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Short communication

# Assay of tianeptine sodium in bulk and its marketed formulations by extraction visible spectrophotometry

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ABSTRACT

A simple, sensitive and cost effective extraction visible spectrophotometric method without using buffer solution has been described for the determination of tianeptine in pure and tablet dosage form. The method is based on the formation of colored ion-association complex between the basic nitrogen of the drug and acidic dye Tropaelin OOO (orange dye II) in the presence of acid medium which is extractable into chloroform with an absorption maximum of 489 nm. The optimum operating conditions necessary for the assaying the drug is established. The Beer's law obeyed in the concentration range of 4–20 μg/ml with correlation coefficient $r^2 = 0.998$. The proposed method is applied to commercial available STABLON tablets and the results are statistically compared with those obtained by the reported UV reference method and validated using recovery studies.



## 1. Introduction

Tianeptine sodium (TIA) (Fig. 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 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 official in European Pharmacopoeia[2] and suggests potentiometric titration method for the assay of TIA in bulk and tablet formulations. 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.

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. Ulu et al reported one visible spectrophotometric method for the determination of tianeptine in tablets using ion pair reagents (BPB, BCG, BTB and MO) but buffer solutions are required in it. To overcome the buffer solution, the author has made some attempts in this direction and succeeded in developing a method using the acid dye technique[14] based on its tendency to form chloroform extractable ion-association complex with acidic dye belonging to Azo (monoazo) category dye TP000 (CI No. 15510) under acidic conditions (0.1 M HCl) by exploiting the basic nature of the drug molecule.

The proposed method for TIA determination has 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. The method can be extended for the routine quality control analysis of pharmaceutical products containing TIA.

## 2. Materials & methods (experimental)

### 2.1. Apparatus and chemicals

A Milton Roy UV/Visible spectrophotometer model-1201 with 10 mm matched quartz cells was used for all spectral measurements. A Systronics digital pH meter model-361 was used for pH measurements. All the chemicals used were of analytical grade.

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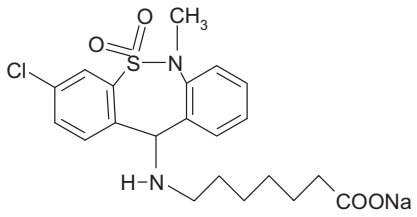

**Fig. 1.** Chemical structure of tianeptine.

STABLON tablets purchased from local market. Tropaeolin 000 (Fluka, 0.2%, $5.7 \times 10^{-3}$ M prepared by dissolving 200 mg of Tropaeolin 000 in 100 ml distilled water and subsequently washed with chloroform to remove chloroform soluble impurities), 0.1 M HCl (prepared by diluting 8.7 ml of Con. Hydrochloric acid to 1000 ml with distilled water and standardized) were prepared.

### 2.2. Preparation of standard stock solution

The standard stock solution (1 mg/ml) of TIA was prepared by dissolving 100 mg of TIA initially in 10 ml of 0.1 M sodium hydroxide, followed by dilution to 100 ml with distilled water. The working standard solution of TIA (100 μg/ml) was obtained by appropriately diluting the standard stock solution with the same solvent. The prepared stock solution was stored at 4 °C protected from light. From this stock solution, a series of standards were freshly prepared during the analysis day.

### 2.3. Preparation of sample solution

About 20 tablets were weighed to get the average tablet weight and pulverized. The powder equivalent to 100 mg of TIA was weighed, dispersed in 25 ml of isopropyl alcohol, sonicated for 10 min and filtered through Whatman filter paper No 41.The filtrate was evaporated to dryness and the residue was dissolved as under standard solution preparation.

### 2.4. Preparation of calibration graph

Aliquots of the standard TIA solution (1.0 ml–5.0 ml, 100 μg/ml) were placed in a series of 125 ml separating funnels. A volume of 6.0 ml of 0.1 M HCl and 2.0 ml of TPOOO were added. The total volume of aqueous phase in each separating funnel was adjusted to 15.0 ml with distilled water. Then 10.0 ml of chloroform was added to each funnel, and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the

**Table 1**
Optical parameters of proposed method.

| Parameter | Values |
|---|---|
| $\lambda_{max}$ (nm) | 489 nm |
| Beer's law limit (μg/ml) | 4–20 |
| Sandell's sensitivity (μg/cm$^2$/0.001 abs. unit) | 0.00152381 |
| Molar absorptivity (litre/mole/cm) | 301172.8125 |
| Correlation coefficient | 0.998 |
| Regression equation ($Y$)* | |
| Intercept (a) | −0.005 |
| Slope (b) | 0.026 |
| % RSD | 1.56 |
| % Range of errors (95% confidence limits) | |
| 0.05 Significance level | 1.64 |
| 0.01 Significance level | 2.58 |

* $Y = a + bx$, where $Y$ is the absorbance and $x$ is the concentration of tianeptine in μg/ml.

**Table 2**
Analysis of tianeptine in pharmaceuticals.

| Method | Formulations[a] | Labeled amount (mg) | Found by proposed method | | | Found by reference method ± SD | % Recovery by proposed method ± SD[c] |
|---|---|---|---|---|---|---|---|
| | | | Amount found ± SD[b] | $t$ | $f$ | | |
| TPOOO | STABLON Tablets | 12.5 | 12.33 ± 0.08 | 0.99 | 1.77 | 12.35 ± 0.109 | 98.62 ± 0.66 |

Reference method (reported UV method) using methanol ($\lambda_{max}$ = 220 nm).
[a] STABLON tablets of Serdia Pharmaceuticals (India) Pvt. Ltd.
[b] 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 $f = 5.05$.
[c] Recovery of 10 mg added to the pre-analyzed sample (average of three determinations).

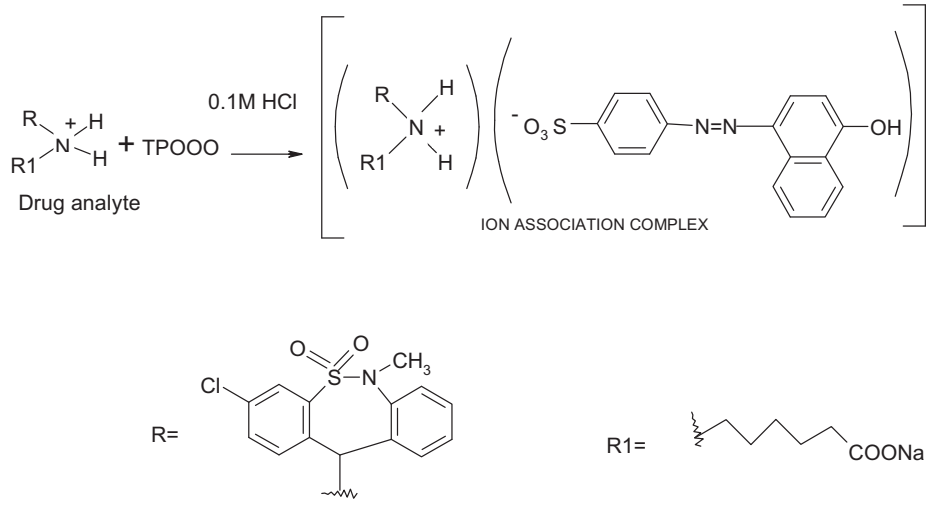


**Fig. 2.** Scheme of the proposed method.

separated chloroform layer was measured at 489 nm against a reagent blank within the stability period 1 h. The calibration graph was constructed by plotting the drug concentration versus absorbance. The amount of drug was computed from its calibration graph.

## 3. Results and discussions

Using OVAT method optimum operating conditions used in the procedure were established .The effect of various parameters such as time, volume and strength of TPOOO reagent, 0.1 M HCl and solvent for final dilution of the colored species were studied. The water immiscible solvents tested for the extraction of colored complex into organic phase include chlorobenzene, dichloromethane, carbon tetra chloride, benzene, n-butanol or chloroform. Chloroform was preferred for its selective extraction of colored drug–dye complex into organic layer from the aqueous phase. The stoichiometric ratio of the drug to dye was determined by the slope ratio method and was found to be 1:1. 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) and % range of error (0.05 and 0.01 confidence limits) were calculated using MS Excel software 2007 version and are shown 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 additional demonstration of accuracy, recovery experiments were performed by adding a 10 mg of the drug to the pre-analyzed formulations at three different concentration levels (80%, 100% & 120%). These results are summarized in Table 2.

## 4. Conclusion

Omission of buffer solution is an added advantage in the proposed method and applicable for the assay of drug in wider range under Beer's law limits and possesses reasonable precision, accuracy and simple, sensitive. The method can be used as alternative method to the reported ones for the routine determination of TIA depending on the need and situation.

### *4.1. Chemistry of colored species*

The positively charged aliphatic secondary nitrogen of TIA molecule in acid medium is expected to attract the negatively charged part of the acidic dye TPOOO and form an ion pair held together through electrostatic attraction. Based on the analogy, the structure of ion-association complex in this method is shown in the scheme (Fig. 2).

## Conflicts of interest

The author has none to declare.

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