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Validated, Ultra High Efficiency RP-HPLC and Stability Indicating Method for Determination of Tranylcypromines Sulphate in Bulk and in Tablet Dosage Forms

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ABSTRACT

Simple, sensitive, rapid and stability indicating ultra high efficiency RP-HPLC method was developed and validated for analysis of Tranylcypromine sulphate in bulk drug and in tablet dosage forms. Well- resolved peaks of target analyte and its degradation products were achieved on a Kinetex® column (75 mm x 4.6 mm ID) 2.6 µm at 30 °C, using simple isocratic mobile phase of acetonitrile - orthophosphoric acid 0.1 % (10: 90, v/v). The flow rate was 1.0 mL/min and the detection was performed at 220 nm. The retention time of the drug was 2 min while for the reported method was 6.7 min. The method was validated according to International Conference on Harmonization (ICH) guidelines. Tranylcypromine was subjected to the stress conditions of hydrolytic acidic, basic, oxidative, and photolytic degradation. The assay was linear over the concentration range of 3-150 µg mL^{-1} and the correlation coefficient was 1. The RSD% of inter and intraday precision was less than 1 %. The % recoveries were found to be 100.58 % proved that the proposed method is sufficiently accurate and precise. The method distinctly separates the drug from its degradation products within 2 min and total run time of 8 min.

INTRODUCTION

Tranylcypromine sulphate (TCP-SO_4) is (1*RS*, 2*SR*)-2-phenylcyclopropylamine sulphate (Fig. 1). It is a monoamine oxidase inhibitor; antidepressant. The British pharmacopoeia recommends non aqueous titration for analysis of the raw material and spectrophotometric method for the dosage forms (The British pharmacopoeia, 2013). Literature survey shows that the methods used for assay of TCP-SO_4 are mainly for its evaluation in bulk biological fluids using HPLC – electrochemical detector (Rashid *et al.,* 2013), determination in plasma using LC-MS/MS (KirchherrKühn-Velten, 2005), in vivo, in urine and pharmaceutical formulation using symmetry column (Aboul-Enein and Abou-Basha, 1996; Taavitsainen *et al.,* 2001) and separation of TCP-SO_4 enantiomers (Aboul-Enein and Serignese, 1995; Spahn *et al.,* 1992). Other methods for determination of TCP-SO_4 involves spectrophotometric methods (Belal *et al.,* 1991; Ibrahim *et al.,* 1991; Knochen *et al.,* 1989; Rizk *et al.,* 2003), a conductometric method (GHANI *et al.,* 2004), gas chromatographic methods (Aspeslet *et al.,* 1992; BaileyBarron, 1980; Baker *et al.,* 1985; Baselt *et al.,* 1977; CrifasiLong, 1997; ValentineMiddleton, 2000), proton magnetic resonance (HannaLau-Cam, 1988) and an enzymatic assay for dextro or levo TCP-SO_4 in the brain (Fuentes *et al.,* 1975). The chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidelines state the requirements of the stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors (Blessy *et al.,* 2014). A stability indicating method is a method that will accurately measure the analyte and resolve the analyte from its degradation products. ICH guidelines requires the establishment of stability indicating methods by conducting of forced degradation studies under different pH, light, oxidation, etc. conditions and separation of the target drug from degradation products (BakshiSingh, 2002). The presence of degradants and impurities in pharmaceutical formulations can result in changes in their chemical, pharmacological, and toxicological properties, which affect their efficacy and safety. Therefore, the development of a sensitive stability-indicating method for the routine analysis of TCP-SO_4 in bulk drug and in pharmaceutical dosage forms is required.

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Yet no report is available on the stability study of TCP-SO_4 according to ICH recommendations forced degradation conditions. Thus, the aim of this work is the development of a stability indicating RP-HPLC method to determine and resolve the main degradation products from the analyte using Kinetex® core – shell column with high efficiency.

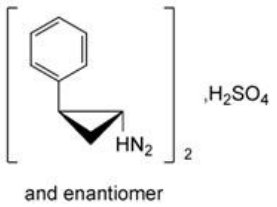


Fig. 1: Tranylcypromine sulphate.

EXPERIMENTAL

Chemicals and reagents

Tranylcypromine sulphate assay 99.98 % and Parentil® Tablets labeled to contain 10 mg TCP-SO_4 (batch number: 01610), were kindly donated by Kahira Pharma & Chem. Ind. Co. (Cairo, Egypt).

HPLC grade Acetonitrile Poch SA (Avantor Performance Materials, Gliwice Poland) and Orthophosphoric acid from Burdick & Jackson (Seelze, Germany). Analytical grade of sodium hydroxide, hydrochloric acid and 30 % hydrogen peroxide were purchased from Sigma–Aldrich (St. Louis, MO, USA) and high purity distilled water was used.

Instrumentation

The HPLC (Agilent 1100 series) instrument equipped with G1310A isocratic quaternary pump with solvent cabinet, G1322A vacuum degasser, G1313A autosampler injector, G1314A variable wavelength detector (VWD) connected to a computer loaded with Agilent Chemstation software. The column used was Phenomenex Kinetex® (75 mm x 4.6 mm, 2.6 µm particle size) (Phenomenex Inc.). UV lamp with short wave length 254 nm was obtained from Desaga (Waldbronn, Germany).

Chromatographic conditions

The isocratic mobile phase was consisted of acetonitrile and orthophosphoric acid 0.1% (10 : 90, v/v) pH 2.3. The auto sampler utilized acetonitrile as a rinse solution, injection volume was 10 µL and flow rate of mobile phase was 1.0 mL min^{-1}. The variable wavelength UV‑visible detector was set at 220 nm. The column temperature was maintained at 30 ºC.

Preparation of standard stock solution

Stock standard solution of TCP-SO_4 was prepared by dissolving 50 mg of TCP-SO_4 in double distilled water and completed to 100 mL volume. The working standard solutions were prepared by diluting aliquots of each stock solution to obtain concentrations ranging from 3 to 150 µg mL^{-1}. Working solutions were stable for one week.

Pharmaceutical sample preparation

The red coat of Parentil® 20 tablets was gently removed with methanol, dried then weighed accurately, finally powdered and mixed well. An accurately weighed amount of powdered tablets equivalent to 50 mg of TCP-SO_4 was dissolved in 80 mL of double distilled water sonicated for 15 min till complete dissolution and made up to 100 mL volume with water. The solution was filtered and the first 10 mL of the filtrate was discarded. The filtrate was taken and diluted to obtain working solutions.

Forced degradation studies

Forced degradation studies were performed to provide an indication of the stability-indicating properties and specificity of the method. Intentional degradation was attempted using acid, base, hydrogen peroxide, and UV-radiation. From the previously mentioned stock solutions of standard drugs, 10 mL aliquots were transferred to each of three 50 mL round bottomed flasks to perform the first three degradation tests. To the first flask, 10 mL of 1N HCl was added for acidic degradation. To the second flask, 10 mL of 1N NaOH was added for basic degradation. To the third flask 10 mL of 30 % H_2O_2 was added for oxidative degradation. All 3 flasks were refluxed for about 1 hr. After the degradation treatment, the samples were allowed to cool to room temperature and treated as follows: The pH values of the first and second flasks were neutralized with 1N NaOH and 1N HCl, respectively. The volume of all the three flasks was adjusted to 50 mL. The samples were injected and analyzed against control samples (without degradation treatment). Another sample solution was left in UV radiation for 1 hr then the radiated solution was diluted to 10 mL, then it was finally injected into HPLC and compared with the control sample

RESULTS AND DISCUSSION

Method development

Different chromatographic conditions were optimized to obtain an acceptable chromatographic resolution between target analyte and its main degradation products.

Type of the column

The ability to obtain ultra-high chromatographic separations on conventional HPLC systems with significant reductions in sample analysis time has been especially beneficial for laboratories tasked with the routine analysis of drug products. The introduction of Kinetex® core-shell columns has brought dramatic benefits to chromatographers (Koerner *et al.*, 2011).

Innovations in LC particle technology are driven by the demand for better chromatographic performance and higher productivity. To achieve performance improvements of greater sensitivity, higher resolution, and faster analysis times, a column requires lower plate height (higher efficiency) at a wide range of linear velocities. With traditional fully porous 3 µm and 5 µm particles, efficiency decreases significantly as flow rate increases.

In most cases, loss of resolution and sensitivity prevents faster analysis times (Kinetex® brochure Technical resource, 2013). So Kinetex® 2.6 µm column was used because ordinary column elongates retention time of TCP-SO_4 and gives broad peaks.

Mobile phase composition

A buffer free method was developed by using acetonitrile - orthophosphoric acid 0.1% (10-90%). Salts used in buffer solution may precipitate in the presence of organic solvents and increase the maintenance cost of HPLC pumps (Kanakal *et al.*, 2014). For many LC-UV, a low pH is more important than the presence of a true buffer, so 0.1% phosphoric acid can be used to satisfy this requirement (Dolan, 2002).

Initially various mobile phase composition were tried in attempts to obtain good resolution of TCP-SO_4 and its degradants. It was found that acetonitrile content greater than 10 % and pH-value greater than 2.3 gave rapid elution of TCP-SO_4 and its degradation products leading to co-elution of the analyte and its degradation products.

On the other hand, decreasing acetonitrile content lower than 10 % and pH value below 2.3 resulted in increase separation time without enhancement in resolution. A mixture of acetonitrile and orthophosphoric acid 0.1 % (10: 90, v/v) pH 2.3 was found to be optimum for separation and quantification of the drug from its degradation products without interference from each other within 7.6 min.

Column oven temperature

Column oven temperature was also studied at room temperature, 30, 35 and 40 °C. It was found that column temperature 30 °C was optimum and there is no need to increase temperature over that.

Choice of detection wavelength

TCP-SO_4 showed main absorption peaks at 220 and 264 nm. Analyte peak were monitored using the two wavelengths; 220 nm was found to be optimum for detection at which the highest detector response was obtained.

Choice of flow rate

The effect of flow rate was studied to optimize the chromatographic efficiency of the proposed method and improve the resolution of the eluted peaks. The flow rate was changed over the range of 0.5-1.5 mL min^{-1} and a flow rate of 1.0 mL min^{-1} was optimum for good separation in a reasonable time. So, the optimum chromatographic performances were achieved when using isocratic mobile phase composed of acetonitrile: 0.1% orthophosphoric acid pH 2.3 (10:90, v/v), injection volume 10 µL, column temperature 30 °C, detection wavelength 220 nm and flow rate 1.0 mL min^{-1}. Symmetrical peak shape Fig. 2 was obtained under the proposed chromatographic condition and TCP-SO4 was separated within 2 minutes. These conditions gave good separation and maximum peak height for the studied drug and its degradants within short time. Also, the developed method has an advantage over the reported HPLC method for determination of TCP-SO4 in tablets dosage forms (Aboul-Enein *et al.*, 1996) as the retention time of TCP-SO4 was 2.08 min, while in reported method was 6.78 min. The proposed method is rapid more than three times shorter than the reported method.

Results of Degradation studies

Tranylcypromine has cyclopropane ring which can undergo different ring opening reactions due to high ring strain (DePuy, 1973), also presence of amino group can undergo oxidation to form N-Oxide.

Alkaline degradation

Heating of TCP-SO_4 with 1N NaOH for 1 hour resulted in approximately 25 % degradation. The degradation peaks at t_R 1.314 well resolved from TCP-SO_4 peak t_R 2 min and two small peaks at 2.7 and 7.6 min as shown in Fig. 4.

Acidic condition

The degradation patterns of TCP-SO_4 in acidic conditions by heating with 1N HCL for 1 hour was found to be similar to that of the alkaline condition but with very small peaks at t_R 2.66 and 7.6 min as shown in Fig. 5.

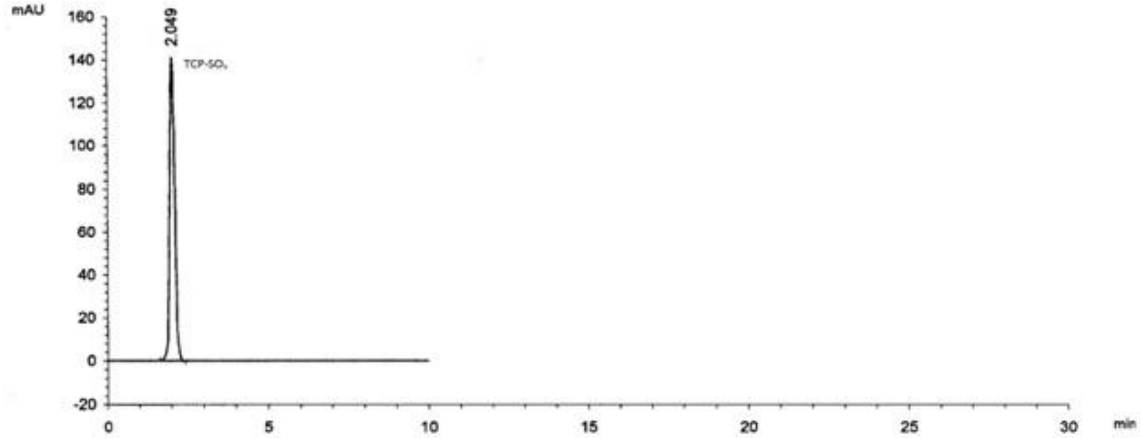


Fig. 2: HPLC Chromatogram of 100 µg of Tranylcypromine sulphate (TCP)

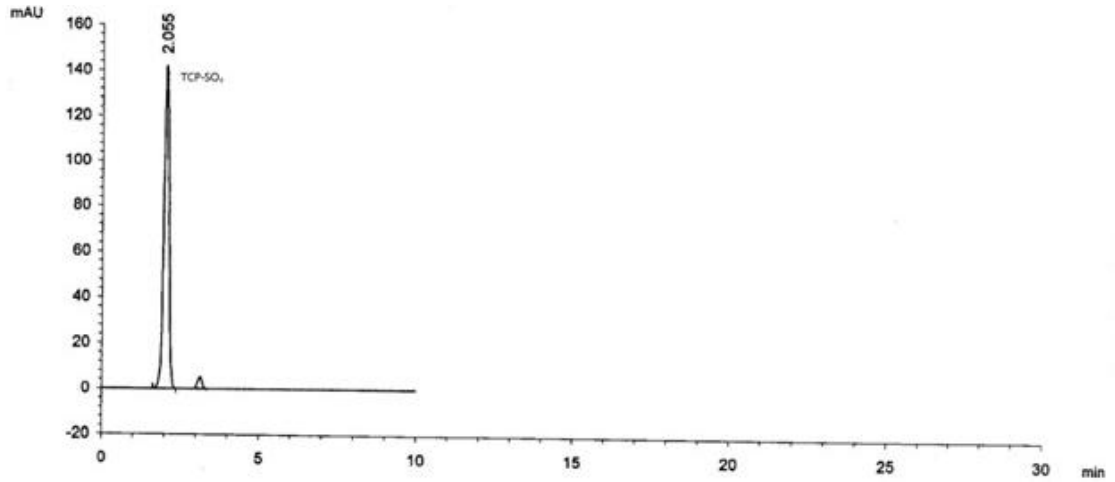


Fig. 3: Chromatogram of 100 µg of tablet Tranylcypromine sulphate (TCP).

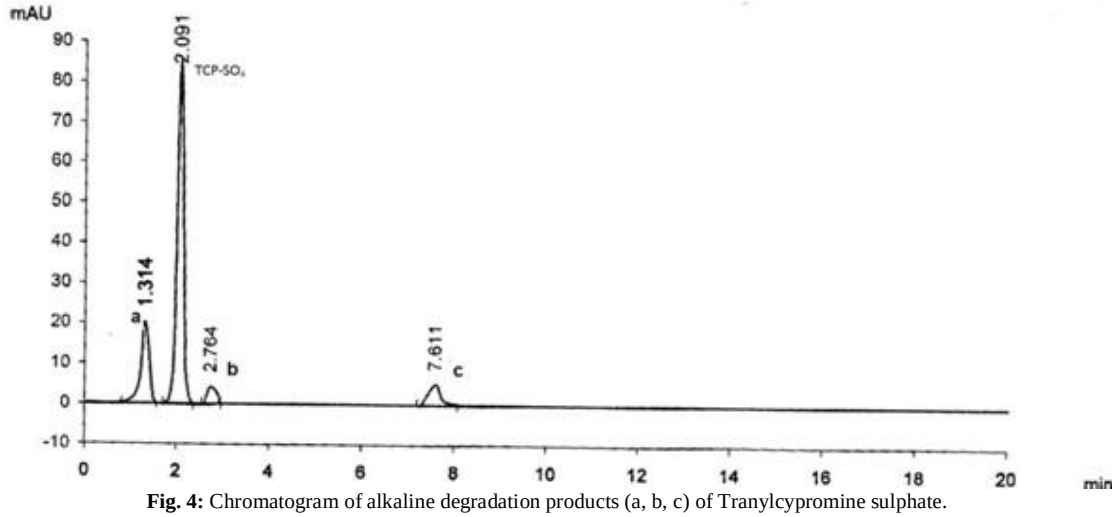


Fig. 4: Chromatogram of alkaline degradation products (a, b, c) of Tranylcypromine sulphate.

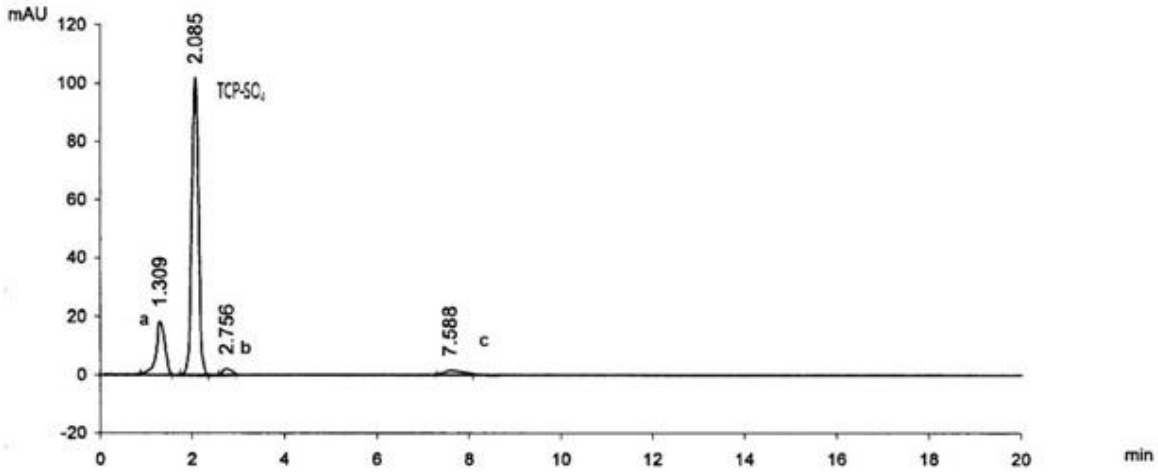


Fig. 5: Chromatogram of acidic degradation products (a, b, c) of Tranylcypromine sulphate.

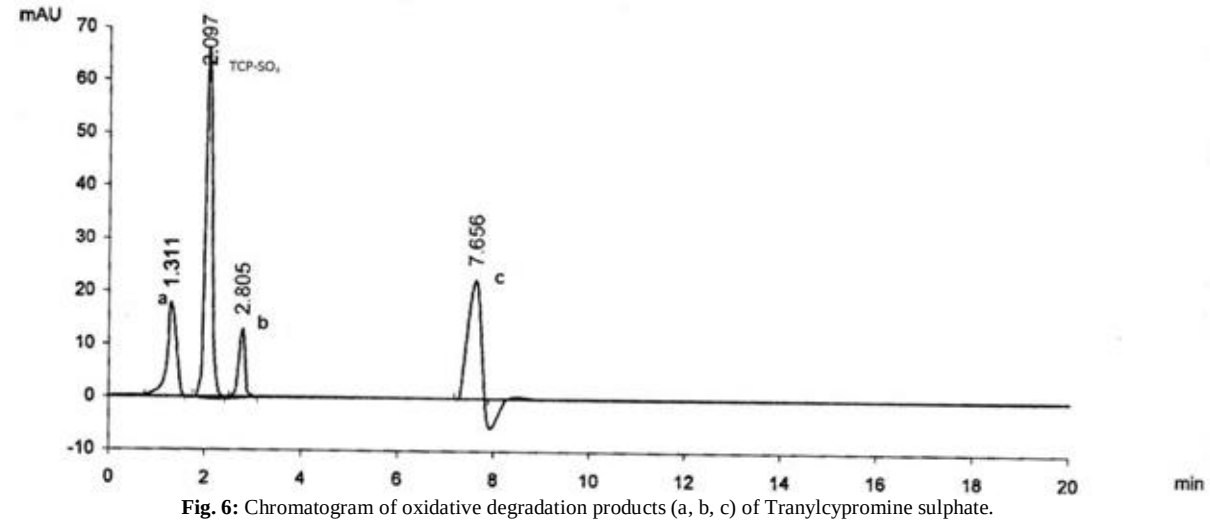


Fig. 6: Chromatogram of oxidative degradation products (a, b, c) of Tranylcypromine sulphate.

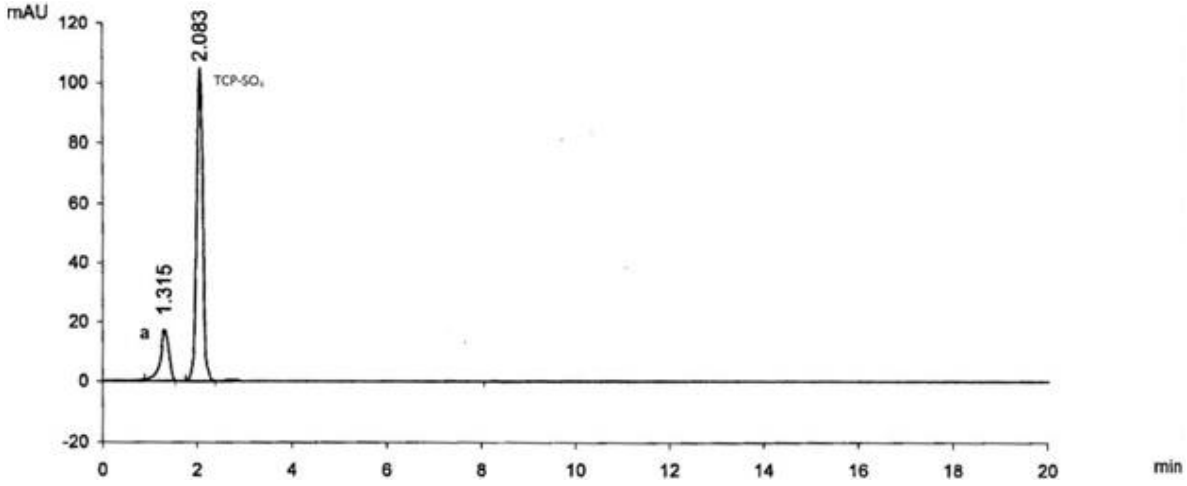


Fig. 7: Chromatogram of photo degradation products (a) of Tranylcypromine sulphate.

Oxidative conditions

TCP-SO_4 was found to be liable to oxidative conditions upon heating with H_2O_2 and approximately showed 40 % degradation. Degradation peaks at t_R 1.3, 2.8 and 7.6 min were found as shown in Fig. 6.

Photolytic conditions

TCP-SO_4 was found to be relatively stable upon exposure to UV and showed only small peak at t_R1.3 min as shown in Fig. 7.

Method validation

The developed method was validated according to the International Conference on Harmonization (ICH) guidelines (*Validation of analytical procedures*, 2005).

Linearity and range

The linearity was studied to determine the range over which the analyte response is a linear function with the concentration. This study was performed by preparing standard solutions at different concentrations. The responses were measured as peak area. The calibration curve was obtained by plotting the peak area against the corresponding concentration, showed linear relationship over a concentration range of 3-150 µg mL^{-1}. The linear regression equation was found to be: y = 11.0887x – 2.0238. The regression coefficient value (r) was found to be 1 indicating a high degree of linearity.

Limits of detection (LOD) and limit of quantitation (LOQ)

The LOD and LOQ were separately determined on the basis of the standard calibration curve. The residual standard deviation of the regression line or the standard deviation of y-intercepts of regression lines was used to calculate LOD and LOQ. The following formulae were used;

LOD = 3.3 × D/S and LOQ = 10 × D/S, where, D is the standard deviation of the y-intercepts of regression line and S is the slope of the calibration curve.

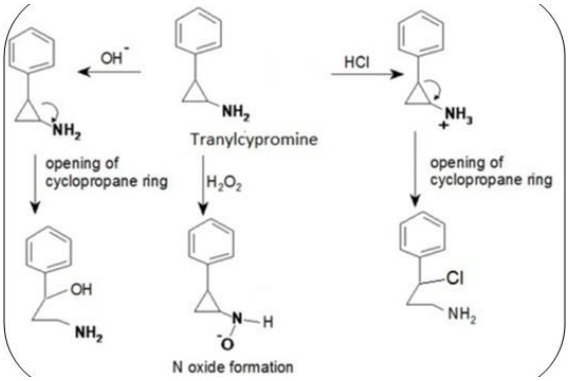
LOD was found to be 0.164 µg mL^{-1} and LOQ was found to be 0.498 µg mL^{-1}. Small values of LOD and LOQ indicate high sensitivity of the proposed method. Regression characteristics of the proposed HPLC method are given in Table 1.

Table 1: Analytical parameters for the determination of Tranylcypromine sulphate by the proposed HPLC method.

Parameter	Tranylcypromine sulphate
Range (µg mL^{-1})	3-150
Correlation coefficient (r)	1
Slope	11.0887
Intercept	-2.0238
LOD (µg mL^{-1})	0.165
LOQ (µg mL^{-1})	0.498

Specificity

Specificity is the ability of the analytical method to discriminate between target analyte and other components that may be present. The specificity of the assay was determined by absence of any excipient interference (such as microcrystalline cellulose, pregelatinised starch, carmellose sodium, calcium sulphate dehydrate, croscarmellose sodium, magnesium stearate which present in Parentil® tablets) since none of peaks appeared at the same retention time of TCP-SO_4. The results revealed that there was no interference of excipients Fig. 3. Also the complete chromatographic separation of TCP-SO_4 peak from its degradation products peaks generated under various stress conditions (Figs. 4-7) indicate the specificity of the proposed method.



Scheme: Proposed pathway for alkaline, acidic and oxidative degradation of Tranylcypromine sulphate.

Table 2: Inter and intra-day precision (%RSD) data for Tranylcypromine sulphate using the proposed method.

Conc. (µg mL^{-1})	Intra-day		Inter-day	
	Mean ±S.D*	RSD	Mean ±S.D*	RSD
20	98.76±0.197	0.200	98.94±0.563	0.569
50	98.32±0.330	0.336	98.37±0.377	0.383
100	98.296±0.639	0.650	98.63±0.364	0.369

Precision

The precision of an analytical method is the closeness of replicate results obtained from analysis of the same homogeneous sample. Precision was considered at two levels, i.e. repeatability and intermediate precision, in accordance with ICH recommendations (Guideline, 2005). Repeatability, or intra-day precision, was determined by performing nine analyses at three concentrations (20, 50, 100 µg mL^{-1}) on the same day. The percent RSD value was found to be in the range of (0.20-0.65 %). Intermediate precision was determined by analyzing the same sample in the same way on different days and the values of RSD ranged from 0.36 to 0.57 %. Results are shown in Table 2. The criterion for intra-day and inter-day precision was a RSD % not more than 2 %.

Accuracy

The accuracy of an analytical method is the closeness of results obtained by that method to the true value for the sample. It is expressed as recovery (%), which is determined by the standard addition method. 10 µg of tablet solution was spiked with 10, 20, 50and 100 µg of the standard and analyzed. The experiment was performed in triplicate. The average % recoveries for TCP-SO_4 in marketed formulation were found to be 99.41%. The results of accuracy are shown in Table 3. Furthermore, recovery data obtained from the developed method were statistically compared with those of the reference HPLC method (Aboul-Enein *et al.*, 1996) using the Student's t test and the variance ratio F test. In both tests, the calculated values did not exceed the theoretical ones at the 95 % confidence level which indicated that there were no significant differences between the recoveries obtained from the developed method and those of the reference method (Table 4).

Table 3: Accuracy (% recovery) data for Tranylcypromine sulphate by the proposed method.

Parameter	Taken µg mL^{-1}	Added µg mL^{-1}	Recovery*
	10	0	100.040
		10	102.277
		20	100.902
		50	99.764
		100	99.933
Mean			100.583
SD			1.044
RSD			1.038
SE			0.467
V			1.091

Table 4: Statistical analysis of results obtained by the proposed method compared with reported methods.

Parameters	Proposed method	Reference Method (Aboul-Enein et al., 1996)**
Mean ± S.D.	99.98±0.552	99.8±1.34
N	7	5
V	0.305	1.8
Student-t (MillerMiller, 2005)	0.326 (2.228)*	
F-test (Miller et al., 2005)	4.229 (4.53)*	

* The theoretical Student t-values and F-ratios at p-0.05.
**based on HPLC method.

Robustness

Robustness is the ability of the analytical method to remain unchanged by small, but deliberate changes in method parameters. To determine the robustness of the proposed method, the experimental conditions were deliberately changed; variation of pH (± 0.1), the mobile phase flow rate (± 0.05 mL $min^{-1)}$, acetonitrile content in the mobile phase (± 2.0 %), column temperature (± 2 °C), working wavelengths (±2 nm). These variations did not have any significant effect on the measured responses; peak area or retention time of TCP-SO_4. Table 5 shows the effects of studied variations on the retention times and peak area of the analyte.

Table 5: Robstness of the proposed method.

Slight change in	pH-value (2.3, 2.2 and 2.2)		flow rate (1,1.1 and 0.9 mL/min)		Acetonitril % (10, 11 and 9%)		Temp. (30, 32 and 28 °C)		Detection wavelength (220, 222and 218)	
Affected parameter	t_R	Peak area	t_R	Peak area	t_R	Peak area	t_R	Peak area	t_R	Peak area
RSD	1.224	0.500	3.465	0.417	2.076	0.352	3.181374	0.1893	0.874	0.345

Table 6: System suitability parameters of Tranylcypromine sulphate and nearest degradation products.

Parameter	Degradant a	Degradant b	TCP-SO_4	Acceptance criteria (Guidance, 1994)
Retention time(t_R)	1.314	2.756	2.085	
Capacity factor($K^{'}$)	1.628	4.512	3.182	1-5
Theoretical plates (N)	2150	2698	3315	> 2000
Asymmetry	1.17	1.2	0.63	≤ 2
Resolution(R_s)	2.39	2.333		> 2
Selectivity (α)	1.954	1.423		> 1

System suitability

System suitability tests are used to verify that results and the reproducibility of the chromatographic system is adequate for the analysis to be performed. It was monitored by number of theoretical plates N, capacity factor $K^{'}$, Asymmetry, Resolution Rs and selectivity α. The parameters were found to be satisfactory for TCP-SO_4 and most closely placed degradation peaks (a and b) indicated that the method is suitable for the purpose. The R_s was always > 2.3 as in Table 6.

CONCLUSIONS

A simple, rapid and stability-indicating ultra high efficiency RP-HPLC method has been developed and validated for the routine analysis of Tranylcypromine sulphate in bulk form and in tablets with ultra high efficiency. The results of stress testing carried out according to the ICH guidelines showed that the proposed method is selective and stability-indicating. The method is capable of separating target analyte from its degradation products within 2 min and total run time was 8 minutes, while the reported HPLC method separates the studied drug at 6.7 min.

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