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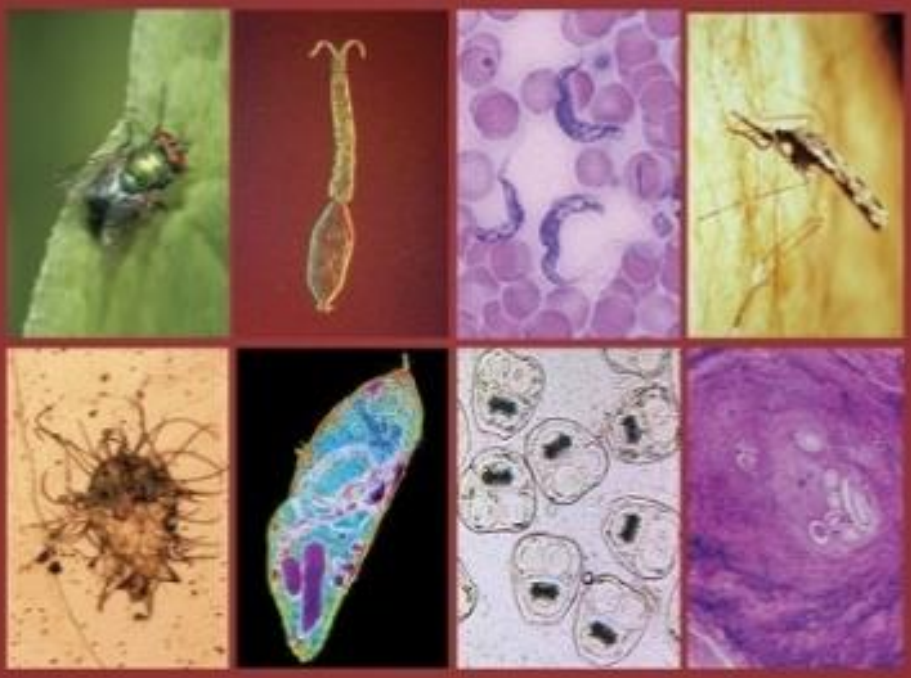

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Utilization of Spectrophotometric Technique for the Quantitative Evaluation of Cefadroxil Monohydrate in its Pure form and Its Therapeutic Doses

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ABSTRACT

Establishing and adopting a quick, easy, and cheap method for determining antibiotic Cefadroxil monohydrate (CFL) in its pure form and pharmaceutical preparations. The method involves adopting spectrophotometry in the visible region. The method adopted the oxidation of the studied medicine by an excess amount of N-Bromo succinamide (NBS), then estimated the NBS Excess by bleaching the dye color of Methylene Blue. The maximum wavelength was measured at λ 586 nm. This approach obeys the Beer-Lambert law for the range (5-20 µg. ml^{-1}), with a correlation coefficient of 0.9980. The calculated molar absorptivity was 1.41×10^3 (L. mol^{-1}. cm^{-1}), and Sandall's sensitivity was 0.27 µg. cm^{-2}. The limit of detection (LOD) was 3.508 µg. ml^{-1}, as well as the limit of quantification (LOQ), was 11.693 µg. ml^{-1}. The precision and accuracy of the method are established and checked.

This study measured the optimal reaction conditions and other analytical variables. It showed decent repeatability, and the relative standard deviation (RSD percentage) was less than 1%.

The proposed methodology identified the effective implementation of an easy, resilient as well as precise spectrophotometric method to determine Cefadroxil employing N-Bromo succinimide as Cefadroxil oxidant factor and also the unreacted N-Bromo succinimide bleached the methylene blue dye. The process has been successfully extended in different pharmaceutical formulations to evaluate the Cefadroxil drug.

INTRODUCTION

Cefadroxil (CFL) has the chemical formula ($C_{16}H_{17}N_3O_5S$) and the systematic name 8-[2-amino-2-(4-hydroxyphenyl)-acetyl] amino-4- methyl-7-oxo-2-thia-6-azabicyclo [4.2.0] oct-4-ene-5-carboxylic acid. Cefadroxil (CFL) is a β-lactam antibiotic and a type of cephalosporin (Magdesian, 2017). The β-lactam ring fuses to a 6-membered dihydro thiazine ring to form a nucleus of cephem. (Hoque *et al.*, 2013) Its chemical composition (Fig.1) is as follows:

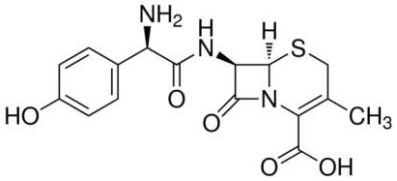

Fig. 1: Chemical structure of Cefadroxil monohydrate**.**

It is a yellow, good water-soluble crystalline powder. It belongs to the 1st generation of cephalosporin. (Kaur *et al.*, 2021) It inhibits the synthesis of the bacterial cell wall (de Marco , B. A. & Salgado, 2017), Which is found in *Streptococcus, Staphylococcus* spp., *and Pasteurella* spp. Etc. (Papich, 2021)

CFX treats many human diseases, such as pharyngitis, tonsillitis, urinary tract infections, and uncomplicated skin infections. (Castle & Medical, 2007) It treats diseases of animals such as infections of the skin, pyoderma, soft tissue infections, other dermal infections, pneumonia, and UTIs. (Papich, 2016)

For the determination of CFX, many Alternative techniques have been published in the literature. These alternative techniques include spectrophotometry, chromatography such as High-performance liquid chromatography(Najia *et al.*, 2015; Rahim *et al.*, 2014; Vittaladevaram & Pragada, 2017), liquid chromatography(Jin *et al.*, 2014)(El-Gindy *et al.*, 2000) and Hydrophilic-interaction planar chromatography(Rageh *et al.*, 2019), Voltammetry and other Electrochemical methods.(Saleem *et al.*, 2022a)(Kassa & Amare, 2021)(Kassa *et al.*, 2022a)(Kassa *et al.*, 2022b)(Saleem *et al.*, 2022b)(Sanz *et al.*, 2020)(Feier *et al.*, 2017)

Under pharmaceutical applications, the technique of choice provides the benefits of simple and low-cost instruments available in all laboratories. The current research described a straightforward and sensitive spectrophotometric method for determining one phenolic drug. To determine CFX, CFX reacts with N-Bromo succinimide in an acidic medium. Then the amount of unreacted NBS is estimated by methylene blue to form a blue-colored substance at λ 586 nm. The quantity of NBS interacting with the colorant is equivalent to the amount of the drug. An easy and quick analytical method is recommended for the simultaneous estimation of Cefadroxil. This research aimed to create quality, reliable and validated economic analytical methods for assessing Cefadroxil in pure form and pharmaceutical formulations.

MATERIALS AND METHODS

Any chemical used has an analytical ranking. Cefadroxil monohydrate (CFL) was obtained as a gift from SDI (State Drug & Clinical Appliances Organization, Samara- Iraq).

Cefadroxil solution, 250 μg ml^{-1}, was prepared by dissolving 0.025 g of Cefadroxil in a volumetric flask of 100 ml of distilled water.

Methylene blue dye solution, 1.6 $x10^{-3}$ M, was prepared by dissolving 0.051 g in a volumetric flask with 100 ml of distilled water.

N-Bromo succinimide solution, 1 $x10^{-3}$ M, was prepared by dissolving 0.0178 g of N-Bromo succinimide in a volumetric flask of 100 ml of distilled water.

Hydrochloric, Nitric, Sulfuric, and Acetic acids solutions, 2M were prepared by diluting 16.66 ml, 17.89 ml, 10.88 ml, and 11.49 ml of concentrated hydrochloric acid 30 %, Nitric acid 70%, Sulfuric acid 98% and glacial Acetic acid 99.6% in volumetric flasks into 100 ml of distilled water. A variety of formulations were studied, including metoclopramide as an effective ingredient.

The Pharmaceutical Formulations: 250 μg. ml^{-1} of Roxil Capsules solution from Tabuk Pharmaceutical Co., KSA, was prepared by calculating the average weight of ten capsules. The weight of the pharmaceutical formulation containing 0.025 g of Cefadroxil was calculated. The calculated weight was transferred to a 100 ml volumetric flask and supplemented with distilled water. 250 μg. ml^{-1} of the Droxicef syrup solution from Pharma International Company, Jordan, was prepared by calculating the volume of the medicine needed to be taken and diluted to prepare 100 ml of the solution. The calculated amount was transferred to a 100 ml volumetric flask, and the volume was supplemented with distilled water.

Equipment and Apparatuses: Certain measurements were carried out using the 303 PD UV-Visible Spectrophotometer, Apel, Japan (Single beam) with 1cm quartz cells. The electronic analytical balance that was used in the method is of the model (BL 210S from Sartorius). Procedure for pharmaceutical preparations: Cefadroxil preparations were evaluated as an active ingredient (Table 1).

Table 1: Pharmaceutical preparation for Cefadroxil monohydrate.

Pharmaceutical preparation	Composition	Pharmaceutical
Roxil	Per one capsule, 0.5 g of Cefadroxil	Tabuk Pharmaceutical Co., KSA
Droxicef	Per 5 ml of syrup 0.25g Cefadroxil	Pharma International Company, Jordan

RESULTS AND DISCUSSION

General Procedure and Calibration:

A system of ten volumetric flasks of 10 ml was used. Increasing volumes of Cefadroxil solution (250µg. ml^{-1}) were placed in it. 0.8 ml of CH_3COOH and 0.3 ml of NBS were added to the system and left at 5 °C for 25 mins. Then 0.12 ml of methylene blue dye was added to the volumetric flasks, and the flasks were completed with distilled water to the mark and left for 10 mins.

Spectral frequencies were scanned from 200-800 nm. It was found that the λ max is at 586 nm. The absorbance of the samples was measured against the same sample except for the dye (as a blank).

Preparation of Standard Solution and Calibration Graph:

To prepare a concentration of 250µg. ml^{-1}, 100 ml from stock solution was produced. It is prepared by dissolving 25 mg of CFL in distilled water. Increasing volumes of the prepared Cefadroxil solution were put into many volumetric flasks of 10 ml. The method was applied by adding the necessary materials in the appropriate. And applying optimal conditions in terms of time and temperature. Then the absorbance (on a UV-visible spectrophotometer) was measured at 586nm against the same solutions except for the dye as a blank solution. The latter process was performed three times. And a median of three absorbance levels was estimated. The data was charted using CFL concentration on the X-axis and the recorded absorptions on the Y-axis (Fig. 2).

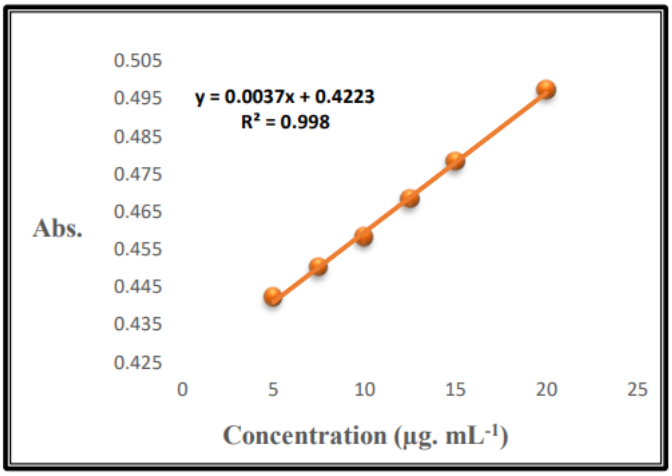

Fig. 2 : Calibration curve of CFL.

Determination in Pharmaceutical Preparations:

Pharmaceutical preparations were taken from local pharmacies in Iraq-Najaf. The medicines quantities needed to prepare 250 µg. ml^{-1} of the CFL pharmaceutical preparation was calculated. The weighted quantities were moved to volumetric flasks (100 ml). Then the method was implemented under optimal conditions on the sections they prepared.

Solvent Effect:

As shown in Table 2**,** several polar and non-polar solvents were used. Water was chosen from among them because it gives the best absorbance in terms of linearity of the response, the extent of compliance with Beer-lambert's law, and the best sensitivity. At the same time, other solvents gave fewer responses or gave Two-layer or turbid mediums.

Table 2: Solvent influence on the absorbance.

Solvent	Absorbance	ε, L. $mol^{-1}.cm^{-1}$
Water	0.442	1.41 $X10^3$
Ethanol	0.458	1.83 $X10^3$
Methanol	0.45	0.442 X 10^3
DMSO	0.153	2.01 X 10^3
DMF	0.940	0.676 $X10^3$
Chloroform	Two layers	
Toluene	Two layers	
DSM	Two layers	
Ethyl acetate	Two layers	
Butyl alcohol	Turbid	

Reaction Time Influence:

The times needed to complete the drug's oxidation and the dye's bleaching were monitored. The NBS was added to a series of volumetric flasks that contained the same quantities of Cefadroxil, which were left for different times before adding the dye and then left for a constant time (Table 3). The time of oxidation that gives the best absorbance was recorded. A volumetric flask was re-prepared, and the other conditions were applied, including the preferred oxidation time. Then the time during which the bleaching was completed was recorded.

Table 3: The effect of time of oxidation and bleaching of the dye.

Time of oxidation (min)	Abs.	Time of the bleaching of the dye (min)	Abs.
5	0.453	5	0.548
10	0.483	10	0.535
15	0.492	15	0.535
20	0.503	20	0.536
25	0.537		
30	0.515		
35	0.505		

Validation of the Proposed Method:

The approach's results were evaluated regarding the linearity of the relationship between concentration and absorbance. The selectivity, sensitivity, LOD, LOQ, precision, accuracy, and Sandall's sensitivity were also evaluated (Table 4). The precision was tested by examining the endpoints and the middle point at least five times. In contrast, the accuracy was tested by calculating the recovery of these points. The method was applied to pharmaceuticals as well. The same previous variables were calculated on the only two preparations available in local pharmacies. The criteria for the t-Test and the F-Test were within the allowed range. The replication of the results was studied, and the percent relative standard deviation (RSD%) was calculated.

Table 4: Experimental limitation qualities from the consistent method of the calibration curve**.**

Parameter	Values of method
Regression equation	y = 0.0037x + 0.422
Molar absorptivity	1.41×10^3 (L. mol^{-1}. cm^{-1})
Correlation coefficient	0.9980
limits of Beer's law (linearity)	(5 – 20) µg. ml^{-1}
Sandell's sensitivity	0.27 µg. cm^{-2}
Slope	0.0037
Limit of detection	3.508 (µg. ml^{-1})
Limit of quantitation	11.693 (µg. ml^{-1})
Intercept,	0.4223
Intraday Precision RSD*	% 0.499
Inter-day Precision RSD*	% 0.928
Accuracy (% mean recovery) *	% 98.18

Absorption Spectra-Results and Discussion:

The aqueous solution of CFL 0.05ml was combined with 0.8ml CH3COOH and 0.3ml N-Bromo succinimide and left at 5C° for 25 minutes. After the combination, the methylene blue 0.12ml was added and left for 10 minutes. An intense blue is produced

spontaneously. λ max was shown at 586 nm (Fig. 3).

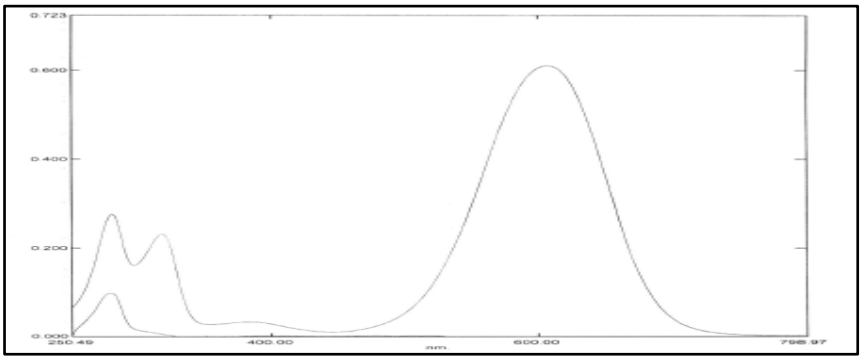

Fig. 3: (A) λ max for dye (methylene blue), (B) λ max for the drug.

Optimizing the Controlled Conditions:

All factors affecting absorption were tested separately. Thus, the optimal conditions for pharmaceutical preparations and future experiments were determined.

The selected dye and concentration:

The effective and optimal concentration of methylene blue and its effect on absorption at λ max were tested. The results showed that 0.12ml of the dye gives the best result with 0.05ml drug, 0.3ml N-Bromo succinimide, and 0.8ml of CH_3COOH (Fig.4).

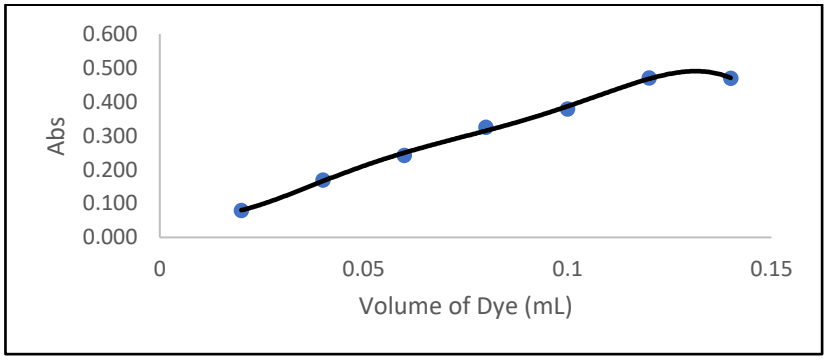

Fig. 4: The perfect volume of methylene blue dye on the absorbance level

Oxidant Amount Influence*:*

The effect of increasing volumes of NBS on the absorbance of methylene blue was tested. Figure 5 shows that 0.3ml of NBS is sufficient to completely oxidize the studied volume of Cefadroxil.

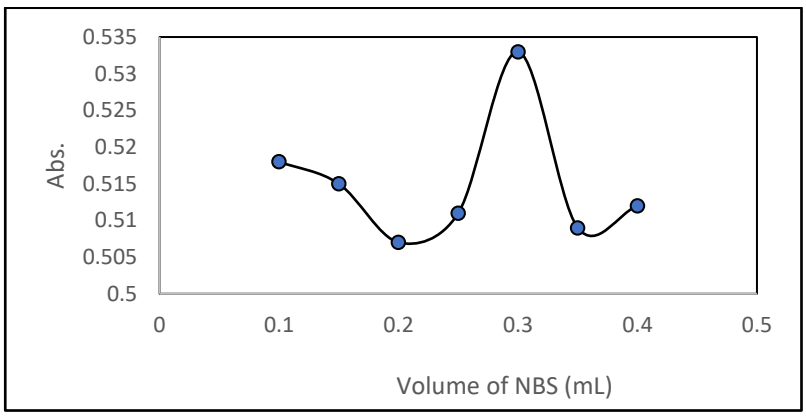

Fig. 5: The perfect volume of NBS on the absorbance level

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Order Of Addition Influence:

Different sequences of experimental materials (CFX, NBS, acetic acid, and dye) were studied *(*Table 5*)*. The sequence that gives the best absorbance is recommended for subsequent application.

Table 5: Order of addition influence**.**

Order of addition	Abs.
Drug – Acid – NBS - Dye	0.468
Drug – NBS - Acid –Dye	0.431
NBS -Drug – Acid –Dye	0.461
Acid – NBS - Drug –Dye	0.437
Acid –Drug –NBS - Dye	0.449

Influence of the Type of Acid in The Determination Process:

The studied reaction should carry out in an acidic medium. The effect of a fixed concentration (2M) of hydrochloric, sulfuric, nitric, and acetic acids on the absorbance was studied. Acetic acid gave the best absorbency. So, it was recommended for subsequent testing. The best volume of acetic acid was also tested to give the optimum absorption (Table 6 and Fig. 6).

Table 6: Influence of the Type of acid.

Absorbance	Acid Type
0.527	Hcl
0.504	H_2SO_4
0.518	HNO_3
0.562	CH_3COOH

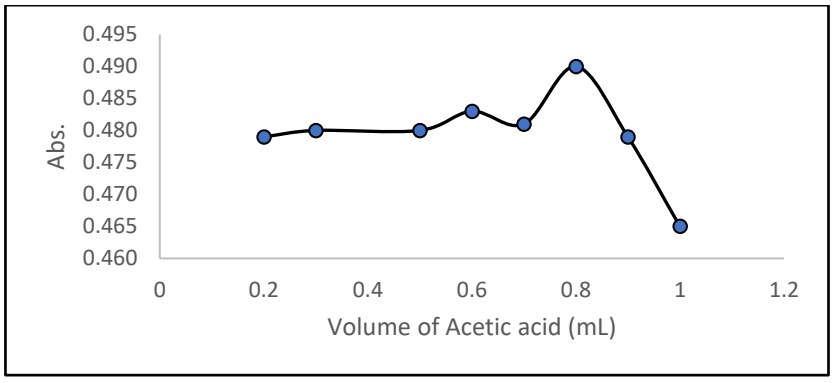

Fig. 6: Influence of the Volume of Acetic acid in the absorbance**.**

Temperature Influence:

The influence of temperature on methylene blue's color intensity has been recorded. When the formed color was at 5°C, a maximum absorbance was obtained, and the observed color was less at lower or higher temperatures. Thus, for subsequent experiments, a temperature of 5°C is recommended (Fig. 7).

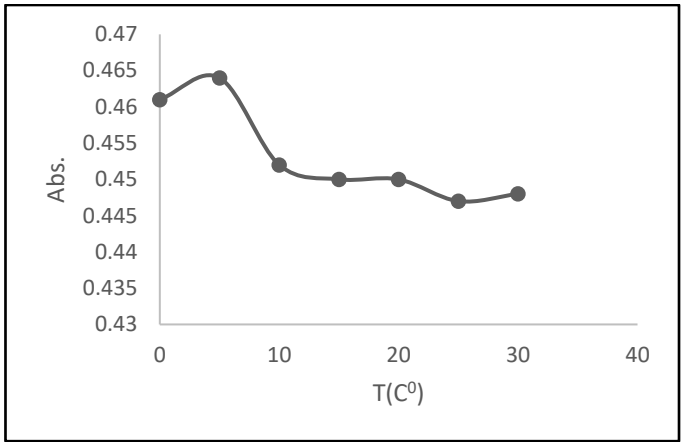

Fig. 7: Influence of temperature on absorbance.

Linearity:

The Calibration curve was generated for serial concentrations of cefadroxil monohydrate. The absorbances given by these concentrations were recorded after applying the method. Concentrations of 5-20µg. ml^{-1} of CFX solution obeys Beer-Lambert's law. Absorbances were plotted against concentrations. The plot showed a straight line with a correlation coefficient of 0.9980 and a regression equation y = 0.0037x + 0.4223 (Fig. 4).

A stable compound at 5 °C was produced from the reaction of CFX with NBS, CH_3COOH, and methylene blue dye in the mentioned quantities. Under optimal conditions, the calibration curve showed a molar absorption coefficient of 1.41 $\times 10^3$ L. mol^{-1}. cm^{-1}. Y-Intercept was discovered to be 0.4223. LOD, LOQ, molar sensitivity, and other parameters are shown in Table 4.

A precision intra-assay was performed to test the repeatability of the method. Two drug samples were examined. RSD% was also calculated.

Influence of Interference:

The influence of certain excipients explicitly labeled in pharmaceutical preparations was evaluated by Cefadroxil determination in the presence of various excipients (Benzoic acid, Sucrose, Sodium disulfate, Magnesium stearate, Starch, Lactose, Calcium chloride, Fructose). Investigational findings revealed no interference with the experimental technique by excipients (Table 7). (Taha *et al.*, 2016).

Table 7: Investigation of 250 µg. ml^{-1} CFL in the presence of excipients**.**

Interference	$E_{rel\%}$	Recovery%
Benzoic acid	0.924	99.076
Calcium chloride	1.458	98.542
Fructose	-1.214	101.214
Lactose	1.565	98.435
Magnesium stearate	0.496	99.504
Sodium bisulfate	0.283	99.717
Sodium sulfate	-0.893	100.893
Starch	0.283	99.717
Sucrose	-1.534	101.534

Application of the Procedure:

In evaluating CFX in numerous pharmaceutical formulations, the validation of the proposed methodology for the quantitative detection of CFX has been checked. In Table 8, the obtained results are

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presented. F-test and student t-test population variance with those attained by British pharmacopeia at a confidence scale of 95 percent with two degrees of freedom. The outcome suggested that the F-test and the t-test were lower than the unrealistic account (F=19.00, t=2.353). The values for the current technique were (F=3.785, t =0.49). The estimates for the current technique (F=3.785, t =0.49) and the values for the Typical Methodology (F=19.00, t=2.353) showed no substantial difference between the system developed and the typical methodology.

Table 8: Evaluation of (CFL) in prescription medicines has complied with the official framework.

Medicinal Products of (CFL)	Modified methodology		Typical methodology		Standard Quantities (t), (F)
	Recovery %	RSD %	Recovery %	RSD %	
Pure CFL	100.09	0.235	100.47	10.89	0.049 (t)Value=2.353 3.785 (F)Value = 19.00
Roxil	100.46	1.269	99.475	10.68	
Droxicef	99.899	0.754	88.710	7.195	

CONCLUSION

The proposed methodology identified the effective implementation of an easy, resilient as well as precise spectrophotometric method to determine Cefadroxil employing N-Bromo succinimide as Cefadroxil oxidant factor and also the unreacted N-Bromo succinimide bleached the methylene blue dye. The process has been successfully extended in different pharmaceutical formulations to evaluate the Cefadroxil drug.

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