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New analytical methods development for estimation of tianeptine in its tablet form by visible spectrophotometry

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ABSTRACT

The aim of the investigation was to see the simple and sensitive visible spectrophotometric methods for the determination of the tianeptine sodium in bulk and tablet dosage forms. Two direct, simple and sensitive visible spectrophotometric methods (M_1 and M_2) are described for the assay of Tianeptine sodium in pure and solid dosage forms. The method M_1 involves oxidative coupling of tianeptine with brucine in presence of sodium meta periodate and purple red colored species is formed and exhibits absorption maxima at 510nm. The method M_2 is based on the formation of yellowish brown colored species by the drug with Folin reagent and exhibits absorption maxima at 450 nm. Beer's law obeyed in the concentration range of 8-24µg/ml and 16-80 µg/ml for methodM_1 and M_2 respectively. No interference was observed from the usually existing additives in pharmaceutical formulations and the applicability of the methods was examined by analyzing STABLON tablets containing TIA and the results are statistically compared with those obtained by the UV reference method and validated with respect to accuracy, precision, linearity, limit of detection, percentage of recovery, repeatability The reported methods for its assay involve sophisticated equipment, which are very costly and pose problems of maintenance. To overcome these problems, the use of visible spectrophotometric technique is justifiable. The statistical data proved the accuracy, reproducibility and the precision of the proposed methods.

KEYWORDS

Assay;
Tri cyclic Anti-depressant;
Brucine-IO_4^-;
Folin reagent;
Nucleophillic substitution;
Oxidative coupling.

INTRODUCTION

Tianeptine sodium (TIA) (Figure 1) is a tri cyclic antidepressant compound of dibenzo thiazepine type neuro protective, anxiolytic and mood-brightening serotonin reuptake enhancer with psycho stimulant, anti-ulcer and anti-emetic properties. Chemically it is designated as (RS)-7-[(3-chloro-6, 11-dihydro-6-methyl dibenzo [c, f] [1, 2] thiazepin-11-yl) amino] heptanoic

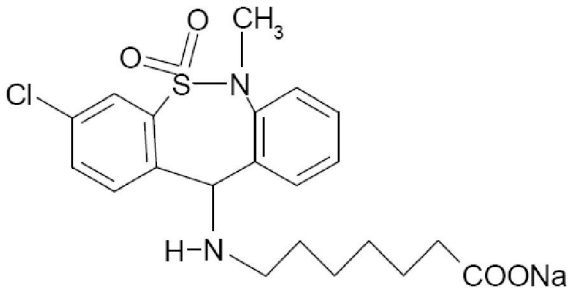

Figure 1: Chemical structure of Tianeptine sodium

acid S, S- dioxide mono sodium salt (1:1)[1].The drug is white powder and freely soluble in water, methanol and methylene chloride. Its molecular formula is $C_{21}H_{24}ClN_2O_4SNa$ with molecular weight 458.93. The drug exists as two isomers, of which the leavo isomer seems to be the therapeutically active form and shows serotonergic activity by enhancing the presynaptic reuptake of serotonin. The drug is selective facilitator of 5HT uptake in vitro and in vivo and has no effect on noradrenalin or dopamine uptake. The drug is mainly metabolized by the external route, β-oxidation of its heptanoic side chain is the major metabolic pathway and the pentanoic (MC_5) and propionic (MC_3) acid side chain derivatives are the major metabolites in urine and plasma. The drug is official in European Pharmacopoeia[2] and suggests potentiometric titration method for the assay of TIA in bulk and tablet formulations.

In the literature, several analytical techniques like HPLC[3-7], PIF methods including Flow Injection analysis[8], Spectrofluorometric[9], Voltametric[10], GC[11], UV[12] and visible spectrophotometric[13] methods have been reported for its determination in biological fluids and formulations. Even though there is one visible spectrophotometric method using acidic dyes namely bromo phenol blue (BPB), bromo cresol green (BCG), bromo thymol blue (BTB), methyl orange (MO) reported for the determination of the drug in tablets, they are tedious and requires extraction and the functional groups present in the drug not fully exploited. For routine quality control analysis, simple, rapid and cost effective visible spectrophotometric methods are required and preferred.

The main purpose of the present study was to establish a relatively simple, sensitive, validated and inexpensive extraction free visible spectrophotometric method for the determination of TIA in pure form and in pharmaceutical preparations. So the author have made some attempts in this direction and succeeded in developing two methods based on the reaction between the drug and BCN-IO_4^- reagent[14] (M_1) or Folin reagent[15] (M_2) under specified experimental conditions.

The proposed methods for TIA determination have many advantages over other analytical methods due to its rapidity, normal cost and environmental safety. Unlike HPLC, HPTLC procedures, the instrument is simple and is not costly. Economically, all the analytical reagents are inexpensive and available in any analytical laboratory. These methods can be extended for the routine quality control analysis of pharmaceutical products containing TIA.

MATERIALS & METHODS (EXPERIMENTAL)

Apparatus and chemicals

A Shimadzu UV-Visible spectrophotometer 1800 with10mm matched quartz cells was used for all spectral measurements. A Systronics digital pH meter mode-361 was used for pH measurements. All the chemicals used were of analytical grade. STABLON tablets purchased from local market. Aqueous solution of brucine (Loba, 0.2%, $506.7x10^{-3}$M prepared by dissolving 200mg of brucine initially in minimum amount of 0.16M sulphuric acid and then made up to 100ml with distilled water), sodium metaperiodate (BDH, 0.2%, $9.35x10^{-3}$M prepared by dissolving 200mg of sodium metaperiodate in 100ml distilled water and standardized iodometrically) and sulphuric acid (Qualigens, 1.2M prepared by diluting 126ml of conc. H_2SO_4 to 100ml of distilled water initially, followed by diluting to 1000ml with distilled water), Folin reagent (NQS) solution (Loba, 0.5%, $1.92x10^{-2}$M prepared by dissolving 500mg of NQS in 100 ml of distilled water), pH 8.0 buffer solution (prepared by mixing 30ml of potassium hydrogen phosphate (0.067M) and 970ml of disodium hydrogen phosphate (0.067M) and the pH of the solution was adjusted to 8.0) were prepared for method M_1 & M_2.

Preparation of Standard stock solution: The standard stock solution (1mg/ml) of TIA was prepared by dissolving 100mg of TIA in 10 ml 0.1M sodium hydroxide and the volume was brought to 100 ml with distilled water. The working standard solutions of TIA were obtained by appropriately diluting the standard stock solution with the same solvent (M_1- 200 μg/ml & M_2- 400 μg/ml). The prepared stock solution was stored at 4p C protected from light. From this stock solution, a series of standards were freshly prepared during the analysis day.

Preparation of Sample solution: About 20 tablets were weighed to get the average tablet weight and pulverized. The powder equivalent to 100mg of TIA was weighed, dispersed in 25ml of Isopropyl alcohol, sonicated for 15 minutes and filtered through

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Whatman filter paper No 41.The filtrate was evaporated to dryness and the residue was dissolved as under standard solution preparation.

Determination of wavelength maximum (λ_{max}):

Method M_1: The 3.0ml of working standard solution of TIA (200µg/ml) was taken in 25ml calibrated tube. To this, 3.0ml brucine, 1.5ml of $NaIO_4$ solution and 2.0ml of sulphuric acid were added successively and the volume was brought up to 10ml with distilled water and kept in boiling water bath for 15min for complete color development. The solution was cooled to room temperature and the volume was made up to the mark with distilled water. In order to investigate the wavelength maximum, the above colored solution was scanned in the range of 400-660 nm UV-Visible spectrophotometers against a reagent blank. From the absorption spectra (Figure 2), it was concluded that 510 nm is the most appropriate wavelength for analyzing TIA with suitable sensitivity.

Method M_2: The 5.0 ml of working standard solution of TIA (400µg/ml) was taken in 25ml standard flask. To this, 1.0ml of folin reagent ($1.092x10^{-2}$M), 5.0 ml of buffer pH 8.0 and 1.5ml of distilled water were added and kept aside for 15 min for complete color development. Then the volume was made up to 25 ml using distilled water and sonicated for 1 minute. In order to investigate the wavelength maximum, the above colored solution was scanned in the range of 360-560nm by UV-Visible spectrophotometer. From the spectra (Figure 3), it was concluded that 450nm is the most appropriate wavelength for analyzing TIA with suitable sensitivity.

Preparation of calibration curve:

Aliquots of the standard TIA solution [1.0-3.0ml, 200µg/ml (Method M_1), 1.0-5.0ml, 400µg/ml (Method M_2)] were placed in a series of 25ml standard flask. Then 3.0ml brucine, 1.5ml of $NaIO_4$ solution and 2.0ml of sulphuric acid were added successively and the volume was brought up to 10ml with distilled water and kept in boiling water bath for 15min for complete color development. The solution was cooled to room temperature and the volume was made up to the mark with distilled water (Method M_1) or 1.0ml of folin reagent ($1.092x10^{-2}$M), 5.0 ml of buffer pH 8.0 and 1.5ml of distilled water were added and kept aside for 15 min for complete color development. Then the volume was made

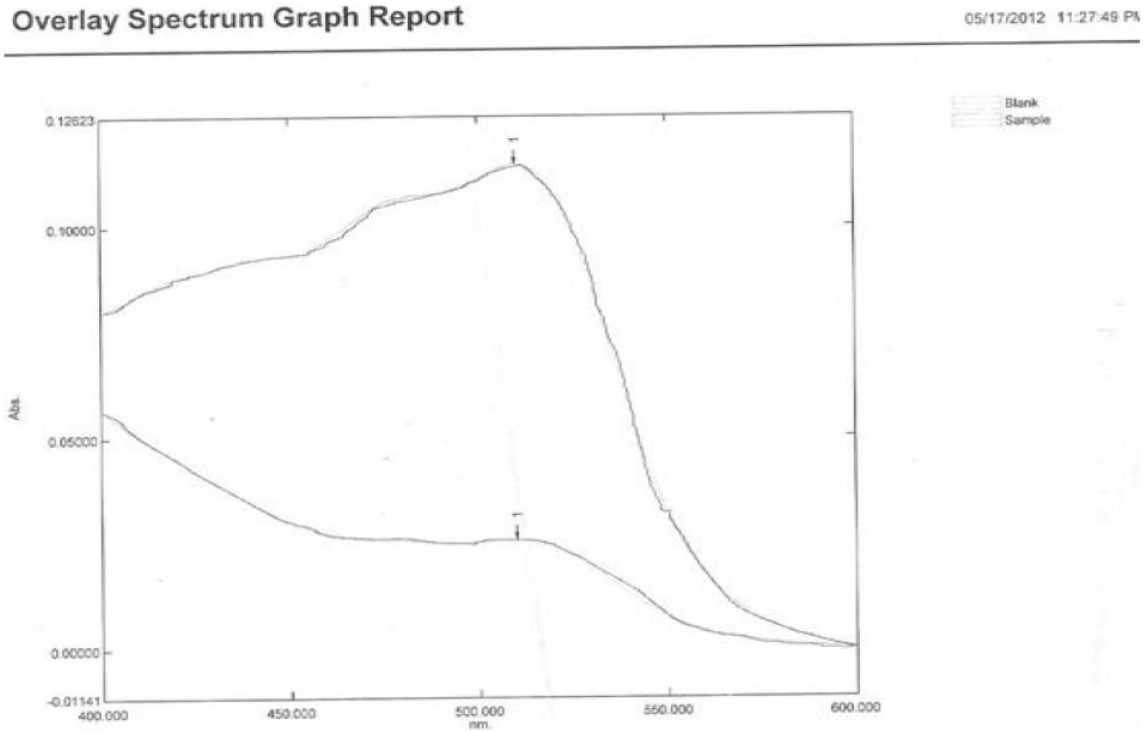

Figure 2 : Absorption spectra of TIA-BCN-IO_4^- system

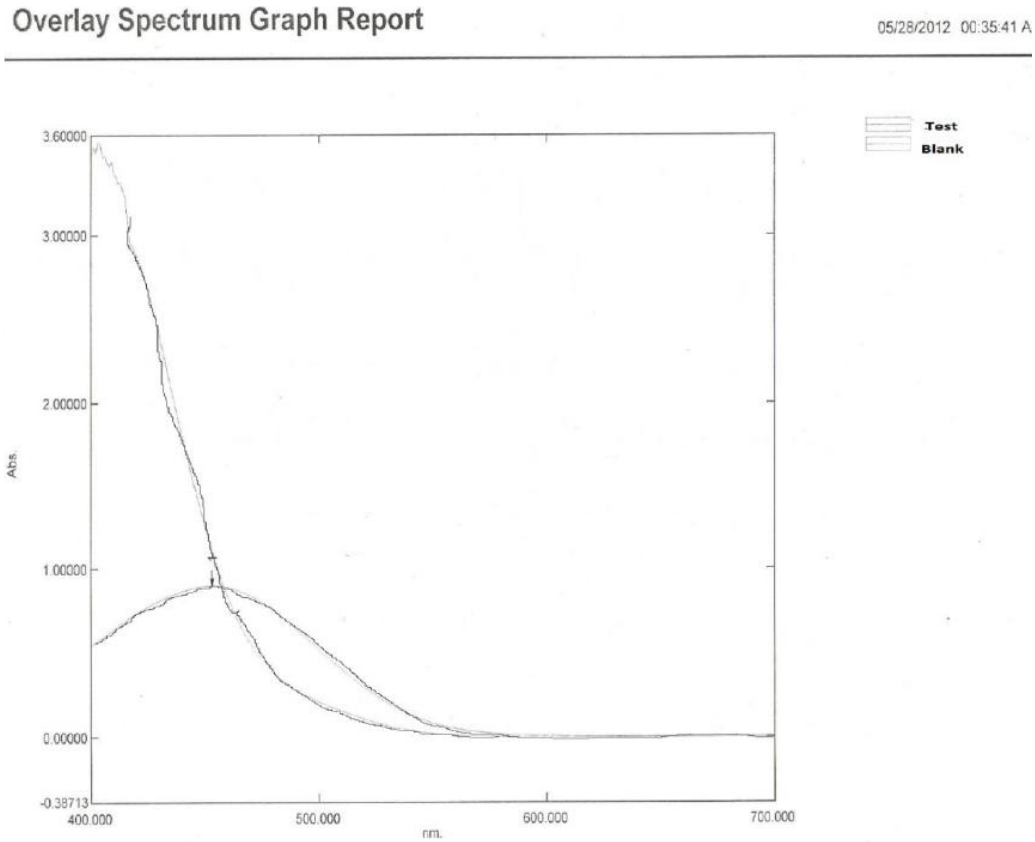

Figure 3 : Absorption spectra of TIA-NQS system

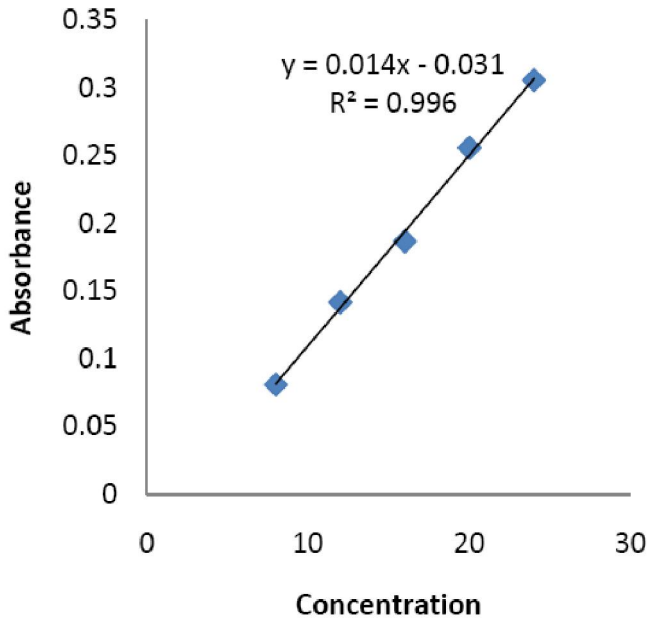

Figure 4: Beer's Law plot of TIA-BCN-IO_4^- system

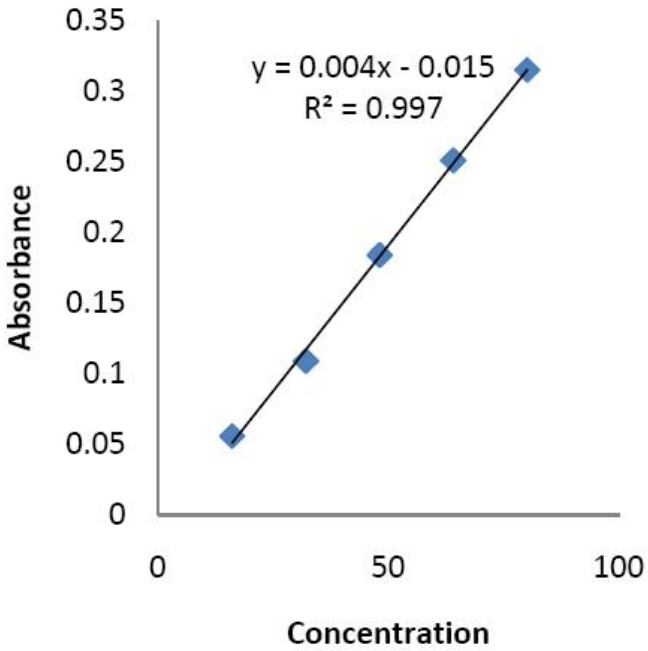

Figure 5 : Beer's Law plot of TIA-NQS system

up to 25 ml using distilled water and sonicated for 1 minute (MethodM_2) The absorbance was measured at 510nm (method M_1) or 450 nm (method M_2) against a reagent blank within the stability period 30min. The calibration graph was constructed by plotting the drug concentration versus absorbance. The amount of drug was computed from its calibration graph (Figure 4&5).

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RESULTS AND DISCUSSION

In the present investigation, the presence of secondary amino group in thiazepine moiety of TIA permits the development of visible spectrophotometric methods for its determination through the oxidative coupling reaction with BCN-IO_4^- reagent (M_1) or the nucleophillic substitution with Folin reagent (M_2).

Optimum operating conditions used in the procedure were established by adopting variation of one variable at a time (OVAT) method. The effect of various parameters such as time, volume and strength of reagents, the order of addition of reagents, pH buffer solutions and solvent for final dilution of the colored species were studied. The other oxidants such as Fe (III), Cr (IV), IO_3^-, and $S_2O_8^{-2}$ were tried in place of $NaIO_4$

TABLE 1: Optical characteristics, precision and accuracy of Proposed methods

Parameter	Method M_1	Method M_2
λ_{max}(nm)	510	450
Beer's law limit(µg/ml)	8-24	16-80
Sandell's sensitivity(µg/cm^2/0.001 abs. unit)	0.00342246	0.010434783
Molar absorptivity (Litre/mole/cm)	134093.6094	43980.79167
Correlation coefficientRegression equation (Y)*	0.996	0.997
Intercept (a)	-0.031	-0.015
Slope(b)	0.014	0.004
%RSD	1.83	1.78
% Range of errors(95% Confidence limits)0.05 significance level0.01 significance level	1.92 3.0	1.86 2.92

***Y = a + b x, where Y is the absorbance and x is the concentration of TIA in µg/ml**

and found to be inferior incase of method M_1. Distilled water was found to be best solvent for final dilution. Other water miscible solvents like methanol, ethanol, propan-2-ol and acetonitrile have no additional advantage in increasing the intensity of the color in both methods. The optical characteristics such as Beer's law limit, Sandell's sensitivity, molar absorptivity, percent relative standard deviation, (calculated from the six measurements containing 3/4th of the amount of the upper Beer's law limits), % range of error (0.05 and 0.01 confidence limits) were calculated using MS Excel Soft ware 2007 version and the results are summarized in TABLE-1.

STABLON tablets containing TIA were successfully analyzed and the values obtained by the proposed method for formulations were compared statistically by the t-and F-test with reported UV reference method and found not to differ significantly. For an additional demonstration of accuracy, recovery experiments were performed by adding a 10mg of the drug to the pre analyzed formulations at three different concentration levels (80%, 100%&120%). These results are summarized in TABLE 2.

Chemistry of colored species: In method M_1, the dimethoxy benzene nucleus of brucine is attacked by IO_4^- with the formation of o-quinone (bruciquinone) which in turn undergo nucleophillic attack on the most electron-rich position of the coupler (secondary amino group in thiazepine moiety of TIA) to give 1-monosubstituted bruciquinone derivative(purple red colored species). In method M_2, yellowish brown colored species (N-alkyl amino napthaquinone) was formed by replacement of the sulphonate group of the napthaquinone sulphonic acid by a secondary amino group of drug. The formation of colored species with these reagents may be assigned through above analogy as shown in

TABLE 2 : Analysis of tianeptine sodium in pharmaceutical formulations by proposed and reference method

Method	*Formulations	Labeled Amount (mg)	Found by Proposed Methods			Found by Reference Method ± SD	#% Recovery by Proposed Method ± SD
			**Amount found ± SD	t	F		
M_1	STABLONTABLETS	12.5	12.16± 0.24	2.40	4.8	12.35±0.109	97.27 ± 1.92
M_2	STABLONTABLETS	12.5	12.25 ± 0.075	1.22	2.1	12.35±0.109	97.97 ± 0.60

*** Stablon tablets of Serdia Pharmaceuticals (India) Pvt. Ltd.; **Average ± Standard deviation of six determinations, the t- and f-values refer to comparison of the proposed method with reference method. (UV). Theoretical values at 95% confidence limits t =2.57 and f = 5.05. ;# Recovery of 10mg added to the pre-analyzed sample (average of three determinations). ; Reference method (reported UV method) using methanol (λ_{max}=220 nm).**

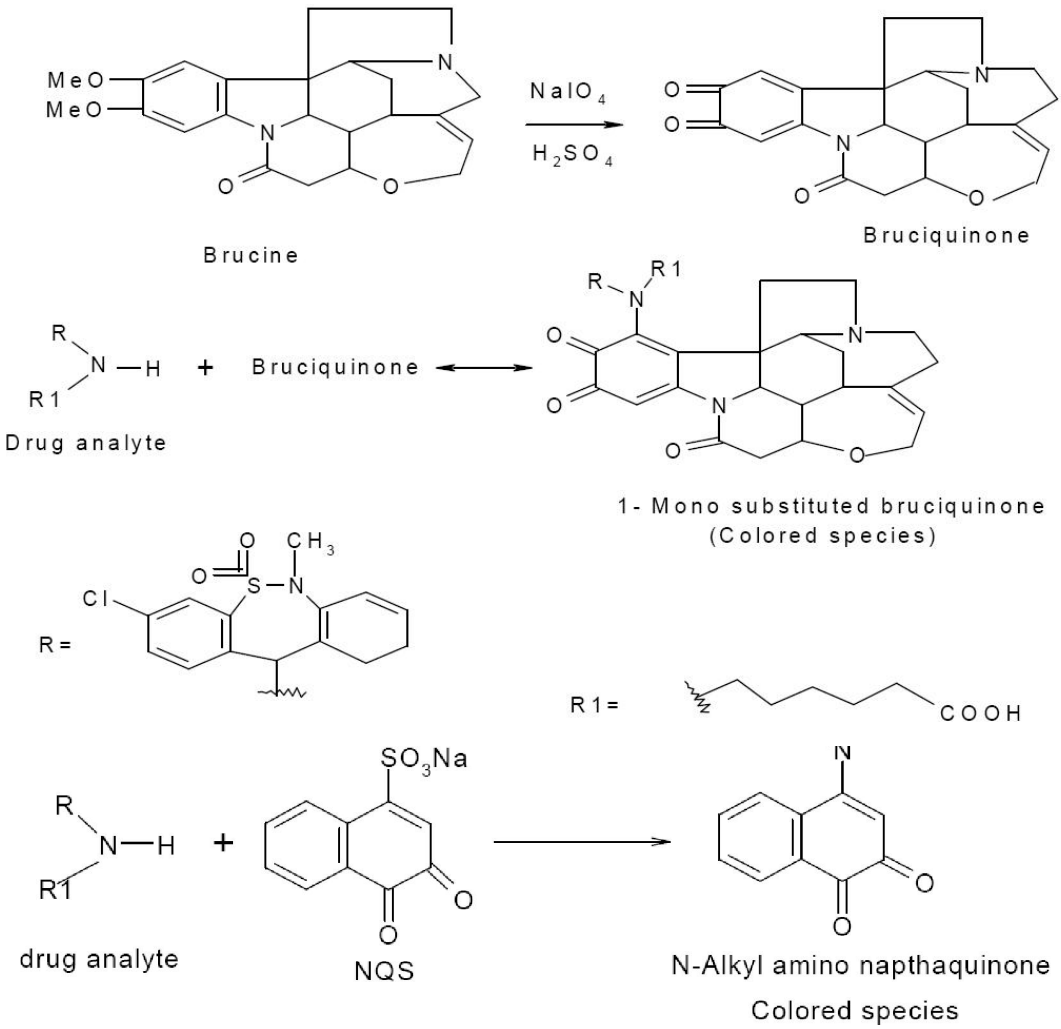

Figure 6: Probable Scheme of reactions for methods M_1&M_2

Schemes (Figure 6).

CONCLUSION

The proposed methods applicable for the assay of drug, the advantage of wider range under Beer's law limits, possess reasonable precision, accuracy, and simple, sensitive. Omission of an extraction step with organic solvents is an added advantage. These methods can be used as alternative methods to the reported ones for the routine determination of TIA depending on the need and situation.

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