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Review Article

A Review on Analytical Applications Of 1,10-Phenanthroline as Chromogenic Reagent

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ABSTRACT

Chromogenic reagents play a pivotal role in pharmaceutical analysis by facilitating the detection and quantification of key analytes through precise colorimetric reactions. Among these, 1,10-phenanthroline is a versatile and highly sensitive reagent that forms stable metal complexes, making it indispensable in spectrophotometric, electrochemical, and chromatographic techniques. This article explores the diverse applications of 1,10-Phenanthroline in the quantitative determination of pharmaceuticals and metal ions, emphasizing its role in quality control, environmental monitoring, and advanced analytical methodologies. Spectrophotometric methods leveraging 1,10-Phenanthroline offer rapid, cost-effective, and highly accurate alternatives for drug and metal ion analysis, demonstrating excellent sensitivity and reproducibility. Additionally, emerging techniques such as flow-injection photometry, FTIR spectroscopy, and electrochemical sensors further expand its utility in modern analytical chemistry. The review underscores the growing significance of 1,10-Phenanthroline -based methodologies in ensuring pharmaceutical safety, regulatory compliance, and enhanced analytical precision.

INTRODUCTION

Chromogenic reagents are vital in pharmaceutical analysis, enabling the detection and quantification of specific analytes through colorimetric reactions. These reagents react with target substances, such as metal ions or drug compounds, producing a measurable color change.[1] This property is widely utilized in spectrophotometry, chromatography, and chemical sensors for precise and reliable analysis. In pharmaceutical quality control, chromogenic reagents help ensure drug purity, potency, and consistency by detecting impurities and verifying active ingredient concentrations. They play a crucial role in the analysis of metals, enzymes, and pharmaceutical formulations, enhancing the accuracy of analytical methods. Their sensitivity and ease of use make them essential in regulatory compliance and batch-to-batch quality assessment. The ability to provide rapid, cost-effective, and non-destructive analysis underscores their importance in drug

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manufacturing and research, ensuring patient safety and therapeutic efficacy.

1,10-Phenanthroline is a heterocyclic aromatic compound with the molecular formula $C_{12}H_8N_2$.[2] Its structure consists of a fused three-ring system with two nitrogen atoms in a bipyridine-like arrangement, allowing it to form highly stable complexes with metal ions (Figure 1). This strong chelating ability makes it a valuable reagent in analytical and coordination chemistry.

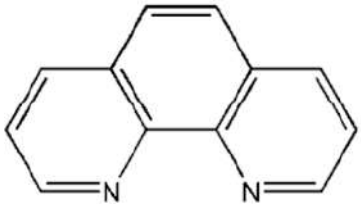

Figure 1: Structure of 1,10-phenanthroline

In redox chemistry, 1,10-phenanthroline (Phen) plays a key role in oxidation-reduction reactions, particularly in the detection of iron. It forms a stable red-colored complex, $[Fe(Phen)_3]^{2+}$, with Fe(II) in the presence of an oxidizing agent like ferric chloride, enabling precise spectrophotometric quantification of iron.[3] This redox reaction is widely used in pharmaceutical analysis, environmental testing, and industrial quality control. As a chromogenic reagent, 1,10-phenanthroline is employed in the spectrophotometric determination of various drugs, including anti-ulcer agents, antiviral compounds, and antibiotics.[4-6] It is also used in metal ion analysis, ensuring the quality and potency of pharmaceutical formulations. Its versatility, sensitivity, and stability make it indispensable in analytical chemistry, facilitating accurate and efficient quantification of key analytes.

Spectrophotometric Methods

Quantification of Pharmaceuticals

Sensitive and precise colorimetric method was developed for quantifying barnidipine hydrochloride in bulk drug. This method involves the formation of an orange-colored complex between barnidipine hydrochloride and 1,10-phenanthroline in the presence of ferric chloride, with a maximum absorption at 510 nm. The method was statistically validated and demonstrated accuracy, precision, and reproducibility. The approach offers reliable alternatives for the routine quality control of barnidipine hydrochloride in pharmaceutical formulations.[4]

Benzimidazole-class anti-ulcer drugs, such as omeprazole (OMZ), lansoprazole (LNZ), pantoprazole (PNZ), rabeprazole (RBZ), and esomeprazole (EMZ) were quantified by a simple and sensitive spectrophotometric method.[5] The method is based on the reaction of these drugs with iron (III), followed by complexation with 1,10-phenanthroline to form an orange-colored complex with a maximum absorption at 510.0 nm. The method demonstrated excellent selectivity, as common excipients and additives did not interfere with the analysis. It allows for the quantification of LNZ, PNZ, and RBZ in the range of 200.0–4000.0 ng/mL, OMZ in the range of 80.0–2800.0 ng/mL, and EMZ in the range of 200.0–3800.0 ng/mL. Analysis of commercial pharmaceutical formulations, including Omelac capsules, Lanpro capsules, Pan tablets, Rabeloc tablets, and Raciper tablets, showed results in good agreement with established methods. This validated method is suitable for routine quality control of anti-ulcer drugs in pharmaceutical formulations.

Both cefepime (CFM) and repaglinide (RGP) were simultaneously estimated in both pure and pharmaceutical formulations, where the drug was oxidized using ferric chloride, and then complexed with 1,10-phenanthroline. The resulting blood-red chromogen absorption maxima was measured at 520 nm for CFM and 515 nm for RPG. The method obeyed Beer's law in the 1.0–7.5 µg/mL range for CFM and 2.5–15.0 µg/mL for RPG. It was successfully applied to pharmaceutical formulations, demonstrating no interference from excipients or diluents. The proposed method provides a reliable, accurate, and reproducible approach for routine quality control analysis of cefepime and repaglinide.[6]

A simple and sensitive spectrophotometric method was developed for the quantitative analysis of dolutegravir in pure form and pharmaceutical formulations. The method is based on a redox reaction between dolutegravir and ferric chloride, leading to the formation of an orange-colored

complex with 1,10-phenanthroline, which exhibits a maximum absorption at 520.0 nm. The method demonstrated linearity within a concentration range of 40.00–140.00 µg/mL and was validated according to International Council for Harmonization (ICH) guidelines. Validation parameters confirmed its accuracy, precision, and reproducibility, with assay results showing 102.5% of the labelled claim, indicating high reliability. Given its sensitivity, simplicity, and compliance with regulatory standards, this redox-based colorimetric method is suitable for routine quality control analysis of dolutegravir in pharmaceutical dosage forms.[7]

Murali *et al.*, 2019 reported two spectrophotometric methods for the quantification of carisoprodol (CCP) in pure form and pharmaceutical formulations using ferric chloride, *o*-phenanthroline, *p*-nitroaniline (PNA), and sodium nitrate as analytical reagents. The first method is based on the oxidation of Fe^{2+} by CCP, followed by complexation with o-phenanthroline under acidic conditions, forming an orange-colored complex. The second method involves the diazotization of PNA, which subsequently couples with CCP in an alkaline medium to produce a yellow-colored complex. Both methods obey Beer's law within the concentration range of 10–60 µg/mL, with high correlation coefficients of 0.9992 and 0.9990. The limits of detection were determined as 1.286 µg/mL and 2.408 µg/mL, respectively. These validated methods offer accuracy, sensitivity, and simplicity, making them suitable for routine quality control analysis of carisoprodol in pharmaceutical formulations.[8]

A simple and sensitive spectrophotometric method was developed for the quantification of mycophenolic acid (MYCO) in bulk and pharmaceutical formulations. The method is based on the formation of a colored complex due to the oxidation of MYCO with Fe(III), followed by complexation with 1,10-phenanthroline to produce Fe(II). The resulting complex exhibits maximum absorption at 510 nm. The method follows Beer's law in the concentration range of 2.0–7.5 µg/mL and provides reproducible results. The percentage recovery of MYCO in pharmaceutical formulations was found to be 99.26–99.86%, indicating high accuracy and reliability. This spectrophotometric approach offers an efficient and validated technique for the routine analysis of mycophenolic acid in various dosage forms.[9]

Quantification of Iron and other metal ions

The stability of the tris(1,10-phenanthroline) iron(II) complex is significantly influenced by the composition of alumina-based composites during total iron measurements. This study aimed to determine the optimal alumina concentration that maximizes complex stability over 45 minutes. Using UV-Vis spectrophotometry, absorbance measurements were conducted to assess complex stability at varying alumina concentrations. The results showed that alumina concentrations of 3 g/200 cm^3 and 4 g/200 cm^3 formed stable complexes, making them suitable for iron analysis. Furthermore, an increase in absorbance with increasing alumina concentration was observed, indicating adherence to Beer-Lambert's law. The findings suggest that the stability of the complex is highly dependent on the composite composition, emphasizing the need for further investigation into the stereochemistry of complex formation in different matrices. This study provides valuable insights for optimizing analytical methodologies involving tris(1,10-phenanthroline) iron(II) complexes in various applications.[10]

A simple and sensitive derivative spectrophotometric method was developed for Fe(II) and Ru(III) determination using the baseline-to-peak measurement technique. 1,10-Phenanthroline (o-phen) was used as a complexing agent, forming a deep red Fe(II)-*o*-phen complex at pH 5 with a peak at 535 nm and a yellow Ru(III)-*o*-phen complex at pH 4 with a peak at 466 nm. The method followed Beer's law in the range of 0.1–2.0 µg/mL for Fe(II) and 5.0–20.0 µg/mL for Ru(III), with correlation coefficients of 0.99853 and 0.99914, respectively. The method was successfully applied for Fe(II) determination in pharmaceutical formulations and Ru(III) in synthetic mixtures, demonstrating accuracy and reliability.[11]

A robust UV-Visible spectroscopic method was developed for iron(III) estimation using a 1,10-phenanthroline reagent, following an experimental

design approach. The method involves forming a colored iron-phenanthroline complex, measured at 509 nm. A full factorial design assessed the influence of reagent concentration, reagent volume, pH, and reaction time, identifying significant factors via Pareto, normal, and half-normal plots. Optimization was conducted using response surface methodology (RSM) through the Box-Behnken design. The method followed Beer's law within a 2.0–10.0 µg/mL concentration range, with a correlation coefficient of 0.998. It was successfully applied for quantitative iron estimation in iron sucrose injection, ensuring accuracy and reliability.[12]

A novel optical sensor for Fe(II) ion detection was developed by immobilizing 1,10-phenanthroline in an alginate/pectin film. The sensor relies on the complexation reaction between Fe(II) ions and 1,10-phenanthroline, resulting in a distinct color change from transparent yellow to orange-red. The film was characterized using Fourier-transform infrared spectrometry (FT-IR) and scanning electron microscopy (SEM). Optimal detection conditions were established at a wavelength of 513 nm, with a response time of 2 minutes at pH 2. The UV-Vis spectrophotometric analysis confirmed the film's excellent linearity, precision, and selectivity, with a detection limit as low as 0.446 mg/L. This immobilized phenanthroline-based sensor provides a simple, rapid, and highly sensitive method for Fe(II) ion detection, making it a promising tool for environmental and industrial applications requiring real-time metal ion monitoring.[13]

An innovative flow-through, double-beam photometric detector with direct injection of reagents (double-DID) was utilized for the first time to determine iron in pharmaceutical formulations. The system integrates double paired emission-detection LED diodes and a log ratio precision amplifier, ensuring stable absorbance measurements. Solenoid micro-pumps were employed for precise solution dispensing and reagent minimization, enhancing automation. Total Fe(II) was determined using 1,10-phenanthroline as a complexing agent, with photometric detection. The method demonstrated linear calibration (1–30 mg/L), a detection limit of 0.5 mg/L, and a throughput of 90 samples/hour. It exhibited excellent repeatability (RSD = 2%, n = 10) and low reagent/sample consumption (20 µL each), generating minimal waste (~540 µL per analysis). The validated method showed high accuracy and precision, with results consistent with manual UV-Vis spectrophotometry and manufacturer specifications. The system remained stable and resistant to bubble interference, making it a highly efficient and automated approach for iron quantification in pharmaceuticals.[14]

Quantification by FTIR Method

FTIR spectroscopic method was developed along with a colorimetric method for quantifying barnidipine hydrochloride in bulk drug. The FTIR method is based on the formation of a yellow-colored complex with isoniazid, exhibiting maximum absorption at 456 nm. The FTIR method quantifies barnidipine hydrochloride by measuring the NH stretching band at 3325 cm^{-1}. The methods were statistically validated and demonstrated accuracy, precision, and reproducibility.[4]

Electrochemical and Photometric Analysis

A stable $[Os(tmphen)_3]^{3+}$ (tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline) complex was synthesized in neutral aqueous solution by oxidizing $[Os(tmphen)_3]^{2+}$ with lead(IV) oxide. The complex was characterized using absorption spectroscopy and compared with its ruthenium analog, $[Ru(tmphen)_3]^{3+}$, in terms of stability under pH 7 conditions. The osmium and ruthenium complexes were evaluated as oxidants in a photoluminescence-following electron-transfer (PFET) system for detecting oxidizable pharmaceuticals, specifically acetaminophen. The method exhibited high sensitivity, with a limit of quantification (LOQ) of 30.2 µg/L and a limit of detection (LOD) of 1.5 µg/L. A 2×1-Dimensional Solid Phase Extraction (2×1D SPE) method was developed to selectively isolate acetaminophen from urine samples using methanol concentration and pH adjustments. Acetaminophen was detected in urine samples within a concentration range of 40.41–360.0 µg/L, achieving recoveries above 90%. This method was successfully applied to the

determination of acetaminophen in pharmaceutical formulations, demonstrating its effectiveness in complex sample matrices and potential for clinical and quality control applications.[15]

Chromatographic and Advanced Analytical Techniques

An isocratic RP-HPLC method (Method-A) and two visible spectrophotometric methods (Methods B and C) were developed and validated for estimating Clobazam in bulk and tablet dosage forms. Method-A employed a PEAK chromatographic system with a Zodiac C-18 column (250mm × 4.6mm, 5µm) and a mobile phase of THF, methanol, and acetonitrile (10:30:60 v/v/v). Detection was performed at 227 nm using a UV detector, with integration by PEAK Chromatographic Software v1.06. Methods B and C used Fe(II)-1,10-phenanthroline and ferricyanide-Fe(III) as chromogenic reagents for visible spectrophotometric analysis. All methods were validated following ICH guidelines and applied successfully for Clobazam assay in bulk and tablet formulations.[16]

The spectro-electrochemical properties of 4,7-di(phenothiazine)-1,10-phenanthrolines as ligands for potential metal complexation was also explored.[17] A combination of electrochemical, spectro-electrochemical, and density functional theory (DFT) studies was employed to analyze the impact of broken symmetry in substituted phenothiazine derivatives. The first oxidation step exhibited a reversible color change, marked by the emergence of a new absorption band around 500 nm due to the formation of a phenothiazine radical cation. Additionally, findings revealed that phenothiazine substituents function as two independent yet electronically isolated redox centers. Furthermore, a mechanistic study of oxidation and reduction processes was conducted, complemented by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) for reaction product identification. These insights contribute to the understanding of redox-active phenanthroline derivatives for advanced electrochemical applications.

CONCLUSION

The versatility and sensitivity of 1,10-phenanthroline make it an indispensable tool in pharmaceutical and metal ion analysis. Its ability to form stable, highly colored complexes enables precise spectrophotometric quantification of active pharmaceutical ingredients, impurities, and metal ions in various formulations. The reviewed methodologies demonstrate its broad applicability across UV-Vis spectrophotometry, FTIR, electrochemical analysis, and chromatographic techniques, offering reliable solutions for quality control and research. Innovations such as immobilized sensors and automated flow-injection systems further enhance the efficiency and accuracy of 1,10-phenanthroline-based assays. As pharmaceutical regulations tighten and analytical demands grow, 1,10-phenanthroline remains a cornerstone of modern analytical chemistry, driving advancements in drug analysis, environmental monitoring, and industrial applications. Future research should focus on refining these methodologies and exploring novel applications in emerging fields such as nanotechnology and bioanalytical chemistry.

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