



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

Development And Validation of The HPTLC Method For the Estimation of Tianeptine Sodium in Bulk and Tablet Formulation and Its Degradation Study

Janvi Chauhan¹, Dr. Hina Bagada*²

¹Assistant Professor, Department of Pharmaceutical Quality Assurance, Sardar Patel College of Pharmacy, Bakrol, Anand, Gujarat, India.

²Assistant Professor, Department of Pharmaceutical Quality Assurance, A.R. College of Pharmacy & G.H Patel Institute of Pharmacy, Vallabh Vidyanagar, Anand, Gujarat, India.

ARTICLE INFO

Published: 03 May 2025

Keywords:

Tianeptine sodium; HPTLC; Validation; Stability indicating; Degradation.

DOI:

10.5281/zenodo.15332855

ABSTRACT

Tianeptine sodium is widely used as an antidepressant agent; hence it is used to treat depression and anxiety. Aim or Objective: Development of a stability-indicating HPTLC Method for the determination of Tianeptine Sodium in bulk and tablet Form. The objective of this study is to establish a simple, precise, and accurate stability-indicating high-performance thin-layer chromatography (HPTLC) method for the determination of tianeptine sodium in bulk and tablet dosage forms. Materials and Methods: The HPTLC method was developed using chromatographic plates pre-coated with silica gel G60 F254. The solvent system employed consisted of chloroform, acetone, and glacial acetic acid in the ratio of 7:3:0.1 (v/v/v). The optimized densitometric scanning was performed at a wavelength of 220 nm. Results: The R_f value for tianeptine sodium was found to be 0.32 ± 0.01. The method showed a good linear relationship, with an R² value of 0.9994, across the standard concentration range of 100–600 ng per spot. The developed method was determined to be precise, accurate, and cost-effective for the analysis of tianeptine sodium in both bulk and tablet dosage forms. Degradation peaks were identified during the degradation study. Conclusion: The study concluded that Tianeptine sodium is highly unstable under acidic conditions compared to other conditions. The developed method is simple, precise, accurate, and robust for the analysis of Tianeptine sodium. The degradation kinetics study revealed that tianeptine sodium follows pseudo-first-order kinetics in both acidic and basic conditions.

*Corresponding Author: Dr. Hina Bagada

Address: Assistant Professor, Department of Pharmaceutical Quality Assurance, A.R. College of Pharmacy & G.H Patel Institute of Pharmacy, Vallabh Vidyanagar, Anand, Gujarat, India.

Email : bagadahina@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



INTRODUCTION

Tianeptine sodium is a serotonin receptor (5 HT₂ receptor) blocker. It improves serotonin and adrenaline in the brain. It leads to preventing stress. Hence it works as an antidepressant. Tianeptine sodium is primarily used to treat major depressive disorder (MDD), and it has also shown benefits in treating anxiety, asthma, and irritable bowel syndrome (IBS) due to its influence on the brain-gut axis. Some studies suggest it might help with certain types of pain, particularly those related to inflammation or stress-induced conditions^{1,2}.

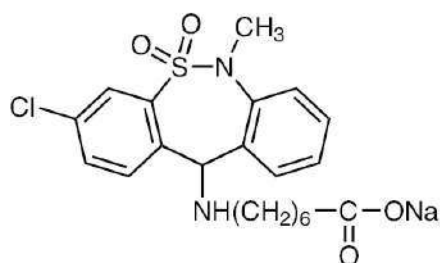


Fig 1: Chemical structure of Tianeptine sodium

In an extensive literature survey, various methods like Gas chromatography (British pharmacopeia³) and liquid chromatography (British pharmacopeia²) were reported for the estimation of tianeptine sodium. HPLC⁴⁻⁸, and UV-UV-visible spectroscopic method^{9,10} are reported for the estimation of Tianeptine sodium. Ulu et al., describe an optimized HPLC method that uses fluorescence detection to measure Tianeptine concentrations in tablet dose forms⁴. Appala et al., present a method for estimating Trimebutine maleate in tablet dose form using reverse-phase high-performance liquid chromatography (RP-HPLC)⁵. Buridi et al. reported an estimation of tianeptine sodium using UV visible spectroscopic methods^{9,10}. Tianeptine, sold as the supplement Tianaa™ in the US, is a synthetic drug linked to opioid addiction. This study found tianeptine

levels ranging from 3.1 to 10.9 mg per capsule across Tianaa™ White, Red, and green products, with significant variation in both capsule mass and tianeptine content¹⁰. Literature survey¹⁻¹⁴ reveals that no method reported using HPTLC for Tianeptine sodium in bulk and marketed products HPTLC is the most sophisticated and automated thin-layer chromatography. HPTLC principle is useful for the separation, identification, and quantification of compounds¹². Hence, it is the best choice to separate degradation products in various conditions (acid, base, oxidative, thermal, and photolytic degradation) for Tianeptine sodium. It is also a very useful technique for the degradation kinetic study¹⁵⁻²⁰. Degradation kinetic studies are useful for understanding a drug's stability, determining its shelf life, and ensuring patient safety by identifying the conditions that lead to degradation. They are also useful for the development of stable formulations and compliance with regulatory requirements, ensuring that the drug remains effective throughout its shelf life¹⁵⁻²⁰. Hence, the work aims to develop and validate stability indicating the HPTLC method for Tianeptine sodium in bulk and tablet dose form.

2. Experimental

2.1. Instruments and Apparatus, Camag HPTLC system with a Linomat V automatic sample applicator (100µl syringe), Camag TLC Scanner-III, Twin-trough TLC developing chamber (10 × 10 cm) was used for this study. Pre-coated silica gel G₆₀F₂₅₄ HPTLC plates were used for the development and validation. Analytical balance (Shimadzu Corporation, Japan) and Digital ultrasonic cleaner (Mumbai, India) sonicator (APL-digital Ultrasonic Cleaner) were used in the study.

2.2. Materials. Tianeptine Sodium was obtained as a gift sample by Vega Biotech Private Limited,

Vadodara, Gujarat. Methanol, acetone, and chloroform were purchased from Loba Chemie Pvt. Ltd. All solvents used for this study, were AR grade. The stable tablet (Serdia Pharmaceuticals Ltd, India.) 12.5 mg was purchased at the local pharmacy, Anand, Gujarat.

2.3. Selection of detection Wavelength. In the present study drug solution of 10 µg/ml of Tianeptine sodium was prepared in methanol. This solution was scanned from 200 to 400 nm in the UV spectrum (UV 1700-Pharmaspec). The detection wavelength (λ_{max}) is 220 nm.

2.4. Selection of mobile phase. The standard solution of Tianeptine sodium was 5000 µg/ml which was used to optimize the mobile phase by trials and error method. In optimization, various solvents with different compositions were studied for the selection of the mobile phase. In the study the optimized mobile phase was found to be chloroform: acetone: glacial acetic acid (7:3:0.1 v/v/v).

2.5. Chromatographic Conditions. Pre-coated silica gel aluminum plate G₆₀ F₂₅₄ with 10 x 10 cm size, layer thickness 0.2 mm was used for the entire study. Prior washing of the HPTLC plate was done with methanol and activated the HPTLC plate with 60°C for 10 minutes to remove the solvent and impurity. For 10 minutes, the HPTLC plate was saturated with the optimal mobile phase chloroform: acetone: glacial acetic acid (7:3:0.1 v/v/v) in the twin-trough chamber. The produced HPTLC plate was scanned using a TLC scanner III to take measurements.

2.6. Preparation of Standard Solution. 10 mg of Tianeptine sodium was accurately weighed and dissolved in a 10 ml methanol (1000 µg/ml). Further dilution with 1 ml of this solution to 10 ml methanol (100 µg/ml).

2.7. Validation of a method: The HPTLC method for Tianeptine sodium was validated as per ICH guideline (Q2) (R1).

2.7.1. Linearity. In methanol, a stock solution of Tianeptine sodium (100 µg/ml) was made. Using the LINOMAT-V automatic sample applicator, Various stock solution volumes of 1, 2, 3, 4, 5, and 6 (100–600 ng per spot) were precisely applied to the TLC plate. After that, the plate was developed using the previously optimized mobile phase and then scanned. Repeat the experiment with five times of TLC plate. Over the concentration range of 100–600 ng/spot, the linearity was determined¹⁵.

2.7.2. Accuracy (% Recovery). The accuracy study was performed by spiking samples of the Tianeptine sodium (100 µg/ml) solution with three different concentrations of the level at 80%, 100%, and 120% and the absorbance of all solutions was taken at 220 nm and percentage recovery of Tianeptine sodium was calculated. The method was repeated three times¹⁵.

2.7.3. Method Precision (Repeatability). By repeatedly spotting the standard solution of Tianeptine sodium (300 ng/spot) and scanning the same place (n = 6) of Tianeptine sodium without moving the plate, the precision was assessed. Relative standard deviation (% RSD) is used to describe the outcomes¹⁵.

2.7.4. Intermediate Precision (Reproducibility). The corresponding responses for three different concentrations of Tianeptine sodium (100, 300, and 500 ng/spot) were calculated three times on the same day and on three other days to assess the Intraday and Interday precisions. The data is shown as a relative standard deviation (% RSD)¹⁵.

2.7.5. Limit of Detection and Limit of Quantitation. Using the formulas provided below,

the LOD and LOQ were derived from the standard deviation (SD) of the intercepts and slope of the calibration curves of Tianeptine sodium¹⁵.

$$\text{LOD} = 3 \sigma/S$$

$$\text{LOQ} = 10 \sigma/S$$

Where σ is the standard deviation (SD) of intercepts and S is the slope of the calibration curve.

2.7.6. Robustness of the Method.

To assess robustness, purposeful variations in technique variables were made, including mobile phase composition (± 0.5 ml for each component), and saturation duration (± 2 min) for the 300 ng/band Tianeptine sodium. The %RSD was computed²¹⁻²³.

2.8. Assay. The weight of the twenty tablets (Stablon) was measured, the average weight was calculated, and then they were crushed into a fine powder. The powder, equivalent to 10 mg of Tianeptine sodium, was placed into a 10 ml volumetric flask along with 5 ml of methanol. After sonication for 15 minutes, the solution was diluted with methanol up to the mark to achieve a concentration of 1000 $\mu\text{g/ml}$. The resulting solution was filtered using filter paper, and from this 1 ml volume was taken and transferred into a 10 ml volumetric flask and diluted to mark with methanol to obtain a working standard solution Tianeptine 100 $\mu\text{g/ml}$. 3 μl of this solution was put on the HPTLC plate at 300 ng per spot. Three times repeat the experiment, with peak areas recorded at 220 nm and sample concentrations calculated²¹⁻²³.

2.8. Forced Degradation study for Tianeptine sodium in API and tablet dose form. To evaluate the stability-indicating method, the standard drug

and tablet sample was subjected to acid, base, oxidative, thermal, and photolytic degradation.

2.8.1 acid-induced degradation study for API. Accurately weighed 10 mg of Tianeptine sodium, transferred it into a 10 ml volumetric flask, and makeup with methanol. Transfer 1 ml of aliquot from the stock solution into a 10 ml volumetric flask. Add 2 ml of 0.1N hydrochloric acid to the flask and allow it to sit for 60 minutes. The neutralized solution was directly applied to the HPTLC plate followed by development and scanning under optimized chromatographic conditions¹⁵⁻¹⁷. Acid-induced degradation study for Tablet sample. Equivalently weighed 10 mg of tablet powder, transferred it into a 10 ml volumetric flask, and makeup with methanol. Sonicated for about 15 minutes with occasional shaking. Transfer 1 ml of aliquot from the stock solution into a 10 ml volumetric flask. Add 2 ml of 0.1N hydrochloric acid to the flask and allow it to sit for 60 minutes. Apply the neutralized solution directly to an HPTLC plate, then proceed with development and scanning under optimized chromatographic conditions¹⁵⁻¹⁷.

2.8.2 Base-induced degradation study for API. Accurately weighed 10 mg of Tianeptine sodium, transferred it into a 10 ml volumetric flask, and made it with methanol. Transfer 1 ml of aliquot from the stock solution into a 10 ml volumetric flask. Add 2 ml of 0.1N sodium hydroxide to the flask and allow it to sit for 60 minutes. Apply the neutralized solution directly to an HPTLC plate, then proceed with development and scanning under optimized chromatographic conditions¹⁵⁻¹⁷. Base-induced degradation study for Tablet sample. Equivalently weighed 10 mg of tablet powder, transferred it into a 10 ml volumetric flask, and makeup with methanol. Sonicated for about 15 minutes with occasional shaking. Transfer 1 ml of aliquot from the stock solution into a 10 ml

volumetric flask. Add 2 ml of 0.1N sodium hydroxide acid to the flask and allow it to sit for 60 minutes. Apply the neutralized solution directly to an HPTLC plate, then proceed with development and scanning under optimized chromatographic conditions¹⁵⁻¹⁷.

2.8.3 Hydrogen peroxide-induced (oxidation) degradation study for API. Accurately weighed 10 mg of Tianeptine sodium, transferred it into a 10 ml volumetric flask, and made it with methanol. Transfer 1 ml of aliquot from the stock solution into a 10 ml volumetric flask. Add 2 ml of 3% w/v H₂O₂ to the flask and allow it to sit for 60 minutes made up to the mark. The solution obtained was applied directly onto the HPTLC plate, and the chromatogram was then documented using optimized chromatographic conditions¹⁵⁻¹⁷. Hydrogen peroxide-induced (oxidation) degradation study for Tablet sample. Equivalently weighed 10 mg of tablet powder, transferred it into a 10 ml volumetric flask, and made up with methanol. Sonicated for about 15 minutes with occasional shaking. Transfer 1 ml of aliquot from the stock solution into a 10 ml volumetric flask. Add 2 ml of 3% w/v H₂O₂ to the flask and allow it to sit for 60 minutes made up to the mark. The solution obtained was applied directly onto the HPTLC plate, and the chromatogram was then documented using optimized chromatographic conditions.

2.8.4 Photolytic degradation study for API. Accurately weighed 10 mg Tianeptine sodium was irradiated with sunlight for 60 min. A solution was prepared by dissolving a drug sample in the diluent. From this stock solution of 1000 µg/ml, a working standard solution of 100 µg/ml was prepared. The resulting solution was applied on a TLC plate and chromatograms were run. Photolytic degradation study for Tablet sample. Equivalently weighed 10 mg of tablet powder of

Tianeptine sodium was irradiated with sunlight for 60 min. A solution was prepared by dissolving a drug sample in the diluent. Sonicated for about 15 minutes with occasional shaking. From this stock solution of 1000 µg/ml, a working standard solution of 100 µg/ml was prepared. The resulting solution was applied on a TLC plate and chromatograms were run¹⁵⁻¹⁷.

2.8.5 Thermal degradation for API. Accurately weighed 10 mg Tianeptine sodium was placed in a hot air oven at 75°C for 60 min. The solution was prepared by dissolving the drug sample in the diluent. From this stock solution of 1000 µg/ml, a working standard solution of 100 µg/ml was prepared. The resulting solution was applied on a TLC plate and chromatograms were run. Thermal degradation for Tablet sample. Equivalently weighed 10 mg of tablet powder Tianeptine sodium was placed in a hot air oven at 75°C for 60 min. The solution was prepared by dissolving the drug sample in the diluent. Sonicated for about 15 minutes with occasional shaking. From this stock solution of 1000 µg/ml, a working standard solution of 100 µg/ml was prepared. The resulting solution was applied on a TLC plate and chromatograms were run¹⁵⁻¹⁷.

2.8.6 Degradation kinetics In acidic medium

The stock solution of Tianeptine sodium was prepared up to 1000 µg/ml. 1 ml of tianeptine sodium was refluxed at different temperatures (40°C, 50°C, 60°C, 70°C, and 80°C). After refluxing, 2 ml of 0.1 N HCl was added. The neutralized solution of Tianeptine sodium was applied on a chromatographic plate under optimized chromatographic conditions. Each study was repeated three times at different temperatures with different internal. The concentration of the drug was calculated. Various parameters like shelf life, degradation rate constant, half-life, and activation energy were

determined by using degradation kinetics and the Arrhenius plot. From the Arrhenius plot, $t_{1/2}$ and t_{90} were determined at 25 °C for acid degradation 15-17.

In a basic medium

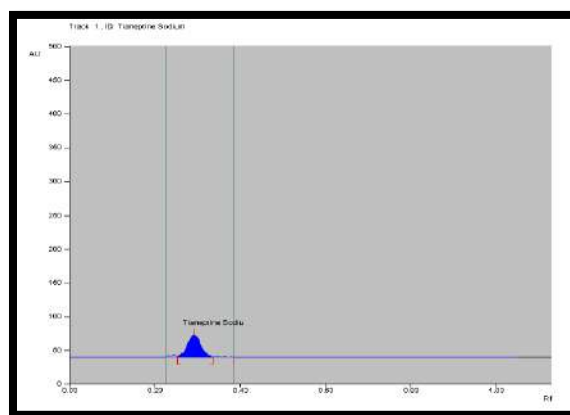
The stock solution of Tianeptine sodium was prepared up to 1000 µg/ml. 1 ml of Tianeptine sodium was refluxed at different temperatures (40°C, 50°C, 60°C, 70°C, and 80°C). After refluxing, 2 ml of 0.1 N NaOH was added. The neutralized solution of Tianeptine sodium was applied on a chromatographic plate under optimized chromatographic conditions. Each study was repeated three times at different temperatures with different internal. The concentration of the drug was calculated. Various parameters like shelf life, degradation rate

constant, half-life, and activation energy were determined by using degradation kinetics and the Arrhenius plot. From the Arrhenius plot, $t_{1/2}$ and t_{90} were determined at 25 °C for basic degradation 16,17.

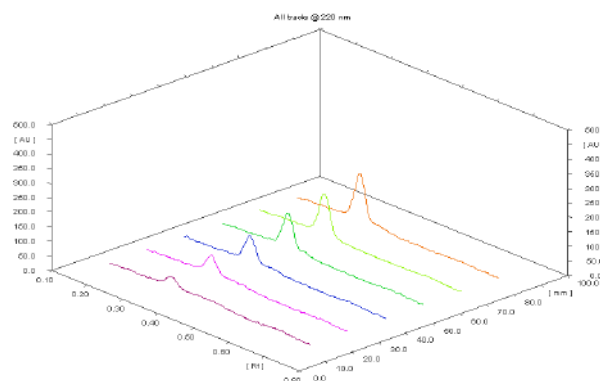
3. RESULTS

3.1. Optimization of Chromatographic condition:

Various solvents with different compositions and ratios were tried for the HPTLC plate for Tianeptine sodium. The optimized mobile phase was chloroform: acetone: glacial acetic acid (7:3:0.1, v/v/v). The optimized saturation time with a twin-trough developing chamber was 10 minutes with the same mobile phase. (Figure 1)



(a)



(b)

Fig 2: (a) Densitogram of Tianeptine sodium standard 100 ng/band using Chloroform: Acetone: Glacial acetic acid (7:3:0.1 v/v/v) as mobile phase (b) View of all tracks of Tianeptine sodium

3.2. Method validation.

3.2.1. Calibration curve

The calibration curve for Tianeptine sodium showed a good linear relationship over the range of 100-600 ng per spot ($r^2 = 0.999$, slope = 4.609, intercept = 148.5). (Table 1 & Figure 2)

Table 1: Linearity study of Tianeptine sodium at 220nm

Sr. no.	Conc.(ng/band)	Mean \pm SD(n=5)	%RSD
1.	100	796.88 \pm 10.07	1.26
2.	200	1388.76 \pm 27.48	1.97
3.	300	2095.84 \pm 41.38	1.97
4.	400	2727.58 \pm 40.19	1.47
5.	500	3378.66 \pm 54.80	1.62
6.	600	3963.00 \pm 21.29	0.53

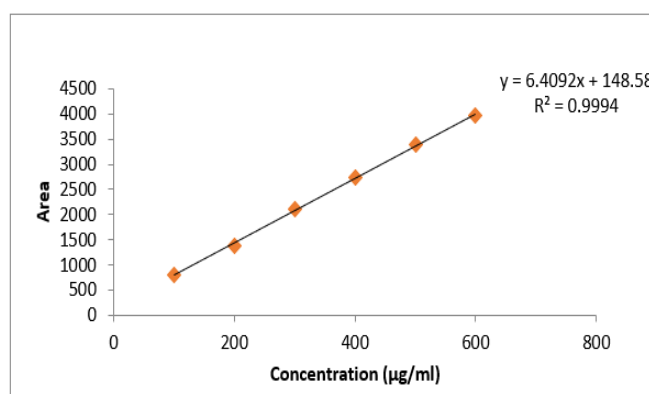


Fig 3: Calibration curve of Tianeptine sodium at 220 nm

3.2.2. Precision

Repeatability for Tianeptine sodium was found to be 0.91% for six replicates with the same concentration. The % RSD values obtained for intraday and interday variation were 0.72-1.51 % and 1.42-1.64 %, respectively.

3.2.3. Robustness

The % RSD value of the robustness study was found to be 0.54 for mobile phase composition and

0.30 for saturation time. The result indicated that the optimized method was robust.

3.2.4. LOD and LOQ

The LOD and LOQ were found to be 16.75 and 50.77 ng per band for Tianeptine sodium.

3.2.5. Specificity

The specificity of Tianeptine sodium was determined by analysis of the standard and sample of the drug. It indicates the no interference of degradation product or impurity (Figure 3).

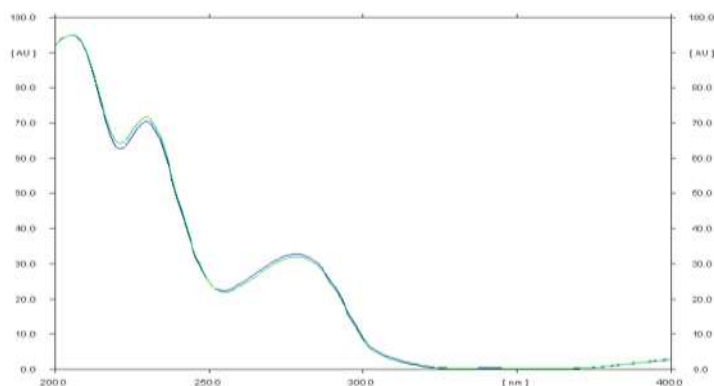


Fig 4: Overlain spectra of standard solution and dose form solution

3.2.6. Accuracy

% Recovery of Tianeptine sodium was found to be 100.4 % which is within the limit (98%-102%) as per ICH guidelines. So, the developed method was found to be accurate.

The amount of Tianeptine sodium (12.1 mg) obtained in tablets concerning the label claim (12.5 mg). The drug content of Tianeptine sodium in tablets was found to be 99.15 % \pm 10.10 %.

There is a summary of validation parameters in Table 2.

3.3. Analysis of marketed formulations.

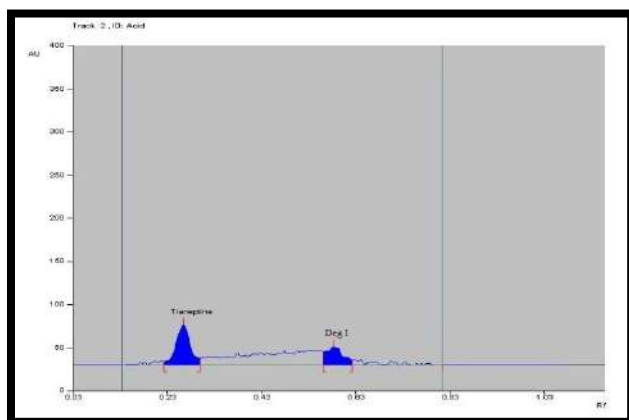
Table 2: Summary of validation parameters of the proposed HPTLC method

Parameters	Result
Linearity(ng/band)	0.999
Recovery%	99.77-101.23
Precision	
Repeatability (%RSD,n=6)	0.91
Intraday (% RSD,n=3)	1.15
Interday (%RSD,n=3)	1.54
Sensitivity	
LOD(ng/spot)	16.75
LOQ(ng/spot)	50.77
Robustness(%RSD)	0.42

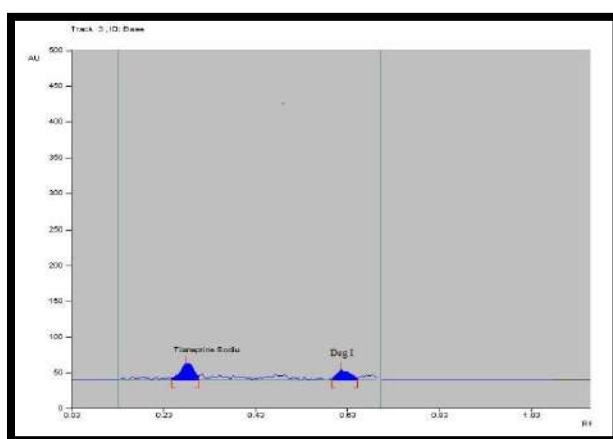
3.4. Forced degradation study for Tianeptine sodium in API and table dose form.

The percentage degradation for Tianeptine sodium was found to be 25.46 % in API and 23.42 % in tablet at R_f value 0.62 in the acid-induced degradation study. In basic conditions, the percentage degradation was found to be 12.20 % in API and 13.87 % in tablet at R_f value 0.61. For their oxidative study one degradation peak was

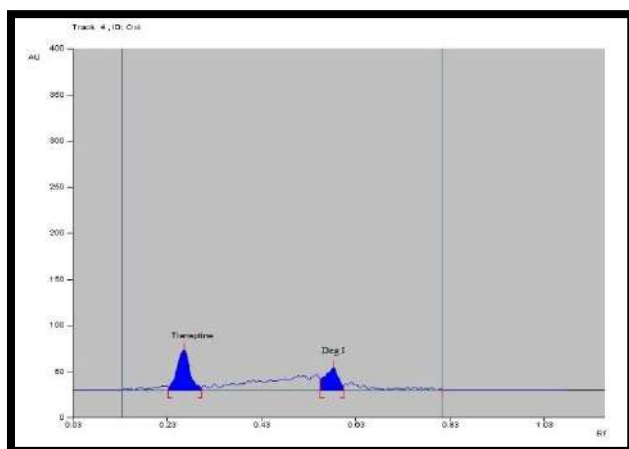
found at 0.61 R_f value (11.64 % in API and 12.25% in tablet). The photolytic degradation was also found at the R_f value of 0.62. The Tianeptine sodium was also susceptible to thermal conditions. The % degradation peak was found 13.67% in API and 14.86% in tablet dose form. The result also indicated that the degradation mixture may be found to be the same. Hence it was obtained at the same R_f value (Figure 4).



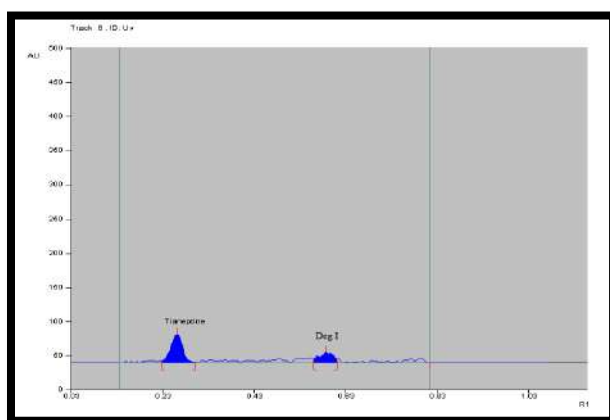
(a)



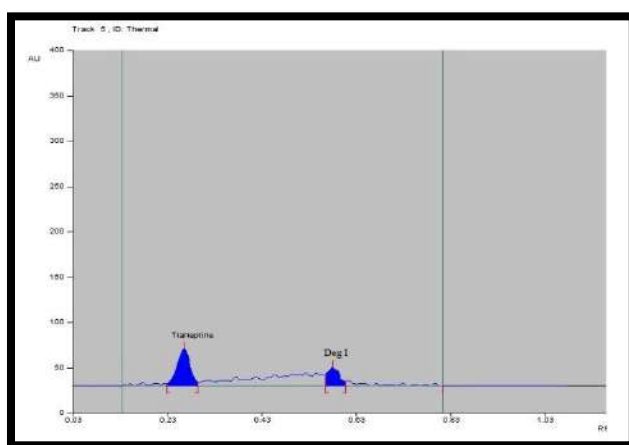
(b)



(c)



(d)



(e)

Fig 5 : Densitogram of API of Tianeptine sodium and its degradation products in the (a) acidic, (b) basic, (c) oxidative, (d) photolytic, and (e) thermal degradation study

3.5 Degradation kinetics

In the data (Table 3,4) and graph (Figure 5) of degradation kinetics, it was observed that the concentration of the drug decreased with time. This means when the time increases, the concentration of the drug also decreases, the effect of temperatures 40°, 50°, 60°, 70° and 80°C in the degradation kinetics was shown in Fig 5 in acidic conditions and basic conditions. The K_{obs} the apparent first-order degradation rate constants, t_{90} , and half-lives ($t_{1/2}$) were calculated from the graph of degradation. In the context of degradation studies, pseudo-first-order kinetics (Figure 5) is a situation where the reaction rate appears to follow

first-order kinetics concerning one reactant. The data obtained from the first-order kinetics treatment were subsequently analyzed using the Arrhenius equation.

$$\text{Log } K = \text{Log } A - E_a/2.303 RT$$

Where K is rate constant, A is frequency factor, E_a is energy of activation (Cal mol^{-1}), R is gas constant ($1.987 \text{ cal/deg} \cdot \text{mol}$) and T is absolute temperature ($^{\circ}\text{K}$), In the Arrhenius plot, a linear relationship was observed between the values of $(2 + \log K_{obs})$ and $(1/T \times 10^3)$ within the temperature range of 40-80°C.

Table 3. Summary Of Degradation Products of Tianeptine Sodium Under Different Stress Conditions.

Degradation Condition	Number of Degradation product	% Degradation based on area for API:	% Degradation based on area for Tablet sample:
Acid	1	25.46	22.43
Base	1	12.20	13.87
Oxidative	1	11.61	12.23
Thermal	1	14.86	13.56
Photolytic	1	18.67	14.86

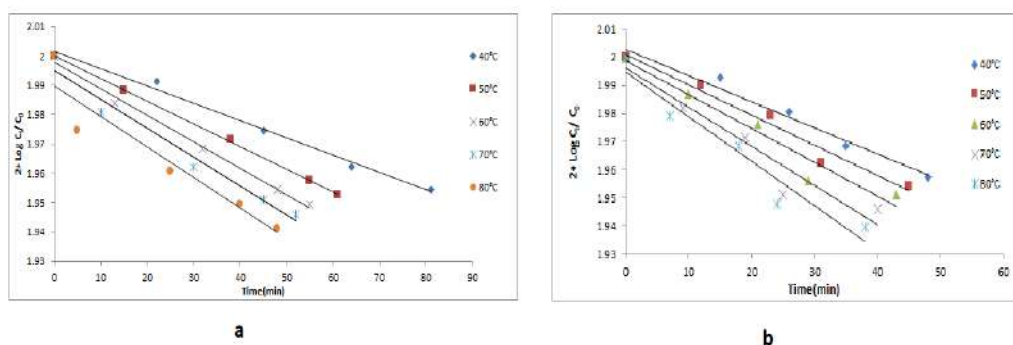


Fig 6: Pseudo first-order plots for the degradation of Tianeptine sodium with (a) 0.1 N HCl and (b) 0.1 N NaOH at various temperatures using the HPTLC method.

Table 4. The degradation rate constant (K_{obs}), half-life($t_{1/2}$), and t_{90} for Tianeptine sodium in the presence of 0.1 N HCl and 0.1 N NaOH.

Temperature (°C)	$K_{obs}(h^{-1})$	$t_{1/2}(h)$	$t_{90}(h)$
In 0.1 N HCl			
40	0.026	0.75	0.133
50	0.115	0.63	0.1
60	0.26	0.58	0.05
70	0.438	0.5	0.033
80	1.139	0.33	0.025
In 0.1 N NaOH			
40	0.082	0.833	0.166
50	0.218	0.466	0.116
60	0.323	0.716	0.066
70	0.493	0.583	0.041
80	0.912	0.45	0.016

DISCUSSION

The developed stability indicating the HPTLC method was found to be simple, precise, and accurate and also identified degradation peaks of Tianeptine sodium. The wavelength selected for the analysis was 220nm as per UV-visible spectra. The optimized mobile phase for the HPTLC

method was found to be chloroform: acetone: glacial acetic acid (7:3:0.1, v/v/v). The calibration curve for Tianeptine sodium showed a good linear relationship over the range of 100-600 ng per spot (Table 1, Figure 2). From the precision data, it was found that method was repeatable. There was no significant change observed during the robustness study through small changes in the mobile phase

and saturation time. Hence developed method was found to be robust. The LOD and LOQ were found to be within the Limit. The specificity of Tianeptine sodium indicated that there is no interference of degradation product or impurity. % Recovery of Tianeptine sodium was found to be in within limit. The Degradation study reveals that Tianeptine sodium (bulk and tablet dose form) was susceptible to acid, basic, thermal, oxidative, and photolytic conditions (Figure 4). The optimized HPTLC method successfully identified the degradation peak from the Tianeptine sodium. Hence, the developed method was found to be stability indicating method for Tianeptine sodium in bulk and tablet dose form. From the data and graph of the degradation process, it was concluded that the degradation process obeys the Pseudo-first order kinetics (Figure 5, Table 3 & 4). It was reported that the Arrhenius equation was found to be linear with a temperature range of 40-80°C. The degradation kinetics study indicated that the drug exhibited higher susceptibility under both acidic and basic conditions.

4. CONCLUSION

The developed stability indicating the HPTLC method was found to be simple, precise, and accurate and also identified degradation peaks of Tianeptine sodium. The degradation peaks were well resolved from the Tianeptine sodium with significantly different R_f values. The degradation of Tianeptine sodium was higher in acidic conditions compared to other degradation conditions (basic, oxidative, thermal, and photolytic). Hence, it was concluded that Tianeptine sodium was acid-susceptible. The optimized method was found to be reproducible and selective for the analysis of Tianeptine sodium in bulk drug and tablet dose form. The result of degradation kinetic for Tianeptine sodium

indicated pseudo-first-order kinetic in acid and basic conditions.

ACKNOWLEDGMENTS

All authors are grateful to the A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy for providing the facilities required to conduct their research.

Conflict of interest

The authors of this study declare that there is no conflict of interest in the publishing of this paper. There was no specific grant for this research from any public, commercial, or non-profit funding agency.

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HOW TO CITE: Janvi Chauhan, Dr. Hina Bagada*, Development and Validation of The HPTLC Method For the Estimation of Tianeptine Sodium in Bulk and Tablet Formulation and Its Degradation Study, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 5, 306-318 <https://doi.org/10.5281/zenodo.15332855>

