloride and triprolidine hydrochloride, respectively.

Zero order spectra were taken for three drugs individually and was derivatized to second order ($\Delta = 10$) spectra. Amplitude was measured at the selected wavelength and was plotted against concentration. Slope, intercept and correlation coefficient were determined using linear regression analysis.

Precision: General standard addition method was applied for quantification of drugs. Quantity added is shown in Table-1. Weighed and powdered, 20 tablets using clean mortar and pestle. Tablet powder containing 50 mg equivalent of paracetamol was transferred in a 50 mL volumetric flask. Added 30 mL methanol and shaken for 15 min. The volume was made up to the mark with methanol. The solution was filtered through a Whatmann filter paper No. 40. From the filtrate 2.5 mL was pipetted out in a 100 mL volumetric flask. In the same volumetric flask, 2.5 mL of phenylephrine hydrochloride and 2.5 mL of triprolidine hydrochloride was added from standard stock solution. The volume was made up by 0.1 M HCl. The final concentration of paracetamol was 25 $\mu\text{g}/\text{mL}$, phenylephrine hydrochloride was 25.5 $\mu\text{g}/\text{mL}$ and triprolidine hydrochloride was 25.25 $\mu\text{g}/\text{mL}$. These solutions were scanned for zero order spectrum and was converted to second order derivative spectra ($\Delta = 10$).

TABLE-1
QUANTITY ADDED FOR GENERAL STANDARD ADDITION METHOD

Drug	Sample conc. taken ($\mu\text{g}/\text{mL}$)	Standard added ($\mu\text{g}/\text{mL}$)	Dilution (mL)	Final conc. ($\mu\text{g}/\text{mL}$)
Paracetamol	2500	–	100	25.00
Phenylephrine hydrochloride	50	2500	100	25.50
Triprolidine hydrochloride	25	2500	100	25.25

For, intra-day precision above procedure was carried out for six replicates in the same day. Inter-day precision was carried out similarly for six replicates, but in two different days. Assay, mean of assay, standard deviation and percentage relative standard deviation (% RSD) were calculated.

Accuracy

Paracetamol: From the tablet stock solution, 1 mL was pipetted out in three different 100 mL volumetric flasks labeled as A, B and C. Known amount of standard paracetamol solution was added, 0.8 mL in A, 1 mL in B and 1.2 mL in C. The volume was made up to the mark with 0.1 M HCl. The experiment was performed in triplicate. Percentage recovery, mean percentage recovery and percentage RSD were determined and reported.

Phenylephrine hydrochloride: From the tablet stock solution, 2.5 mL was pipetted out in three different 100 mL volumetric flasks labeled as A, B and C. Then 2.5 mL of standard phenylephrine hydrochloride solution was added from standard stock solution in each volumetric flask. Again, known amount of standard phenylephrine hydrochloride solution were added, 1 mL in A, 1.5 mL in B and 2 mL in C. The experiment was performed in triplicate. Percentage recovery, mean percentage recovery and percentage RSD were calculated.

Triprolidine hydrochloride: From the tablet stock solution, 2.5 mL was pipetted out in three different 100 mL volumetric flasks labeled as A, B and C. Then 2.5 mL of standard triprolidine hydrochloride solution from standard stock solution was added. Again, known amount of standard triprolidine hydrochloride solution was added, 1 mL in A, 1.5 mL in B and 2 mL in C. The experiment was performed in triplicate. Percentage recovery, mean percentage recovery and percentage RSD were calculated.

Robustness and ruggedness: Robustness was performed by varying spectrophotometric conditions like solvent strength by $\pm 0.05M$ and wavelength by ± 2 nm. Ruggedness was performed by carrying out analytical procedures with different analysts.

Limit of detection (LOD): LOD was determined by using formula:

$$LOD = \frac{SD \text{ of amplitude} \times 3.3}{\text{Slope}}$$

where, standard deviation (SD) of amplitude was obtained from six replicates of amplitude obtained from the sample solution and the slope was obtained from the linearity curve.

Limit of quantification (LOQ): LOQ was determined by using formula:

$$LOQ = \frac{SD \text{ of amplitude} \times 10}{\text{Slope}}$$

where, standard deviation (SD) of amplitude was obtained from six replicates of amplitude obtained from the sample solution and the slope was obtained from the linearity curve.

Assay of tablet formulation: Weighed accurately 20 tablets and was powdered using mortar and pestle. From the tablet powder, 50 mg equivalent of paracetamol was weighed and transferred in a 50 mL volumetric flask. It was dissolved with 30 mL methanol by shaking it for 15 min. The volume was made up to the mark by methanol. The solution was filtered

through a Whatman filter paper No. 40. From the filtrate, 2.5 mL was pipetted out in a 100 mL volumetric flask. In the same volumetric flask, 2.5 mL of phenylephrine hydrochloride and 2.5 mL of triprolidine hydrochloride was added from standard stock solution. The volume was made up by 0.1M HCl. These solutions were scanned for zero order spectrum and was converted to second order derivative spectrum ($\Delta = 10$). Percentage purity was calculated. The procedure was performed in triplicate.

RESULTS AND DISCUSSION

Selection of wavelength: For paracetamol 244 nm, phenylephrine hydrochloride 276 nm and for triprolidine hydrochloride 297 nm was selected as wavelength for quantification purpose. The overlaid zero and second order spectra are shown in Figs. 1 and 2.

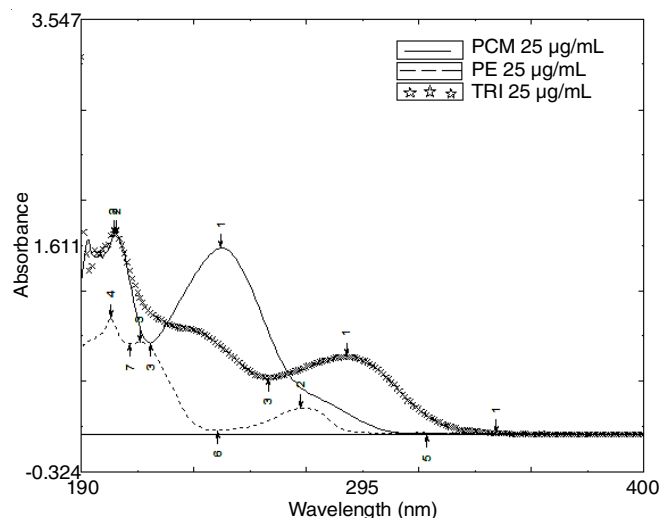


Fig. 1. Overlaid zero order spectra of mixture of 25 µg/mL of paracetamol (PCM), phenylephrine hydrochloride (PE) and triprolidine hydrochloride (TRI) solution

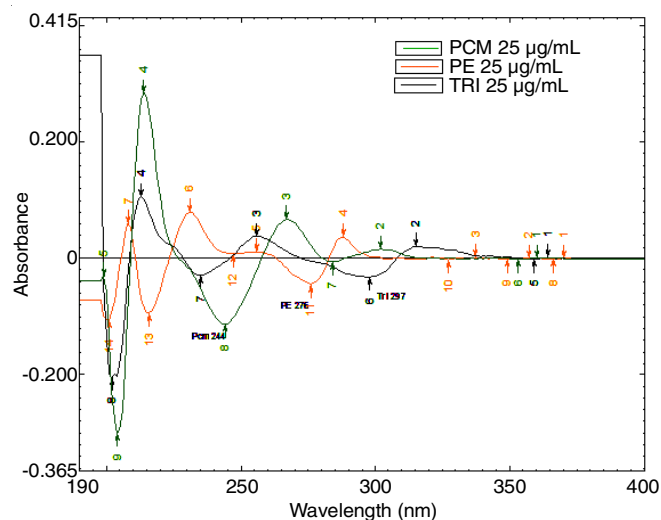


Fig. 2. Overlaid second order derivative spectra of mixture of 25 µg/mL of paracetamol (PCM), phenylephrine hydrochloride (PE) and triprolidine hydrochloride (TRI) solution

Linearity: The calibration curve for paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride were linear over the concentration range of 5-40 µg/mL having

correlation coefficient value 0.9990, 0.9991 and 0.9995, respectively. The regression equation were $y = 0.0048x - 0.0047$ for paracetamol, $y = 0.0018x - 0.0003$ for phenylephrine hydrochloride and $y = 0.0013x + 0.0000$ for triprolidine hydrochloride. Linearity spectra and calibration curve are shown in Figs. 3-8.

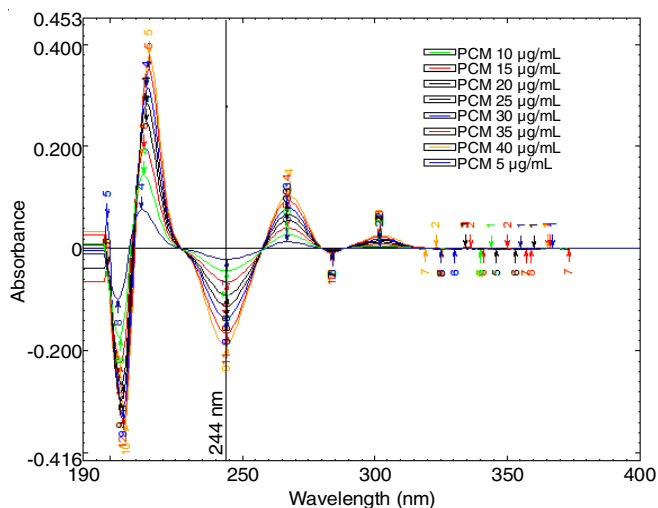


Fig. 3. Overlaid second order derivative spectra of paracetamol (PCM) 5-40 µg/mL

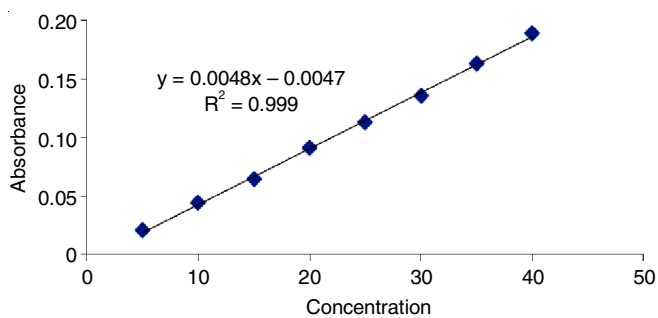


Fig. 4. Standard calibration curve obtained for paracetamol (PCM) by second order derivative spectroscopy

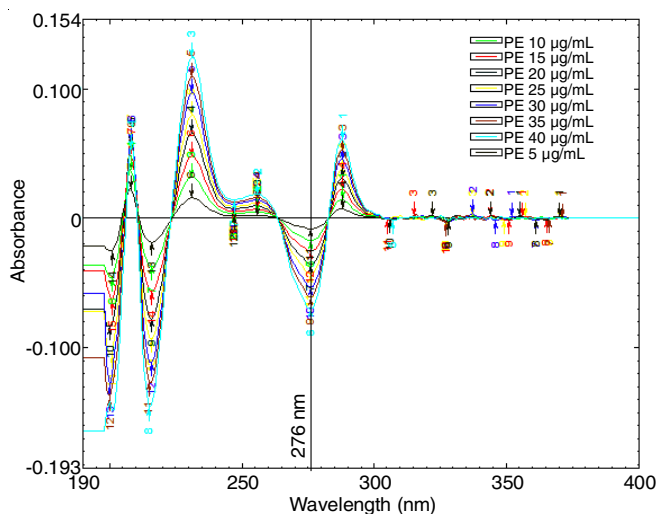


Fig. 5. Overlaid second order derivative spectra of phenylephrine hydrochloride (PE) 5-40 µg/mL

Precision: Intra-day and inter-day precision studies were carried out by taking six replicate samples. Values of percent-

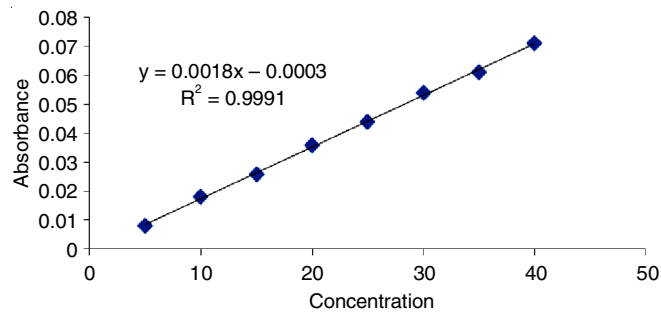


Fig. 6. Standard calibration curve obtained for phenylephrine hydrochloride (PE) by second order derivative spectroscopy

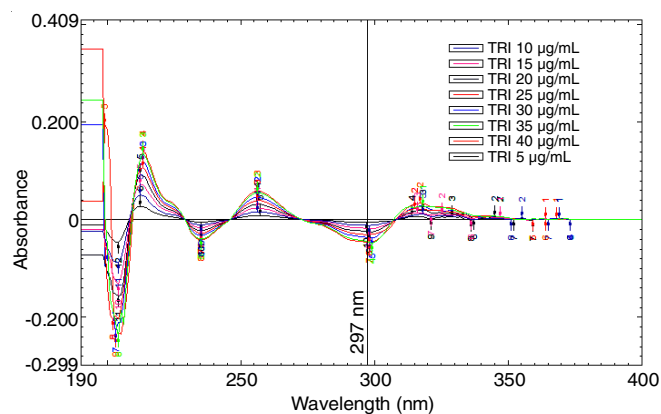


Fig. 7. Overlaid second order derivative spectra of triprolidine hydrochloride (TRI) 5-40 µg/mL

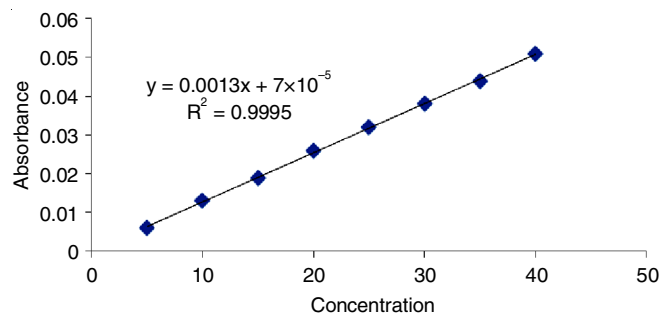


Fig. 8. Standard calibration curve obtained for triprolidine hydrochloride (TRI) by second order derivative spectroscopy

tage RSD for intra-day precision were 1.94, 2.03 and 1.98 for paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride, respectively. Similarly, for inter-day precision percentage RSD were found to be 0.65, 2.27 and 1.60 for paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride, respectively. Results of intra-day and inter-day precision is shown in Table-2.

Robustness and ruggedness: Robustness data shows that small variation in spectrophotometric conditions like varying solvent strength and wavelength does not affect the method. The percentage RSD shows the method was robust and having good ruggedness. The value for robustness and ruggedness are shown in Tables 3 and 4.

LOD and LOQ: LOD and LOQ was calculated using formula given by ICH guidelines. The LOD value obtained were 0.56, 1.11 and 0.83 µg/mL for paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride, respectively. The values of LOQ were 1.87, 3.33 and 1.62 µg/mL for paracetamol,

TABLE-2
RESULTS OF INTRA-DAY AND INTER-DAY PRECISION

	Intra-day precision			Inter-day precision		
	Paracetamol	Phenylephrine hydrochloride	Triprolidine hydrochloride	Paracetamol	Phenylephrine hydrochloride	Triprolidine hydrochloride
Assay	98.08	100.68	98.25	97.25	100.67	98.25
	97.25	96.22	98.25	96.47	96.22	98.25
	99.75	100.67	101.31	98.08	100.67	101.32
	101.41	96.22	95.16	96.47	96.22	98.46
	102.25	98.44	98.24	97.25	98.44	98.31
	98.91	98.45	98.21	97.25	96.22	101.32
Mean	99.61	98.44	98.75	97.12	98.07	99.31
Std. Dev.	1.93	1.98	1.94	0.63	2.19	1.55
RSD (%)	1.94	2.03	1.98	0.65	2.27	1.60

n = 6

TABLE-4
RESULTS OF RUGGEDNESS OF PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE AND TRIPROLIDINE HYDROCHLORIDE

Drug	Analyst I: Amount found % \pm SD	% RSD	Analyst II: Amount found % \pm SD	% RSD
Paracetamol	96.26 \pm 0.96	0.99	97.25 \pm 1.18	1.21
Phenylephrine hydrochloride	98.44 \pm 2.22	2.25	97.64 \pm 1.40	1.44
Triprolidine hydrochloride	99.27 \pm 1.77	1.78	97.97 \pm 1.35	1.37

n = 3

TABLE-3
RESULTS OF ROBUSTNESS IN SMALL VARIATION IN SOLVENT STRENGTH AND WAVELENGTH

Parameters	% RSD		
	Paracetamol	Phenylephrine hydrochloride	Triprolidine hydrochloride
Solvent strength (0.1 M \pm 0.05)	0.17	0.21	0.35
Wavelength (\pm 2)	1.24	2.36	2.21

n = 3

TABLE-5
RESULTS OF LOD AND LOQ OF PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE AND TRIPROLIDINE HYDROCHLORIDE

Drug	LOD (μ g/mL)	LOQ (μ g/mL)
Paracetamol	0.56	1.87
Phenylephrine hydrochloride	1.11	3.33
Triprolidine hydrochloride	0.83	1.62

phenylephrine hydrochloride and triprolidine hydrochloride, respectively. The values of LOD and LOQ are shown in Table-5.

Accuracy: Recovery study was performed by standard spiking method with the aim of justifying the accuracy of the proposed method. Previously analyzed samples were spiked with known amount of standard paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride. The experiment was performed in triplicate. The percentage recovery, mean percentage recovery and percentage RSD were calculated. The method has good and consistent recoveries ranging from 96.79-97.43 % for paracetamol, 97.22-99.33 % for phenylephrine hydrochloride and 97.98-99.43 % for triprolidine hydrochloride. Table-6 data shows the accuracy of the method.

Assay of the tablet formulation: Calculated mean assay for the tablet formulation was found to be 98.25 % for paracetamol, 98.54 % for phenylephrine hydrochloride and 99.73 % for triprolidine hydrochloride. The results of assay are shown in Table-7.

TABLE-6
STATISTICAL EVALUATION OF DATA SUBJECTED TO ACCURACY OF PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE AND TRIPROLIDINE HYDROCHLORIDE

Drug	Conc. of sample (μ g/mL)	Conc. of standard added (μ g/mL)	Mean % Recovery (n = 3)	% RSD
Paracetamol	10	8	96.79	1.35
	10	10	97.43	1.93
	10	12	97.28	1.03
Phenylephrine hydrochloride	25.5	10	97.63	1.44
	25.5	15	99.33	2.37
	25.5	20	97.22	1.74
Triprolidine hydrochloride	25.25	10	99.28	1.55
	25.25	15	99.43	2.013
	25.25	20	97.98	1.38

n = 3

TABLE-7
ASSAY RESULTS OF TABLET FORMULATION CONTAINING PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE AND TRIPROLIDINE HYDROCHLORIDE

Drugs	Mean assay (%)	SD	% RSD
Paracetamol	98.25	1.39	1.41
Phenylephrine hydrochloride	98.54	1.87	1.90
Triprolidine hydrochloride	99.73	1.63	1.64

n = 3

Conclusion

A simple, sensitive, accurate and reproducible second order derivative UV spectrophotometric method was developed for simultaneous estimation of mixture of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in tablet dosage form. The method isolates the individual peaks of the mixture drugs and overcomes the problem of merging and interference of mixture peaks with each other. This method was validated as per the ICH guidelines for all the parameters and the results passed the criteria set forth by ICH guidelines.

Hence, the method stands validated and can be used for the routine quality control analysis of paracetamol, phenylephrine hydrochloride and triprolidine hydrochloride in tablet dosage form.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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