Spectrophotometric Determination of Amoxicillin Trihydrate in Pharmaceutical Preparation

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Abstract
A new, fast, and sensitive spectrophotometric analysis method has been modified to assess amoxicillin trihydrate drug traces in aqueous mediums. This method depends on the "oxidative coupling reaction" between the drug and the promethazine hydrochloride as a reagent in the presence of potassium persulfate as an oxidizing agent. The resulted purple product was absorbed in the visible region of ultraviolet at (517 nm) and soluble in distilled water with a stability duration of (70 min). the product followed Lambert-Beer law in a series of concentrations of (20 –50 µg/ml) and molar absorbance of (7255 L /mole.cm), the Sandel index was (0.057808 µg/cm) and a rational standard deviation that do not exceed (RSD %=1.03). The rational error was less than (RE%=2.5). The limit of quantitation was equal to (L.O.Q.= 7.746x10-6µg/ml), and the limit of detection was (L.O.D.= 2.334x10-7µg/ml). The correlation factor was (R=0.9993) and the evaluation factor (R2=0.9987). This method has been successfully applied on the assessment of the amoxicillin trihydrate in the pharmaceutical drug (Promox-500 mg).
Keywords: Amoxicillin trihydrate, oxidative coupling reaction, (Promox-500 mg).

1. Introduction

Amoxicillin trihydrate is a pink powder, slightly soluble in water and alcohol and insoluble in oils and ether. The solubility of this drug increases in diluted basic and acidic aqueous mediums. The molecular weight is (419.4 g/mol) and the molecular formula is C16H19N3O5S1.3HCl. The scientific name of this drug is (α-amino-p-hydroxybenzyl penicillin). The chemical structure is depicted in figure 1 below.

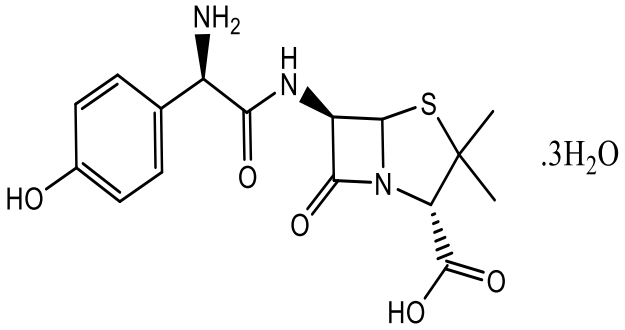

Figure 1: Chemical structure amoxicillin Trihydrate

The amoxicillin trihydrate drug is commercially available as tablets, and its commercial names are as follow; Promox (India), Pulmoxyl (India), Ogmacil (Syria), Amoxicillin (Germany) [1]. This drug is mainly prescribed for the treatment of several inflammations including Larynx, gonorrhea, middle ear, sinuses, chronic bronchi, pharynx, urinary tract, meningitis, inner lining of the heart and gastric ulcers. This drug is listed as one of the penicillin drugs. However, like any synthesized drug, this drug has some side effects including Nausea, rash, vomiting, allergy, anxiety, insomnia and mental disorders [2].

The applications of the molecular absorption extend within the regions of ultraviolet rays (200-350nm) and the visible range (350-750nm). Absorption in this latter zone is one of the most important means of quantitative analysis because of its accuracy, sensitivity, and high selectivity [3]. The oxidative coupling reaction is one of the most important applications of molecular absorption spectrometry as this reaction involves a mixture of two organic compounds in the presence of an oxidizing agent and ideal conditions to produce a colored product, and this product can be estimated using spectrophotometry in the visible region of the electromagnetic spectrum. The oxidative coupling reaction was applied to determine amoxicillin Trihydrate in its pharmaceutical drug (Promox-500 mg) [4-9].

Amoxicillin trihydrate was extensively determination using chromatography methods [10-22] and spectrophotometric methods [23-44] and Degradation reaction [45] and Adsorption method [46-47] and iodometric method [48] and Electrochemical analysis [49-53] and nanoparticles Applications [54-55].

2. 2. Experimental

2.1 Apparatus and Equipment Used

Balance (KERN), Glass cell (1 cm), Spectrophotometer (Shimadzu), Distilled water (GFL), Water bath (Memmert) and Heater with magnetic stirrer (Heidolph).

2.2 Chemicals used

Chemical used are listed in (Table 1) below:

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Table 1: Chemicals used.				
Molecular Weight g/mole	Formula	Company	of Compound Name	NO.
18	H2O	Lab.	Water Distillation	1
419.4	C16H19N3O5S. 3HCl	Iraq / SDI	Amoxicillin Trihydrate	2
270.33	K2S2O8	BDH	Potassium persulfate	3
320.88	C17H20N2S. HCl	Iraq / SDI	Promethazine Hydrochloride	4

2.3 Preparation of Solutions

2.3.1 Amoxicillin Trihydrate (Stock Solution) (1000 µg/ml)

Amoxicillin trihydrate (0.1 g) was dissolved in (3 mL) of ethanol and (50 mL) of distilled water. The solvent was heated above water bath for (5 min), then the samples were diluted to the mark of a (100 mL) volumetric flask using distilled water.

2.3.2 Amoxicillin Trihydrate (500 µg/ml)

(Promox-500 mg/India) that contains amoxicillin trihydrate was used as tablets. A solution of (500 ppm) was prepared by using (10 grounded tablets) of the drug weigh (7.192 g), the average weight taken was (0.07192 g) of one tablet, this amount was dissolved in (3 mL) of ethanol and (50 mL) of distilled water and heated above water bath for (5 min) at (30˚ C) until fully dissolved. The solution was filtered twice and the sample was diluted to the mark of a (100 mL) volumetric flask using distilled water.

2.3.3 Amoxicillin Trihydrate (500 µg/ml) (Working Solution)

Drug solution (50 mL) of (1000 µg/ml) was transferred to a (100 mL) volumetric flask and the volume was completed to the mark using distilled water. This solution was measured using spectrophotometer against water as a blank by using (1 mL) of the solution and the sample was diluted to the mark of a (25 mL) volumetric flask using distilledwater, which corresponds the concentration of (20 µg/ml). The highest absorption wavelength was (272 nm), and the absorbance of the solution was (0.153) as it is depicted in (figure 2) below.

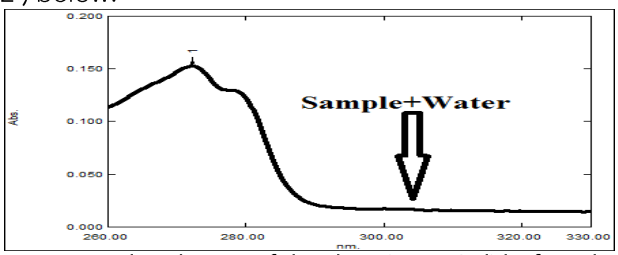


Figure 2: Absorbance of the drug (20 µg/ml) before the reaction.

2.3.4 Promethazine Hydrochloride Solution (Reagent) (5×10-3 M)

Promethazine Hydrochloride (0.1604 g) was dissolved in a (100 mL) volumetric flask with distilled water.

2.3.5 Potassium Persulfate Solution (Oxidizing Agent) (1×10-2 M)

Potassium persulfate (0.2703 g) was dissolved in a (50 mL) volumetric flask, the solution was then heated above water bath for (5 min) at (35˚ C) due to the weak solubility in cold water. After dissolved, the solution was diluted to the mark of a (100 mL) volumetric flask using distilledwater..

2.4 General Procedure

The colorless solution of the reagent was added to the colorless solution of the oxidizing agent, this step was followed by the addition of the drug solution to afford a purple solution that can be absorbed in the visible region of the electromagnetic spectrum [56].

3. 3. Results and Discussions

3.1 Primary Tests

Amoxicillin Trihydrate drug (1 mL) was added to (1 mL) of the oxidizing agent (potassium sulfate), followed by the addition of the reagent (1 mL). A purple-colored product was produced as a result of the oxidation and combination reaction. the sample was diluted to the mark of a (100 mL) volumetric flask using distilledwater, and the sample was measured and the recorded spectra showed that the highest wavelength seen at (517 nm).

3.2 Adjusting the Ideal Conditions

Several studies were conducted to obtain the ideal conditions, starting with the concentration of (10 µg/ml, 0.0000011 M, 0.5 mL) of the amoxicillin trihydrate drug in a (25 mL) volumetric flask, the spectra was measured using a (1 cm) glass cell at (517 nm).

3.3 Quantity of Oxidizing Agent

Different volumes (0.5- 2.5 mL) of the (1×10-2 M) oxidizing agent were reacted with (1 mL) of potassium persulfate and (1 mL) of (5×10-3 M) of the reagent promethazine hydrochloride. The samples were diluted to the mark of a (25 mL) volumetric flask using distilled water, then the solutions and the blank were measured for each sample at (517 nm). Results are depicted in (Table 2) below:

Table 2: The oxidizing agent quantity	
Abs. of Drug	mL of Oxidant
—	0.5
0.020	0.8
0.055	1.0
0.041	1.3
0.040	1.7
0.037	2.0
0.031	2.2
0.029	2.5

Results showed that (1.0 mL) volume has given the highest absorbance value, therefor it was chosen for the next steps.

3.4 Quantity of the Combining Reagent

Different volumes (0.5- 2.0 mL) of (5×10-3 M) of the promethazine hydrochloride reagent were reacted with (1 mL) of the amoxicillin trihydrate and (1 mL) of the oxidizing agent (potassium persulfate). All samples were diluted to the mark of a (25 mL) volumetric flask using distilledwater, then the solutions and the blank were measured for each sample at (517 nm). Results are shown in (Table 3) below.

Table 3: The combining reagent quantity

Abs. of Drug	mL of Reagent
—	0.5
0.038	0.8
0.054	1.0
0.043	1.3
0.035	1.7
0.029	2.0

Results showed that (1.0 mL) volume has given the highest absorbance value, therefor it was chosen for the next steps.

3.5 Quantity of the Drug

Different volumes (1.0-2.8 mL) which represents (20 - 56 µg/mL) of the amoxicillin trihydrate with (1 mL) of the promethazine hydrochloride and (1 mL) of the oxidizing agent (potassium persulfate). Samples were diluted to the mark of a (25 mL) volumetricflask using distilled water, then the solutions and the blank were measured for each sample at (517 nm). Results are shown in (Table 4) below.

Table 4: The drug quantity.

Abs. of Drug	mL of Drug
0.055	1.0
0.098	1.5
0.121	1.7
0.168	1.8
0.184	2
0.211	2.2
0.199	2.5
0.195	2.8

Results showed that (2.2 mL) volume has given the highest absorbance value, therefor it was chosen for the next steps.

3.6 The Addition Sequence Effect

This was achieved by changing the sequence in which the reactants are added. See (Table 5) below.

Table 5: Addition sequence effect.

Order of addition	Color	Absorbance	Order NO.
D + R + O	Violet	0.210	1
R + O + D	Violet	0.251	2
O + R + D	Violet	0.162	3

Results showed that the ideal addition sequence is (reagent + oxidant + drug), therefor, this sequence was followed for the next steps.

3.7 Time Effect on Results

Reaction was studied in terms of how time affects the absorbance of the resulted product, this was achieved via the addition of (1 mL) of (5×10-3 M) promethazine hydrochloride to (1 mL) of (1×10-2 M) of the oxidizing agent potassium persulfate then the addition of (2.2 mL) of (500 µg/ml) of the amoxicillin trihydrate. The waiting time range was (5-25 min) along with the continuous stirring of the solution before the dilution with. The samples were diluted to the mark of a (25 mL) volumetricflask using distilledwater. Results are shown in (Table 6) below.

Table 6: Time effect on absorbance.

Absorbance	Time (min.)
0250	0
0.293	5
0.355	10
0.329	15
0.281	20
0.247	25

Results indicated that the ideal time was (10 min), which gives the highest absorbance value, therefore, it was chosen for the next steps.

3.8 Solvent Effect

This step was conducted via the dilution of the resulted product to the mark of a (25mL) volumetric flask using different solvents. (Table7) below shows the results of this step.

Table 7: Solvent effect on absorbance.

Solvent	Abs.	No.
Water	0.360	1
Methanol	0.327	2
2-Propanol	Turbid	3
Acetone	0.294	4

(Table 7) shows that water is the best solvent to be used with the highest absorbance value due to its abundance, being non-toxic, and its low-cost. Therefore, water was chosen for the next steps.

3.9 Temperature Effect

The effect of applied temperature on absorbance value has been studied. Temperature range was (10-40 ˚C), and the results are shown in (Table 8) below.

Table 8: Temperature effect on absorbance.

Absorbance	Temperature 0C
0.277	10
0.291	15
0.349	20
0.365	25
0.354	30
0.327	35
0.311	40

Results from (Table 8) shows that the ideal temperature was (25 ˚C), therefore, this temperature was selected for the next steps.

3.10 Time Effect on Product Stability

Three different concentrations (28, 32, and 50 µg/ml) of the amoxicillin trihydrate were taken respectively, these concentrations were added to the other reactants to study the stability of the resulted product within (10-70 min). The

absorbance for the three resulting solutions was measured at (517 nm). The result are shown in (Table 9) below.

Table 9: Time effect on product stability within different time durations.										
Absorbance / minute										Concentration µg / ml
870	760	650	540	435	330	25	20	15	1 0	
00.166	00.166	00.165	00.166	0.166	00.167	0.169	0.168	0.168	0.167	28
00.215	00.215	00.217	00.217	00.217	00.216	0.217	0.215	0.216	0.216	32
00.474	00.475	00.476	00.475	00.476	00.477	0.476	0.457	0.475	0.475	50

Results from (Table 9) shows that the absorbance value is stable within (70 min), which can be considered a perfect feature for the resulted product, the reaction, and the modified procedure.

3.11 Final Absorption Spectra

The ideal conditions of the reaction were applied as shown in (Table 10) below.

Table 10: The ideal conditions of the reaction.		
Experimental Conditions		
Water	Solvent	1
25 0C	Temperature	2
517 nm	λ max	3
1 ml	Oxidant / Potassium persulfate (1x10-2 M)	4
2.2 ml	Drug / Amoxicillin Trihydrate (500 µg/ml)	5
1 ml	Reagent / Promethazine Hydrochloride (5x10-3 M)	6
Violet	Color	7
0.365	Absorbance	8

The final results were as shown in (Table 11) and (Figure 3) below.

Table 11: Final results of the modified procedure.	
Sample Solution – Blank Solution	Variable
0.365	Absorbance
517 nm	Wavelength

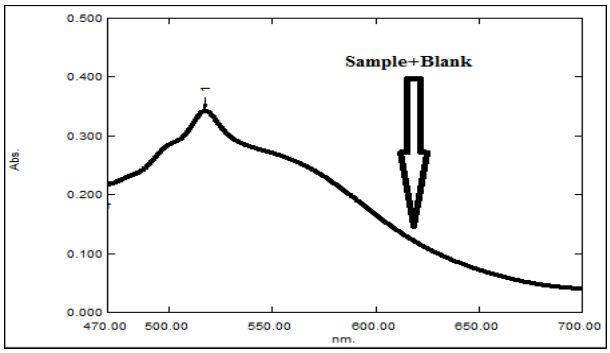


Figure 3: Final absorption spectra of the product after using the ideal conditions.

3.12 Calibration Curve

The calibration curve [57-59]. has been set by using different volumes (1.0-2.5 mL) of (500 µg/mL) of the amoxicillin trihydrate drug, the volumes correspond to (20-50 µg/mL) the concentrations. These volumes were added to a series of (25mL) volumetric flasks that contain (1.0mL) of (5×10-3 M) of promethazine hydrochloride and (1.0 mL) of (1×10-2 M) the oxidizing agent (potassium persulfate). The prepared samples were measured using spectrophotometer at (217 nm) according to the ideal conditions that have been studied earlier. It has been clearly seen that the calibration curve follows the Lambert-Beer law at a concentration of (20-50 µg/mL), (4.7×10-5-1.1×10-4 M), assessment factor value of (R2=0.9987), correlation factor value of (R=0.9993), (slope=0.0173), (Molar absorptivity=7255 L/mol.cm), and (Sandel index=0.057808 µg/cm). figures (4) and (5) below show the final results of this study.

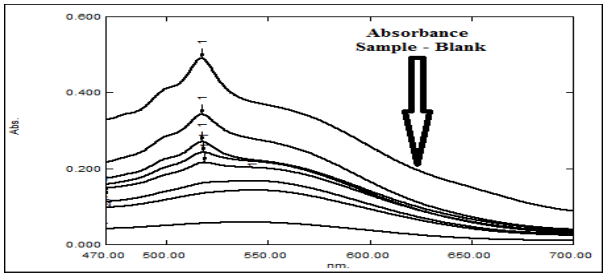


Figure 4: Calibration curve spectra.

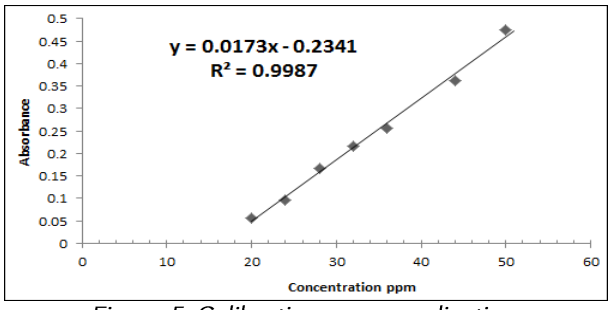


Figure 5: Calibration curve application.

3.13 Accuracy and Precision

Volumes of (1.4, 1.8, and 2.5mL) correspond to amoxicillin trihydrate concentrations of (28, 36, and 50 µg/mL) respectively were taken, other reactants were added to yield the product under the ideal conditions as shown in (Table 12).

Table 12: Accuracy and precision				
Recovery %	RE %	RSD %	Average Abs.	Conc. Present µg/ml
102	2.0	0.15	0.166	28
102.5	2.5	0.24	0.255	36
101	1.0	1.03	0.473	50

3.14 Limit of Quantification (L.O.Q.) and Limit of Detection (L.O.D.)

Limit of quantification and limit of detection were

evaluated via the measurement of the absorption of six samples of amoxicillin trihydrate, each sample volume is (1 mL) which corresponds the concentration of (4.7×10-5 M). The absorbance was measured using ideal conditions that have been previously studied. It has been confirmed that the value of (L.O.Q.) equals (7.746×10-5 µg/mL) and the value of (L.O.D.) equals (2.334×10-7 µg/mL). Results of (L.O.Q.) and (L.O.D.) are shown in (Table 13) below.

Table 13: (L.O .Q) and (L.O .D).				
Concentration	X^-	S	L.O.Q.	L.O.D.
4.7x10-5	0.054	0.00089	7.746x10-6 µg/ml	2.334x10-7 µg/ml

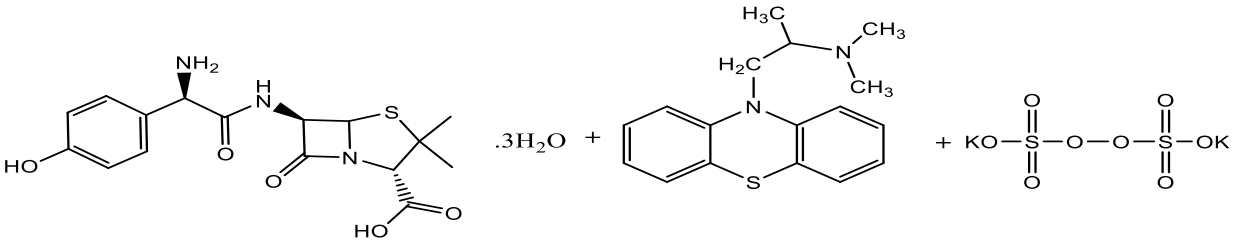
3.15 Applications/ Direct Method

In order to know the selectivity and activity extent of the modified method along with knowing the reduction of interferences in this method, as well as the application of this method in high sensitivity on pharmaceuticals to assure the effective concentrations in these drugs. This method has been applied on amoxicillin trihydrate (Promox-500 mg/Indian) as tablets via taking volumes of (1.4, 1.8, and 2.5 mL) respectively, these volumes correspond (28, 36, and 50 µg/mL) of the drug solution. Result are shown in (Table 14) below.

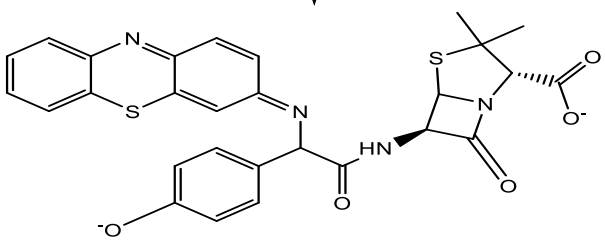
Table 14: Applications/direct method.				
Recovery %	RE %	RSD %	Average Absorbance	Concentration **Present** µg / ml
101.4	1.4	0.13	0.164	28
101.7	1.7	0.21	0.253	36
100.7	0.7	0.93	0.474	50

Results from (Table 14) that the modified method of assessing amoxicillin trihydrate was successful in (Promox-500 mg).

3.16 Suggested Reaction Equation



Amoxicillin trihydrate Promethazine hydrochloride Potassium persulfate



(2*S*,6*R*)-6-(2-(((*Z*)-3*H*-phenothiazin-3-ylidene)amino)-2-(4-oxidophenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

3.17 Comparing the modified method to other methods

(Table 15) below shows the comparison between the modified method and other methods.				
Literature [61] method	Literature [60] method	Current Method	Analytical Parameter	No.
Direct method	Spectral method	Oxidative coupling	Reaction	1
_____	_____	Promethazine Hydrochloride	Reagent	2
_____	_____	Potassium Persulfate	Oxidant	3
Color less	Color less	Violet	Color of the dye	4
2.5 – 50	9-350	20 – 50	Beer's Law Range µg/ml	5
1.0020 x 10^4	6000	7255	Molar Absorptivity $L.mol^{-1}.cm^{-1}$	6
0.03906	0.1	0.05788	Sandel Index $\mu g/cm^2$	7
_____	_____	25	Temperature ^0C	8
0.3360	0.49	1.03	RSD %	9
_____	0.14	2.334x10-7	L.O.D µg/ml	10
0.0244	0.0085	0.0173	Slope	11
_____	_____	70	Stability minute	12
0.9996	0.9997	0.9993	R	13
_____	_____	7.746x10-6	L.O.Q µg/ml	14
213	211 - 300	517	Wavelength nm	15

4. Summary

The newly modified analysis method is an economical spectrophotometric method to analyze traces of amoxicillin trihydrate in (Promox-500 mg) pharmaceutical drug tablets using the oxidative coupling reaction with promethazine hydrochloride as the reagent and potassium persulfate as the oxidizing agent. The resulted purple-colored product is absorbed at (217 nm), soluble in water, stable for (70 min) at ambient temperature (25 ˚C). The product follows the Lambert-Beer law in a concentration of (20-50 µg/mL), with a molar absorbance of (7255 L/mol.cm), Sandel index (0.05788 µg/cm) that do not exceed (RSD% = 1.03) and (RE% = 2.5). (L.O. D. = 2.334×10-7), (L.O .Q = 7.746×10-6), (R = 0.9993), and (R2 = 0.9987).

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