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Optimizing Ciprofloxacin Detection: Spectrophotometric Method Validation across Chemical and Thermal Parameters

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Abstract: A simple, rapid, and reliable direct spectrophotometric method for the determination of ciprofloxacin has been proposed and validated to overcome the lack of comprehensive reports on its estimation under different chemical conditions. Ciprofloxacin (CIP) was reported to be a well-known broad-spectrum fluoroquinolone antibiotic with activity against both Gram-positive and Gram-negative bacteria pathogens. The spectroscopic analysis of CIP includes the impact of solvent, ionic strength, pH, and temperature on the intrinsic spectroscopic features of CIP. A linear calibration curve was constructed with a correlation coefficient of 0.99 over concentration values (5-30 mg/l). The molar absorptivity (ε) and mean recovery were investigated to be 22.2 x 10^3 $L.mol^{-1}.cm^{-1}$ and 99.2%, respectively. The limit of detection (LOD) and quantification (LOQ) were assessed in accordance with ICH guidelines. The developed approach has been successfully validated for simultaneous determination of Ciprofloxacin, as evidenced by the high recovery values.
Keywords: Ciprofloxacin, Spectrophotometric method, Fluoroquinolone antibiotics, LOD and LOQ.

1. Introduction

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4 dihydro-4-oxo-7-(piperazinyl) quinolone-3 carboxylic acid) is globally classified as a fluoroquinolone antibiotic with a wide spectrum response [1, 2]. In recent years, a lot of emphasis has been placed on developing novel chemicals and assessing these drugs' antibacterial efficacy [3, 4]. Additionally, it is recognized that a large number of medications have altered pharmacological and toxicological characteristics [5]. Therefore, it was applied as a standard model to measure bacterial resistance [6, 7]. Interestingly, fluoroquinolones have great influence via both Gram-negative and Gram-positive bacteria, excluding *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, due to the interaction of C_7 piperazine and C_6 fluorine [8, 9]. According to the World Health Organization (WHO), five antibiotics were more frequently used in 2017, including ciprofloxacin and levofloxacin (quinolones), azithromycin and clarithromycin (macrolides), and cefixime (third-generation cephalosporin) [10]. Therefore, CIP could be a candidate for bacterial infection remediation such as the gastrointestinal, urinary tract, typhoid fever, bones, and joints [11]. It principally prevents DNA replication by interacting with the enzymes of bacterial DNA gyrase and topoisomerase (IV) [12-15].

Lipophilicity, ionization, and solubility are physicochemical features that affect the absorption, distribution, metabolism, and excretion processes [16, 17]. Hence, experimental drug behavior is frequently assessed in different kinds of solvents, as the solubility of active pharmaceutical ingredients is an important property to be considered in medicines' design duties [18]. Moreover, the drug's lipophilicity is a crucial physicochemical characteristic [19]. The majority of pharmacologically active substances have an acidic or basic form. Additionally, an amphoteric nature exists [20]. Chemical forms can differ from one another, including cations, anions, neutral, and zwitterion [21]. In water, the ionic substance dissolves more readily. But the neutral one enters the tissues more effectively. There are two types of amphoteric compounds: zwitterionic amphoteric and conventional amphoteric [22]. Fluoroquinolones belong to the second category. Protons can attach to fluoroquinolones at two different locations: the carboxyl group and the nitrogen atom in the piperazine ring. The renal tubular cells' organic anion and organic cation transporters are both likely to react with zwitterion [23].

Based on the reported literature, novel antimicrobial agents such as Pd(II), Cu(II), and Cu(I) complexes of (Z)-2-(phenylamino)-N'-(thiophen-2-ylmethylene)acetohydrazide [24], Co(II), Ag(I), and Cd(II) complexes of 2-(phenylglycyl)-N-(p-tolyl)hydrazine-1-carbothioamide [25], a series of Zr(IV), V(IV), Ru(III), and Cd(II) complexes with the ligand N-((5-hydroxy-4-oxo-4H-pyran-3-yl)methylene)-2-(p-tolylamino) acetohydrazide [26], and Ni(II) and Co(II) complexes with thiosemicarbazone ligand [27] have been studied. In contrast, extensive studies on the physical properties of antimicrobial agents are rare. Therefore, this work began with the study of the spectroscopic analysis of ciprofloxacin.

Generally, many approaches have been directed toward the identification of ciprofloxacin in biological material, pure form, and pharmaceutical formulations owing to the broad usage of this class of medications and the medicinal significance of ciprofloxacin [28]. Numerous analytical methods for drug determination have been documented in the scientific literature, like Rayleigh light scattering technique,

Capillary electrophoresis, High-performance liquid chromatography, Atomic absorption spectrometry, UV-vis spectrophotometry, and optical sensors [29]. Although some of these techniques entail highly skilled operations and expensive equipment, the spectrophotometric pathway is favorable due to being an inexpensive, highly sensitive, simple, and accurate technique [30, 31]. The majority of the time, spectrophotometry is utilized as a practical and affordable analytical technique in pharmaceutical analysis [32].

Recently, many physicochemical methods were reported to estimate CIP, including electrochemical sensing via Zn-doped CeO_2 [33], Ruthenium-doped Cu-MOF [34], and N or S co-doped porous carbon/silver nanoparticles [35]. Although the spectrophotometric assay for different brands of ciprofloxacin has been discussed by Naveed et al. [23], no reports have appeared on the effect of experimental variables on the studied statistical parameters. Therefore, much debate has arisen about the impact of experimental variables on the regression analysis of CIP. Hence, the purpose of the current study is to elaborate and validate an accurate, precise, and repeatable UV-vis spectrophotometric method for ciprofloxacin detection. An affordable approach was created and verified to analyze some spectroscopic parameters of the proposed drug at different experimental variables (pH, ionic strength, and temperature). A sufficient statistical analysis was conducted to confirm the method's reproducibility.

2. Materials and methods

2.1. Materials

Ciprofloxacin hydrochloride $C_{17}H_{19}ClFN_3O_3$ was generously provided by Anhui medipharm (China, M.wt.=385.8177 g/mol). Dimethyl sulphoxide (Sigma-Aldrich, M.wt.=78.13 g/mol, 99%), Ethanol (Sigma-Aldrich, 46.07 g/mol, 99.8%), Dimethyl formamide (Sigma-Aldrich, 78.09 g/mol), Sodium chloride (Sigma-Aldrich, M.wt.=58.44 g/mol, 99%), Sodium hydroxide, (Sigma-Aldrich, M.wt.=40 g/mol), Phosphoric acid (Sigma-Aldrich, M.wt.=95 g/mol, 85%). All reagents were of analytical grade.

2.2. Experimental:

2.2.1. Apparatus

All spectrophotometric measurements were collected by Perkin Elmer Lambda 35 spectrophotometer.

2.2.2. Preparation of standard solutions

A stock solution of CIP was prepared by dissolving 50 mg of the sample in 500 ml of bidistilled water. Different aliquots of the stock solution were diluted with diverse volumes to prepare proper concentrations of CIP (3-30 µg/ml).

2.2.3. Chemical and function groups analysis

Fourier transform-infrared (FT-IR) spectroscopy in the attenuated total reflectance (ATR) mode of samples was carried out using the Bruker Alpha FT-IR instrument in the range 400-4000 cm^{-1} using KBr methodology to investigate the functional groups in the studied antibiotic.

2.2.4. Spectrophotometric measurements

UV-Vis absorption spectra of the solutions were obtained in the range from 200 to 500 nm by Perkin Elmer Lambda 35 spectrophotometer. The spectroscopic detection of ciprofloxacin hydrochloride was determined via a wide range of pH values from 2 to12. The pH values of the solutions were adjusted with a buffer solution from NaOH and H_3PO_4 solutions. The behavior of ciprofloxacin was studied against different types of solvents (DMF, ETOH, and DMSO), different ionic strength by various contents of NaCl, and different temperatures from 10 to 40 ^0C. The proposed temperature was optimized by a thermostated cell compartment. The validity of Beer's law was checked in the concentration range of 5-30 ppm for each pH, solvent %, ionic strength, and temperature.

2.2.5. Effect of experimental variables

The influence of concentration, ionic strength, pH, solvent type, and temperature on the absorbance of ciprofloxacin was studied. The rationale for choosing specific solvents, concentration ranges, and other experimental conditions is based on several considerations:

- **Solvents (DMSO, ETOH, and DMF):** These solvents were selected due to their differing polarities and ability to dissolve ciprofloxacin, allowing us to study how CIP's spectroscopic properties vary in different solvent environments. DMF, ETOH, and DMSO are commonly used in pharmaceutical and biochemical research, making them relevant for practical applications.
- **Concentration Ranges:** The concentration ranges were chosen to cover both the expected therapeutic levels of ciprofloxacin and the potential environmental concentrations that might be encountered in real-world scenarios. This ensures that the study's findings are applicable to both clinical and environmental contexts.
- **Ionic Strength (NaCl):** Sodium chloride was used to vary the ionic strength of the solutions. The selected concentrations reflect typical ionic strengths found in physiological and environmental samples, allowing us to assess the impact of ionic strength on CIP's spectroscopic behavior in realistic conditions.
- **pH Levels (2-12):** The pH levels were chosen to represent a wide range of conditions that ciprofloxacin might encounter, from acidic to neutral to basic environments. This range covers the physiological pH of human body fluids as well as potential pH variations in environmental waters.
- **Temperature Range (10°C to 40°C):** The temperature range was selected to encompass typical ambient and physiological temperatures. This allows us to study the stability and behavior of ciprofloxacin under conditions it might experience during storage, transport, and use.

These choices were made to ensure that the study's findings are robust, relevant, and applicable to both laboratory research and practical applications in pharmaceutical and environmental contexts.

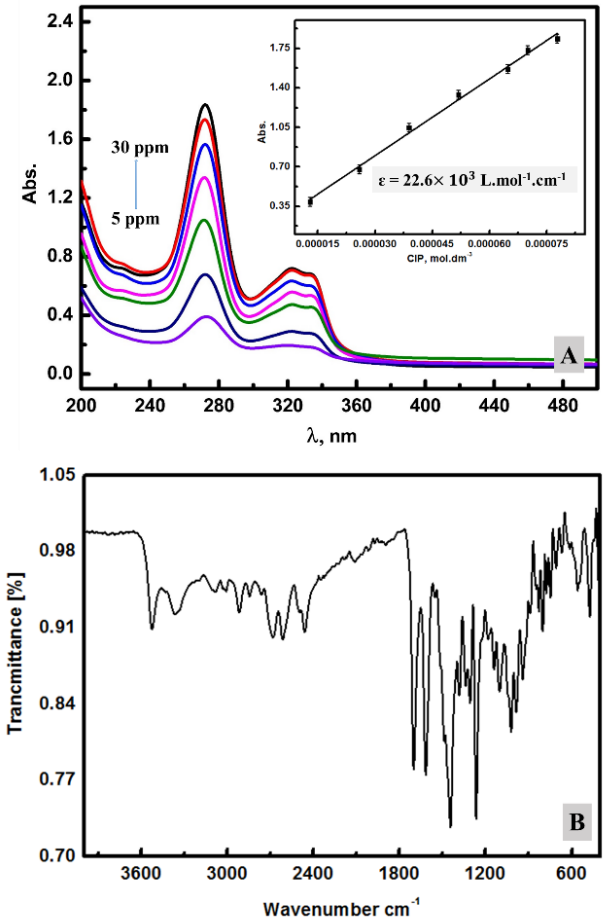

Fig. 1: The absorption spectra of: A) different concentrations of CIP (5-30 ppm), B) FT-IR chart of CIP.

2.2.6. Construction of calibration curves

Separate aliquots of the working standard solutions of CIP were diluted in 100 ml volumetric flasks to construct calibration standards involving 5-30 µg/ml of CIP at different experimental conditions (solvent, pH, ionic strength, and temperature).

2.2.7. Validation of method

Validation was considerably estimated following ICH recommendations for linearity, accuracy, limit of detection, and limit of quantitation.

2.2.7.1. Linearity

Linearity was demonstrated by analyzing the calibration curve using least squares linear regression. The acquired absorbance was plotted against the corresponding concentrations, and the resulting curves were subjected to a linear regression analysis. The results are used to display the calibration curves' means and standard deviations. The evaluation parameters were computed and reported as slope, intercept, and correlation coefficient.

2.2.7.2 Accuracy

The suggested method's accuracy was investigated through recovery experiments. Hence, the accuracy was demonstrated by computing the mean recovery (%).

2.2.7.3. Limit of detection and quantification

The LOD and LOQ were calculated depending on ICH guidelines by using the equation [36]:

$$LOD = 3.3(SD/a), LOQ = 10(SD/a)$$

Where "SD" is the standard deviation of the intercept and "a" refers to the slope value.

3. Results & Discussion

The aim of the study is to establish a pharmaceutical assay of CIP with different experimental variables via spectrophotometric measurements. Solutions of 5, 10, 15, 20, 25, 27, and 30 ppm were prepared in bidistilled water, and the related spectra were detected along 200-500 nm. Two absorption peaks appeared at 275 and 325 nm, attributed to the absorption ring and n-π*, respectively [37]. The intensity of both peaks gradually increased with increasing the concentration of CIP from 5 to 30 µg/ml, as recorded in (Fig. 1A). The opposite absorbance at λ_{max}=275 nm was recorded, and the linearity was confirmed by plotting the concentration vs. absorbance, which clarifies their perspicuous direct relationship. Hence, ciprofloxacin obeys Beer's Lambert law over a concentration range of 5-30 ppm with a regression coefficient (0.99). The pertinent statistical data are cited in Table S1 (Supplementary Material). Molar absorptivity was estimated to be ε =22.2 x 10^3 $L.mol^{-1}.cm^{-1}$ according to the previous calibration curve. Therefore, the detection of unknown CIP contents could be easily found via its absorbance.

3.1. IR analysis

The FTIR spectrum of ciprofloxacin shows many absorption bands as recorded in (Fig. 1B). The most characteristic bands can be attributed to the O–H stretching in COOH at 3527-3368 cm^{-1}, N–H stretching at 2683-2462 cm^{-1}, C=O stretching in COOH and 4-quinolone ring at 1702 cm^{-1} and 1617 cm^{-1}, respectively, the C=C stretching in aromatic ring at 1553-1489 cm^{-1}, C–H bending at 1445 cm^{-1}, C–N stretching at 1384 cm^{-1}, C–O stretching in COOH at 1266 cm^{-1}, and C–F stretching vibrations in the range of 1266-1103 cm^{-1}.

3.2. Effect of solvent

CIP consists of several interconnected aromatic cores and numerous substituents, including heteroatoms like O, F, N, and Cl. Therefore, the molecule possesses high polarizability due to the existence of an electronegative heteroatom and aromatic delocalized π-electrons [38]. The behavior of CIP with different solvents was checked by the power of the absorbance response against increasing solvent quantity via UV-vis measurements. By adding different ratios of DMSO, ETOH, and DMF (10-60 %) to 5 µg/ml of CIP as depicted in (Fig. 1B) and (Fig. 2(A-C)). The fineness of the virtual absorption bands is deeply affected by the selected type of solvent. In the case of DMF, the absorbance is directly proportional to the DMF ratio until 40 %, and up to this ratio, the absorbance decreased or almost became stable at 50% and 60% (Fig. 2A).

By comparing the position of λ_{max} of CIP solution in the case of H_2O and DMF, it was observed that λ_{max} shifted to a lower value (275-273 nm) as the polarity of the solvent reduces (cf. Fig. **2B**) [**39**]. This is most likely caused by a superior n-π^* transition, resulting in a blue shift in the instance of H_2O over DMF. The same procedure was optimized in the presence of ETOH as solvent (cf. Fig. **2C**). The absorbance increases with increasing ETOH ratio until 40% and then decreases at 50%. ETOH shows a clear impact on the shape of CIP peaks at λ= 275 and 325 nm. On the other hand, the absorbance increases with increasing quantities of DMSO until reaching 50%, and upon reaching this ratio, the absorbance slightly decreases as shown in (Fig. **2D**). The clear influence of CIP absorbance by changing the type and quantity of solvent is due to being susceptible to various particular interactions with polar solvents, such as hydrogen bonding, protonation, electrostatic interactions, and specific solvation [**38**].

3.3. Effect of pH

The protonable groups of CIP molecules are based on the pH of the solution [**40**]. Hence, the sensitivity of CIP absorbance against the pH of the medium was studied at different pH values via UV-vis measurements. pH of CIP aqueous solutions was adjusted by different ratios of buffer solution (NaOH (0.1 N)/ H_3PO_4 (0.1 N)). With varying pH values, the intrinsic spectroscopic features of CIP still exist with a stamped change which lies in the position and intensity of the proposed peaks at 275 and 325 nm. As the pH value increases, the first peak intensity at λ=275 nm decreases with a lower shift in wavelength. In contrast, the second peak intensity at λ=325 nm increases. These results could be due to the probable ionization of the carboxylic group during the deprotonation at a higher pH [**41**]. At low pH values where the cationic or zwitterionic form of CIP is dominant, the absorbance promotes with a higher shift in wavelength as the solubility of CIP increases at lower pH, as investigated in (Fig. **3A**).

Besides, this behavior was discussed by following the absorbance of different concentrations of CIP (3-15 µg/ml) at pH=2, where CIP molecules exist in cationic form due to the protonation of the amino group in an acidic medium [**15**]. As the concentration of CIP increases, the absorbance increases, as cited in (Fig. **3B**). CIP exhibits maximum absorbance at low pH, as stability and solubility clearly increase at pH=2. CIP is regarded as an amphoteric drug, which can be found in different structural species in aqueous solutions: anionic, cationic, and zwitterionic based on the pH values [**15**].

Therefore, the effect of different pH on the structure of CIP was studied along different concentrations (3-10 ppm), as recorded in (Fig. **4A**). The absorbance elevated with decreasing pH and was almost fixed at higher pH. The maximum value of absorbance was detected at pH=3. The molar absorptivity of calibration plots under the applied pH (2-12) was calculated in the concentration range from 3 to 15 µg/ml (Fig. **4B**). Additionally, the linear equation and molar absorptivity values at different pH values were recorded in Table S2 (Supplementary Material), followed by LOD, LOQ, and recovery percentage in Table **S3** (Supplementary Material).

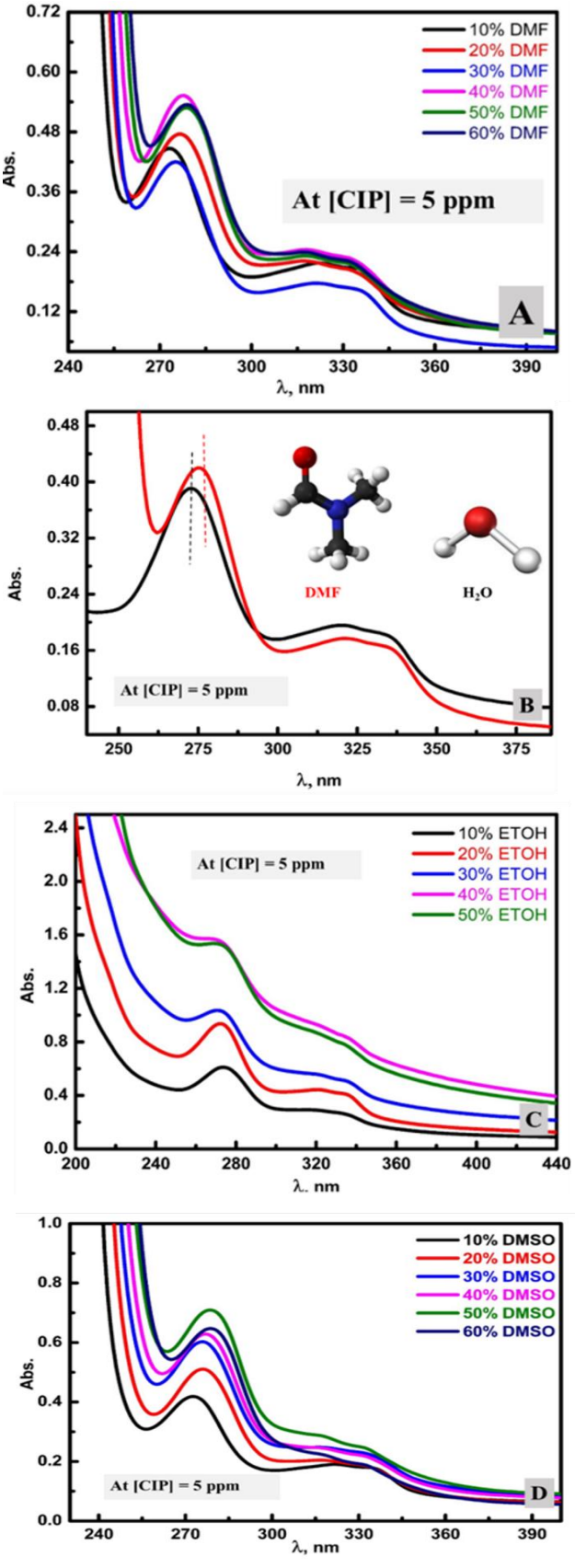

Fig. 2: The absorption spectra of CIP at 5 ppm: A) different ratios of DMF (10-60%); B) in aqueous solution and in organic solvent (DMF), C) in different ratios of co-organic solvent ETOH (10-50%) and D) in different ratios of co-organic solvent DMSO (10-60%).

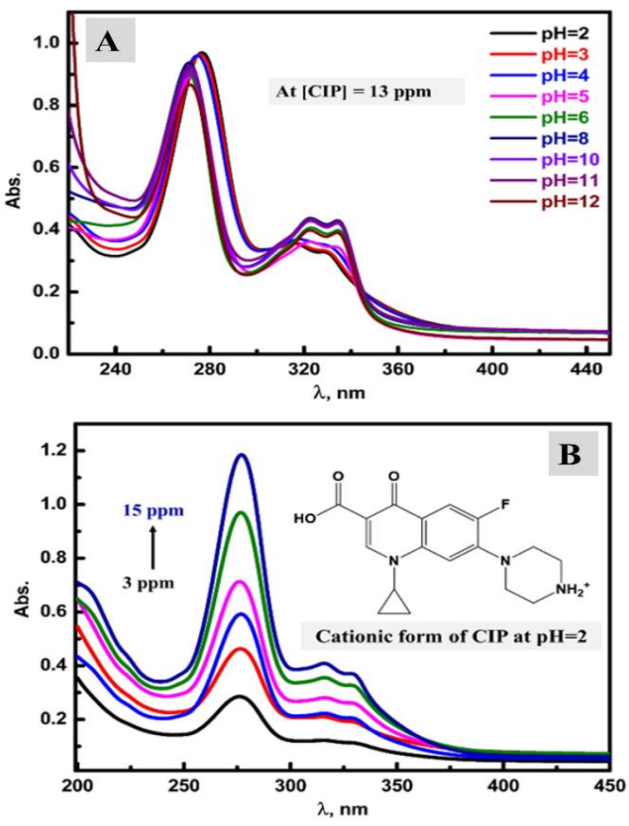

Fig. 3: Spectral scans of: **(A)** CIP = 13 ppm in different pHs; (B) CIP from 3 ppm to 13 ppm in acidic medium.

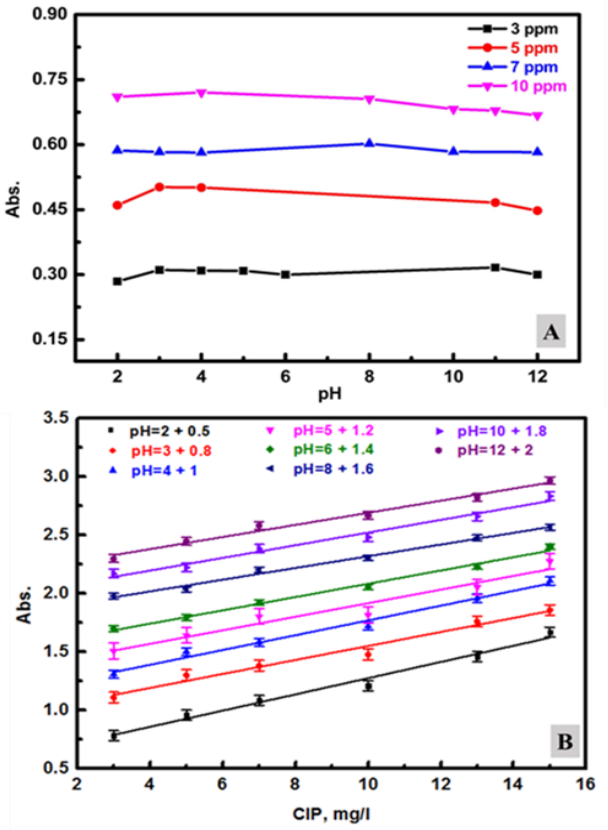

Fig. 4: (A) The spectroscopic response of different CIP at λ max = 275 nm against various pH values; (B) The relation of absorbance vs. CIP under the influence of different pH values (2-12).

From the displayed regression data, the spectrophotometric method, especially the recovery (%) was verified in neutral media better than what was seen in strong acidic or alkaline mediums, which could be due to the formation of cationic or anionic forms in acidic or alkaline medium, respectively as depicted in Figure **S1** (Supplementary Material). This could be attributed to the expected electrostatic attraction between the chemistry of CIP and hydronium ions [**42**]. Therefore, there are two dissociation constants for CIP molecules, which could be found as different ionic species at different pH values. In short, the preferred pH for CIP detection is the neutral medium away from high or low pH values to provide a suitable chance for the zwitterion to be dominant if compared with anionic or cationic form.

3.4. Effect of ionic strength

Generally, ionic strength is a crucial factor in electrolytic solutions [**43**]. Different concentrations of NaCl (0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mol.dm^{-3}) were prepared to verify the impact of ionic strength on absorption bands of 7 µg/ml CIP. It was observed that the absorption band intensity barely changed as the electrolyte concentration increased, which proves the stability of ciprofloxacin along a wide range of ionic strength (0.05-0.5 mol.dm^{-3}), as viewed in (Fig. **5A**). The same trend was observed by differentiating CIP concentration to 10 µg/ml at different ionic strength demonstrating the great stability of the proposed drug in the presence of various electrolyte contents as recorded in (Fig. **5B**). As evidenced, the influence of ionic strengths on various concentrations of the studied drug (3-15 µg/ml) was clarified, and the absorption was either minimally altered or remained nearly constant (cf. Fig. **6A**). This behavior can be due to the absence of competition effect between anions or cations in the solution [**44**]. Moreover, the molar absorptivity of ciprofloxacin solutions (from 3 to 15 µg/ml) at the first absorption band (λ_{max}=275 nm) was calculated by blotting the CIP concentration vs. the resultant absorbance at different concentrations of electrolyte as investigated in (Fig. **6B**). Besides, the linear equation and molar absorptivity values at different ionic strength values were recorded in Table **S4** (Supplementary Material) followed by LOD, LOQ, and recovery percentage in Table **S5** (Supplementary Material). The LOD and LOQ values were found between 1.7-5.2 and 5.2-15.7, respectively. All these estimated results confirmed the chemical stability of the proposed drug in presence of various electrolyte content.

3.5. Effect of temperature

It is widely acknowledged that the UV spectrum is a temperature-dependent analysis. The spectroscopic response of various concentrations of ciprofloxacin was studied under the influence of different temperatures (10-40 ºC). The absorbance detection was carried out in a thermostated cell compartment at the appropriate temperature. CIP stock solution (50 µg/ml) was prepared in bidistilled water and diluted to obtain the proposed concentrations (3-15 µg/ml). The absorbance of the prepared solution (3 µg/ml) was investigated at different temperatures as shown in (Fig. **7A**). The intensity of the proposed bands increases with elevating temperature from 10 to 40ºC. The same conclusion was imitated at various concentrations of CIP as appeared in (Fig. **7B** and **8A**).

In addition, the linear equation and molar absorptivity values at different temperature values were recorded in Table S6 (Supplementary Material), followed by LOD, LOQ, and recovery percentage in Table S7 (Supplementary Material). The LOD and LOQ values were found between 7.9-9.4 and 23.80-28.40, respectively. In general, the compounds that exhibit n-π^* transition display a different temperature-related effect. The total absorption intensity gradually reduced with decreasing temperature, even in the absence of a particular interaction between the solvent molecules and the solute in agreement with what was previously discussed [45]. The molar absorptivity of ciprofloxacin solutions at the first absorption band (λ_{max}=275 nm) was calculated at different temperatures (10-40 °C) as settled in (Fig. 8B) by blotting the absorbance against concentration. All these estimated results confirmed that low-temperature is favored for the chemical stability of the proposed drug to get the best values from LOD and LOQ.

3.6. Validation method

3.6.1. Linearity

The calibration graphs were created by graphing the response absorbance values against the drug concentration (µg/ml). The linearity of the calibration curves was supported by the high value of the regression coefficient (R^2 = 0.99) over differentiating experimental variables [46]. The performance data and statistical parameters at different pH values (2-12) within the concentration range of 3-15 µg/ml are summarized in Tables S2 and S3. Additionally, the linearity of the plot between absorption and concentrations was attained under the influence of multiple concentrations of sodium chloride 0.05-0.5 mol dm^{-3}. The related linearity equation found concentration, and other statistical computations are involved in Tables S4 and S5. The linearity was also achieved at different values of temperatures 10-40 ^{0}C as depicted in Tables S6 and S7. The linearity of the spectrophotometric method is achieved with different slope and intercept values according to the variation of pH, ionic strength, and temperature conditions.

3.6.2. Limit of detection and quantification LOD and LOQ

LODs and LOQs were computed following ICH guidelines depending on regression data under the impact of experimental circumstances. The proper values of LODs and LOQs were obtained at different contents of CIP 3-15 µg/ml which was 5.73 and 17.38 µg/ml were slightly different to that reported elsewhere [28]. As previously confirmed, CIP is undoubtedly impacted by the variation of pH values [47]. Furthermore, LODs and LOQs calculations proceeded at multiple pH levels (2-12) as recorded in Tables S2 and S3. LODs were found within the range of 3.2 - 9.3 µg/ml and LOQs within 9.7 -28.2 µg/ml. CIP was also affected by other excipients which could be taken into consideration such as ionic strength and temperature. Hence, LODs and LOQs were assessed at different ionic strength values (0.05-0.5 mol.dm^{-3}) and different temperature values (10-40^{0}C) as depicted in Tables S4, S5, S6, and S7. Other related statistical parameters were discussed as recovery, mean recovery, and found concentration which prove the sensitivity of the utilized methods. In short, low-temperature and neutral pH are the preferred chemical and thermal environments, and slight change could be seen in the case of ionic strength change.

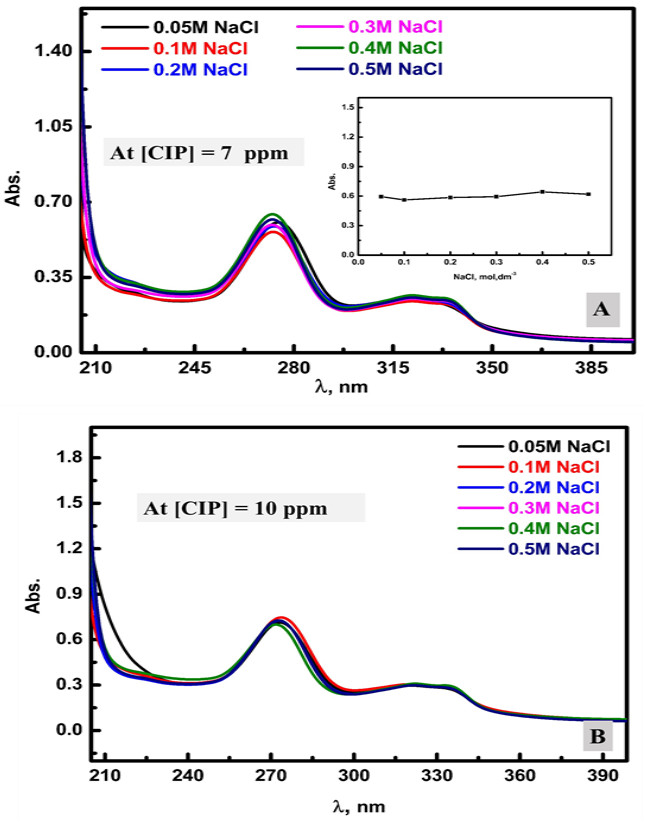

Fig. 5: The influence of different ionic strength on the absorption of CIP; (A) CIP = 7 ppm, (B) CIP = 10 ppm.

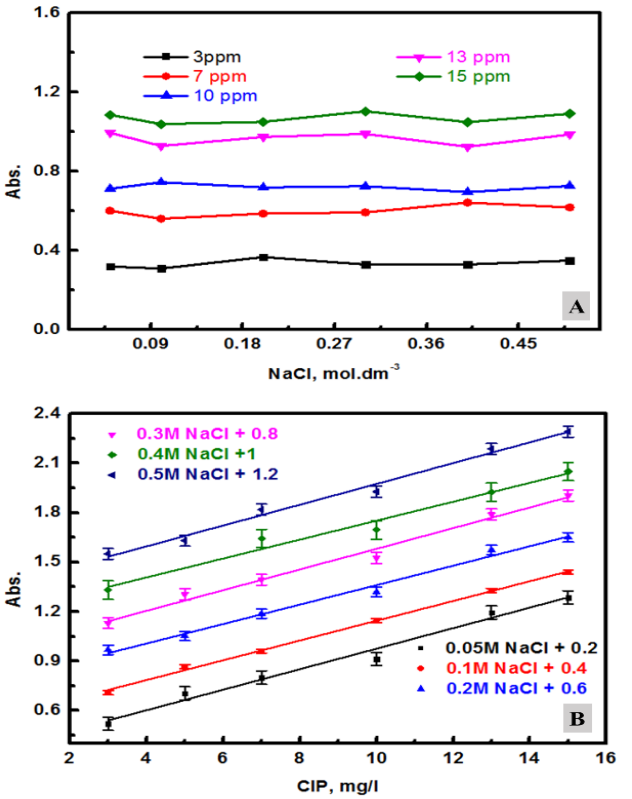

Fig. 6: (A) The spectroscopic response of different CIP at λ_{max}=275 nm against various electrolyte concentrations; (B) The relation of absorbance vs. CIP in the presence of different ionic strength.

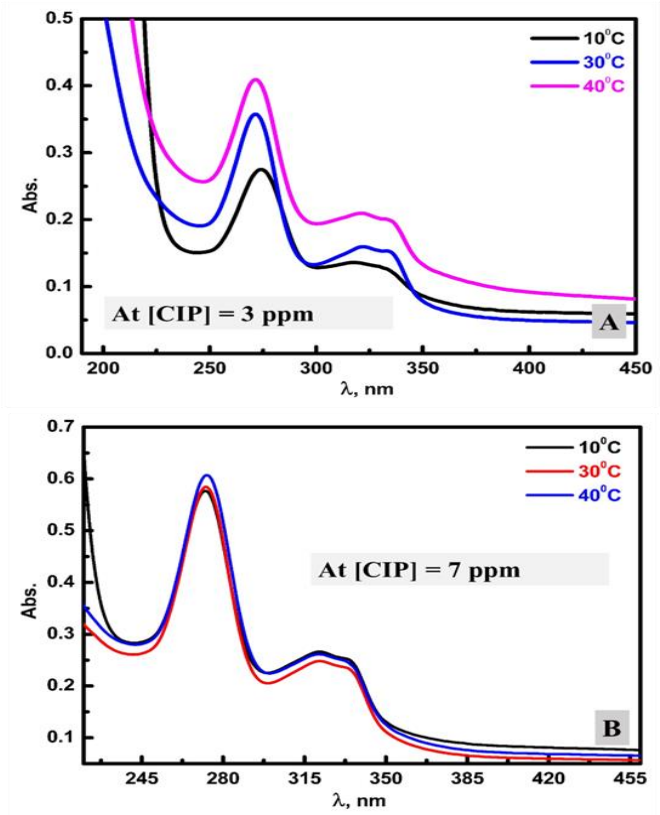

Fig. 7: The impact of different temperature on the absorption of CIP: (A) CIP = 3 ppm, (B) CIP = 7 ppm.

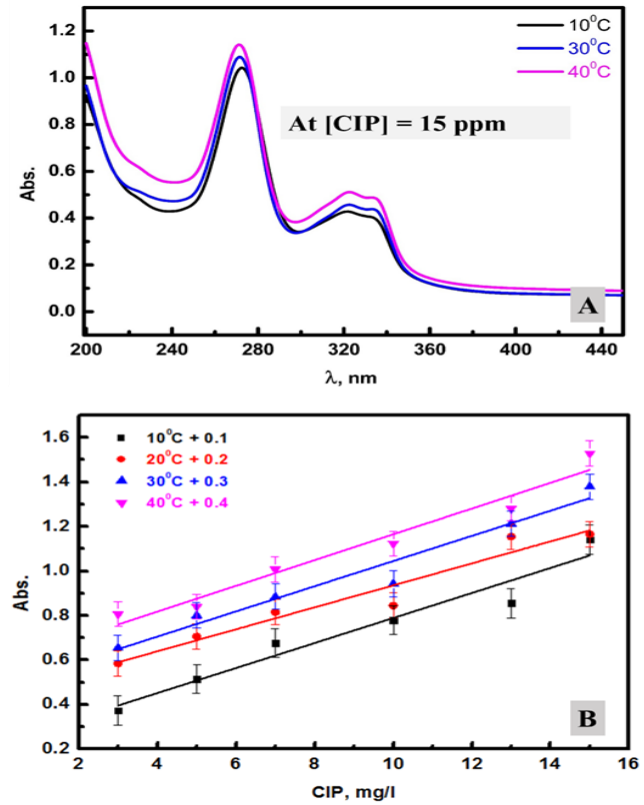

Fig. 8: (A) The impact of temperature variation on the absorption of CIP = 15 ppm, (B) The relation between absorbance and CIP at different temperature.

4. Conclusion

The developed spectrophotometric method is convenient and efficient for the detection of CIP. In contrast to chromatography, spectrophotometry doesn't demand any pretreatment or laborious sample preparation. Linearity was demonstrated by analyzing the calibration curve using least squares linear regression. A strong linear correlation was noticed in the concentration levels of 5 ppm, 10 ppm, 15 ppm, 20 ppm, 25 ppm, 27 ppm, and 30 ppm. The obedience of the studied drug to Beer's law was supported by the apparent linearity between concentration and absorbance over different experimental conditions with r^2 = 0.99. In conclusion, low-temperature and neutral pH are the preferred chemical and thermal environments that have better LOD and LOQ, and a slight change could be detected in the case of ionic strength change. The accuracy of the developed method with different linear equations was substantiated by the computed statistical parameters. Furthermore, the utilized approach is regarded as safe, environmentally friendly, and non-hazardous or sophisticated in the estimation of ciprofloxacin in different chemical or biomedical environments.

CRediT authorship contribution statement:

Author Contributions: Conceptualization, I.M.A.M and Y.A.; methodology, Y.A.; software, L.A.E.N, A.M.S.; validation, L.A.E.N, Y.A., A.M.S. and I.M.A.M.; formal analysis, L.A.E.N., Y.A.; investigation, Y.A., I.M.A.M.; resources, L.A.E.N., A.M.S.; data curation, Y.A.; writing—original draft preparation, L.A.E.N., Y.A., and I.M.A.M.; writing—review and editing, L.A.E.N., Y.A., and I.M.A.M.; visualization, L.A.E.N., A.M.S.; supervision, L.A.E.N., A.M.S., and I.M.A.M. project administration, L.A.E.N., A.M.S., and I.M.A.M.; funding acquisition, L.A.E.N., A.M.S., and I.M.A.M. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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