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Article

Visible Spectrophotometric Methods for the Determination of Triprolidine Hydrochloride in pure and Pharmaceutical Formulations Using Cobalt Thiocyanide And Citric Anhydride

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ABSTRACT

Two visible spectrophotometric methods were developed A and B for the determination of Tripolidine Hydrochloride in pure and pharmaceutical formulations. Method A is based on the formation of co-ordination complex of tertiary amine of TPH (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 TPH. The coloured products exhibit absorption λ_{max} at 623 nm and 546nm. Regression analysis of Beer-Lambert plots showed good correlation in the concentration ranges 8-48 µg/ml, correlation co-efficients are 0.9999(A), 0.9822(B);the Sandell's sensitivities are 2.7705 x 10^{-3} , 1.5058 x 10^{-3} (1 mole cm^{-1}); molar absorptivity values are1.1364 x 10^5, 2.0908 x 10^5 (µg cm^{-2})for methods A,B respectively.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. The results are found satisfactory and reproducible. These methods are applied successfully for the estimation of the TPH 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.

Key words: Coordination complex, Dehydration product, Tertiary amino group, Sandells sensitivity

1. INTRODUCTION

Triprolidine hydrochloride (TPH) is chemically 2-[(1E)-1-(4-methylphenyl)-3-(pyrrolidin-1-yl)prop-1-en-1-yl] pyridine (Figure 1). This is anti-allergic, Histamine H1 antagonist that blocks the action of endogenous histamine, which subsequently leads to temporary relief of negative symptoms brought on by histamine. It is used for the treatment of seasonal or perennial allergic rhinitis or non-allergic rhinitis, conjunctivitis, and mild urticaria and angioedema [1]. The most common side effects are sedation, dizziness, gastrointestinal disturbances, nausea, vomiting, and diarrhea. It may also produce blurred vision, dryness of mouth, tight of chest, blood disorders including agranulocytosis, and hemolytic anemia [2]. Literature survey revealed that few analytical methods have been reported for the determination of TPH in plasma using Thin-layer chromatography [3] simultaneous determination of TPH with other anti-histamines [4-6] other agents [7,8]. Few methods have been developed for the determination of triprolidine by high-performance liquid chromatography (HPLC) [9] and spectrophotometric method [10]. Spectrophotometric and HPLC [11] determination of TPH and its metabolite in biological samples using liquid chromatography-mass spectrometry [12]. Capillary Zone Electrophoresis Method for Quality Control Analysis of TPH with other drugs [13] degradation studies of TPH and Stability indicating Ultra Performance Liquid Chromatography method [14]. New plastic membrane and carbon paste ion elective electrodes for the determination of triprolidine [15]. TPH is usually administered in combination with dextromethorphan and/or phenylpropanolamine and also with paracetamol [16].

The analytical useful functional groups in TPH 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 the proposed methods. All these methods have extended to pharmaceutical formulations as well. Reported HPLC methods have lesser output and are occasionally lacking the stress behavior studies. Hence, there is no simple, cost-effective individual method has been reported. Validation as per USFDA and ICH guidelines [17,18] is done along with stress degradation studies. The applications of Cobalt thiocyanide and citric anhydride reagents [19-28] in spectrophotometric analysis were also reviewed whether any method developed for the selected drug by the authors is reported.

1.1. Instruments Used

A Shimadzu ultraviolet-visible spectrophotometer 1801 with 1 cm matched quartz cells was used for all spectral and absorbance

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measurements. A Systronics digital pH meter 361 was used for pH measurements.

1.2. Preparation of Standard Drug Solution

The stock solution (1 mg/ml) of TPH was prepared by dissolving 100 mg of it in 100 ml of milli pore-distilled water. A portion of this stock solution was diluted stepwise with the distilled water to obtain the working standard TPH solution of concentrations 240 µg/ml for the method.

1.3. Procedure of Assay of TPH in Formulations

An accurately weighed amount of formulation (tablet) 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 solution of drug in formulations. One ml of this solution was furthered diluted to 25 ml to get 40 µg ml^{-1} solutions. 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.

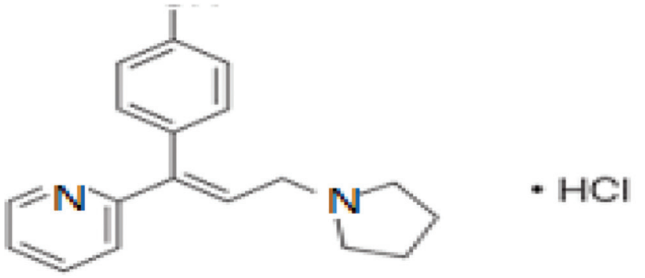


Figure 1: Chemical structure of triprolidine hydrochloride

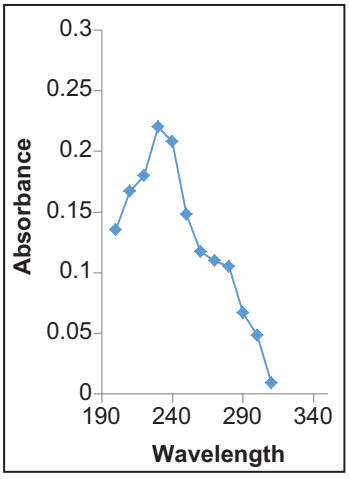


Figure 2: Absorption spectra of triprolidine hydrochloride in methanol (ultraviolet reference method)

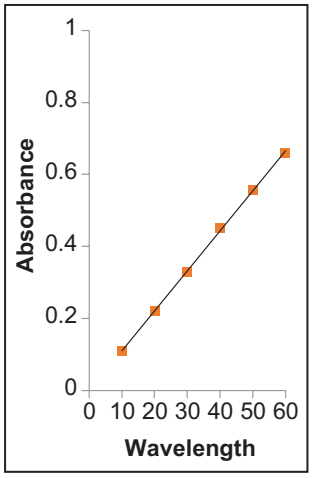


Figure 3: Beer's law plot of triprolidine hydrochloride in methanol (ultraviolet reference method)

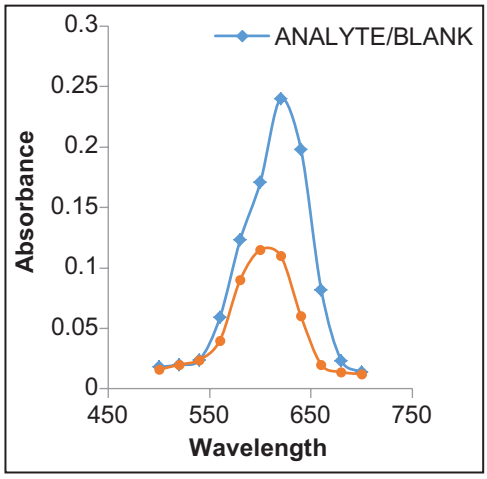


Figure 4: Absorption spectra of triprolidine hydrochloride: Cobalt thiocyanate

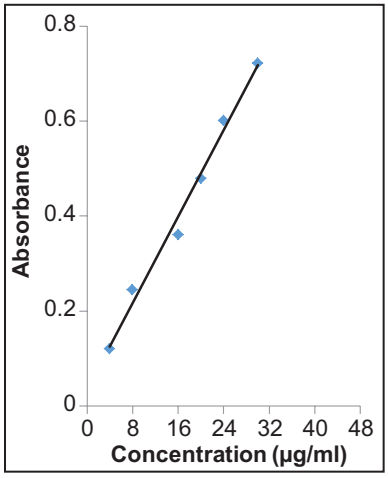


Figure 5: Beer's plot of triprolidine hydrochloride: Cobalt thiocyanate

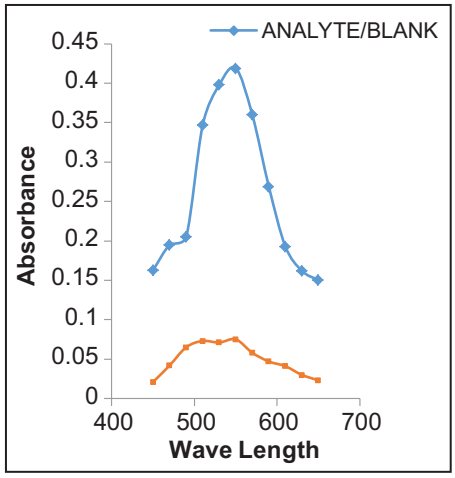


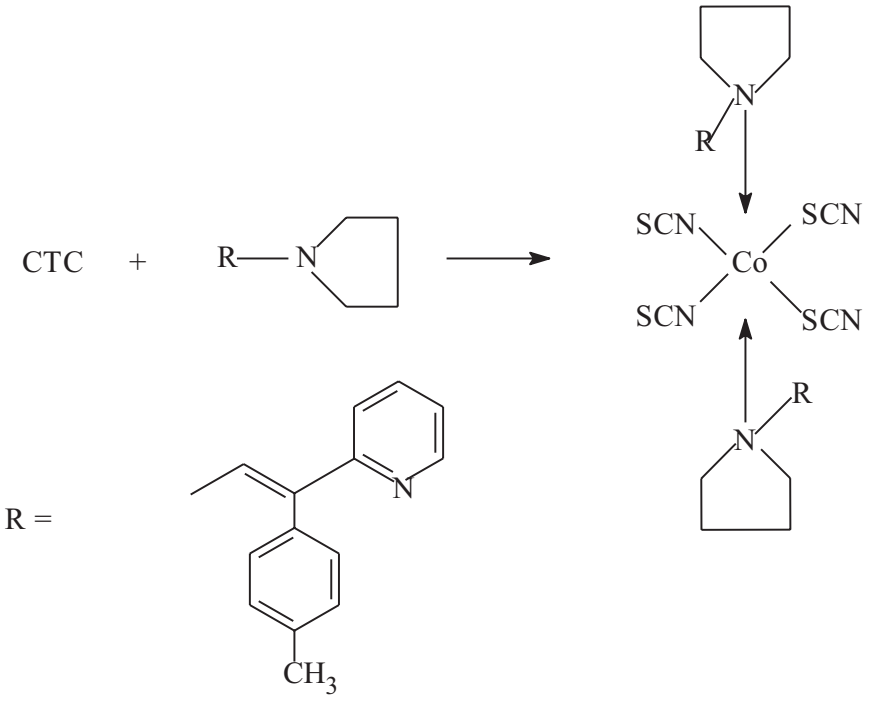
Figure 6: Absorption spectra of triprolidine hydrochloride: CiA/AC2O

2. METHOD-A

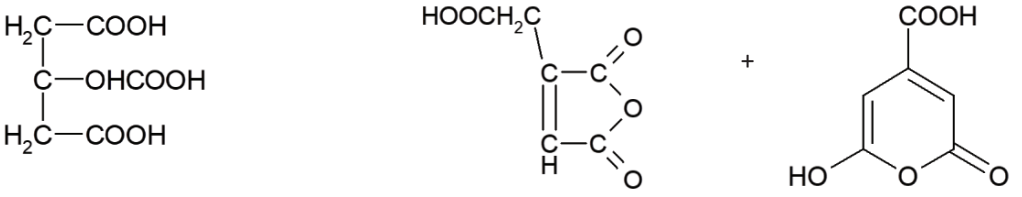
Aliquots of standard drug solution (0.1–0.6 ml, 48 µg/ml) were delivered into a series of calibrated tubes. Then, 2.0 ml of buffer (pH 2.0) and 5.0 ml of Cobalt thiocyanate (CTC) solutions were added and the total volume in each tube was adjusted to 15 ml with distilled water. The solutions in the tubes were transferred to 125 ml separating funnels. 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 TPH in the sample was obtained from the Beer's law plot (Figure 5)

2.1. Method-B

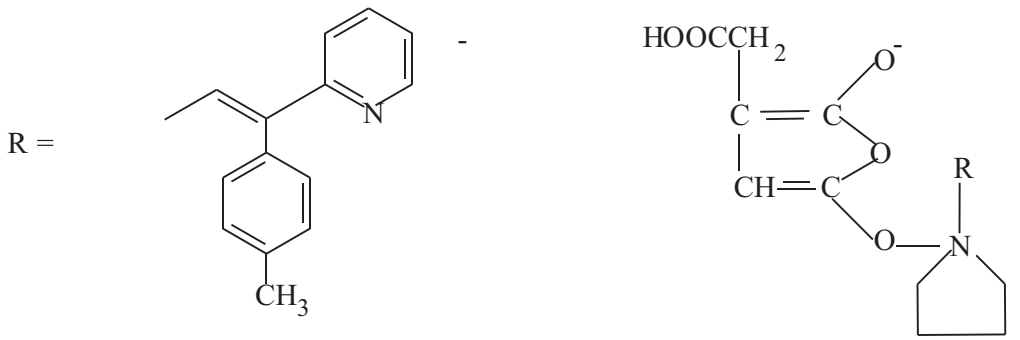
Aliquots of standard TPH in free base form 0.1 to 0.6 ml, 48 µg/ml were taken into a series of 25 ml graduated tubes and evaporated to dryness on a water bath. The tubes were cooled at room temperature and then 10 ml of CiA-AC_2O reagent was added to each tube. The tubes were placed in boiling water 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} 550 nm (Figure 6) against reagent blank. The quantity of TPH in the sample was obtained from the Beer's law plot (Figure 7).



Scheme 1



Aconitic anhydride



Scheme 2

2.2. Chemistry of the Colored Species in the Present Investigation

TPH possesses different functional moieties such as tertiary amino group and indole of varied reactivity. An attempt has been made to indicate the nature of colored species formed in each proposed method for TPH determination tentatively based on analogy.

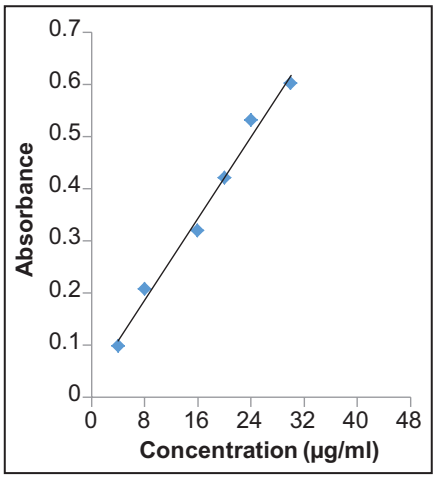


Figure 7: Beer's plot of triprolidine hydrochloride: CiA/AC_2O

2.3. Method-A

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 colored species formed is the co-ordination complex of tertiary amine of TPH (electron donor) and central metal of the CTC (acceptor) which is extractable into nitrobenzene from aqueous solution. The reactions are described in Scheme 1

2.4. 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 color developed due to the formation of internal salt. In the present investigation, the author has successfully developed procedure for the visible spectrophotometric determination of TPH 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 TPH. The reactions are described in Scheme 2

Table 1: Optical and regression characteristics, precision, and accuracy of the proposed methods for triprolidine hydrochloride

Sl. no.	Parameter	Method-A	Method-B
1.	Wave length λ_{max} (nm)	623	550
2.	Beer's law limits (µg ml^{-1})	8–48	8–48
3.	Detection limits (µg ml^{-1})	0.5754	6.2896
4.	Molar absorptivity (1 mole cm^{-1})	1.1364×10^{5}	2.0908×10^{5}
5.	Sandell's sensitivity (µg cm^{-2}/0.001 absorbance unit)	2.7705×10^{-3}	1.5058×10^{-3}
6.	Regression equation (Y = a+bC) Slope (b)	0.0239	0.0271
7.	Standard deviation of slope (S_b)	1.4714×10^{-4}	1.8236×10^{-3}
8.	Intercept (a)	0.0069	0.0409
9.	Standard deviation of intercept (S_a)	4.5843×10^{-3}	5.6816×10^{-2}
10.	Standard error of estimation (S_e)	4.9244×10^{-3}	6.1030×10^{-2}
11.	Correlation coefficient (r^2)	0.9999	0.9822
12.	Relative standard deviation (%)*	0.6928	0.8632
13.	% Range of error(Confidence Limits) 0.05 level*	0.7271	0.9060
14.	% Range of error(Confidence Limits) 0.01 level	1.1404	1.4209
15.	% Error in bulk samples**	0.342	0.234

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

Table 2: Assay and recovery of triprolidine hydrochloride in formulations

Sample	Amount taken (mg)	Amount found by proposed methods		Reference Methods	Percentage recovery by proposed methods	
		Method-A	Method-B		Method-A	Method-B
Tablet I	2.5	2.489±0.0032 F=1.13 *t*=0.57	2.493±0.0028 F=1.147 *t*=0.22	2.495±0.003	99.875±0.17	99.563±0.20
Tablet II	2.5	2.488±0.0019 F=1.108 *t*=1.21	2.494±0.0015 F=1.777 *t*=0.43	2.496±0.002	99.810±0.12	99.718±0.19

*: 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 two different amounts of the pure labeled to the formulations, each value is an average of three determinations

3. RESULTS AND DISCUSSION

Optimum operating conditions used in the procedure were established adopting variation of one variable at a time (OVAT) method. Optimum operating conditions used in the procedure were established adopting variation of one variable at a time (OVAT) method. To develop an exact method ,the effect of various parameters such as pH of Buffer on color development to know the better absorption, volume of buffer required for maximum intensity of color in Nitro Benzene layer and effect of shaking time were taken for method-A, and for method-B,volume of Citric Anhydride, effect of reaction time on color development, solvent for final dilution, stability of the colored. 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 such as 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 TPH 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.

4. CONCLUSION

The proposed methods for TPH determination have many advantages over other analytical methods due to its rapidity, lower cost. Unlike HPLC, LC procedures, the instrument is simple. The proposed methods report new ways for the determination of TPH in commercial formulations.

5. REFERENCES

1. Drug Profile. Triprolidine. Available from: http://www.mims.com/troprolidine. [Last accessed on 2015].
2. J. E. F. Reynolds, (1982) Promethazine and other anti-histamine In: ***Martindale: The Extra Pharmacopoeia***, Vol. 28. The Pharmaceutical Press, London, p1294.
3. R. L. Deangelis, M. F. Kearney, R. M. Welch, (1997) Determination of triprolidine in human plasma by quantitative TLC, ***Journal of Pharmaceutical Sciences***, **66**: 841-843.
4. A. Gupta, R. K. Nema, A. Sahu, (2009) Simultaneous estimation of phenylpropanolamine hydrochloride and triprolidine hydrochloride in pharmaceutical preparations by RP-HPLC method, ***The Pharma Research***, **1**: 67-71.
5. Caglar H, Buyuktunce E, (2014) HPLC method development and vaidation :simultaneous determination of active ingredients in cough and cold pharmaceuticals, ***International Journal of Pharmacy and Pharmaceutical Sciences***, **6**: 421-428.
6. Y. EL-Shabrawy, A. El-Gindy, M. A. S. Shoeib, Y. El-Gindy, (2014) An HPLC method for determination of 15 pharmaceutical compounds in anti-cold products, ***Standard Research Journal of Pharmacy and Pharmacology***, **1**: 86-94.
7. A. El-Gindya, K. A. S. Attiab, M. W. Nassarb, H. Abu Aeadab, M. A. S. Shoeibc, (2013) HPLC method for determination of paracetamol, psudoephedrine, triprolidine, methylparaben, propylparaben, sodium benzoate and other related substances in pharmaceutical syrup, ***Journal of Liquid Cheomatography and Related Technologies***, **36**: 1251-1263.
8. B. M. Saida, S. A. Alabjaw, F. Deabas, M. M. Saket, R. Shareiah, E. S. M. Abu Nameh, (2014) Liquid chromatographic method for the determination of triprolidine, liquid chromatographic method for the determination of triprolidine, ***Journal of Chemical and Pharmaceutical Research***, **6**: 327-332.
9. A. Mumtaz, A. A. Kazi, T. Aman, M. U. Sabri, F. Noureen, (2005) Dtermination of troprolidine-Hcl by spectrophoto metric method in pure and pharmaceutical preparartions using dichloronitrobenzene as a new cheomagenic reagent, ***Proceedings of the Pakistan Academy of Sciences***, **42**: 253-259.
10. M. Hinge, K. R. Patel, R. J. Mahinda, (2015) Spectrophotometrioc and high performance liquid chromatographic determination (HPLC) of triprolidine and pseudoephedrine hydrochloride in tablet dosage form, ***Pharmaceutical Methods***, **15**: 87-93.
11. E. B. Jr. Hansen, T. A. Getek, W. A. Korfmacher, (1989) Application of HPLC-thermospray ionization mass spectrometry for the analysis of triprolidine and its metabolite hydromethytriprolidine in biological samples, ***Journal of Analytical Toxicology***, **13**: 185-187.
12. S. Di Berardino, R. Jasionowska, (2014) Rapid and sensitive CZE (capillary zone electrophoresis) method for quality control analysis of pharmaceuticals containing pseudoephedrine, triprolidine and paracetamol, ***American Journal of Analytical Chemistry***, **5**: 613-619.
13. M. K. Moneab, K. B. Chandrasekh, S. Vyasa, (2011) Degradation studies of troprolidine: Isolation, characterization of oxidative degradationproducts and development of a validated stability indicating indicating method UPLC method, ***Journal of Chromatography and Related Technologies***, **34**: 652-669.
14. S. I. Zayed, (2004) New plastic membrane and carbon paste ion selective electrodes for the determination of troprolidine, ***Analytical Sciences***, **20**: 1043-1048.
15. C. E. Bye, J. Cooper, D. W. Empey, A. S. Fowle, D. T. Hughes, E. Letley, J. O'Grady, (1980) Effects of pseudoephedrine and triprolidine, alone and in combination, on symptoms of the common cold, ***The BMJ***, **281**: 189-190.
16. Guidance for Industry, (2000) ***Analytical Procedure and methods Validation: Chemistry, Manufacturing and Controls Documentation; Draft Guidance***. Rockville, MD. UD FDA.
17. International Conference on Hormonization, (1995) Q_2A: Text on validation of analytical procedures, ***Federal Register***, **60**: 11260-11262.
18. A. V. Subbayamma, C. Rambabu, (2009) Cobalt thiocyanate as chromogenic reagent for determination of trandolapril and aripiprazole, ***Asian Journal of Chemistry***, **21**: 4285-4288.
19. G. Tuljarani, D. G. Sankar, P. Kadgapathi, B. Satyanarayana, (2011) Novel visible spectrophotometric method for determination of few selected drugs using cobalt thiocyanate as chromogenic reagent, ***International Journal of Chemical Sciences***, **9**: 255-264.
20. V. M. Sarma, B. V. Rao, T. V. V. Satyanarayana, V. Sridhar, (2015) A novel method for the assay of metoprolol by visible spectrophotometry using cobalt thiocyanate, ***International Journal of Advanced Research in Science and Technology***, **4**: 456-461.
21. V. Rajendran, N. S. R. Yerrapothini, S. K. Guntamukkala, K. Sugandha, D. M. Dasaratha, (2015) Method development for quantification of donor-acceptor complexes of alverine citrate and tapentadol by visible spectrophotometry, ***Journal of Applied***

Pharmaceutical Science, **5**: 68-72.
22. W. D. Langley, (1967) Reaction of tertiary amine, quaternary ammonium, and inorganic salts with citric acid in acetic anhydride, ***Analytical Chemistry***, **39**: 199-202.
23. A. Unnisia, K. V. G. Raju, A. N. Jyothi, K. Balaji, (2014) New spectrophotometric methods for estimation of perindopril erbumine in bulk and pharmaceutical formulations, ***Journal of Scientific Research***, **6**: 319-327.
24. J. R. Marier, D. M. Boulet, (1958) Direct determination of citric acid in milk with an improved pyridine-acetic anhydride method, ***Journal of Dairy Science***, **41**: 1683-1692.
25. Y. A. Beltagy, (1976) Citric acid-acetic anhydride reagent for determining some alkaloids and organic bases, ***Pharmazie***, **31**: 483-484.
26. K. R. Raju, S. R. K. Akella, N. Lingaiah, A. R. Reddy, U. T. B. Rao, (1997) Spectrophotometric determination of isoproturon and metoxuron in technical and formulation grade samples using citric acid-acetic anhydride reagent, ***Indian Journal of Chemical Technology***, **4**: 196-200.
27. K. R. Babu, L. S. Swarup, B. K. Ramu, M. N. Rao, C. R. Das, (2012) Simple and inexpensive methods development for determination of venlafaxine hydrochloride from its solid dosage forms by visible spectrophotometry, ***E-Journal of Chemistry***, **9**: 1645-1654.
28. H. Auterhoff, I. Schwingel, (1975) The reaction of citric acetic anhydride and pyridine, ***Archiv der Pharmazie***, **308**: 583-587.

****Bibliographical Sketch***

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