

RESEARCH ARTICLE

NEW METHODS FOR DETERMINATION OF AMBROXOL HYDROCHLORIDE IN PURE FORM AND FARMACEUTICAL FORMULATIONS BASED ON SPECTROPHOTOMETRY

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Abstract

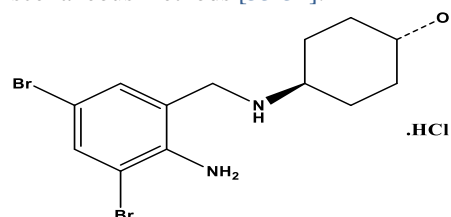
The proposed methods are simple, rapid, and accurate, used for the determination of Ambroxol Hydrochloride (AMB.HCl). There were two methods, the First method included chromotrope 2R, chromotrope 2B, arsenazo I, ASPANDS, and chromotrope 2C for the determination of AMB.HCl in its pure and pharmaceutical forms. The first method is based on the drug oxidation with Potassium permanganate in excess. The unreacted potassium permanganate was determined by measuring the absorbance of colored chromotropic acid azo dyes namely chromotrope 2R, chromotrope 2B, arsenazo I, SPADNS, and chromotrope 2C. The suitable λ_{max} were 500, 510, 500, 510, and 520 nm, respectively. Under optimized conditions, Beer's Law showed good correlation and obeyed in the concentration range 1.51-7.46, 0.82-4.97, 1.65-6.63, 0.82-6.63, and 1.73-8.29 $\mu\text{g mL}^{-1}$ for chromotrope 2R, chromotrope 2B, arsenazo I, SPADNS, and chromotrope 2C. The apparent molar absorptivity, Sandell sensitivity, LOD, and LOQ were calculated. Pure and pharmaceutical forms containing AMB.HCl were analyzed and tested for the validity of the proposed methods. The Second method spectrophotometric titration is based on the determination of unreacted potassium permanganate using spectrophotometric titration against ferrous ammonium sulfate, where the end-point was detected spectrophotometrically using ferrion indicator at 510 nm, the Relative standard deviation where 0.23-2.04 with average recovery 100.35-103%.

Keywords: Spectrophotometry, Ambroxol hydrochloride, Oxidation-reduction reaction, Chromotropic acid azo dyes.

1. Introduction

Ambroxol Hydrochloride is chemically known as trans-4-(2-amino-3,5-dibromobenzylamino)cyclohexanol hydrochloride. AMB.HCl is very important for improving the drug in the pharmaceutical industry [1] Although, AMB.HCl (AMB.HC) is a mucolytic drug that reduces the thickness of the sputum [2] also used to treat conditions with abnormal mucus secretion [3] allowing the patient to breathe freely and deeply by promoting mucus clearance, facilitating expectoration and easing productive cough [4,5]. It is soluble in hot water and practically insoluble in dichloromethane and soluble in methanol [6]. A supramolecular assembly of pure AMB.HCl with cyclodextrin molecules tagged with a protein or enzymes could make it a potent mucolytic and mucokinetic agent. Some recent studies include the drugs

having a role in the treatment of Gaucher's disease [7], Parkinson disease [8], and other aging-associated diseases involving dysfunction of autophagy [9]. AMB.HCl is a mucolytic drug as a salt form of Ambroxol (Scheme 1), a metabolite of bromohexine [10]. Several different methods have been used for the determination of AMB.HCl including UV/Vis spectrophotometric [11-22], high-performance liquid chromatography [23-32], and miscellaneous methods [33-34].



Scheme 1: Structure formula of Ambroxol HCl

Aim of The Present Work

The aim of this work is to develop new spectrophotometric methods.

The first method is based on the oxidation of the ambroxol hydrochloride (AMB-HCl) with excess potassium permanganate in the presence of chromotropic acids azo dyes such as C2R C2B, ARZO I, SPADNS, and C2C. The second method is spectrophotometric titration based on an unreacted oxidant with a standard Fe (II) solution.

The main objectives that were taken into consideration during the present study are:

- Investigating the optimum conditions for determination of ambroxol hydrochloride by oxidation with potassium permanganate in the excess and back titration of the unreacted oxidant.
- Suggestion of new analytical methods characterized by high sensitivity for determination of drugs.
- To validate the suggested methods through the determination of quantification ranges, sensitivities, limits of quantification, and limits of detection, in addition to comparison of the results with previously reported ones statistically using student t-and F-test.

The Importance of Research in Relation to Previous Research

Previous studies help the researcher avoid making mistakes that previous researchers made because they make them aware of their mistakes. The researcher benefits from previous studies in developing the study questions, because he looks at the previous studies carried out by the previous researchers, and learns about the way in which they formulated their scientific research questions.

In addition, the literature review revealed that there were no previous analytical methods have the same concept of analysis which was simple, economical and accurate.

2. Experimental

2.1 Apparatus

All the spectral measurements were carried out using a Jenway 6300 Visible single-beam spectrophotometer with a range of 200-1000 nm equipped with glass or quartz cells of 1 cm optical path length. Micro-burette was used for measuring volumes of solution. A Scientech SA210 digital balance was used for Weighing throughout the study.

2.2 Materials

All chemicals used were of analytical grade, and double distilled water was used throughout all experiments. Pure grade AMB.HCl was provided by chemical industries development Co, (CID, Giza Egypt). The Pharmaceutical formulation of AMB.HCl capsules 30 mg/cap was obtained by the local market Glaxo welcome pharm. Co, Cairo, Egypt. Chromotrope 2R, Chromotrope 2B, Arsenazo (I), spadns, (SPADNS) were provided by (Sigma –Aldrich), while Chromotrope 2C, was prepared locally in the laboratory of the Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt, 1,10 phenanthroline, ferrous ammonium sulfate hexa-hydrate and potassium permanganate were obtained from (Sigma-Aldrich).

2.3 Solutions

AMB.HCl (AMB.HCl) stock solution ($414.5 \mu\text{g mL}^{-1}$) was prepared by dissolving an accurate amount of 0.4145 g, of the pure solid in double distilled water, the solution was transferred into 100 mL volumetric measuring flask and made up to the mark by using double distilled water. Potassium permanganate Mn(VII) stock solution ($158.0339 \mu\text{g mL}^{-1}$) was prepared by dissolving

Table 1: Some spectrophotometric determination methods for AMB.HCl

Methods	Reagent	λ_{max} (nm)	Linear-range ($\mu\text{g mL}^{-1}$)	Ref
Redox-reaction	P-dimethylbenzaldehyde	420	40-80	[11]
	Folin-Ciocalteu	704	30-70	
	Cerric Amm. Sulphate	540	10-50	
Vis/Spectro (diazotized)	Catechol	425	1.0-16	[12]
	Resorcinol	425	10-60	
	β -naphthol	425	1.0-20	
Vis/Spectro (Extraction)	Bromophenol blue	412	0.4-19	[13]
	Bromocreasol green	414	0.4-37	
Charge transfer	Chloranillic	430	5.0-40	[14]
Derivative UV/ (Spectro)	-	272	10-50	[15]
UV/ (Spectro)	-	245	2.0-6.0	[16]
UV/ (Spectro)	-	245	40-200	[17]

accurately weighed 1.580 g of the solid in double distilled water the solution was transferred into 100 mL volumetric measuring flask and made up to the mark by dilute sulfuric acid 2 $\mu\text{g mL}^{-1}$ Standard stock solutions of 468 $\mu\text{g mL}^{-1}$ of chromotrope 2R, 513.3 $\mu\text{g mL}^{-1}$ chromotrope 2B (C2B), 548 $\mu\text{g mL}^{-1}$ arsenazo I, 570.4 $\mu\text{g mL}^{-1}$ SPADNS, and 345.1 $\mu\text{g mL}^{-1}$ chromotrope 2C, were prepared by dissolving accurately weighed 0.4680, 0.5133, 0.548, 0.5704, and 0.3451 g, respectively, in 100 mL volumetric measuring flask using double distilled water.

Preparation of reagent for spectrophotometric titration: The solution of 1,10 phenanthroline 0.01 mol L^{-1} was prepared by dissolving 1.820 g in dilute sulfuric acid in a 100 mL measuring flask, then 182 $\mu\text{g mL}^{-1}$, was prepared by the diluting stock solution. Fe(II) solution 392.1 $\mu\text{g mL}^{-1}$ was prepared from ammonium ferrous sulfate hexahydrate by dissolving 3.921 g into a 100 mL measuring flask and made up to the mark by double distilled water. Then 196.05 $\mu\text{g mL}^{-1}$ Fe(II) was prepared by diluting the stock solution. The solution of the ferrion indicator was prepared by mixing 1,10 phenanthroline and Fe(II) sulfate in 3:1 molar ratio

2.4. Analytical Procedure

2.4.1. Spectrophotometric calibration curve using chromotrope 2R (I), chromotrope 2B (II), arzo I (III), SPADNS (IV), and chromotrope 2C (V)

For the plotting of the calibration curve, different series solutions containing (0-10 $\mu\text{g mL}^{-1}$) AMB.HCl was added to 94.82 $\mu\text{g mL}^{-1}$ Mn(VII) solution in a 10 mL test tube. After heating these solutions for 10 min at 100 °C, then cooling for 5 min a constant concentration of chromotropic acid azo dyes was added. After several trials, it was found that the best result was obtained upon using 1.5, 1.2, 0.8, 1.0, and 1.0 mL^{-1} from 9.36 $\mu\text{g mL}^{-1}$ Chromotrope 2R, 10.26 $\mu\text{g mL}^{-1}$ Chromotrope 2B, 10.96 $\mu\text{g mL}^{-1}$ Arzo I, 11.4 $\mu\text{g mL}^{-1}$ SPADNS, and 6.9 $\mu\text{g mL}^{-1}$ Chromotrope 2C respectively. The content of each tube was transferred into a 10 mL measuring flask and completed to the mark by the solution of sulfuric acid 2.0 $\mu\text{g mL}^{-1}$. The calibration curve was obtained by measuring the color at 500, 510, 500, 510, and 520 nm in the case of C2R, C2B, ARZO I, SDS, and C2C respectively. The calibration curve was plotted in each case by using the concentration of AMB.HCl against the corresponding absorbance at the selected wavelengths.

2.3.2. Ringbom Curve for AMB.HCl

Since absorbance is a linear function of concentration for solutions conforming to Beer's Law, a straight line indicates such conformity. Ringbom suggested plotting working curves as transmittance versus the logarithm of concentration to emphasize the importance of making

measurements within a certain transmittance range where the error in the measurements is smallest [34].

2.4.3. Spectrophotometric Titration

Into a series of test tubes, constant volumes of 4.145 $\mu\text{g mL}^{-1}$ AMB HCl pure solutions were added to 94.82 $\mu\text{g mL}^{-1}$ excess MnO_4^- , and heated at 100 °C. After cooling, the titration was carried out against 196.05 $\mu\text{g mL}^{-1}$ Fe(II) as titrant using ferrion indicator. The absorbance was measured at λ_{max} (510 nm). A titration curve between volumes of added Fe(II) on the X-axis and absorbance on Y- the axis were plotted. The endpoint was determined from the intersection between two straight lines.

2.4.4. Procedure for Pharmaceutical Formulation

The contents of ten capsules (30 mg/capsule) were accurately weighed and ground using a mortar. The average weight (equivalent to one capsule was calculated). An accurately weighed amount of the ground content capsule powder equivalent to 30 mg AMB.HCl was dissolved in a small amount of double distilled water. The resulting solution was filtered and remained excipients were washed several times by double distilled water to make sure that the entire active ingredient in the powder was dissolved. Finally, the volume was then completed to 500 mL in a volumetric flask, and the concentration of AMB-HCl is 60 $\mu\text{g mL}^{-1}$. Different volumes of this solution were taken and treated by the same procedures.

3. Results and discussion

The absorption spectra of the chromotropic an azo dyes, the drug product of oxidation of the drug with Mn(VII), and the product of oxidation of excess Mn(VII) with chromotropic azo dyes were plotted in the range 200-800 nm to record the maximum absorbance at which the measurement would be carried out. Absorption spectra of AMB.HCl did not exhibit any absorption in the visible region. The maximum absorption was observed at 500, 510, 500, 510 and 520 nm for Chromotrope 2R, Chromotrope 2B, Arzo I, Spadns, and Chromotrope 2C, respectively. As Shown in Figure. (1)

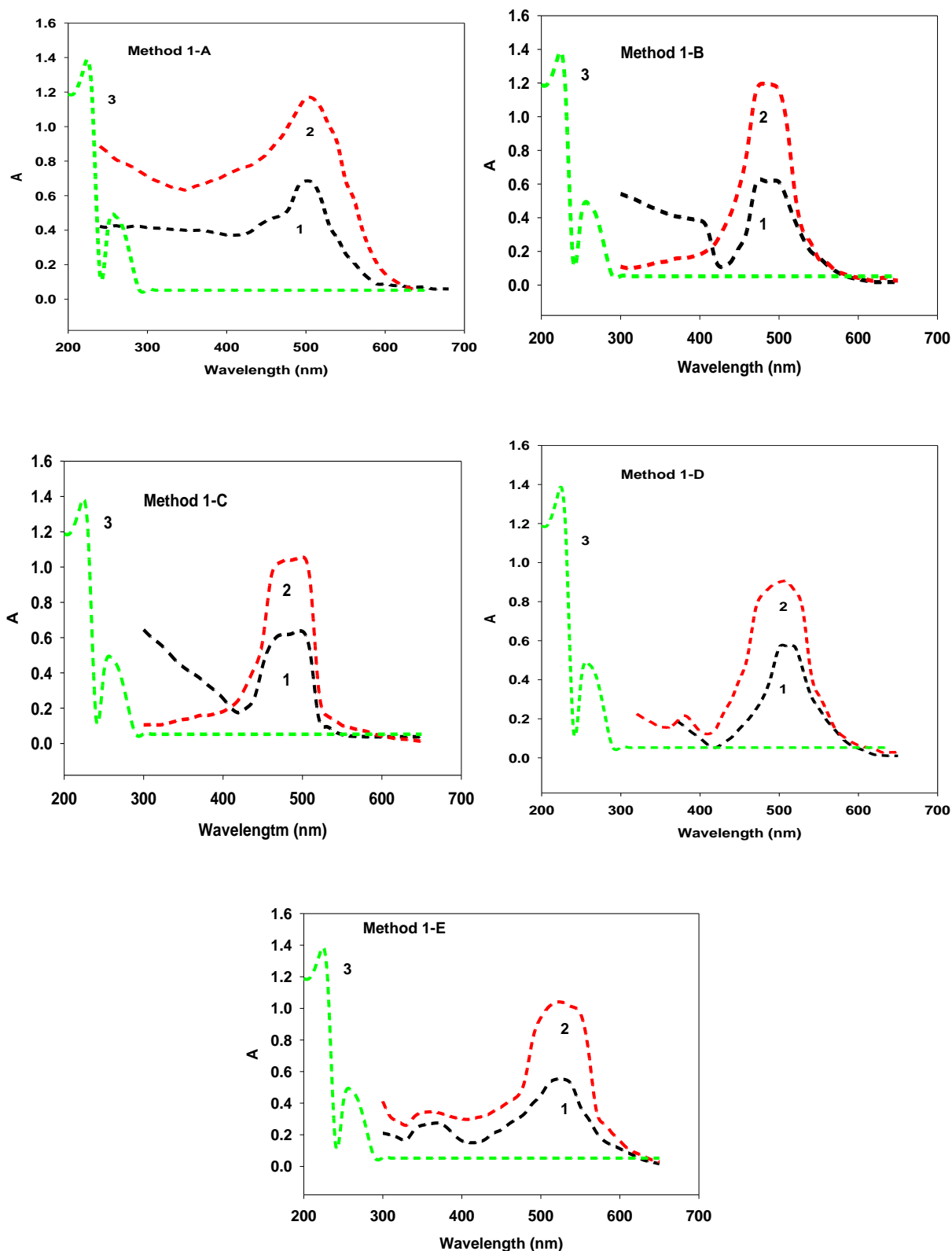
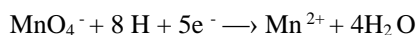
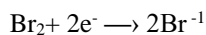


Fig. 1: (A) Absorption spectra of production of oxidation excess Mn(VII) and C2B (1), C2B (2) AMB-HCl (3)
 (B) Absorption spectra of production of oxidation excess Mn(VII) and C2B (1), C2B (2) AMB-HCl (3)
 (C) Absorption spectra of production of oxidation excess Mn(VII) and ARZO 1 (1), ARZO 1 (2) AMB-HCl (3)
 (D) Absorption spectra of production of oxidation excess Mn(VII) and SPADNS (1), SPADNS (2) AMB-HCl (3)
 (E) Absorption spectra of production of oxidation excess Mn(VII) and C2C (1), C2C (2) AMB-HCl (3).

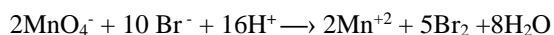
Potassium permanganate is prepared in an acidic medium so it is reduced by 5 electrons according to the equation:



The molecular structure of the AMB-HCl contains one molecule of the bromine reduced to the following:



The essential equations for the Absorption spectra of production of oxidation excess Mn(VII) and azo dyes



$\text{MnO}_4^- + 5\text{e}^- \longrightarrow \text{Mn}^{2+}$ (Reduction) acts as an oxidizing agent (half-reaction)

$10\text{Br}^- \longrightarrow 5\text{Br}_2 + 2\text{e}^-$ (Oxidation) acts as a reducing agent

These equations are applicable for all the methods (from 1-A to 1-E).

3.1. Spectrophotometric Calibration Curve

Methods I-A, I-B, I-C, I-D, and I-E involve two stages, oxidation of AMB HCl with excess Mn(VII) solution in acid medium under the effect of heating, and determination of the unreacted oxidant by measurement of the decrease in absorbance at 500, 510, 500, 510 and 520 nm for Chromotrope 2R, Chromotrope 2B, Arzo I, SPADNS, and Chromotrope 2C, respectively.

3.1.1. Effect Of Acid Concentration

Several trials were carried out using 0.1, 0.5, 1.0, 1.5, and 2.0 mol L⁻¹ of sulfuric acid, it was found that 2.0 mol L⁻¹ of acid, should be used as the acidic medium in the chemical mixture.

3.1.2. Effect of Temperature and Time

The component of the mixture solution containing AMB HCl, Mn(VII), and H₂SO₄ was heated at different temperatures ranging from 40 to 100 °C. The obtained results indicated that the reaction is catalyzed by heating at 100 °C for 10 min.

3.1.3. Effect of cooling

Different cooling times were taken into consideration after heating and before the addition of chromotropic azo dyes from 1-5 min. It was found that the solution must be cooled for at least 5 min before the addition of chromotropic acid azo dyes.

3.2. Calibration Graphs of AMB.HCl Using the Reagent Under Study

3.2.1. Methods 1-A, 1-B, 1-C, 1-D, and 1-E

The calibration curves of the spectrophotometric determination of AMB. HCl using methods from (I A to I-E) were shown in Figure 2. Beer's law limits, molar absorptivity, Sandell sensitivities, regression equation, and correlation coefficients, all these parameters are shown in Table 2.

The molar absorptivity shows a high value in the case of Chromotrope 2R $5.5 \times 10^4 \text{ L}^{-1} \text{ mol}^{-1} \text{ cm}^{-1}$. The LOD and LOQ were calculated.

Table 2: Optical parameters for pure AMB.HCl.

Parameters Methods	C2R	C2B	ARZO I	SDS	C2C
$\lambda_{\text{max}}(\text{nm})$	500	510	500	510	520
Beer's Law limit ($\mu\text{g mL}^{-1}$)	1.51-7.46	0.82-4.97	1.65-6.63	0.82-6.63	1.73-8.29
Ringbom range ($\mu\text{g mL}^{-1}$)	0.17-0.87	-0.086-0.69	0.22-0.82	-0.086-0.82	0.23-0.92
Molar absorptivity $\text{L mol}^{-1} \text{ cm}^{-1}$	5.5×10^4	4.7×10^4	3.9×10^4	3.4×10^4	3.8×10^4
Sandell sensitivity ($\mu\text{g cm}^{-2}$)	1.3×10^{-2}	8.8×10^{-2}	5.2×10^{-2}	1.9×10^{-2}	5.8×10^{-2}
LOD ($\mu\text{g mL}^{-1}$)	0.45	0.20	0.49	0.09	0.51
LOQ ($\mu\text{g mL}^{-1}$)	1.51	0.67	1.65	0.32	1.73
Intercept	0.044	0.023	0.023	0.010	0.017
Slope	0.11	0.11	0.095	0.08	0.093
Correlation coefficient (r^2)	0.998	0.993	0.995	0.995	0.996

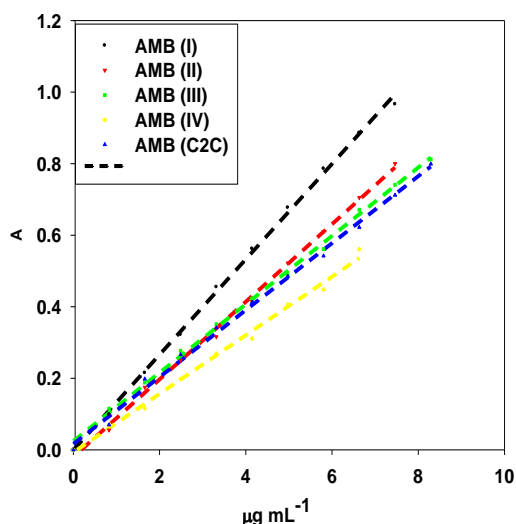


Fig. 2: Calibration curve of determination of AMB.HCl using chromotropic acid azo dyes.

3.2.2. Ringbom curves

Ringbom plot [34] is the established standard method adopted to know the optimum of concentration for the system that obeys Beer's law

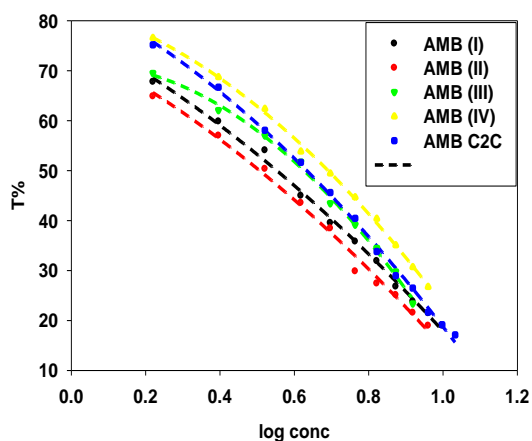


Fig. 3: Ringbom curve for AMB.HCl using chromotropic acid azo dyes C2R, C2B, ARZO I, SPADNS and C2C.

3.3.2. Spectrophotometric Titration Method.

This method depends upon the titration of the excess Mn(VII) using Ferrous ammonium sulfate hexahydrate, the results showed that spectrophotometric titration curves give a sharp inflection for the concentration varied from 7.0-14.0 $\mu\text{g mL}^{-1}$ of AMB.HCl. Figure. (3) shows the spectrophotometric titration curve of 7.0, 10.0, and 14.0 $\mu\text{g mL}^{-1}$ AMB.HCl. It was applied to the pharmaceutical formulation capsule. The recovery values were found to be in the application range (100.0-103 %) with RSD values of 0.21.

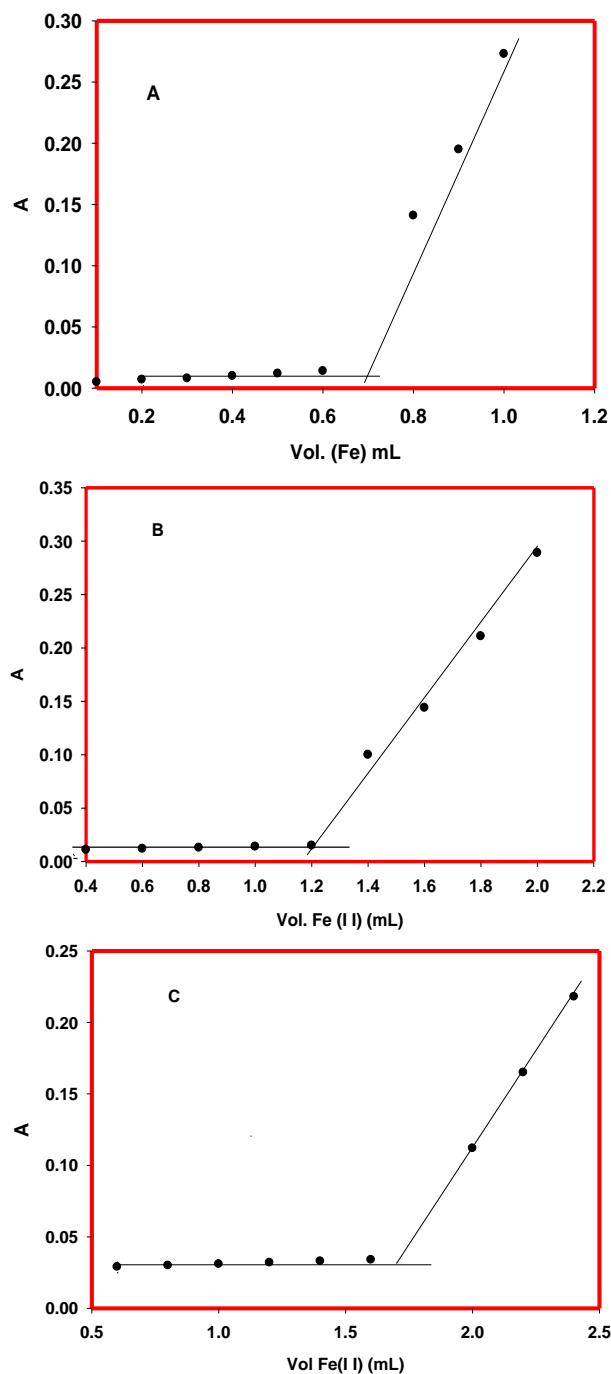
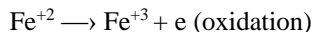
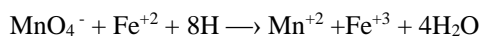


Fig. 4: (A) Spectrophotometric titration of (AMB.HCl) 7.0 $\mu\text{g mL}^{-1}$ against 196.05 $\mu\text{g mL}^{-1}$ Fe (II).
 (B) Spectrophotometric titration of (AMB.HCl) 10.0 $\mu\text{g mL}^{-1}$ against 196.05 $\mu\text{g mL}^{-1}$ Fe (II)
 (C) spectrophotometric titration of AMB.HCl 14 $\mu\text{g mL}^{-1}$ against Fe(II)196.05 $\mu\text{g mL}^{-1}$

Equations for spectrophotometric titration

Potassium permanganate is prepared in an acidic medium.

So, the equation:



In this study, Fe (II) acts as a reducing agent for the excess Mn (VII) which acts as an oxidizing agent. The excess Mn (VII) was determined by Fe (II) in the presence of ferrion indicator.

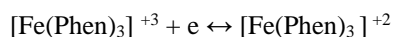


Table 3: Results for spectrophotometric titration methods

Pure AMB.HCl	Found $\mu\text{g mL}$	Recovery
7.0	710	101.43 \pm 0.29
10.0	10.20	102.0 \pm 1.0
14.0	14.05	100.35 \pm 0.61
30mg/caps		
7.0	7.15	102.14 \pm 0.71
10.0	10.15	101.50 \pm 0.28
14.0	14.30	103.33 \pm 1.1

4. Statistical Analysis

The proposed method was developed to determine AMB.HCl in its dosage forms. The results obtained were compared statistically by student-test (for accuracy) and variance ratio F-test (for precision) with the reference method [13]. Extractive spectrophotometric methods for the determination of AMB.HCl using bromophenol blue and bromocresol green, the method obeyed Beer's law and showed a good correlation. The results showed that the t- and F- values indicate that there was no significant difference between the proposed and reference method, the result illustrated in Table 4. The proposed methods were more accurate with high recoveries than the reference method so the proposed methods can be used for routine quantitative of AMB.HCl in pharmaceutical formulation.

4.1 Precision and Accuracy

In order to determine the accuracy and precision of the proposed methods, solutions containing three different concentrations of the studied drug, pure AMB-HCl, under the prescribed conditions within the calibration curve. The result shown in Table 5 indicated a good precision with RSD 0.2-0.61. Recovery studies were carried out by the calibration curve method in using of C2R, C2B, ARZO I, SPADNS and C2C. The recovery percentages are within the range of 96.97- 99.79

Table 4: Statistical Evaluation of Results

Method	Taken	%Recovery \pm SD%	t-value	F-value	%Recovery [13]
C2R	1.65	99.58 \pm 0.36	2.64	1.0	98.67
C2B	2.48	100.1 \pm 0.92	2.42	1.25	98.84
ARZO I	3.10	99.59 \pm 0.12	3.46	1.0	97.55
SPADNS	4.1	98.79 \pm 0.24	1.8	0.25	98.84
C2C	5.8	98.3 \pm 0.72	2.81	0.71	-

Table 5: Evaluation of Precision of the proposed methods on AMB.HCl pure sample and pharmaceutical formulations 30 mg/caps.

Methods	Pure			Formulations 30 mg/cap		
	Taken $\mu\text{g mL}^{-1}$	SD%	RSD%	Taken $\mu\text{g mL}^{-1}$	Recovery \pm SD%	RSD%
C2R	3.10	\pm 0.33	0.33	3.06	98.70 \pm 0.8	0.81
	4.90	\pm 0.82	0.83	4.88	99.59 \pm 0.47	0.47
C 2B	3.10	\pm 0.24	0.24	3.06	98.70 \pm 0.48	0.49
	4.90	\pm 0.43	0.43	4.89	99.79 \pm 0.91	0.91
ARZO I	3.10	\pm 0.61	0.61	3.05	98.38 \pm 0.84	0.85
	4.90	\pm 0.41	0.41	4.87	99.38 \pm 0.40	0.40
SPADNS	3.10	\pm 0.20	0.20	3.03	97.74 \pm 0.86	0.88
	4.90	\pm 0.25	0.25	4.77	97.34 \pm 0.31	0.32
C2C	3.10	\pm 0.26	0.26	3.01	97.09 \pm 0.30	0.31
	4.90	\pm 0.20	0.20	4.75	96.93 \pm 0.23	0.24

Conclusion

The wide use of spectrophotometry is due to its high precision, sensitivity, and availability of the required facilities and instrumentation. The field of application of spectrophotometry continues to increase. Spectrophotometric methods of analysis are preferred over other methods because they give simple, rapid, and easy assays for the determination of pharmaceutical compounds. In this work, the proposed methods are accurate, precise, fast, and affordable, for the determination of AMB.HCl in pure form and pharmaceutical formulation. The methods were divided into two ways. The first method depends on the oxidation AMB.HCl utilizing an excess of MnO_4^- in an acidic medium with azo dyes then non-reacted Mn(VII) is determined by reaction with the 5 chromotropic azo dyes. While the second method depends on spectrophotometric titration. The suggested methods have wide Beer's law and Ringbom range, low LOD and LOQ values, and low RSD values. The methods were successfully applied for the determination of the different concentrations of AMB.HCl in capsules, with excellent recovery (100.05-103.33). The developed methods could be used for routine quantitation of AMB.HCl in pharmaceutical formulation.

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مقالة بحثية

التقدير الطيفي لعقار هيدروكلوريد الأمبروكسول في صورته النقية لمستحضراته الدوائية

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المُلخَص

هذه الدراسة تقدم مقترحاً جديداً يهدف إلى تقدير الكمية الفائضة، وتقييم هذه الدراسة ومقارنتها بالطرق السابقة. ويتضمن هذا البحث الطريقتين الآتيتين ذكروهما: الطريقة الأولى: وهي أكسدة عقار هيدروكلوريد الأمبروكسول باستخدام المنجنيز السباعي بكمية زائدة، التي تُقَدَّر باستخدام أصباغ الأحماض الكروموتروبيك؛ إذ أنها -أي الكمية الزائدة- من المنجنيز المستخدم لأكسدة الصبغات، وقياس النقص في الألوان بالطرق الطيفية عند الطول الموجي المناسب لكل صبغة مع تطبيق الطريقة على المستحضرات الصيدلانية، وقد تُبَيَّن مدى فاعلية الطريقة ودقتها وبساطتها. الطريقة الثانية: وهي أكسدة العقار مع كمية زائدة من المنجنيز السباعي بتحديد الفائض منه عن طريق التقطير الطيفي باستخدام الحديد الثنائي عند وجود كاشف الفروين كدليل لنقطة النهاية، وقد تمَّ تطبيق العقار في الصورة الصيدلانية، وتُبَيَّن مدى دقة الطريقة وسهولتها وسرعته.

الكلمات المفتاحية: القياس الطيفي، هيدروكلوريد الأمبروكسول، تفاعل الأكسدة والأختزال، أصباغ حمض الكروموتروبيك أزو.

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