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ION ASSOCIATION METHODS FOR THE SPECTROPHOTOMETRIC DETERMINATION OF TRIPROLIDINE HYDROCHLORIDE USING ACIDIC DYES TPOOO, ACG AND EBT IN PURE AND PHARMACEUTICAL FORMULATIONS

P.V.S.R.Mohana Rao*, Raghu Babu. K[1], Ch. V. R. Murthy[2], M. L. N. Acharyulu[3]

*Research Scholar, Department of Engineering Chemistry, A.U.Collegeof Engineering (A)
[1] Professor, Department of Engineering Chemistry, A.U.College of Engineering (A)
[2] Principal and professor, Department of Chemical Engineering, A.U.College of Engineering (A)
[3] Professor, Department of Applied Sceinces and Humanities, VITAM College of Engineering, Mindivanipalem, Visakhapatnam, Andhra Pradesh- 530017, India

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Corresponding author:
P. V. S. R. Mohana Rao, Research Scholar, Department of Engineering Chemistry, A. U. College of Engineering, Visakhapatnam, Andhra Pradesh

ABSTRACT

Three simple and sensitive extractive visible spectrophotometric methods (A,B and C) for the assay of Triprolidine hydrochloride (TPH) in pure and pharmaceutical formulations based on the formation of colored chloroform soluble ion-association associates under specified experimental conditions are described. Threeo dyes namely acidic dye TropaeolineOOO (TPOOO, method A), Azocarmine-G (ACG, method B), Erio chrome Black-T (EBT, method C) are utilized. The extracts of the ion-associates exhibit absorption λ_{max} at 486 nm and 538 nm, 510nm for methods A, B and C respectively. Regression analysis of Beer-Lambert plots showed good correlation in the concentration ranges (4-24) µg/ml for method A, (20-120) µg/ml for method B, (40-240) µg/ml For method-C and correlation co-efficients are 0.9986(A), 0.9994 (B), 0.9998(C) 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 Triprolidine hydrochloride (TPH) in the presence of other ingredients that are usually present in formulations.

INTRODUCTION

Triprolidine hydrochloride (**Fig.1**) is chemically 2-[(1E)-1-(4-methylphenyl)-3-(pyrrolidin-1-yl)prop-1-en-1-yl] pyridine. 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 perenial allergic rhinitis or non-allergic rhinitis, conjunctivitis and mild utricaria and angioedema

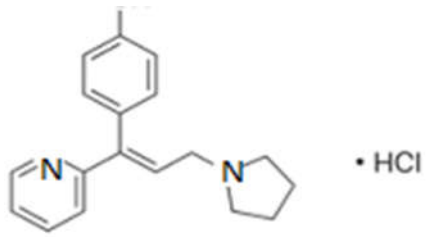

Fig.1 Chemical Structure of Triprolidine hydrochloride

Literature Survey on the analytical methods for TPH

Triprolidine hydrochloride is chemically 2-[(1E)-1-(4-methylphenyl)-3-(pyrrolidin-1-yl)prop-1-en-1-yl] pyridine. 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 utricaria and angioedema[1]. The most common side effects are sedation, dizziness, in co-ordination, gastrointestinal disturbances, nausea, vomiting and diarrhea. It may also produce blurred vision, dryness of mouth, tight of chest, blood disorders including agranulocytosis and haemolyticanaenia[2]. Literature survey revealed that few analytical methods have been reported for determination of TPH in plasma using Thin layer chromatography[3] simultaneous determination of TPH with other anti-histamines[3-5] other agents[6, 7]. Few methods have been developed for determination of Triprolidine by HPLC [8] and Spectrophotometric method[9]. Spectro photometric and High Performance Liquid Chromatographic [10] determination of TPH and its metabolite in biological samples using liquid chromatography-mass spectrometry[11]. Capillary Zone Electrophoresis Method for Quality Control Analysis of TPH with other drugs[12] degradation studies of TPH and Stability indicating UPLC method[13]. New plastic membrane and carbon paste ion elective electrodes for determination of Triprolidine[14]. TPH is usually administered in combination with dextromethorphan and/or phenylpropanolamine and also with paracetamol[15]. Validation as per USFDA and ICH guidelines[16, 17] is done along with stress degradation studies. Upon thorough survey of literature there is no single method

available for the estimation by visible spectrophotometry which is far simpler and economical and less time consuming as compared to above mentioned methods. So, the author made some attempts in developing visible spectrophotometric methods and succeeded in developing three methods based on the reaction between the drug and acidic dyes namely TPOOO, ACG and EBT under specified experimental conditions. As the extraction spectrophotometric procedures are popular for their sensitivity and selectivity in the assay of drugs, the extractive spectrophotometric acid-dye technique was therefore, utilized in the present work for the estimation of TPH. The present paper describes three simple and sensitive extraction visible spectro photometric methods for the determination of TPH, based on its tendency to form chloroform extractable ion-associates with acidic dyes TPOOO[18-22] belonging to Azo category dye (method A), Azocarmine G[23-24] belonging to Phenazine category dye (method B) and EBT[25-31] belonging to Azo category dye (method C), or under experimental conditions by exploiting the basic nature of nitrogen in tertiary amine of the drug molecule. According to the literature, it is the first time for TPH determination in bulk as well as formulations by visible spectrophotometry.

Methods

Instruments used

A 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) of Triprolidine Hydrochloride (TPH) 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 TPH solution of concentrations 4-240 µg/m*l*. A reported UV spectrophotometric method has been adopted for the determination of TPH in pharmaceutical formulations (tablets). The absorbance of the solution was determined λmax 223 nm (**Fig.2**). The quantity of the drug was computed from the Beer's law plot (**Fig. 3**) of the standard drug in distilled water.

Procedure of Assay of TPH in formulations

An accurately weighed amount of formulation (injection powder) 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} solution.

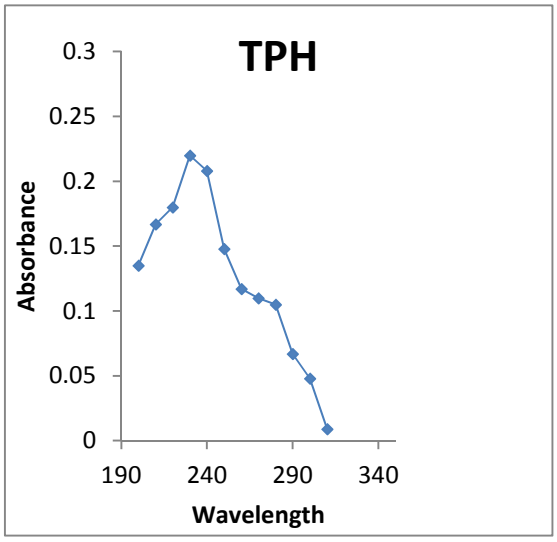

Fig.2 Absorption spectra of TPH in methanol (UV reference method)

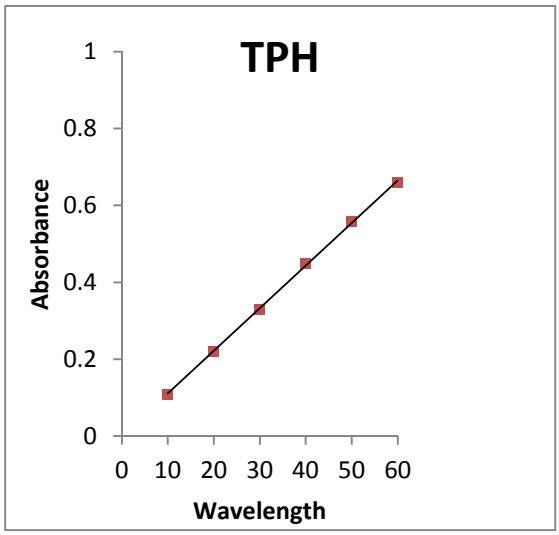

Fig.3 Beer's law plot of TPH in methanol (UV reference method)

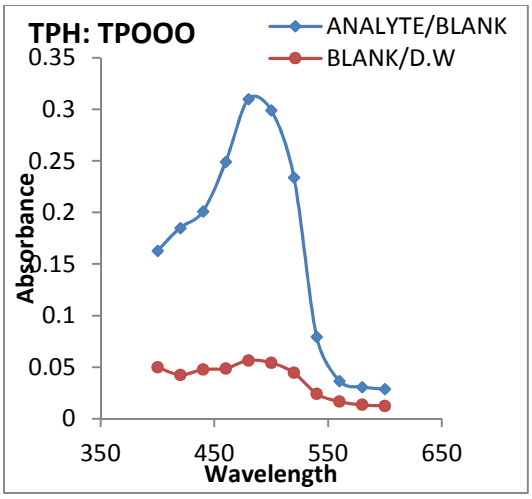

Fig.4 Absorption spectra of TPH: TP000

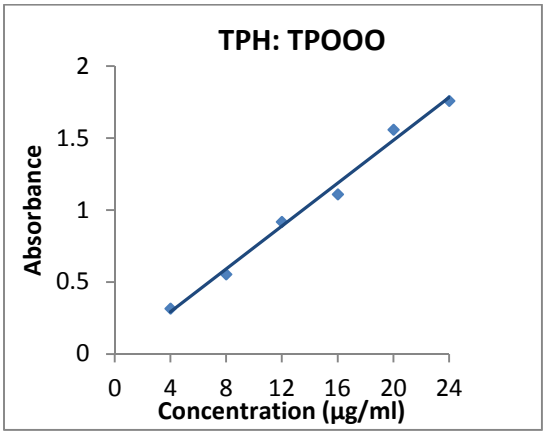

Fig.5 Beer's plot of TPH: TPooo

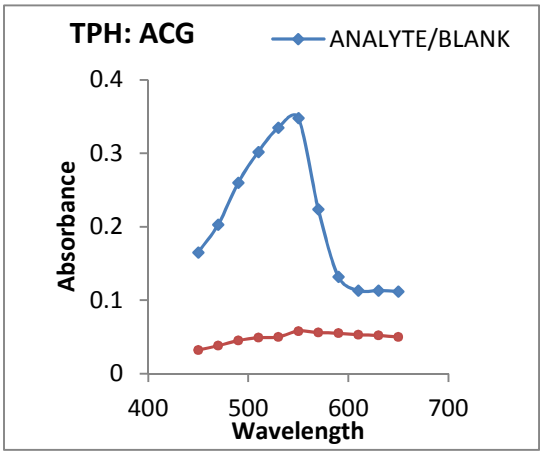

Fig.6 Absorption spectra of TPH: ACG

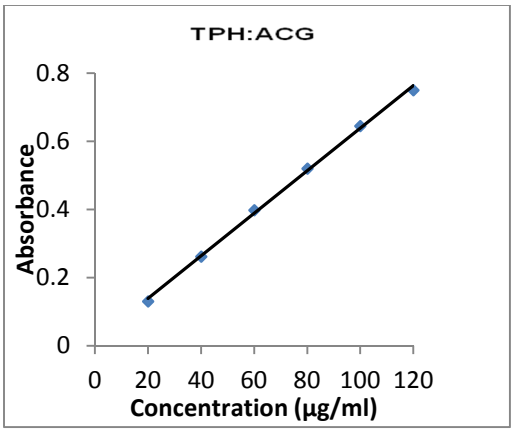

Fig.7 Beer's plot of TPH: ACG

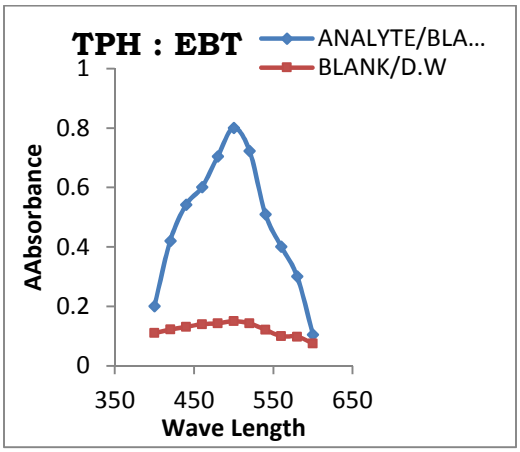

Fig.8 Absorption spectra of TPH: EBT

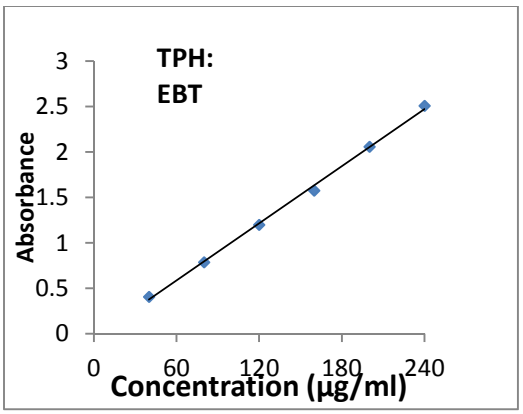

Fig.9 Beer's plot of TPH: EBT

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 TPH in bulk samples.

Method –A:

Into a series of 125 ml separating funnels containing aliquots of standard TPH solution (0.1-0.6 ml; 24 µg/ml), 6.0 ml of 0.1M HCl and 2.0 ml of dye solution (TPooo) were added. The total volume of aqueous phase in each separating funnel was adjusted to 15 ml with distilled water and then10 ml of $CHCl_3$ was added. The contents were shaken for 2 minutes. The two phases were allowed to separate and the absorbances of the separated organic layer were measured at λ_{max} 485 nm(**Fig.4**) against a similar reagent blank. The colored species was stable for 1 hour. The amount of TPH in sample solution was obtained from the Beers-Lambert's plot (**Fig.5**).

Method –B:

Aliquots of standard TPH solution (1.0 – 6.0 ml, 120 µg/ml) were placed in a series of 125 ml separating funnels. A volume of 6.0 ml of buffer (pH 1.5) and 2.0 ml of ACG were added respectively. The total volume of aqueous phase in each separating funnel was adjusted to 15.0 ml with distilled water. Then 10 ml of $CHCl_3$ was added to each separating funnel and the contents were shaken for 2 min and allowed to separate. The organic layer was collected through cotton plug and the absorbance was measured immediately at λ_{max} 538 nm (**Fig.6**) against a

reagent blank. The colored species was stable for 1 hour. The amount of TPH in sample solution was obtained from the Beers-Lambert's plot (**Fig.7**)

Method -C:

Into a series of 25 ml calibrated tubes, aliquots of standard TPH solution (1-6ml, 240 µg /ml) were transferred and then solutions of 2 ml methanol and 2 ml of 0.1% Erichrome Black-T solution was added successively and the volume was made to 15 ml by the addition of water and final volume made to 25 ml by the addition of chloroform. Thus the formed solution allowed to stand for clear separation of the two phases. The chloroform was transferred into test tube by separating funnel. The absorbance was measured at λ_{max} 510 nm(**Fig.8**) against reagent blank prepared similarly. The content of the drug was calculated from its calibration graph (**Fig.9**).

RESULTS AND DISCUSSION

Parameters Fixation:

In developing the proposed methods, a systematic study of the effects of various relevant parameters in the methods concerned were undertaken by varying one parameter at a time and controlling all other parameters to get maximum color development, minimum blank color, reproducibility and the responsible period of stability of final colored species formed. In order to test whether the coloured species formed (or diminished) in the above methods adhere to Beer-Lambert's plot, the absorbance at appropriate wavelength of a set of solutions containing different amounts of TPH and specified amounts of reagents (as described in the recommended procedures of each method) were noted against appropriate reagent blanks or distilled water. The absorption spectras were shown in (**Figs.4, 6, 8**). The Beer-Lambert's plots of the systems were illustrated graphically (**Figs.5, 7, 9**). Least square regression analysis was carried out for the slope, intercept and correlation coefficient. Beer-Lambert's limits, molar absorptivity, and Sandell's sensitivity for TPH with each one of the mentioned reagents were calculated.To determine the accuracy of the proposed methods, different amounts of bulk sample of the TPH within the Beer – Lambert's limits were taken and analysed by the proposed methods. The results of Methods A, B, C for TPH given in the T**able-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.**

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

Sl.No	Parameter	Method-A	Method-B	Method-C
1	Wave length λ_{max} (nm)	485	538	510
2	Beer's law limits (μg ml^{-1})	4-24	20-120	40-240
3	Detection limits (μg ml^{-1})	0.8795	2.8500	4.7193
4	Molar absorptivity (1 mole cm^{-1})	2.0514×10^5	2.8730×10^4	3.2141×10^4
5	Sandell's sensitivity (μg cm^{-2} / 0.001 absorbance unit)	1.2075×10^{-4}	1.0958×10^{-2}	9.7959×10^{-3}
6	Regressionequation (Y = a + bC) Slope (b)	0.0325	0.0061	0.0041
7	Standard deviation of slope (S_b)	6.1164×10^{-4}	7.4402×10^{-5}	4.1403×10^{-5}
8	Intercept (a)	0.0067	0.0043	0.0047
9	Standard deviation of intercept (S_a)	9.5280×10^{-3}	5.7951×10^{-3}	6.4498×10^{-3}
10	Standard error of estimation (S_e)	1.0234×10^{-2}	6.2249×10^{-3}	6.9282×10^{-3}
11	Correlation coefficient (r^2)	0.9986	0.9994	0.9998
12	Relative standard deviation (%)*	0.6716	1.9628	1.3441
13	% Range of error(Confidence Limits) 0.05 level*	0.7049	2.0602	1.4108
14	% Range of error(Confidence Limits)0.01 level	1.1055	3.2309	2.2125
15	% Error in bulk samples**	0.317	0.201	0.168

*: 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		
		Method A	Method B	Method C		Method A	Method B	Method C
Tablet-I	2.5	2.490 ±0.0031 F=1.06 t=0.43	2.492 ±0.0027 F=1.23 t=1.647	2.496 ±0.0029 F=1.07 t=1.25	2.495 ±0.003	99.608 ±0.15	99.752 ±0.13	99.562 ±0.18
Tablet-II	2.5	2.491 ±0.0019 F=1.10 t=0.43	2.495 ±0.0017 F=1.38 t=0.57	2.493 ±0.0021 F=1.10 t=0.22	2.496 ±0.002	99.870 ±0.20	99.506 ±0.29	99.480 ±0.11

*: 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 3 different amounts of the pure labeled to the pharmaceutical formulations, each value is an average of 3 determinations.

DECLARATION

I hereby declared that the work submitted by me is my original work and I haven't submitted either part of it or full to any of the journal.

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