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SIMULTANEOUS ESTIMATION OF RABEPRAZOLE SODIUM AND CINITAPRIDE HYDROGEN TARTRATE IN COMBINED PHARMACEUTICAL FORMULATION

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ABSTRACT: Three simple, rapid, precise and accurate spectrophotometric methods have been developed for simultaneous analysis of Cinitapride Hydrogen Tartrate (CNT) and Rabeprazole Sodium (RAB) in their combined dosage form. Method A, Simultaneous equation method (Vierodt's method) applies measurement of absorptivities at two wavelengths, 265.6 nm (λ_{\max} of Cinitapride Hydrogen Tartrate) and 282.6 nm, (λ_{\max} of Rabeprazole Sodium) in zero order spectra. The concentrations can be calculated from the derived equations. Method B, Q-Absorbance equation method. It involves formation of Q-absorbance equation at 279.00 nm (isoabsorptive point) and 265.60 nm (λ_{\max} of Cinitapride Hydrogen Tartrate) in zero order spectra. Method C, Zero crossing first derivative spectrophotometry involves measurement of absorbance at 246.30 nm (for Cinitapride Hydrogen Tartrate) and 304.00 nm (for Rabeprazole Sodium) in first derivative spectra. Developed methods were validated according to ICH guidelines. The calibration graph follows Beer's law in the range of 4.0 to 20.0 $\mu\text{g/ml}$ for Cinitapride Hydrogen Tartrate and 4.0 to 20.0 $\mu\text{g/ml}$ for Rabeprazole Sodium in water as a solvent with R square value greater than 0.999. Accuracy of all methods was determined by recovery studies and showed % recovery between 98 to 102%. Intraday and inter day precision was checked for all methods and mean %RSD was found to be less than 2 for all the methods. The methods were successfully applied for estimation of Cinitapride Hydrogen Tartrate and Rabeprazole Sodium in marketed formulation.

INTRODUCTION: Cinitapride hydrogen tartrate (CNT), 4-Amino-N-[1-(3-cyclohexen-1-ylmethyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide hydrogen L-(+)-tartarate (**Figure 1**), is a gastroprokinetic drug.

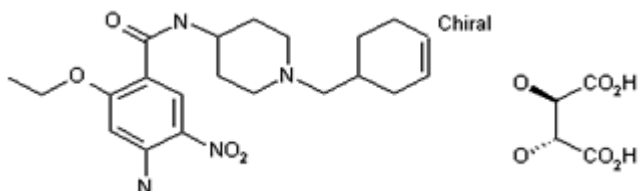


FIGURE 1: CINITAPRIDE HYDROGEN TARTRATE (CNT)

Cinitapride hydrogen tartrate is a benzamide derivative used in the treatment of Delayed gastric emptying, Gastro-esophageal reflux disease, Non-ulcer dyspepsia¹.

Rabeprazole sodium (RAB), 2-([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl) sulphonyl-1 H-benzimidazole sodium (**Figure 2**), is a proton pump inhibitor (PPI) that suppresses gastric acid secretion through an interaction with (H⁺/K⁺) ATPase in gastric parietal cells.

Rabeprazole sodium is effective in the treatment of various peptic diseases, including gastric and duodenal ulcer, gastroesophageal reflux disease (GERD). Rabeprazole sodium is official in Indian pharmacopoeia and describes liquid chromatography method for its estimation².

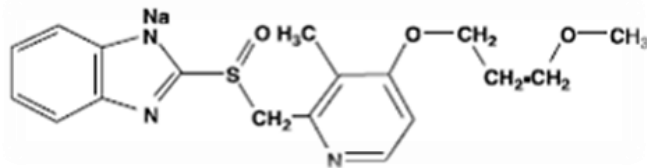


FIGURE 2: RABEPRAZOLE SODIUM (RAB)

Objective of Study: Survey of literature revealed that numbers of method have been reported in literature for the individual analysis of Cinitapride hydrogen tartrate and Rabeprazole sodium by UV spectrophotometric and RP-HPLC method. UV spectrophotometric method available in literature for simultaneous determination of Rabeprazole Sodium with other drugs like Domperidone and Diclofenac^{3, 4, 5, 6}. RP-HPLC method available in literature for simultaneous determination of Rabeprazole Sodium with Domperidone^{7, 8}.

UV spectrophotometric method available in literature for simultaneous determination of Cinitapride hydrogen tartrate with other drugs like Omeprazole and Pantoprazole^{9, 10, 11}. RP-HPLC method available in literature for simultaneous determination of Cinitapride hydrogen tartrate with Pantoprazole¹². However, to our knowledge, there is no reported UV-Spectrophotometric method available for simultaneous estimation of Cinitapride hydrogen tartrate and Rabeprazole Sodium.

The aim of the present work was to develop easy, economic, accurate, specific and precise spectrophotometric methods for simultaneous estimation of Rabeprazole Sodium and Cinitapride Hydrogen Tartrate in combined pharmaceutical formulations and validation of newly developed analytical methods.

MATERIALS AND METHODS:

Apparatus and Software: Shimadzu UV-1800 double beam spectrophotometer connected to a computer loaded with Shimadzu UV Probe 3.34 software was used for all the spectrophotometric measurements. The absorbance spectra of the

reference and test solutions were carried out in 1cm quartz cells over the range of 200-400 nm. The samples were weighed on Contech analytical balance.

Reagents and Chemicals: Distilled Water, Methanol AR grade.

Preparation of Stock Solution: Accurately weighed CNT and RAB (in quantities of 50.0 mg) were transferred to two separate 50 ml volumetric flasks, dissolved with the use of 2 ml methanol. About 10 ml water was added and sonicated for 10 minute. Then volume was made up to the mark with water to obtain stock solution of CNT (1000 µg/ml) and RAB (1000 µg/ml).

Preparation of Working Standard Solution: From the above solution, standard stocks solutions of CNT (100 µg/ml) and RAB (100 µg/ml) were prepared by transferring 10 ml aliquots to 100 ml volumetric flasks and making up the volume with water.

Preparation of Calibration Curve of Standard CNT and RAB: From working std. solution of CNT (100 µg/ml) and RAB (100 µg/ml) 0.4, 0.8, 1.2, 1.6, and 2.0 ml were transferred to 10 ml volumetric flasks and volume were made up to the mark with water. This gives 4.0 to 20 µg/ml for both CNT and RAB.

Method A:

Simultaneous equation method (Vierodt's method): If a sample containing two absorbing drug (X and Y) each of which absorbs at λ_{max} of other. It may possible to determine both drugs by the technique of simultaneous equations (Vierodt's method) provided that certain criteria apply. The information required is the absorptivities of X at λ_1 and λ_2 i.e. a_{x1} and a_{x2} respectively; (a) The absorptivities of Y at λ_1 and λ_2 i.e. a_{y1} and a_{y2} respectively (b). The absorbances of the diluted sample at λ_1 and λ_2 i.e. A_1 and A_2 respectively.

Let C_x and C_y be the concentrations of X and Y respectively in the diluted sample. Two equations are constructed based upon the fact that at λ_1 and λ_2 the absorbance of the mixture is the sum of the individual absorbance of X and Y. From the stock solutions, working standard solutions of CNT (100 µg/ml) and RAB (100µg/ml) were prepared. By appropriate dilutions, the solutions with

concentrations 4.0-20 $\mu\text{g/ml}$ (for both CNT and RAB) were prepared and scanned between 200 to 400 nm (Fig. 3). calibration curve of absorbance versus concentration were prepared. The calibration curves were found to be linear in the concentration range under study (Fig. 4.1 & 4.2). For CNT and RAB, analytical wavelengths of 265.60 nm and 282.60 nm were selected respectively. Absorptivity of CNT and RAB were calculated at both the wavelengths. The concentrations of CNT and RAB can be calculated from following equations¹³:

$$C_x (\text{CNT}) = (A_2 a_{y1} - A_1 a_{y2}) / (a_{x2} a_{y1} - a_{x1} a_{y2})$$

$$C_y (\text{RAB}) = (A_1 a_{x2} - A_2 a_{x1}) / (a_{x2} a_{y1} - a_{x1} a_{y2})$$

Where; C_x & C_y are concentrations of CNT and RAB respectively in gm/100 ml in the sample solution. A_1 & A_2 are the absorbances of the mixture at 265.60 nm & 282.60 nm respectively; a_{x1} and a_{x2} = Absorptivity of CNT at 265.60 nm and 282.60 nm; a_{y1} and a_{y2} = Absorptivity of RAB at 265.60 nm and 282.60 nm.

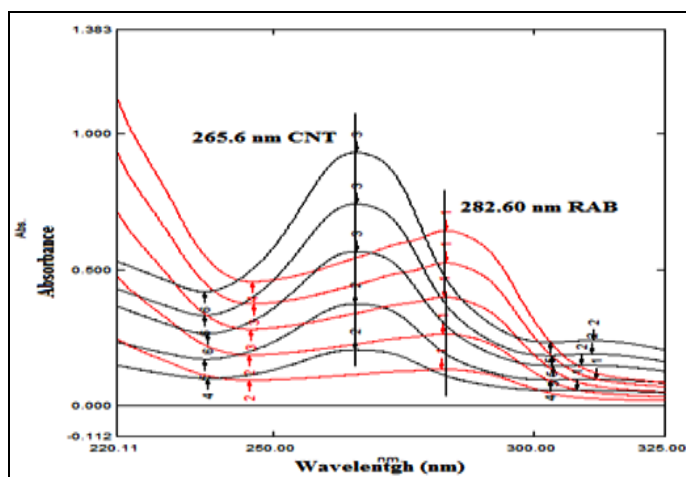


FIGURE 3: ZERO ORDER OVERLAIN SPECTRA OF CNT (4, 8, 12, 16, 20 $\mu\text{g/ml}$, AT 265.6 nm) AND RAB (4, 8, 12, 16, 20 $\mu\text{g/ml}$, AT 282.60 nm).

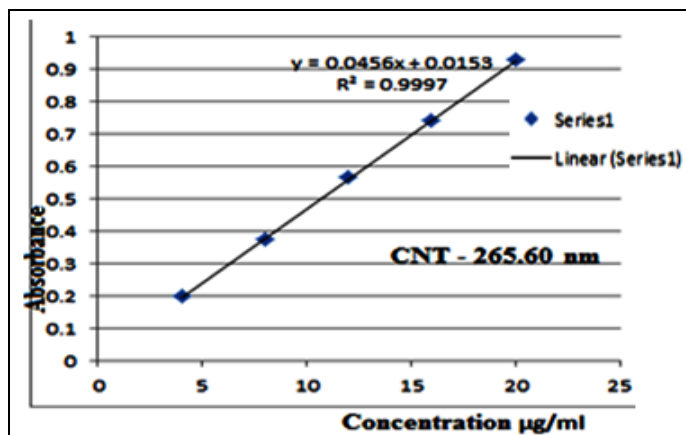


FIGURE 4.1: CALIBRATION GRAPH OF CNT

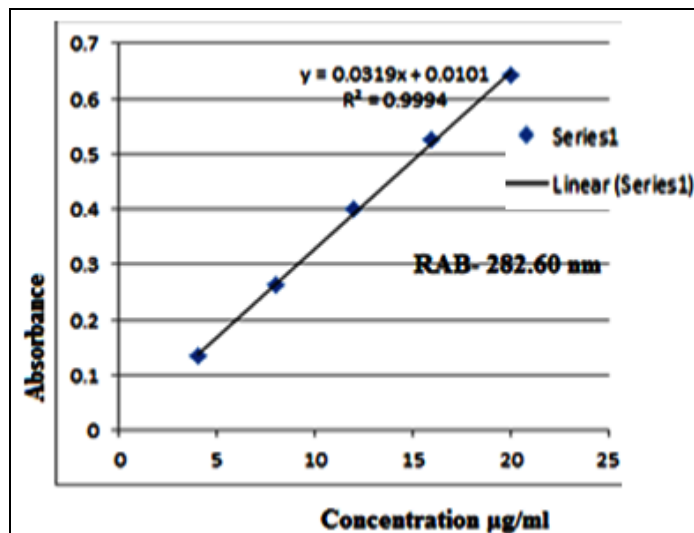


FIGURE 5.2: CALIBRATION GRAPH OF RAB

Method B:

Q-Absorbance ratio method: Q method uses the ratio of absorbances at two selected wavelengths, one at isoabsorptive point and other being the λ_{max} of one of the two compounds. From the stock solutions, working standard solutions of CNT (100 $\mu\text{g/ml}$) and RAB (100 $\mu\text{g/ml}$) were prepared. By appropriate dilutions, the solutions with concentrations 4.0-20 $\mu\text{g/ml}$ (for both CNT and RAB) were prepared and scanned between 200 to 400 nm (Fig. 5).

Series of standard solutions ranging from 4.0-20 $\mu\text{g/ml}$ (for both CNT and RAB) were prepared and the absorbance of solutions was recorded at 265.60 nm (λ_{max} of CNT) and 279.00 nm (isoabsorptive point) to plot a calibration curve of absorbance versus concentration (Fig. 6.1 & 6.2). Calibration curves were found to be linear in the concentration range under study. Absorptivity values of CNT and RAB were determined at selected wavelengths. The concentration of two drugs in mixture was calculated by using following equations¹³:

$$C_X = [(Q_M - Q_Y) / (Q_X - Q_Y)] \times A_1/a_{x1}$$

$$C_Y = [A_1/a_{x1}] - C_X$$

Where; $Q_m = A_2/A_1$, $Q_x = a_{x2}/a_{x1}$, $Q_y = a_{y2}/a_{y1}$; A_1 and A_2 are absorbance of mixture at 279 nm and 265.60 nm respectively; a_{x1} and a_{x2} is Absorptivity of CNT at 279 nm and 265.60 nm respectively; a_{y1} and a_{y2} is Absorptivity of RAB at 279 nm and 265.60 nm respectively.

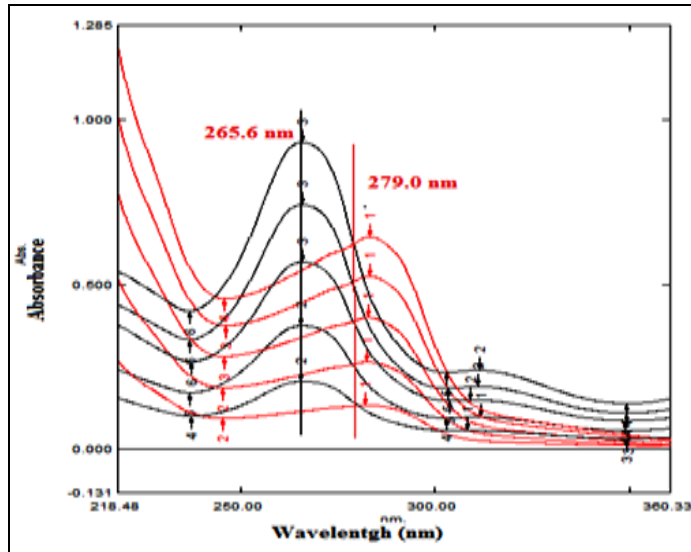


FIGURE 5: ZERO ORDER OVERLAIN SPECTRA OF CNT (4, 8, 12, 16, 20 µg/ml, AT 265.6 nm) AND RAB (4, 8, 12, 16, 20 µg/ml, AT 279.00 nm).

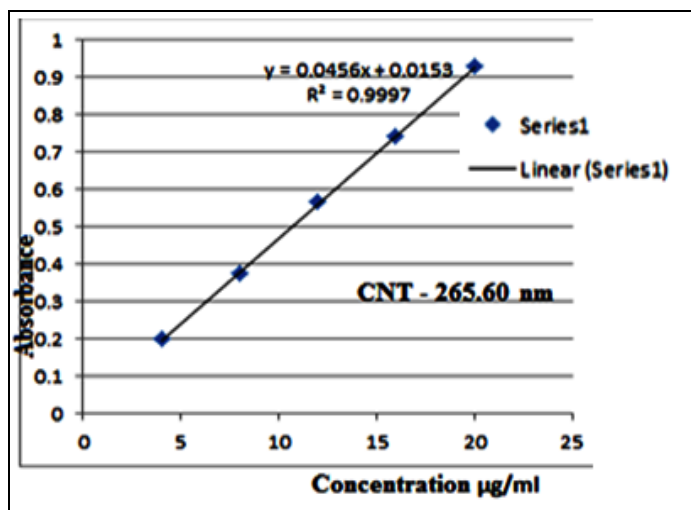


FIGURE 6.1: CALIBRATION GRAPH OF CNT

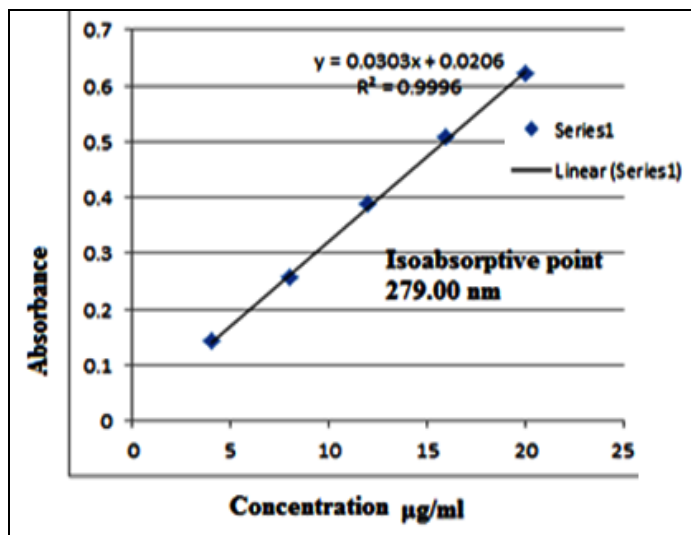


FIGURE 6.2: CALIBRATION GRAPH OF RAB AT ISOABSORPTIVE POINT

Method C:

Zero crossing first derivative spectrophotometry:

The solutions of standard CNT and RAB were prepared in the range of 4.0 to 20.0 µg/ml. The absorption spectra of the solutions of CNT and RAB were recorded in the range of 200 nm to 400 nm and were stored in the memory of the instrument and transformed to first derivative with $\Delta\lambda = 8\text{nm}$ and scaling factor 50 (Fig. 7). At 246.30 nm, RAB is having zero crossing point and CNT can be determined. At 304.00 nm, CNT is having zero crossing point and RAB can be determined. The amplitudes at 246.30 nm were plotted against respective concentrations of CNT and the amplitudes at 304.00 nm were plotted against the respective concentrations of RAB for the preparation of calibration graph. Calibration graph for CNT and RAB are shown (Fig. 8.1 & 8.2).

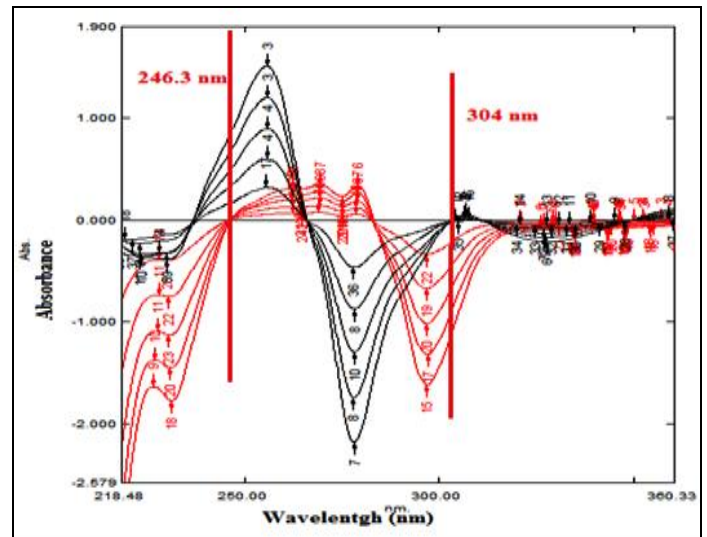


FIGURE 7: FIRST ORDER OVERLAIN SPECTRA OF CNT (4, 8, 12, 16, 20 µg/ml, AT 246.30 nm) AND RAB (4, 8, 12, 16, 20 µg/ml, AT 304.00 nm).

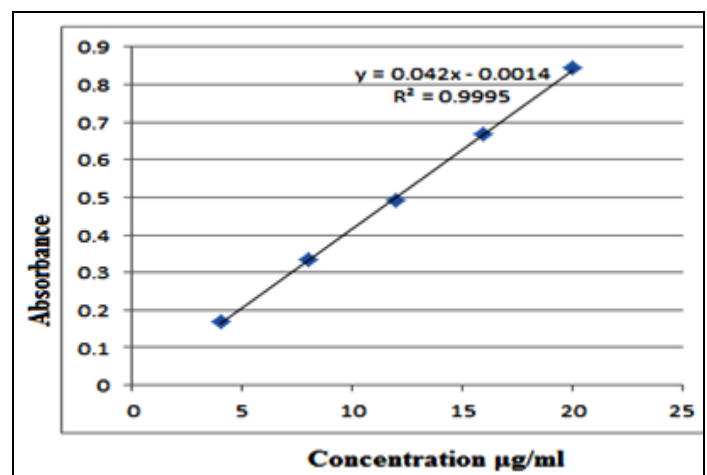


FIGURE 8.1: CALIBRATION GRAPH OF CNT

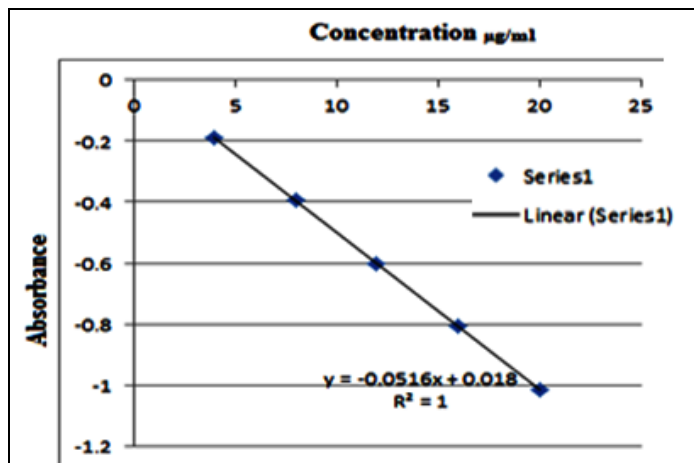


FIGURE 8.2: CALLIBRATION GRAPH OF RAB

TABLE 1: RESULTS OF SIMULTANEOUS ESTIMATION OF MARKETED FORMULATION FOR METHOD A, B, AND C:

Labelled Claim :- CNT : RAB (3mg : 20mg)		
Method	CNT*± SD	RAB*± SD
A	99.41 ± 0.0122	100.93 ± 0.0457
B	100.02 ± 0.0133	100.20 ± 0.1496
C	100.05 ± 0.0295	99.67 ± 0.1579

*Mean value of three determinations

RESULTS AND DISCUSSION: Developed spectrophotometric methods for the simultaneous estimation of CNT and RAB were validated according to ICH¹⁴ guidelines and data complying

with the standards were obtained. The results of validation parameters for all the three developed methods are reported (Table 2 and 3).

TABLE 2: SUMMARY OF VALIDATION PARAMETERS BY DEVELOPED METHODS:

Parameters	Method - A		Method - B		Method - C	
	CNT	RAB	CNT	RAB	CNT	RAB
Analytical wavelength (nm)	265.60 & 282.60		265.60 & 279.00		246.30	304.00
Beer's range (µg/ml)	4.0 -20.0	4.0 -20.0	4.0 - 20.0	4.0 - 20.0	4.0 - 20.0	4.0 - 20.0
Slope	0.0456	0.0319	0.0456	0.0303	0.0042	0.0516
Intercept	0.0153	0.0101	0.0153	0.0206	0.0014	0.018
Correlation coefficient	0.9997	0.9994	0.9997	0.9996	0.9995	1.0
Sandell's sensitivity (µg/cm ² /0.001 A.U)	0.02109	0.03010	0.02109	0.03074	0.02386	0.02018
Repeatability (% RSD, n=6)	0.3111	0.4455	0.3111	0.8196	0.3843	0.4467
Intraday precision (%RSD) (n=3)	0.7564	1.0167	0.7564	0.8154	0.8610	0.9654
Interday precision (%RSD) (n=3)	1.0355	1.2065	1.0355	1.2331	0.9319	1.0607
LOD (µg/ml)	0.156	0.1039	0.156	0.3084	0.2221	0.2989
LOQ (µg/ml)	0.463	0.3148	0.463	0.9345	0.6729	0.9059

TABLE 3: RESULTS OF RECOVERY STUDY OF CNT AND RAB BY DEVELOPED METHODS:

METHODS	% SPIKING	% RECOVERY ± S.D.	
		CNT	RAB
A	50	100.61 ± 0.0329	99.26 ± 0.0613
	100	99.17 ± 0.1132	101.22 ± 0.0047
	150	99.49 ± 0.0386	98.85 ± 0.0591
B	50	99.74 ± 0.1115	99.41 ± 0.1034
	100	99.86 ± 0.0478	99.72 ± 0.1302
	150	99.73 ± 0.1296	98.16 ± 0.0249

C	50	99.67 ± 0.0634	99.89 ± 0.0779
	100	99.55 ± 0.0649	100.39 ± 0.1482
	150	99.96 ± 0.0711	100.11 ± 0.0499

* Mean of three determinations

CONCLUSION: Three Spectrophotometric methods (Simultaneous equation method, Q-Absorbance equation method, Zero crossing first derivative spectrophotometry) were developed for simultaneous estimation of CNT and RAB in their combined formulation. Methods were found to be precise and accurate as can be reflected from validation data. Developed methods were successfully applied for estimation of CNT and RAB in marketed formulation.

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