

Validated and Sensitive Spectrophotometric Method for the Determination of Amitriptyline Hydrochloride

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Abstract

A simple, rapid, selective and highly sensitive spectrophotometric method is described for the quantitative determination of a tricyclic antidepressant drug, amitriptyline hydrochloride (AMT) in pure and in pharmaceutical preparations. The method is based on the bromination of AMT with known excess of bromine. The unreacted bromine is determined based on its ability to bleach the dye Eriochrome blue black R quantitatively at 530 nm. Beer's law was obeyed over the concentration range 0.0–15 µg/mL. The molar absorptivity value was found to be 1.345×10^4 L/mol/cm, with the corresponding Sandell's sensitivity values of 0.0233 µg/cm². The limits of detection and (LOD) and quantification (LOQ) are also reported for the developed method. Intra- and inter-assay precision and accuracy of the method was established according to the current ICH guidelines. Applications of the procedure to the analysis of various pharmaceutical preparations gave reproducible and accurate results. Further, No interferences were observed from excipients and the validity of the method was tested against reference method. Percent of relative recoveries values were 98.57% to 100.52%.

Keywords: Eriochrome blue black R; Antidepressant drug; Amitriptyline; Brominated product; Pharmaceuticals

Introduction

Tricyclic antidepressants (TCAs) are heterocyclic chemical compounds used primarily as antidepressants. The TCAs were first discovered in the early 1950s and were subsequently introduced later in the decade [1] they are named after their chemical structure, which contains three rings of atoms. AMT belongs to tricyclic dibenzocycloheptadiene derivatives and chemically AMT is 3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride (Figure 1). AMT is official in European Pharmacopoeia [2]. The report describes a potentiometric titration of AMT using 0.1 M sodium hydroxide as titrant in acidic medium.

In view of its pharmacological importance, considerable work has been done for the detection and quantification of AMT. Several researchers have been reported the determination of the AMT in biological fluids and/or pharmaceutical formulations. These include chromatographic techniques like HPTLC [3], HPLC with liquid-liquid micro extraction technique [4], GC [5], GC-MS [6], LC-MS [7], UPLC-MS [8], electro generated chemiluminescence [9], chemometric methods [10] and spectrophotometry [11-18].

The reported chromatographic techniques (HPLC/GC/LC-MS/UPLC-MS) require expensive experimental set-up and are not affordable in every laboratory for routine analysis. The reported chemometric method [10] is less sensitive, whereas the reported spectrophotometric methods are less accurate and less sensitive [13,15-18] and some are time consuming, requires tedious extraction procedures [13,18] and costly reagents [16]. Thus, there is a need to develop simple, sensitive, accurate and cost-effective method for its determination. Comparison of the performance characteristics of the proposed method with the existing spectrophotometric methods for AMT is shown in Table 1.

The objective of the present investigation is to develop a highly sensitive, selective, reproducible and economically viable method that could be used to determine AMT in bulk drug and in pharmaceutical dosage forms. The method employs the use of bromate-bromide solution and Eriochrome blue black R as reagents. The proposed

method is based on the bromination of AMT with known excess of bromine followed by reaction with Eriochrome blue black R to produce violet colored dye. The developed method is validated for linearity, accuracy, precision, selectivity and recovery as per the current ICH guidelines.

Experimental Procedure

Apparatus

All absorbance measurements were performed using a Systronics Model 166 digital spectrophotometer provided with 1-cm matched quartz cells.

Reagents and standards

Analytical reagent grade chemicals and reagents were used, and double distilled water was used throughout the experiment to prepare all solutions.

Standard AMT solution: Pharmaceutical grade AMT certified to be 99.95% pure was used and received as a gift sample from La Pharma, Ahmedabad, India. A stock standard solution equivalent to 100 µg/mL of AMT solution was prepared by dissolving 10 mg of the pure drug in 100 mL distilled water. Working solutions were prepared as required by dilution in water.

Pharmaceutical formulations of AMT such as Tryptomer [Wockhardt (Merind)] and Latilin (La Pharma) tablets were purchased from local commercial sources.

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Sl. No.	Reagent's used	Methodology	Linear range, µg/mL	Remarks	Ref
1	Methanol-0.1 N HCl	chemometric methods (Double-divisor spectra derivative and partial least squares methods)	4.83–24.19	Less sensitive	[10]
2	NaClO ₄ -buffer-ethanol	derivative spectrophotometry	0.63–10.04 0.62–10.14	Sensitive but lack of selectivity	[11]
3	Methanol	UV-spectrophotometric method	2.0–12.0	Sensitive but lack of selectivity	[12]
4	AMT-Eriochrome cyanine R (ECR) AMT-pyrocatechol violet (PCV)	The absorbance of AMT- ECR complex was measured at 518 nm and for AMT- PCV at 445 nm	8.0–80 1.5–15.0	Less sensitive, involves strict pH control and extraction procedures Sensitive but involves tedious extraction procedures	[13]
5	Chloranilic acid	purple colour complex showed maximum absorption at 520 nm	€=4.67×103	Less sensitive	[15]
6	3-methylbenzothiazolin-2-onehydrazone-iron(III) chloride	Oxidative coupling of the drugs with 3-methylbenzothiazolin-2-onehydrazone which shows maximum absorption at 630 nm	0.0–25 (€=3.20×103)	Less sensitive and uses costly reagent	[16]
7	Ferric ammonium sulphate-mercuric thiocyanate	Ligand exchange on mercuric ion	0–60	Less sensitive	[17]
8	AMT-methyl orange (MO) and bromocresol green (BCG)	Formation of ion-pairs between MO and BCG reagents and the absorbance was measured at 420 and 410 nm	1–25	Less sensitive and requires extraction procedures	[18]
9	Eriochrome blue black R-Bromate bromide mixture	Bromination of the AMT with known excess of bromine followed by reaction with Eriochrome blue black R and exhibits absorption maximum at 530 nm	0.0–15	Highly sensitive, selective, less time consuming, no heating is required, eco-friendly (no use of organic solvents) and inexpensive	Developed method

Table 1: Comparison of the performance characteristics of the proposed method with the existing visible spectrophotometric/chromatographic methods.

Bromate-bromide solution (10 µg/mL): It was prepared by mixing potassium bromate (0.05 g or 5.98×10^{-4} M) and potassium bromide (0.5 g or 8.40×10^{-4} M) in 500 mL calibrated flask with water. A volume of 20 mL of the mixture was transferred in to a 100 mL calibrated flask and diluted up to the mark with water. Then, a volume of 50 mL of diluted solution was transferred into a 100 mL calibrated flask containing 40 mL of sulfuric acid (4.25 M) and diluted up to the mark with water. Freshly prepared solution was used every day.

Others: 4.25 M H₂SO₄ and 0.1% EBBR were used.

General procedures

Calibration curve: Various aliquots of standard solution containing 0.0, 0.1, 0.2, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mL of AMT (50 µg/mL) were transferred into a series of 10 mL calibrated flasks using a micro burette. To each flask were added 6 mL of bromated-bromide mixture (10 µg/mL w.r.t KBrO₃), and the flasks were stoppered. Finally, 0.75 mL of 0.1% EBBR was added to each flask and mixed well before diluting to 10 mL with distilled water and the absorbance of the bright pink colour solution was measured at 530 nm against the reagent blank. The reagent blank was prepared similarly, but without AMT.

The amount of the AMT present in the sample was computed from the concurrent calibration curve or the regression equation. All measurements were made at room temperature ($26 \pm 3^\circ\text{C}$).

Procedure for commercial samples: Twenty tablets of AMT (10 and 25 mg), were weighed accurately and ground into fine powder. An amount of the powder equivalent to 10 mg of each drug was weighed accurately into a two separate 100 mL calibrated flasks and 50 mL distilled water was added. The content was shaken for about 30 min; the volume was diluted to the mark with water and mixed well and filtered using a Whatman No. 41 filter paper. The filtrate containing the cited drugs were at a concentration 100 µg/mL was subjected to analysis by the procedure described above after suitable dilution step.

Analysis of placebo blank: A placebo blank of the composition: talc (25 mg), acacia (15 mg), starch (15 mg), methyl cellulose (20 mg),

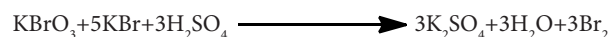
sodium citrate (20 mg), magnesium stearate (25 mg) and sodium alginate (10 mg) was made and its solution was prepared in 50 mL calibration flask as described under Section 4.3.2, and then subjected to analysis using the procedure described under Section 4.3.1.

Analysis of synthetic mixture: To the placebo blank of the composition described above, 10 mg of AMT was added into a 100 mL calibrated flask and homogenized, and the solution was prepared as described under Section 4.3.2, and then subjected to analysis by the procedure described under Section 4.3.1. The analysis was used to study the interferences of excipients such as talc, acacia, starch, methyl cellulose, sodium citrate, sodium alginate and magnesium stearate.

Results and Discussion

Chemistry of the method

The reaction to be studied in this experiment is between bromate and bromide ions in the presence of acid and occurs according to the equation,



Since, the aqueous bromine solutions are unstable because of the high vapour pressure of bromine [19]. In the present investigation, a known excess of bromine is used to brominate AMT in an acidic condition. The unreacted bromine bleaches the color of the azo-dye, EBBR, thereby a decrease in bromine concentration. This reaction formed the basis of AMT determination. When EBBR is bleached (brominated) completely with bromine, the absorbance at 530 nm decreases and reaches minimum value. In the presence of AMT concentration, bromine is reduced to bromide and the unreacted bromine decolorized the EBBR. Thus, with increasing concentration of AMT, higher amount of bromine is reduced and this is observed by a linear increase in the absorbance due to the unbleached EBBR at 530 nm.

The difference in concentration of unbleached EBBR and the reacted bromine in the reaction mixture give the exact concentration of AMT. The absorption spectra (Figure 2) show that, a linear increase in

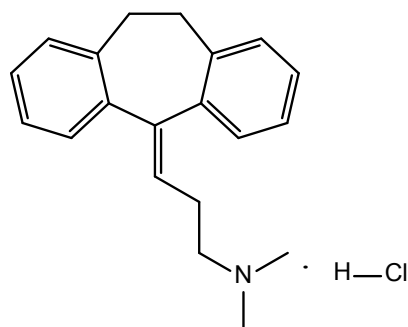


Figure 1: Structure of AMT.

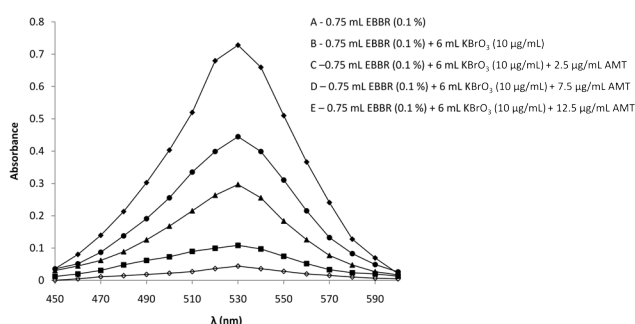


Figure 2: Absorption spectra for AMT.

absorbance with increasing drug concentration. The possible reaction pathway is given in Scheme 1.

Absorption spectra

EBBR has a maximum absorbance at 530 nm (curve A), on treatment with bromine, the color of the EBBR bleaches due to bromination. When EBBR is bleached completely with bromine, the absorbance at 530 nm decreases and reaches minimum value (curve B). With an increase in AMT concentration, there is a corresponding decrease in bromine concentration, and as a result less brominated/bleached EBBR is obtained (curves C, D and E). The concentration of bromine, EBBR and AMT are given in Figure 2.

Optimization of variables and method development

In order to develop a rapid, highly sensitive and stable method, several experimental parameters (effect of dye, bromine concentration and standing time) were studied separately by measuring the absorbance of the colored product at 530 nm by varying one parameter at a time and keeping the others constant.

Effect of dye and reagent concentration: Preliminary experiment was performed to fix the upper and lower limits of the dye that could be determined spectrophotometrically at 530 nm. The upper limit was of the absorbance (0.728) adjusted was obtained by the addition of 0.75 mL of 0.1% EBBR in 10 mL of the reaction mixture. The lower limits of the absorbance was reached by the addition of 6 mL of bromate-bromide mixture (10 µg/mL w.r.t. KBrO₃) in the same volume. The absorbances of these are given in Figure 2.

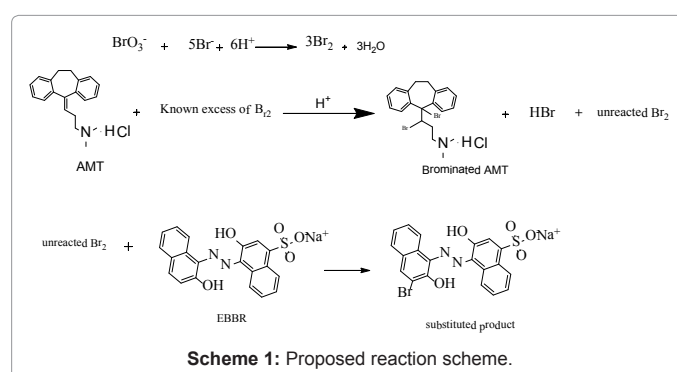
Reaction time and color stability: The quantitative reaction between the drug and the bromine generated *in situ* was completed in 3 min (Figure 2, curves C, D and E). After completion of the reaction between the drug and the bromine, a 5 min standing time was necessary

for the complete bleaching of the dye color by the residual bromine and this bromination process was instantaneous and found to be complete within 8 min. The absorbance of the measured species was stable up to 30 min.

Method validation

The developed method for the assay of drugs under investigation was validated for linearity, sensitivity, precision, accuracy, selectivity and recovery as per the current ICH guidelines [20].

Linearity: Under the experimentally defined conditions for AMT, a linear correlation was found between the absorbance at 530 nm and the concentrations ranges are given in Table 2. Regression analysis of the calibration curve using the method of least-squares was made



Scheme 1: Proposed reaction scheme.

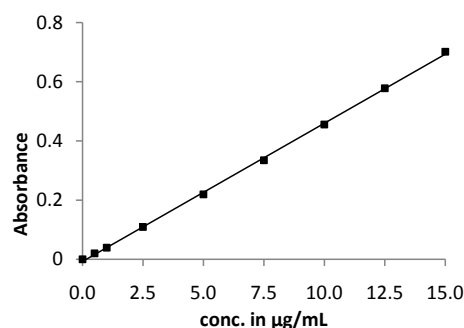


Figure 3: Calibration curve for AMT.

Parameter	AMT
λ_{max} nm	530
Beer's law range (µg/mL)	0.0–15
Linear range (µg/mL)	0.3–15
Molar absorptivity (ϵ), (L/mol/cm)	1.345×10^4
Sandell sensitivity (µg/cm ²)	0.0233
Regression equation, Y*	
Intercept (a)	-0.0040
Slope (b)	0.0445
Correlation coefficient (r)	0.999
S_a	0.1971
S_b	0.0138
LOQ (µg/mL)	0.2430
LOD (µg/mL)	0.0802

* $y = a + bx$, where x is the concentration of AMT in µg/mL and y is the absorbance at 530 nm., S_a is the standard deviation of the intercept, S_b is the standard deviation of the slope.

Table 2: Analytical and regression parameters of the proposed method.

Drug	Drug added, µg/mL	Intra-day accuracy and precision (n=5)			Inter-day accuracy and precision (n=5)		
		Drug found, µg/mL	%RE	%RSD	Drug found, µg/mL	%RE	%RSD
AMT	2.5	2.47	0.84	1.19	2.51	-0.24	1.12
	7.5	7.48	0.22	0.67	7.53	-0.33	0.36
	12.5	12.45	0.44	0.76	12.54	-0.35	0.67

%RE: Percent relative error; %RSD: Percent relative standard deviation.

Table 3: Evaluation of intra-day and inter-day accuracy and precision.

t=1.66, F=3.91	Nominal amount mg per tablet	Found** (% of nominal amount ± SD)	
		Reference method [16]	Proposed method
Tryptomer ^a	10 mg	99.16 ± 0.50	99.95 ± 0.25 t=1.66, F=3.91
Latilin ^b	25 mg	99.25 ± 0.35	99.25 ± 0.35 t=1.53, F=1.64

*Marketed by: a. [Wockhardt (Merind)], b. (La Pharma).

**Mean value of five determinations

Tabulated t- and F-values at 95% confidence level are 2.77 and 6.39, respectively.

Table 4: Results of determination of AMT in dosage form and statistical comparison with the reference method.

Tablet studied	AMT tablet added, µg/mL	Pure AMT added, µg/mL	Total found, µg/mL	Pure AMT recovered*** ± SD
Tryptomer	5	2.5	7.479	99.16 ± 0.11
	5	5	10.02	100.44 ± 0.23
	5	7.5	12.52	100.25 ± 0.41
Latilin	5	2.5	7.490	99.60 ± 0.13
	5	5	9.978	99.56 ± 0.29
	5	7.5	12.529	100.39 ± 0.39

***Mean value of three determinations

Table 5: Results of recovery experiments via the standard addition technique.

to calculate the slope (b), intercept (a) and correlation co-efficient (r) for each drug and the values are presented in Table 2. The optical characteristics such as absorption maxima, Beer's law limits, molar absorptivity and Sandell's sensitivity values [21] are also given in Table 2. The calibration curve is given in Figure 3.

Sensitivity: The detection limits (LOD) and limits of quantitation (LOQ), for the proposed method was evaluated as per ICH guidelines using the formula:

$$LOD = \frac{3.3 \times \sigma}{s} \text{ and } LOQ = \frac{10 \times \sigma}{s}$$

Where σ is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte and s is the slope of the calibration graph. The high values of molar absorptivity (ϵ) and low values of Sandell's sensitivity and LOD indicate the high sensitivity of the proposed method (Table 2).

Intra-day and inter-day precision and accuracy: In order to determine the accuracy and precision (intra- and inter-day) of the proposed method, solutions containing three different concentrations (low, medium and high) (Table 3) within the working limits of drugs were prepared and analyzed in five replicates in the same day (intra-day precision) and in after 3 days (inter-day precision). The relative error, RE (%) and relative standard deviation, RSD (%) values of both intra and inter-day studies were satisfactory and showed that the best appraisal of the procedure in daily use. The results obtained are presented in Table 3 and show that the accuracy and precision of the proposed method have good repeatability and reproducibility.

Interferences: The selectivity of the proposed method to pharmaceutical samples was tested by a systematic study under the optimum experimental conditions which were made for the effect of the additives and excipients. The recommended procedure was applied

to the analysis of both placebo blank and synthetic mixtures prepared in the laboratory as described under Sections 4.3.3 and 4.3.4. The usual diluents and excipients such as starch sodium alginate, talc, gelatin, dextrose, methyl cellulose and acacia were found not to interfere with the analysis by the proposed method and the results were obtained in the range 98.57% to 100.52%. These results further showed clearly the accuracy and precision of the developed method.

Application to analysis of pharmaceutical samples: The proposed method was applied successfully to the determination of AMT in commercial tablets and injection. The same batch tablets were also assayed by the reference method [16] which consisted of measurement of absorbance of AMT at 530 nm. The results of an assay were statistically compared with the reference method [16] by applying the Student's t-test for accuracy and F-test for precision. The results in the Table 4 showed that there is no significant difference between the proposed and reference method [16] at the 95% confidence level with respect to accuracy and precision, they could therefore be used easily for the routine analysis of pure AMT in its dosage forms.

Evaluation of accuracy by recovery study (standard addition technique): The accuracy of the proposed method was further ascertained by performing recovery studies via the standard addition technique. Pre-analyzed tablets powder was spiked with pure drugs at three different concentrations (50, 100 and 150%) and the total was found by the proposed method. Each determination was repeated three times. The recovery of the pure drug added was quantitative and the recovery percentage value ranged between 99.18–101.59% with standard deviation in the range 0.06–0.73% and is close to 100% indicating that the recovery was good, and that the co-formulated substance did not interfere in the determination. The results of recovery study are compiled in Table 5.

Conclusion

In the present investigation, a highly sensitive, accurate and precise spectrophotometric method for the determination of AMT in pure and in pharmaceutical formulations is described. The proposed method is simple and not required expensive experimental set up like HPLC and other chromatographic methods. The proposed method is free from the usual analytical complications like heating or extraction steps and free from interference by common additives and excipients. Further, the proposed method using EBBR-bromate bromide mixture as reagent can be applied at ambient temperature and color development is instantaneous. Another advantage of the developed method is more sensitive than most of the reported spectrophotometric methods [10,13,15-18]. These advantages give the proposed method a great value and make it suitable for routine clinical use, as it is simple and does not involve any complicated extraction procedures and was found to be simple, selective and cost-effective compared too many reported methods.

Competing Interests

The authors declare that they have no competing interests.

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