Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2020, 9 (4): 567-574

(International Peer Reviewed Journal)

Determination of Eletriptan Hydro Bromide in pure and Pharmaceutical Formulations Using Cobalt Thiocyanide and Citric Anhydride by Spectrophotometric Method

M.L.N. Acharyulu[1]*, P.V.S.R. Mohana Rao[2] and I. Siva Ramakoti[3]

1. Centurion University of Technology and Management, Andhra Pradesh- 530017, **INDIA**
2. Department of Engineering Chemistry, A.U.College of Engineering (A), Visakhapatnam-530003, **INDIA**
3. Department of Chemistry, Centurion University of Technology and Management, Odisha- 761211, **INDIA**

Email: acharyulu@cutmap.ac.in

Accepted on 20th July, 2020

ABSTRACT

Two visible spectrophotometric methods were developed A and B for the determination of Eletriptan hydrobromide in pure and pharmaceutical formulations. Method A is based on the formation of co-ordination complex of tertiary amine of EHB (electron donor) and the central metal of the cobalt thiocyanate (acceptor) and Method B is based on internal salt formation involving aconitic anhydride (dehydration product of CiA) and the tertiary amine of EHB. The coloured products exhibit absorption λ_{max} at 623 nm and 546 nm for methods A and B respectively. Regression analysis of Beer-Lambert plots showed good correlation in the concentration ranges 4-24 $\mu g\ L^{-1}$, correlation co-efficients are 0.9886(A), 0.9877(B) respectively. The Sandell's sensitivities are 2.7739 $x10^{-3}$, 1.9933x 10^{-3} (1 mole cm^{-1}) and molar absorptivity values are1.6706 $x10^{5}$, 2.3248 $x10^{5}$($\mu g\ cm^{-2}$).The proposed methods are applied to commercial available formulations and the results are statistically compared with those obtained by the UV reference method and validated by recovery studies.

High Lights:

- The results are found satisfactory and reproducible.
- These methods are applied successfully for the estimation of the EHB in the presence of other ingredients that are usually present in formulations.
- These methods offer the advantages of rapidity, simplicity and sensitivity and low cost without the need for expensive instrumentation and reagents.

Keywords: Coordination complex, Dehydration Product, Tertiary Amino group, Regression Analysis.

INTRODUCTION

Eletriptan hydrobromide (Figure 1) is a second generation triptan drug and it intended for treatment of migrane headache [**1, 2**]. It is used as an abortive medication, and blocks migrane attack which is already in progress. EHB chemically known to be 3-[(-1-methylpyrrolidin-2-yl)methyl]-5-(2-phenylsul fonylethyl)-1H-indole. It is selective at 5-HT1B/1D receptor agonist; thought to be due to the agonist effects at the 5-HT1B/1D receptors located on intracranial blood vessels (including arteriovenous anastomoses) and sensory nerves of the trigeminal system that results in cranial vessel constriction and inhibition of pro inflammatory neuropeptide release [**3**]

Literature survey reveals few chromatographic methods to determine the EHB by HPLC [**4-9**], TLC [**10**] and Liquid Chromatography coupled with tandem mass spectroscopy [**11**], simultaneous determination of EHB with other anti-migraine drugs [**12, 13**], determination of EHB in plasma using Forced degradation studies, development of stability indicating method [**14**] Spectrophotometric method [**15-20**],determination of Process related impurities in Eletriptan using UPLC method [**21**], TLC-Densitometric method [**22**], Fluorimetric and Colorimetric method [**23**], Capillary Electrophoresis [**24**] and Thermal diffractometric studies [**25**] Ionn association Method [**26**] were reported.

The analytical useful functional groups in EHB have not been fully exploited for designing suitable visible spectrophotometric methods and so still offer a scope to develop more visible spectrophotometric methods with better sensitivity, precision and accuracy. The author has made some attempts in this direction and succeeded in developing two methods for determination and validation of EHB in Pharmaceutical dosage forms.

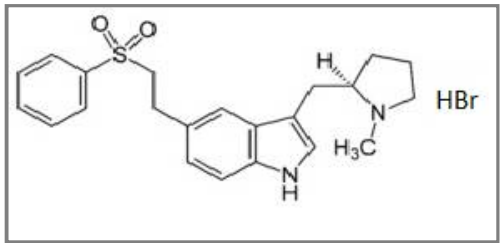


Figure 1. Structure of EHB.

MATERIALS AND METHODS

Instruments Used: Schimadzu UV-Visible spectrophotometer 1801 with 1 cm matched quartz cells was used for all spectral and absorbance measurements. A Systronics digital pH meter 361 was used for pH measurements.

Preparation of standard Drug solution: The stock solution (1 mg mL^{-1}) of Eletriptan Hydrobromide (EHB) was prepared by dissolving 100 mg of it in 100 mL of millipore-distilled water. A portion of this stock solution was diluted stepwise with the distilled water to obtain the working standard EHB solution of concentrations 30 µg mL^{-1} for the proposed methods respectively.

Procedure of Assay of EHB in formulations: An accurately weighed amount of formulation (tablets) equivalent to 100 mg of drug was dissolved in 20 mL of distilled water, shaken well and filtered. The filtrate was further diluted to 100 mL with distilled water to get 1 mg mL^{-1} solution of drug in formulations.

1 mL of this solution was furthered diluted to 25 mL to get 40 µg mL^{-1} solution. The absorbance of the solution was determined λ_{max}223 nm (Figure 2). The quantity of the drug was computed from

the Beer's law plot (Figure 3**)** of the standard drug in distilled water.

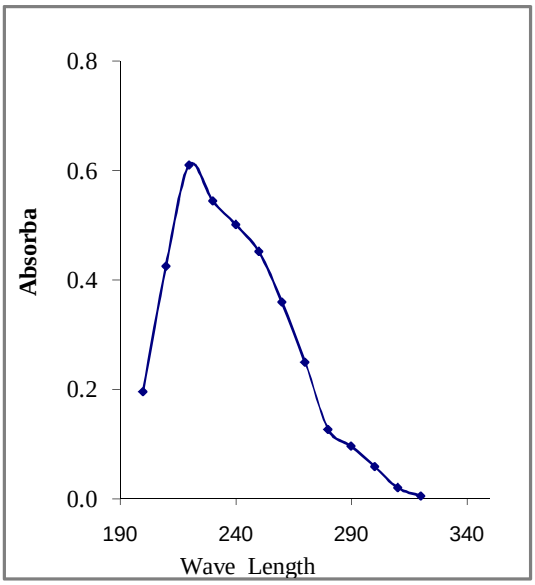


Figure 2. Absorption Spectra of EHB in Methanol (UV Reference method).

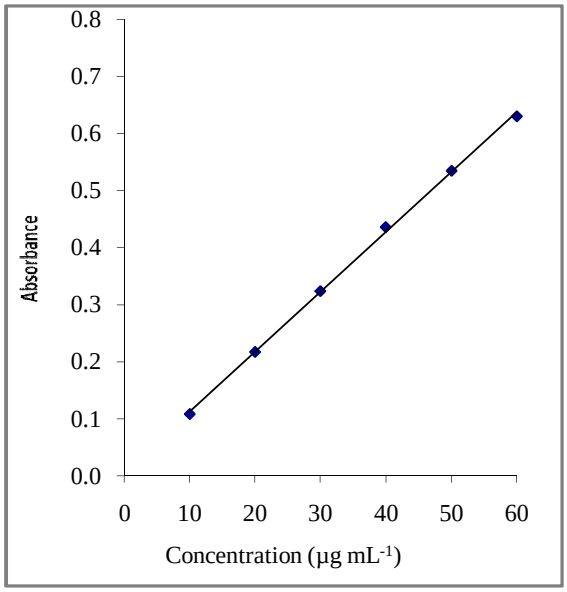


Figure 3. Beer's Law plot of EHB in methanol (UV Reference method)

Recommended Procedures: After systematic and detailed study of the various parameters involved, as described under results and discussion in this chapter, the following procedures were recommended for the determination of EHB in bulk samples.

Method-A: Aliquots of standard EHB solution (0.1- 0.6 mL, 30 µg mL^{-1}) were delivered into a series of calibrated tubes. 2.0 mL of buffer (pH 2.0) and 5.0 mL of CTC solutions were added and the total volume in each tube was adjusted to 15 mL with distilled water. The solutions in the tubes were transferred to 125 mL separating funnel. To each separating funnel 10 mL of nitrobenzene was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated nitrobenzene layer was measured after 20 min. at λ_{max} 623 nm (Figure 4) against a similar reagent blank. The amount of EHB in a sample was obtained from the Beers – Lambert's plot (Figure 5)

Method-B: Aliquots of standard EHB in free base form (0.1-0.6 mL, 30 µg mL^{-1}) were taken into a series of 25 mL graduated tubes and evaporated to dryness on a water bath. The tubes were cooled to room temperature and then 9 to 9.4 mL of CiA-AC_2O reagent was added to each tube. The tubes were placed in boiling water bath for 30 min. The solutions were cooled to room temperature; the volume in each tube was made up to the mark with acetic anhydride. The absorbance of colored solution was measured at λ_{max}546 nm against reagent blank (Figure 6). The quantity of the EHB in the sample was obtained from the Beer's law plot (Figure 7).

Chemistry of the coloured species in the present investigation: EHB possesses different functional moieties such as tertiary amino group and indole of varied reactivity. The methods complex formation with CTC, internal complex formation with aconitic anhydride (dehydration product of citric acid) under experimental conditions is the basis for its determination.

The reviews concerning the reagents used for colour development by exploring appropriate functional groups in EHB are presented in schemes 1,2 respectively. An attempt has been made to indicate the nature of coloured species formed in each proposed method for EHB determination tentatively based on analogy

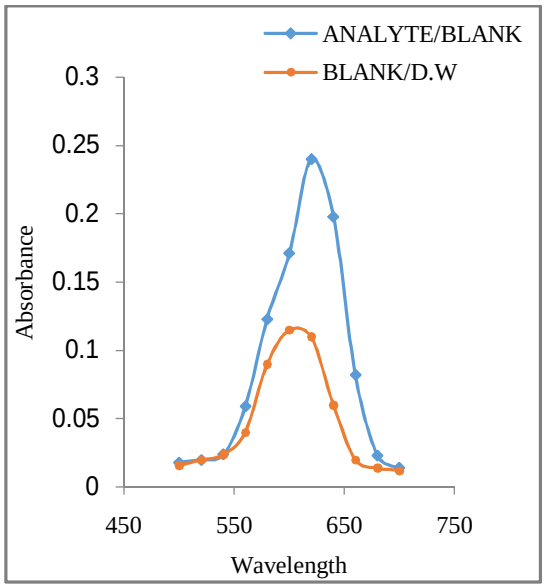


Figure 4. Absorption spectra of EHB: CTC

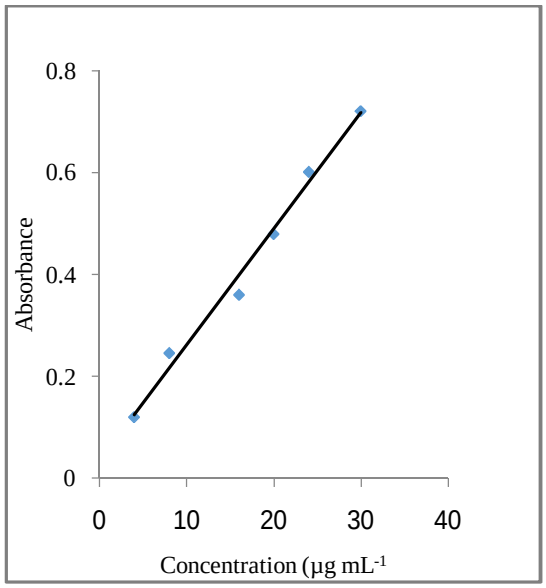


Figure 5. Beer's plot of EHB: CTC

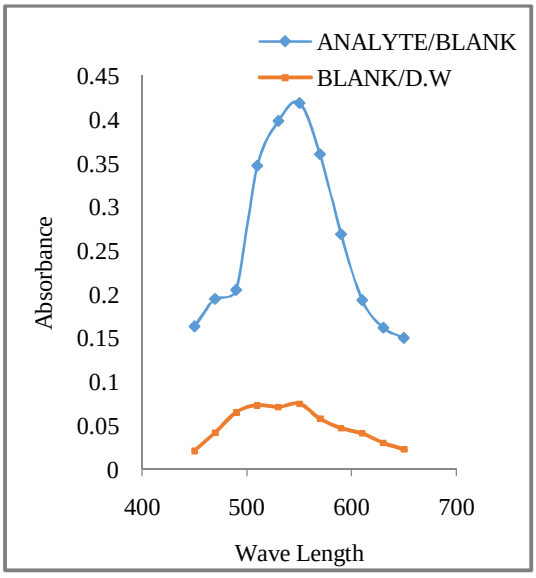


Figure 6. Absorption spectra of EHB:CiA/ AC_2O.

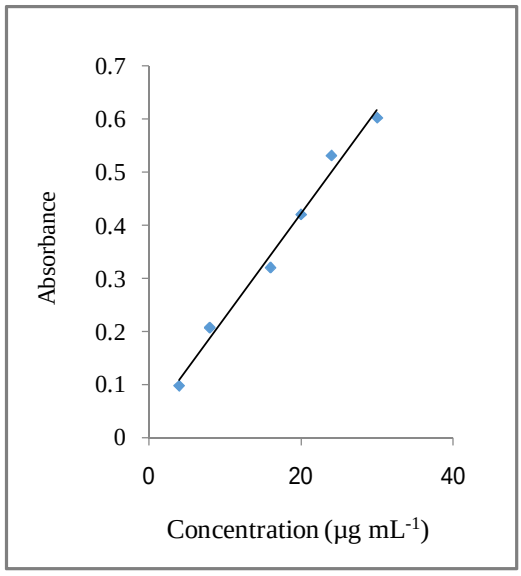
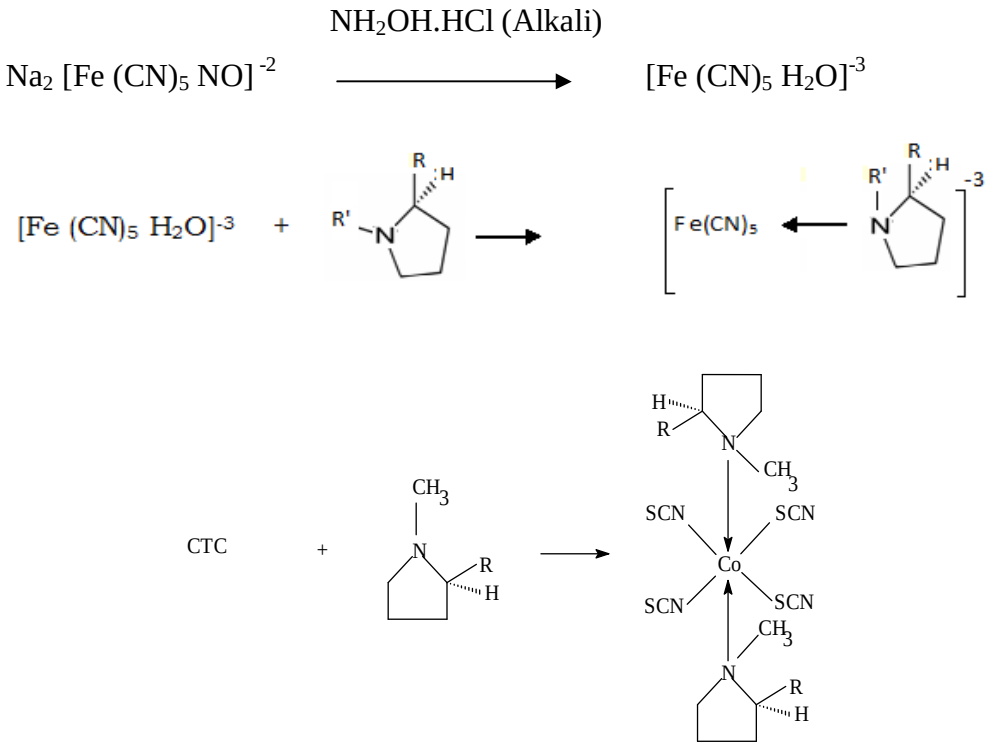


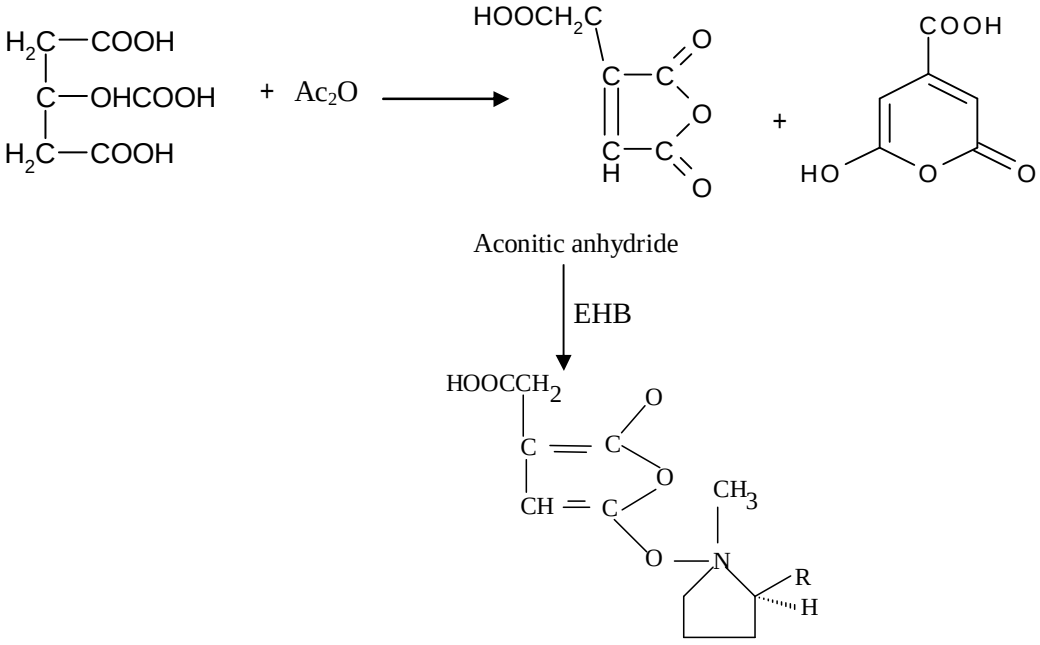
Figure 7. Beer's plot of EHB: CiA/AC_2O.

Method-A: Cobalt thiocyanate (CTC) [formed from the combination of ammonium thiocyanate and cobalt nitrate] has been proved to be a valuable reagent for the determination of amino compounds. In the present investigation the coloured species formed is the co-ordination complex of tertiary amine of EHB (electron donor) and the central metal of the cobalt thiocyanate (acceptor) which is extractable into nitrobenzene from aqueous solution. The reactions are described in the scheme1.

Method-B: There are reports in the literature that when distinctly basic amines (especially tertiary) are heated with either citric acid in acetic anhydride or its dehydration product, aconitic anhydride in Ac_2O red to violet colour develop due to the formation of internal salt. In the present investigation, the author has successfully developed procedure for the visible spectrophotometric determination of EHB by heating it with CiA/ Ac_2O probably due to the internal salt formation involving aconitic anhydride (dehydration product of CiA) and the tertiary amine of EHB. The reactions are described in the scheme 2.



Scheme 1. Coordination Complex of Tertiary Amine in EHB with CTC.



Scheme 2. Internal Salt formation between Acotinic Anhydride and Tertiary amine of EHB.

RESULTS AND DISCUSSION

Optimum operating conditions used in the procedure were established adopting variation of one variable at a time (OVAT) method. The effects of various parameters such as were studied. Effect of buffer pH on colour development, volume of buffer required for maximum intensity of colour, choice of organic solvent for extraction of coloured complex, effect of the ratio of organic to aqueous phase

on the extraction, effect of shaking time (min) were studied for method-A, and volume of CiA/AC_2O, effect of reaction time on colour development, solvent for final dilution, stability of the coloured product were studied for method-B. The optical characteristics such as Beer's law limit, Sandell's sensitivity, molar absorptivity, percent relative standard deviation, (calculated from the six measurements, Regression characteristics like standard deviation of slope (S_b), standard deviation of intercept (Sa), standard error of estimation (S_e) and % range of error (0.05 and 0.01confidence limits) were calculated and the results are summarized in table 1. Commercial formulations containing EHB were successfully analyzed by the proposed methods. The values obtained by the proposed and reference methods for formulations were compared statistically by the t-test and F-test and found not to differ significantly. As an additional demonstration of accuracy, recovery experiments were performed by adding a fixed amount of the drug to the pure analyzed formulations at three different concentration levels. These results are summarized in table 2.

Table 1. Optical and Regression characteristics, precision and accuracy of the proposed methods for EHB

S .No	Parameter	Method-A	Method-B
1	Wave length λ_{max} (nm)	623	546
2	Beer's law limits (µg ml^{-1})	4-30	4-30
3	Detection limits (µg ml^{-1})	3.0958	3.2043
4	Molar absorptivity (1 mole cm^{-1})	1.6706 x 10^5	2.3248 x 10^5
5	Sandell's sensitivity (µg cm^{-2} / 0.001 absorbance unit)	2.7739 x 10^{-3}	1.9933 x 10^{-3}
6	Regressionequation (Y = a + bC) Slope (b)	0.0228	0.0196
7	Standard deviation of slope (S_b)	1.2253 x 10^{-4}	1.0963 x 10^{-3}
8	Intercept (a)	0.0336	0.0306
9	Standard deviation of intercept (S_a)	2.3528 x 10^{-2}	2.0934 x 10^{-2}
10	Standard error of estimation (S_e)	2.6790 x 10^{-2}	2.3837 x 10^{-2}
11	Correlation coefficient (r^2)	0.9886	0.9877
12	Relative standard deviation (%)*	0.6363	1.1870
13	% Range of error(Confidence Limits) 0.05 level*	0.6678	1.2459
14	% Range of error(Confidence Limits)0.01 level	1.0474	1.9540
15	% Error in bulk samples**	0.6489	0.372

*: Average of six determinations considered**: Average of three determinations

Table 2. Assay and recovery of EHB in Pharmaceutical Formulations

Sample	Amount taken (mg)	Amount found by proposed methods		Reference Methods	Percentage recovery by proposed methods	
		M_A	M_B		M_A	M_B
Tablet I	40	39.785 ±0.019 F=1.41 t=0.71	39.824 ±0.017 F=1.12 t=0.59	39.92 ±0.016	99.459 ±0.175	99.476 ±0.149
Tablet II	40	39.815 ±0.026 F=1.159 t=1.13	39.793 ±0.031 F=1.229 t=1.10	39.88 ±0.028	99.765 ±0.106	99.580 ±0.240

Average ± standard deviation of six determinations; the t- and F- values refer to comparison of the proposed method with the reference method. Theoretical values at 95% confidence limit t=2.57, F=5.05.
After adding 2 different amounts of the pure labeled to the pharmaceutical formulations, each value is an average of 3 determinations.

APPLICATION

The present method is rapid and cost is low compare to other methods. This method is economical.

CONCLUSION

The proposed methods for EHB determination have many advantages over other analytical methods due to its rapidity, lower cost and environmental safety. Unlike HPLC, LC procedures, the instrument is simple and is not costly. Economically, all the analytical reagents are in expensive and available in any analytical laboratory. The proposed methods report new ways for the determination of EHB in pharmaceuticals

REFERENCES

[1]. L. R. Snyder, J. J. Kirkland, Introduction to Modern Liquid Chromatography, 2nd Ed., John Wiley and Sons, Inc., p.292.
[2]. Sean C Sweetman, Martindale, The complete drug reference, Pharmaceutical Press, London, Chicago, 34th edition **2005**.
[3]. http://en.wikipedia.org/wiki/Eletriptan.
[4]. E. John Macor, J. Martin Wythes, Indole Derivates. U.S. Patent no. 5545644, **1996**.
[5]. D. Suneetha and A.Lakshmana Rao, A Validated RP-HPLC Method for the Estimation of Quetiapine in Bulk and Pharmaceutical Formulations, *Int.J.Chem Envir and Pharm Research*. **2010**, 1(2), 95-99.
[6]. Gadi Raju Ramalinga Raju, Raju V. K Vegesna, G. S. Prasad, Estimation of Eletriptan Hydrbromide in tablet dosage form by RP-HPLC, *Indo American Journal Pharmaceutical Research*, **2013**, 3(9), 7299-7306.
[7]. Dheeravath Saida Naik, Kasani Ramadevi, Bhagawan.D, Method Development and Validation of Eletriptan Hydrobromide pharmaceutical Dosage form by RP-HPLC, *Int.J.Engineer.Res and Applications*, **2013**, 3(6), 1-5.
[8]. S. Sirish Chandra, T. Priyanka, Naga Sowjanya, A. Ajitha, Uma Maheswara Rao, A New Method Development and validation for Estimation of Eletriptan by using RP-HPLC, *Int. J of Pharm Res and Anal*, **2014**, 4(5), 344-347.
[9]. V. Venugopal, G. Ramu, A. Biksham Babu, C. Rambabu, An Isocratic reverse phase HPLC method Development for the Determination of Eletriptan Hydrobromide in pure and pharmaceutical formulations, *Int. J. Pharm Tech. Res*, **2012**, 4(4), 1504-1507.
[10]. Ramzia I. El-Bagary, Nashwah G. Mohammed and Heba A. Nasr Two Chromatographic Methods for the Determination of Some Antimigraine Drugs, *Analytical Chemistry Insights*, **2012**, 7, 13-21.
[11]. Miraz Zrcevic, Biljana Jocic, Snezana Agatonovic-kustrin and Ljiljana Zvanoic, Validation of an HPLC method for the simultaneous determination of Eletriptan and UK 120.413, *J. Serb. Chem. Soc.*, **2006**, 71(11), 1195-1205.
[12]. G. Mani Kumar, J.V. L.N. Seshagiri Rao, N. Jyothi, Reversed phase High performance Liquid chromatographic method for the estimation of Eletriptan in Bulk drug and In Pharmaceutical Formulations, *Int. J. Inv. Pharm. Sci.*, **2013**, 1(4), 397-403.
[13]. N. Usha Rani, R. Sreenivasa Rao, K. Saraswathi, T. E. G. K. Murthy, RP-HPLC method for Simultaneous estimation of Avitriptan and Eletriptan in Pharmaceutical dosage forms, Novus *International Journal of Analytical Innovatons*, **2012**, 1(3), 19-29
[14]. B. Jocia, M. Zecevia, L. Zivanovia, A. Protia, M. Jadranin, Study of Forced degradation behavior of Eletriptan hydrobromide by LC and LC-MS and development of stability-indicating method, *J.Pharm.Biomed Anal*. **2009**, 50, 622-629.
[15]. P. Sunitha, Ch. Jhansirani, B. Kavitha, N. Sirisha, A. Pavan, Method Development and validaton of Eletriptan hydrobromide tablets by UV-Visible Spectrophotometric method. *Int.J.Pharm.Chem and Bio.Sci*. **2012**, 2(4), 427-430.
[16]. G. Kumara Swamy, J.M.R. Kumar, J.V.L.N. Sheshagiri Rao, U. Ashok Kumar, E. Vinaya Snehalatha, Spectrophotometric Method for the Estimation of Eletriptan Hydrobromide in pure and tablet dosage forms, *Int.J.Chem and Anal. Sci*., **2011**, 2(8), 123-125

[17]. D. Murali, T. Neeharika, C. Ram babu, Spectrophotometric Determination of Nebivolol Hydrochloride in Bulk and Pharmaceutical Formulations, *Asian Journal of Chemistry*, **2013**, 25(6), 2981-2984
[18]. Amina Mohamed El-Brashy,Mohamed El-Sayed MetwallyFawzi Abdallah El-Sepai, Spectrophotometric Determination of Some Fluoroquinolone Antibacterials by Ion-pair Complex Formation with Cobalt (II) Tetrathiocyanate, *Journal of the Chinese Chemical Society*, **2005**, 32, 77-84.
[19]. MustafaJamal KhaleelBichan, Fadam Muteb Abadoon, A Novel Spectrophotometric Determination of Methyl Dopa Through Ternary Complexation Procedure Using Fe(III),Mn(II) With b2-Amino Pyridine, *Asian J Pharm Clin Res*, **2019**, 12(3), 366-371
[20]. Sabri khalil,Analytical applications of ion-associate complexes for the microdetermination of loratadine hydrochloride in pharmaceutical formulations and urine samples, *ACAIJ*, **2014**,14(12), 481-86
[21]. N. Balaji, V. R. Sivaraman, P. Neeraja, A Validated UPLC method for the determination of process related impurities in Anti-migraine bulk drug. *J. Appl. Chem*, **2013**, 3(4), 20-28.
[22]. A.Suneetha, R. Naga Pradeep and A. Pratyusha, TLC-Densitometric method for Estimation of Eletriptan Hydrobromide in Bulk and Pharmaceutical Dosage forms. *Int J. Pharm and Chem science*, **2014**, 3(1), 66-70.
[23]. Ramzia I. El-Bagary, Nashwah G. Mohammed and Heba A. Nasr, Fluorimetric and colorimetric methods for the determination of some anti-migraine drugs. *J.Chem.Pharm.Res*, **2011**, 3(4), 340-314.
[24]. Weiss, David J, Saunders, Kenneth, Lunte, Craig E, PH-Mediated field-amplified sample stacking of pharmaceutical cations in high-ionic strength samples. *Inter.J. Res. Pharmaceu. & Biomed. Sciences*, *Electrophoresis*. **2001**, 22(1), 59-65.
[25]. Pavan Kommavarapu, Arthanareeswari Maruthapillai, Kamarai Palanisamy, Identification and quantitative determination of Eletriptan hydrobromide polymorphs: Thermal, diffractometric and spectrometric studies. *J .Taibah University for Science*, **2015**, 9(4), 586-593.
[26]. Analytical Applications of E.B.T in Spectrophotometric Determination of Eletriptan Hydro Bromide, *Innovare Journal of Sceinces*, **2016**, 4(2), 5-8