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Little-Cost Potentiometric and Spectrophotometric Procedures for Cephalothin Assessment in Pure and Biological Fluids

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ABSTRACT: Low-cost potentiometric and spectrophotometric procedures for cephalothin (CPI) determination in pure and biological fluids were investigated. The potentiometric technique is created through titration of CPI with an aqueous medium of 0.1 M NaOH at an ionic strength of μ = 0.3 M sodium chloride and room temperature by a combined glass pH electrode. Using the standard addition method, we found that the detection and quantitative limits were 0.042 mg/mL, with the standard deviation SD = 0.011, correlation coefficient R = 0.9880 (n = 5), and linear concentration ranges from 0.042 to 0.82 mg/mL. This technique was utilized to assess CPI in pure solutions, urine, and serum with suitable results. No interference was exposed in the presence of public components of the samples under study. Recovery of CPI for pure and biological fluids is in the range of 98.2−101%. Also, the spectrophotometric method has been performed through the formation of the Prussian Blue (PB) complex. The reaction between the

acidic hydrolysis product of CPI (T = 60 °C) and the mixture of Fe^{3+} with hexacyanoferrate (III) ions (HCF(III)) was detected for the spectrophotometric determination of the drug. The maximum absorbance of the formed complex was measured at λ = 283 nm with 2.0×10^3 L mol^{-1} cm^{-1} molar absorptivity. Reaction states have been advanced to acquire the PB complex of great sensitivity and longer stability. In optimal states, the absorbent of the PB compound was attained to grow linearly with the increase in the concentration of CPI, which agrees with the correlation coefficient values. The detection and quantitative limits were 0.000036 and 0.0012 mg/mL, respectively, with the standard deviation, SD = 0.0005, correlation coefficient, R = 0.9955 (n = 5), and the linearity range of the calibration plot 0.0005−0.02 mg/mL CPI. The planned technique was positively utilized for the detection of CPI in both urine and serum models. The results fit well with the data found from the potentiometric method.
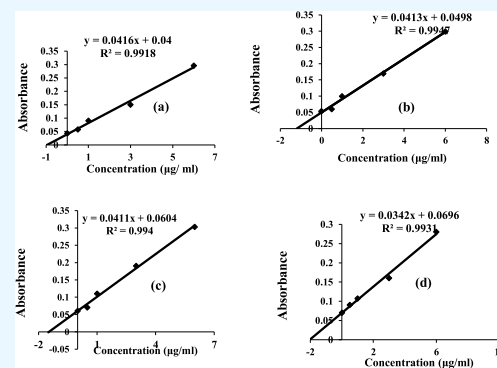
1. INTRODUCTION

As shown in Figure 1, cephalothin (CPI) is an antibiotic that is used to modify a few bacterial infections. It is the first group of
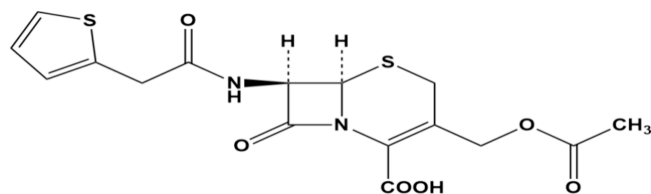

Figure 1. Structure of the CPI.

cephalosporin and is the greatest efficient cephalosporin versus resistant microorganisms. A review of analytical techniques for sodium cephalothin was conducted.[1,2]

While reviewing the literature, several methods to determine the CPI either in pure, pharmaceutical, or biological fluids were revealed. These methods include chemiluminescence,[3] chromatography,[4−9] potentiometry,[10] differential pulse polarography,[11−13] micellar electrokinetic capillary chromatography,[14]

and stripping voltammetric procedures.[15] Stripping voltammetry was advanced to adjust CPI activity. This technique is established on the adsorptive deposition of CPI at the electrode and then scans in a negative sweep. The applicability of this method was confirmed by resolving CPI in therapeutic preparations and biotic liquids such as serum and urine. The conformation of a pseudopotential-determination phase designed for the CPI-selective electrode has been governed and the basic electrode factors are measured.[1] Spectrophotometric,[16] first-derivative spectrophotometry,[17] and fluorimetry[18] procedures were found in the literature for CPI determination. A stability-signifying gradient reversed-phase liquid chromatography procedure has been advanced for the quantifiable resolve of CPI, an antimicrobial compound, in the attendance of its
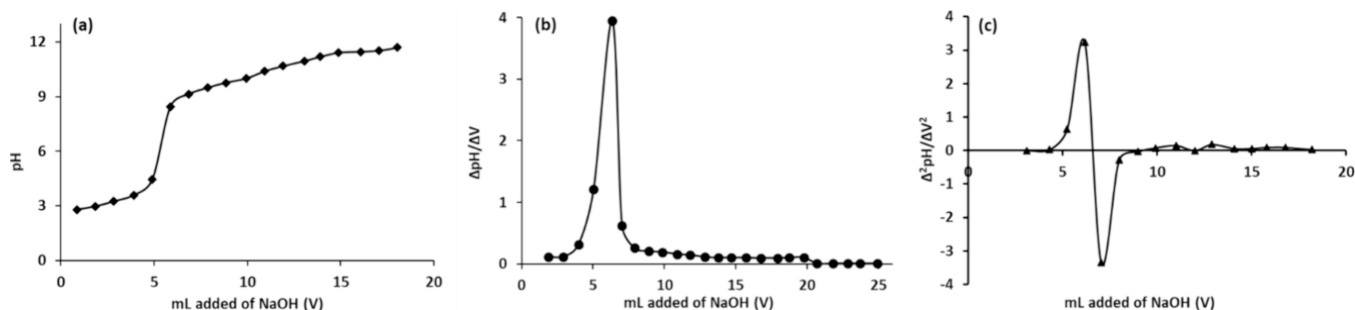
Figure 2. Representative potentiometric titration curve of CPI (pure): (a) blank titration curve, (b) 1st derived curve and (c) 2nd derived of curve, $\mu = 0.3$ M NaCl at room temperature.

impurities and degradation products produced from the required degradation investigation.[1]

Although these analytical methods are more sensitive and accurate, they are high-cost and time-consuming and require complex procedures for sample preparation and analysis protocols. Thus, the use of potentiometric and spectrophotometric procedures to analyze binary and trinary complexes formed between metals and biological and pharmacological compounds has attracted a lot of interest in analytical chemistry.[19−25] In biological fluids, the presence of certain ions is thought to have a major impact on the pharmacological actions of some chemical substances.[26]

The potentiometric technique has been employed greatly in various branches of liquid chemistry; it is by far the greatest precise and broadly appropriate procedure currently existing for ionic balances.[27−33] As an analytical application of potentiometric studies, the equivalence point of the produced titration curves was identified using a Gran plot.[34] Sundry applications of the Gran plot have been published in the literature.[27,30,33,35] For this purpose, the purpose of this work was to grow, for the first time, a potentiometric technique for direct analysis of CPI based on a potentiometric titration of the drug in aquatic solutions with NaOH solution by means of a combined glass electrode.

Also, we state here that the formation and use of the Prussian Blue (PB) complex in the growth of spectrophotometry technique for the assessment of cefuroxime, cefotaxime, and ceftriaxone in dosage forms have been advanced and proven. The procedure is built on the creation of the PB complex. The reaction among the acid hydrolysis product of the CPI at 60 °C among the combination of Fe^{3+} and HCF(III) ions was estimated for the spectrophotometric assessment of the CPI. Therefore, we will use this method for the analysis of CPI in pure, urine, and serum trials.

2. EXPERIMENTAL SECTION

2.1. Reagents and Instruments. Cephalothin sodium salt was obtained from Sigma-Aldrich (Steinheim, Germany) and used without further refinement. Standard solutions were prepared daily by dissolving an appropriate quantity of CPI in bidistilled water. From this solution, a series of dilutions were prepared in water to gain a range of suitable concentrations. All other solutions were able to be obtained via bidistilled water and analytical reagents. Urine and serum samples used in the current analysis were pooled from healthy volunteers.

pH experiments were performed on a pH-meter model (JENWAY) via a combined glass electrode (Precise 0.01 pH unit). Spectrophotometric assessments were operated using the single beam spectrophotometer model JENWAY 6305 by using 1 cm quartz cells.

2.2. Methods. *2.2.1. Preparation of Sample Solutions. 2.2.1.1. Pure Form.* A standard solution (25 mL) of CPI (1 × 10^{-2} M) (ionic strength adjusted to 0.3 M with NaCl) was prepared by the suitable dilution of the stock solution with doubly distilled water. Then, an aliquot of 15 mL of CPI solution was transferred to a thermostatic glass cell (25 ± 0.1 °C) and then potentiometrically titrated with a standard solution of NaOH ($I = 0.3$ M). The same procedures were carried out in other biological samples.

2.2.1.2. Spiked Urine. In a test tube, 1 mL of the standard solution of the drug in methylene chloride (0.0003−0.0008 mg mL^{-1}) was pipetted and evaporated until dryness in a water bath. One milliliter of urine sample from healthy volunteers was added and shaken well on a vortex. The spiked urine was extracted twice 4 mL each in the methylene chloride, and the total extract was collected in a 10−mL standardized flask and evaporated until dryness in a water bath. The flask was cooled, and the technique was completed at the same described for CPI determination in the pure form under the conventional assay methods.

2.2.1.3. Spiked Serum. One milliliter of human serum sample from healthy volunteers was diluted to 10 mL via the recommended medium. Various concentrations from CPI were added, and the process was done as described in the pure form using the entire universal assay techniques.

2.2.2. Potentiometric Measurements. A solution of 25 mL of 1 × 10^{-2} M CPI (I is adapted to 0.3 M by NaCl) was prepared by appropriate dilution with doubly distilled water. After that, 15 mL of CPI was transferred to a thermostatic cell (25 ± 0.1 °C) and then titrated by a standard solution of NaOH ($I = 0.3$ M). The same procedures were carried out in other biological samples.

2.2.3. Spectrophotometric Measurements. 2.2.3.1. Absorption Spectra. The chromogenic reagent was prepared as earlier stated[36] by mixing 1 mL of 0.02 M $FeCl_3$ (0.02 M) and 0.25 mL of HCF (III) (0.008 M) and made up to 10 mL, and the absorption spectra were determined. An aliquot of CPI was mixed with 2 mL of hydrochloric acid (0.1 M) in a tube, and the solution was heated to 60 °C for 20 min. The mixture was allowed to cool, and 1 mL of 0.02 M ferric chloride and 0.25 mL of HCF (III) of 0.008 M were added and the mixture was made up to 10 mL with distilled water. An intense blue color was formed after 20 min, and absorption λ_{max} was determined. The proposed spectrophotometric method was made on the aliquot part of the resultant solutions.

2.2.3.2. Calibration Curve. A 0.1 mg/mL portion of the standard solution of CPI was transferred to a 10 mL volumetric flask having 2 mL of hydrochloric acid (0.1 M). The mixture was put in a thermostat and adjusted to 60 °C for 20 min, and the

chromogenic substances were added as depicted above. The absorbance was judged at λ_{max} = 283 nm wavelength against blank after 20 min. The calibration plots were depicted, and the quantity of CPI present in the sample solution was calculated.

2.2.4. Statistical Analysis. Gran Plot was created, and the limit of detection (LOD), the limit of quantitation (LOQ), and the standard deviation (SD) were computed using the standard addition method. Previously, Microsoft Excel and the standard addition method were successfully applied for the same purpose.[19,27,30,33]

3. RESULTS

3.1. Potentiometric Determination of CPI. As shown in Figure 2, curve (a) displays the curve with only one inflection. In

Table 1. Ionic Strength Effect on the Detection of CPI by the Potentiometric Technique at 25 $\pm$ 0.1 °C

ionic strength (M)	add (CPI) (mg)	found (mg)	recovery $\pm$ SD (%)
0.05	10.46	9.06	86.6 $\pm$ 0.12
0.1	10.46	9.76	93.3 $\pm$ 0.15
0.3	10.46	10.48	100.2 $\pm$ 0.11
0.5	10.46	11.15	106.5 $\pm$ 0.2
0.75	10.46	12.0	114.7 $\pm$ 0.24

Table 2. Recovery Range for CPI in Pure Forms

add pure (mg/mL)	found (mg/mL)	recovery (%)	SD (n = 5)	confidence (α = 0.05)
0.04184	0.0399	95.3	0.20	0.14
0.16736	0.1631	97.4	0.18	0.16
0.29288	0.2871	98.0	0.14	0.13
0.37656	0.374	99.3	0.11	0.21
0.5684	0.576	101.3	0.22	0.19
0.8116	0.838	103.2	0.30	0.23

the planned procedure, change at the titration endpoint was distinct and adequate to give a potentiometric titration curve of suitable shape for a precise and reproducible endpoint. Curve (b) displays the first derivative of the potentiometric titration curve by a combined glass pH-electrode, and curve (c) represents the second derivative.

3.2. Effect of Ionic Strength on CPI Determination. As shown in Table 1, different ionic strength ranges from 0.05 to 0.75 M NaCl via the potentiometric method. We noticed that the highest and best recovery percent was 100.2 $\pm$ 0.11

(enclosed 100%) at 0.3 M NaCl. Thus, 0.3 M ionic strength can be used for CPI determination in pure and biological fluids.

3.3. Determination of CPI in the Pure Form. Table 2 indicates that the range of recovery for pure CPI using the potentiometric method is linear from 95.3−103.2% and was obtained under optimized conditions (I = 0.3 M NaCl). The percentage recoveries were present to be accurate to 100%, with a standard deviation range, SD (n = 5), of 0.2−0.3 and a confidence range of 0.14−0.23 at a 95% confidence level. The method was validated as guidelines for linearity, precision, accuracy, LOD, LOQ, and robustness.[37] These results point to the precision and accuracy of the technique.

Detection limits are calculated as $3\sigma/b$ and the quantitative limits are also computed as $10\sigma/b$.[37] Wherever b is the slope and σ = SD (standard deviation), CPI can be detected from 0.042 mg/mL, and the correlation coefficient was R = 0.9880 (n = 5) with standard deviation (SD = 0.11). Linear concentration ranging from 0.042 to 0.81 mg/mL can be determined successfully, as shown in Figure 3.

3.4. Analytical Application. *3.4.1. In Spiked Urine Sample.* As shown in Figure 4, curves a, b, and c are representative titration curves with only one variety point, the first, and second derivative of the potentiometric curve, respectively.

Figure 5 and Table 3 show that the range of recovery for spiked urine samples using the potentiometric method is linear from 96.6 to 104.4%, which were found under adjusted conditions (I = 0.3 M NaCl). The percentage recoveries were noticed to be close to 100%, with a standard deviation range, SD (n = 5), of 0.13−0.32. These results opinion out the precision and accuracy of the technique.

3.4.2. In Spiked Serum Sample. Figure 6 and Table 4 reveal that the recovery range for spiked serum samples by the proposed method is linear from 97.5 to 102% and were gathered under optimized conditions (I = 0.3 M NaCl). The percentage recovery appeared to be close to 100%, with a standard deviation range, SD (n = 5), of 0.1−0.33. These results indicated the precision and accuracy of the technique.

3.4.3. Spectrophotometric Measurements. Figure 7a shows the UV spectra of the Fe (III) with HCF (III) in the presence of HCl, which did not show a robust absorption in the UV region of the spectrum. Then, during the addition of the CPI hydrolysis product, the absorption band at λ_{max} = 283 nm appeared, which indicates the formation of the PB complex, as shown in Figure 7b. This complex has been used to detect CPI. The method is based on the formation of the PB complex.
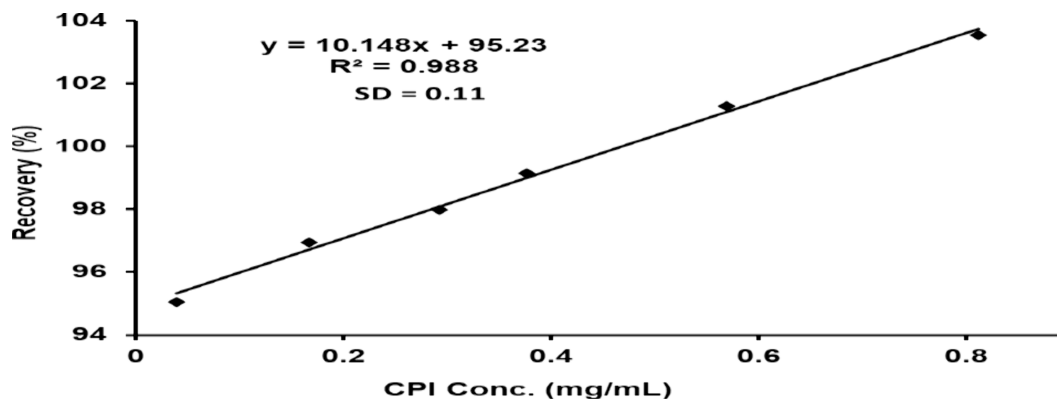
Figure 3. Linearity range of CPI at 0.3 M NaCl and room temperature.
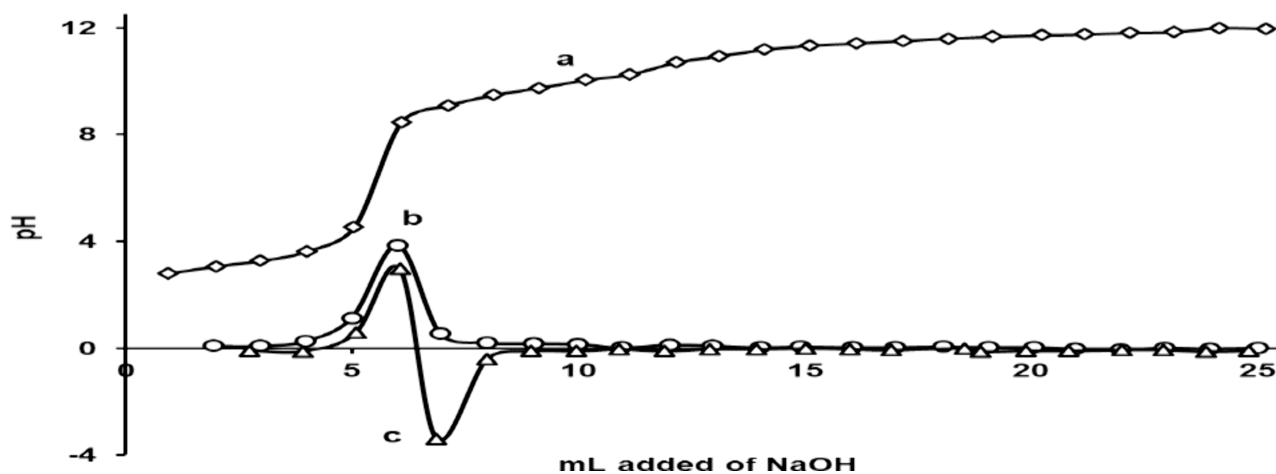
Figure 4. pH−metric titration curve of CPI in spiked urine sample: (a) blank titration curve, (b) 1st derived curve and (c) 2nd derived of curve, $\mu = 0.3$ M NaCl and at 25 ± 0.1 °C.

y = 0.1664x + 93.624
R^2 = 0.9923
SD = 0.32
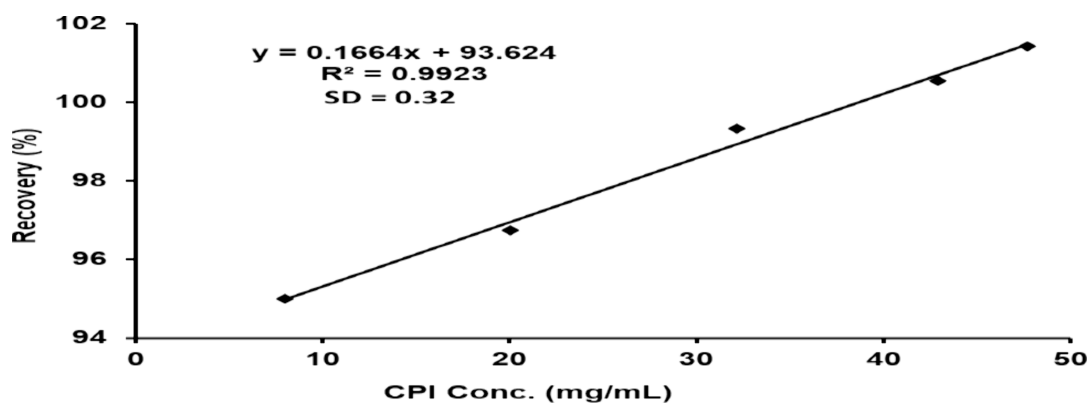
Figure 5. Relation between the recovery and the concentration of CPI in spiked urine sample at $\mu = 0.3$ M NaCl and 25 ± 0.1 °C.

Table 3. Recovery Data for Potentiometric Determination of CPI in the Spiked Urine Sample at $\mu = 0.3$ NaCl and 25 ± 0.1 °C

add pure (mg)	found (mg)	recovery (%)	SD ($n = 5$)	confidence ($\alpha = 0.05$)
1.046	1.011	96.6	0.32	0.17
2.092	2.092	98.3	0.16	0.13
4.18	4.253	101.6	0.21	0.21
6.27	6.55	104.4	0.13	0.26

Table 4. Recovery Data for Potentiometric Detection of CPI in the Spiked Serum Sample at 25 ± 0.1 °C

add pure (mg)	found (mg)	recovery (%)	SD ($n = 5$)	confidence ($\alpha = 0.05$)
1.046	1.02	97.5	0.16	0.14
3.13	3.075	98.2	0.23	0.23
5.23	5.16	98.6	0.33	0.20
7.30	7.25	99.3	0.10	0.11
10.0	10.20	102.0	0.22	0.31

y = 9.33x + 97.015
R^2 = 0.9856
SD = 0.12
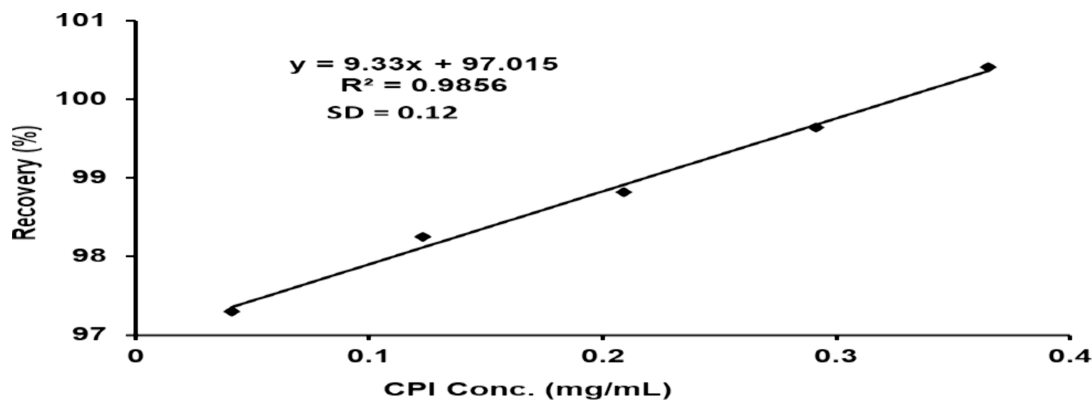
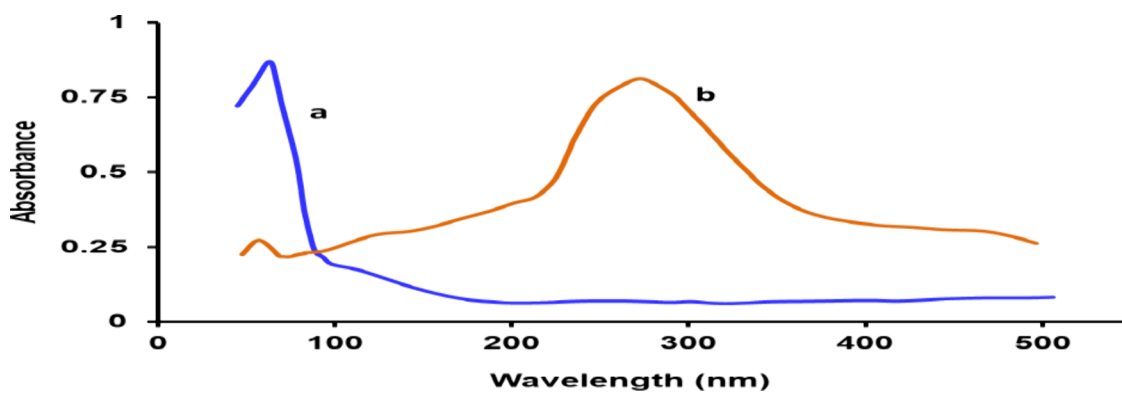**Figure 6.** Linearity range of CPI in spiked serum sample, $\mu = 0.3$ M NaCl at 25 ± 0.1 °C.

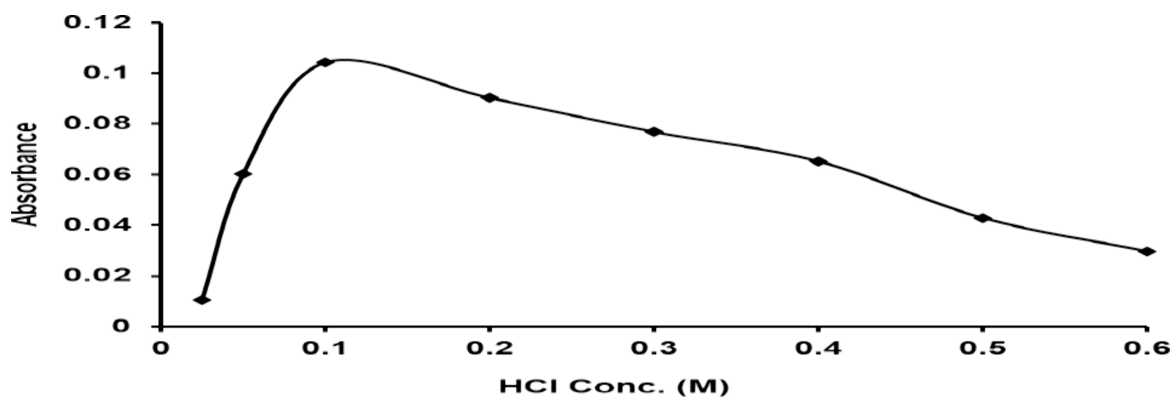**Figure 7.** UV spectra of (a) chromogenic substance $[FeClO_4 + HCF\ (III)]$; and (b) a + CPI hydrolysis product.

Figure 8. Concentration influence of HCl used for hydrolysis of CPI over a period of 20 min at temperature 60 °C on the absorption of PB complex.

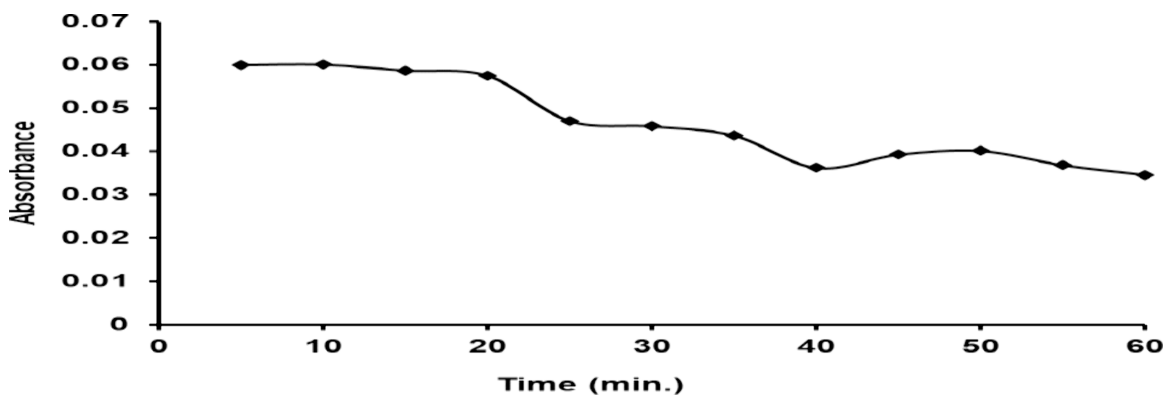**Figure 9.** Time effect study on 2 ppm of CPI (pure) absorption pH = 1 and λ_{max} = 283 nm.
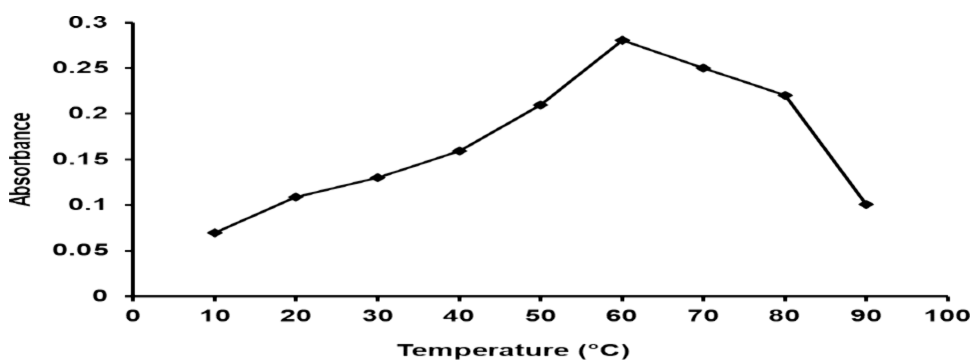

Figure 10. Influence of acidic hydrolysis temperature over a period of 20 min acid hydrolysis on the absorbance of PB complex associated with the hydrolysis of 2 ppm of CPI.
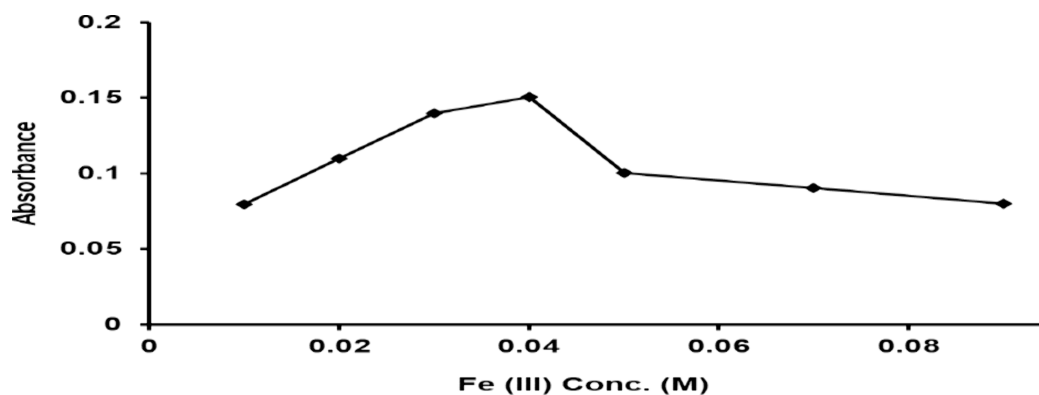
Figure 11. Effect of concentration of Fe (III) on absorbance of 2 ppm of CPI (pure), at λ_{max} = 283 nm, pH = 1 and temperature 60 °C.
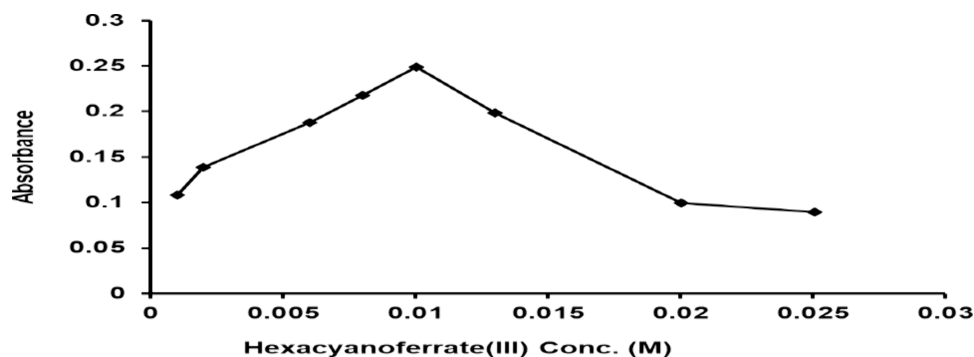

Figure 12. Effect of concentration of HCF (III) on absorbance of 2 ppm of CPI (pure), at λ_{max} = 283 nm, pH = 1, and temperature 60 °C.
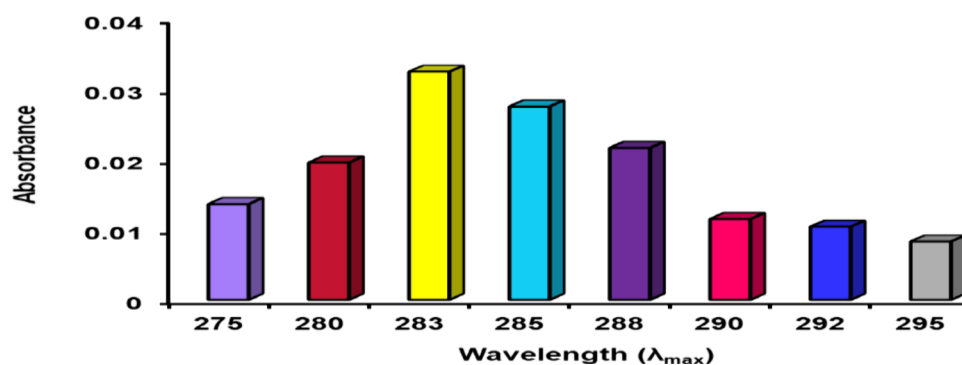
Figure 13. Effect study of wavelength on absorbance of 20 ppm of CPI (pure).
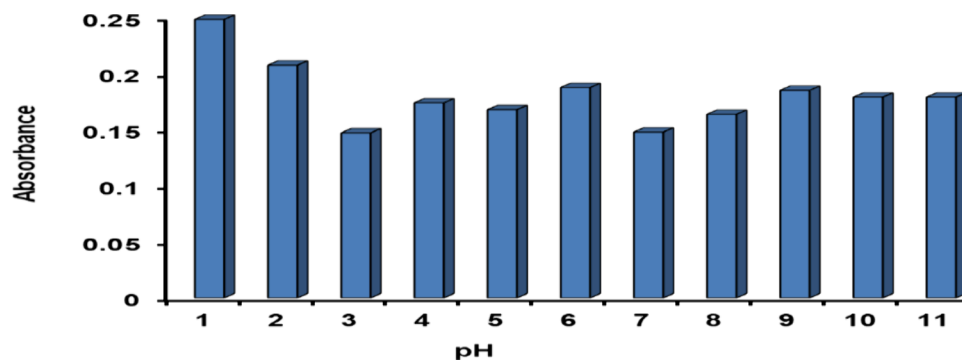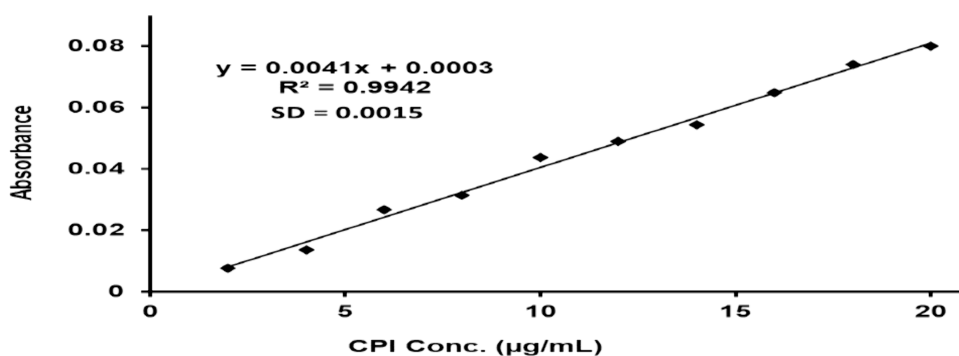

Figure 14. Effect study of pH on 20 ppm of CPI (pure) at λ_{max} = 283 nm.

The effect of the several concentrations of HCl used in the acid hydrolysis step of CPI is revealed in Figure 8. Maximum absorbance was gained at 0.1 M HCl. Therefore, this concentration was selected for extra study. Also, the influence of time and temperature of hydrolysis of CPI displayed in

Figure 15. Linearity range for spectrophotometric determination of CPI (pure), at pH = 1 and λ_{max} = 283 nm using the standard addition method.

Figures 9 and 10 shows that hydrolysis is complete at 60 °C after 20 min.

The influence of the reagent concentration on the color strength of the complex was examined. As explained in Figures 11 and 12, it was observed that 0.04 M FeCl$_3$ and 0.01 M HCF (III) were suitable for great color advancement.

The addition of HCF(III) as a predicted oxidation product did not considerably change the oxidation rates. The acquired oxidation products were recognized by using spot testing and Fourier transform infrared spectra. Also, the wavelength effect and pH on the absorbance of the hydrolysis product of CPI are investigated, as shown in Figures 13 and 14. The maximum absorbance was attained at λ_{max} = 283 nm and pH = 1.0.

4. DISCUSSION

The planned technique was successfully applied for CPI detection in spiked urine and serum samples. To detect the

Table 5. Recovery Range of Spectrophotometric Determination of CPI (pure) at pH = 1 and (λ = 283 nm) Using the Standard Addition Method

add (mg)	found (mg)	recovery (%)	SD ($n = 5$)	confidence ($\alpha = 0.05$)
0.05	0.0483	96.6	0.21	0.18
0.1	0.0981	98.1	0.17	0.14
0.15	0.1462	97.4	0.15	0.13
0.25	0.2485	99.4	0.11	0.09
0.35	0.355	101.4	0.24	0.21

utility of the planned technique, the effects of the additives and excipients, which regularly accompany CPI in the pure form such as NaCl and sodium acetate and (D (+) lactose monohydrate, were examined in a concentration range of 100 periods developed compared to that of CPI. No interference was noticed in the investigated concentration range.

The reaction between the acidic hydrolysis product of CPI with a mixture of Fe^{3+} and HCF (III) ions was evaluated for the spectrophotometric determination of CPI. The β−lactam ring present in this drug molecule has been shown to be enormously liable to nucleophilic attack in the presence of acid and alkali or even neutral molecules. Several methods for quantitative estimation of β−lactam antibiotics have been based on the measurement of the color reaction of their degradation products and are used as well-accepted methods. This property has been exploited in the present investigation.[36,38]

The complex has a λ_{max} = 283 nm and molar absorption of 2.0 × 10^{-3} L mol^{-1} cm^{-1}. Different experiments were performed to obtain the optimum conditions. Between the mineral acids, the purpose of adding HCl to the reaction mixture is to act as a catalyst and speed up the reaction. It is a strong acid that can help break down the reactants and facilitate the formation of the products. Therefore, HCl was displayed to offer good intensity color and rapidity reaction.[39] It was also taken that an extreme absorbance of the PB complex was achieved at 20 min. The color was steady for up to 40 min at the optimal conditions selected for the reaction.

Fawzy et al.[40] stated that the kinetics and mechanistic aspects of the oxidation of two β−lactam antibiotics, ampicillin and flucloxacillin, by alkaline HCF (III) were examined using spectrophotometry at a fixed temperature. The oxidation reactions showed a 1:4 (drug: HCF(III)) stoichiometry. The reaction kinetics were found to follow the first-order dependence for the oxidant and fractional first-order dependence for the drug and [OH$^-$]. The enhancement of the ionic strength and dielectric constant was found to increase the oxidation rates. Free radical tests of the reactions showed positive results. As revealed in Figure 15, a linearity range was created at absorbance (λ_{max} = 283 nm) of the PB complex and CPI concentration ranging from 0.002−0.02 mg/mL through correlation coefficient R^2 = 0.9942 and standard deviation ($n = 5$) SD = 0.0015.

Table 6. Comparative Analysis between Potentiometric and Spectrophotometric Data of CPI in Pure, Spiked Urine, and Serum Trials[a]

	regression equation	LR × 10^{-3} (mg/mL)	n	R^2	DL × 10^{-3} (mg/mL)	QL × 10^{-3} (mg/mL)	SD
CPI (pure)	$y = 10.15 \times + 95.2$	0.042−0.82	5	0.9880	0.042	0.05	0.11
	($y = 0.0041 \times + 0.002$)	(0.5−20.0)	(5)	(0.9955)	(0.36)	(1.20)	(0.0005)
CPI in the spiked urine sample	$y = 0.166 \times + 93.6$	1.05−10.0	5	0.9923	1.01	1.05	0.32
	($y = 0.0309 \times + 0.0412$)	(1.7−15.0)	(5)	(0.9891)	(0.97)	(3.20)	(0.01)
CPI in the spiked serum sample	$y = 9.33 \times + 97.02$	0.05−0.35	5	0.9856	0.05	1.02	0.16
	($y = 0.0019 \times + 0.5702$)	(1.0−8.0)	(5)	(0.9929)	(0.31)	(1.05)	(0.0002)

[a]Where data between brackets () are from the spectrophotometric method, LR, linearity range; DL, detection limit; QL, quantification limit.

CPI was detected by the proposed procedure in the pure form. Table 5 summarizes the results found for CPI, showing that the recovery is good. The recovery percent of the method ranged from 96.6 to 101.4%, via standard deviations varying from 0.11 to 0.24 and confidence limits from 0.18 to 0.21. The results attained via the suggested technique were located to be in good agreement with those achieved in the potentiometric manner (95.3–103.2%, SD = 0.2–0.3). Also, the results achieved by the proposed approaches were created to be in good agreement with those observed in a spectrofluorimetric manner (98.7 ± 1.3%).[36]

Regression considerations of the Beer's law plot indicate great correlation, and the estimated detection and quantification limit specify the great precision of the planned technique (Table 6).

The registered drugs including CPI were evaluated by the planned technique. Five repeats, determinations were kept out and the results acquired, as shown in Figure 15, seem to be greatly reasonable. The proposed technique is easy, precise, exact, and cheap. The components occupied are cheaper and instantly available, and the equipment is resourceful and adaptable. The technique is mentioned for the tedious analysis of the CPI in pure, urine, and serum samples, as displayed in Table 6.

5. CONCLUSIONS

Cephalothin was determined via the proposed techniques in pure, urine, and serum samples. The results acquired for cephalothin showing recovery are satisfactory. The recovery percentage of the two techniques ranged from 96.6 to 101.4%, with standard deviation varying from 0.001 to 0.01 and confidence limits from 0.02 to 0.11, respectively. The results achieved by our method were created to be in appropriate agreement with those observed via the spectrofluorimetric technique (98.7 ± 1.3%). Compared with several previously existing procedures for the estimation of cephalothin, which require a special instrument, reagent, and experience, our procedures revealed the advantage of simple processes, fast response, little cost, and adequate precision in the analysis of cephalothin in pure and biotic samples (urine and serum).

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Notes
The author declares no competing financial interest.

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