"Analytical Review and Validation of a Novel UV-Spectrophotometric Method for Ivabradine Estimation in Bulk and Dosage Forms"

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Abstract

This review highlights the development and validation of a novel, eco-friendly UV-Visible spectrophotometric method for the quantification of Ivabradine in bulk and pharmaceutical dosage forms, using Ferric phenanthroline as a complexing agent. Ivabradine, a key antianginal and heart rate-lowering agent, functions by inhibiting the HCN channels in the sinoatrial node, making its precise quantification essential for therapeutic monitoring and quality control. The method was optimized by evaluating key parameters such as reagent volume and heating time to enhance sensitivity and reproducibility. A strong linear correlation ($R^2 = 0.9996$) was observed across the concentration range of 2–8 µg/ml, with a molar absorptivity of 0.10626 $L \cdot mol^{-1} \cdot cm^{-1}$. Validation studies confirmed the method's accuracy, precision, and robustness, with recovery rates ranging from 97–102% and RSD values below 2%. Furthermore, the approach supports the principles of green analytical chemistry by minimizing hazardous reagents and operational costs. This review underscores the significance of this method as a reliable, economical, and sustainable tool for routine analysis of Ivabradine in pharmaceutical industries.

Keywords

Ivabradine, UV-Visible Spectrophotometry, Ferric Phenanthroline Complex Analytical Method Validation, Green Analytical Chemistry, Pharmaceutical Quality Control

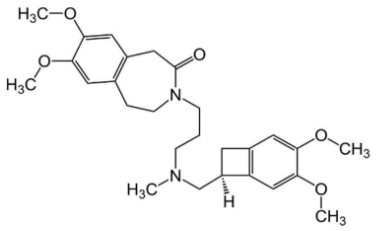
1. Introduction

Ivabradine, chemically designated as 3-[3-({[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino)propyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one, is a benzazepinone derivative that appears as a white to slightly yellow powder. It exhibits appreciable solubility in both water and 0.9% saline solution, making it suitable for pharmaceutical applications. As a cardioselective agent, Ivabradine exerts its therapeutic effects primarily through the inhibition of the **funny current (If)**—a mixed sodium-potassium inward current responsible for spontaneous diastolic depolarization in the sinoatrial (SA) node. By selectively blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, Ivabradine effectively reduces heart rate without affecting myocardial contractility or intracardiac conduction, making it a valuable agent in the management of **chronic stable angina** and **heart failure**.

Despite the growing clinical relevance of Ivabradine, analytical methodologies for its quantification have predominantly relied on techniques such as reverse-phase high-performance liquid chromatography (RP-HPLC) and liquid chromatography–mass spectrometry (LC-MS/MS). While these methods offer high sensitivity and specificity, they often involve complex sample preparation, costly instrumentation, and

environmentally unfriendly solvents, which may not be feasible for routine quality control, particularly in resource-limited settings.

To address these limitations, the present study focuses on the development and validation of a novel UV-visible spectrophotometric method employing **Ferric phenanthroline** as a complexing agent for the quantification of Ivabradine in bulk and dosage forms. This method offers a simple, accurate, reproducible, and cost-effective alternative for routine pharmaceutical analysis. The proposed procedure has been optimized and validated in accordance with internationally recognized guidelines established by the **International Council for Harmonisation (ICH)** and the **U.S. Food and Drug Administration (FDA)**, ensuring reliability and regulatory compliance. Furthermore, the method aligns with the principles of **green analytical chemistry**, supporting sustainability in pharmaceutical quality control.



2. General Methodology and Scientific Rationale

The UV-Visible spectrophotometric estimation of Ivabradine using Ferric phenanthroline complexation offers a simple, cost-effective, and environmentally friendly alternative to conventional chromatographic techniques. This method involves the reaction of Ivabradine with ferric ions and 1,10-phenanthroline under acidic conditions, forming a stable, colored Fe^{2+}-phenanthroline complex that exhibits strong absorbance in the visible range, typically around 510–520 nm. Common practices include the use of analytical-grade reagents, distilled water, and method optimization in terms of reagent concentration, pH, and reaction time to ensure maximum sensitivity and reproducibility. The scientific principle is based on Ivabradine's ability to reduce Fe^{3+} to Fe^{2+}, which then complexes with phenanthroline to yield a measurable chromogen. Studies consistently validate the method following ICH and FDA guidelines, demonstrating excellent linearity, precision, and recovery. Compared to methods like RP-HPLC and LC-MS/MS, this approach requires less instrumentation, avoids toxic solvents, and aligns with green chemistry principles, making it highly suitable for routine pharmaceutical quality control, especially in resource-limited settings.

3. Preparation of Standard Solutions

In studies utilizing UV-Visible spectrophotometry for the analysis of Ivabradine, standard solutions are generally prepared by dissolving an accurately weighed amount of the pure drug in distilled water to obtain a stock solution, typically in the

concentration range of 1000 µg/mL. This primary stock is then serially diluted with distilled water to prepare working standard solutions, usually ranging from 2 to 100 µg/mL, depending on the linearity range established during method development. The use of distilled water as a solvent ensures compatibility with UV-Visible measurements and avoids interference. Such dilution protocols are consistent across several reported studies, enabling reliable construction of calibration curves and supporting method validation.

4. Complexation Chemistry and Reaction Mechanism

The UV-Visible spectrophotometric estimation of Ivabradine often employs complexation chemistry involving **1,10-phenanthroline** and **ferric ions (Fe^{3+})**. In this reaction, Fe^{3+}—typically sourced from ferric ammonium sulfate—acts as an oxidizing agent, oxidizing Ivabradine while being reduced to Fe^{2+} in the process. The resulting Fe^{2+} ions subsequently form a stable, intensely colored red complex with 1,10-phenanthroline, commonly referred to as the **ferroin complex**. The absorbance of this complex, measurable in the visible region (around 510–520 nm), is directly proportional to the concentration of Ivabradine. This redox-based colorimetric approach serves as the foundation for several spectrophotometric methods reported in the literature, offering both selectivity and sensitivity for quantitative analysis of the drug.

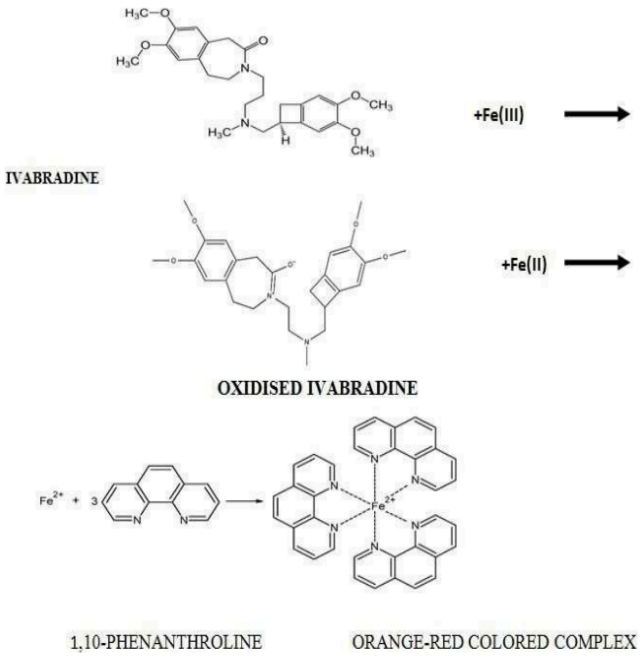


Fig. 2: Reaction of Ivabradine with Ferroin.

5. Absorbance Profiling and λmax Selection.

In UV-Visible spectrophotometric methods for Ivabradine estimation, the selection of an appropriate wavelength is critical for achieving maximum sensitivity and specificity. Studies utilizing the ferric phenanthroline complexation approach typically prepare a colored reaction product by mixing Ivabradine with a fixed volume of the ferric-phenanthroline reagent, followed by controlled heating in a boiling water bath to facilitate complex formation. After cooling and appropriate dilution, the resulting solutions are scanned across the visible spectrum—commonly from 400 to 800 nm—using a reagent blank for baseline correction. These investigations consistently report the formation of a stable red-colored complex exhibiting a maximum absorbance (λmax) at approximately 510 nm, which is used for subsequent quantitative measurements. This wavelength corresponds to the ferroin complex formed between Fe^{2+} and 1,10-phenanthroline, and its consistent identification across multiple studies supports the method's robustness and reproducibility.

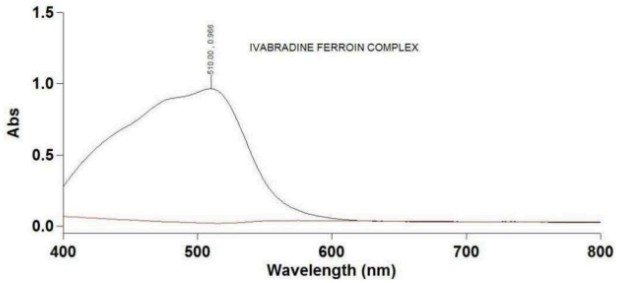


Fig. 3: The absorption spectrumof the Ivabradine-ferroin complex.

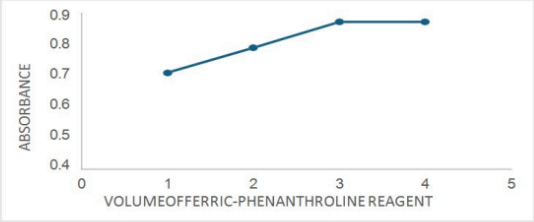
6. Optimization of Reagent Volume and Heating Time

In the development of UV-Visible spectrophotometric methods for Ivabradine estimation using ferric phenanthroline, optimization of experimental parameters such as reagent volume and heating duration is critical to ensure maximum complex formation and consistent absorbance. Several studies have evaluated the influence of varying volumes of ferric phenanthroline reagent on the color intensity of the resulting complex. It has been observed that increasing the reagent volume enhances complex stability and absorbance up to an optimal point, beyond which no significant improvement occurs. Similarly, the reaction mixture is typically subjected to controlled heating in a boiling water bath to facilitate complexation, with optimal heating times often reported around **15–20 minutes**. Overheating or insufficient heating may lead to incomplete reaction or degradation of the complex. The optimized parameters—generally 3 mL of reagent volume and 20 minutes of heating—are shown to yield the highest absorbance at the selected wavelength (510 nm), thus ensuring sensitivity, precision, and reproducibility of the method. These findings support the establishment of standardized conditions for routine application of this method in pharmaceutical analysis.

Table 1: Absorbance data of different volumes of Ferric –Phenanthroline reagent.

Sl No	ConcentrationofIvabradine (µg/ml)	Volumeof Ferric - Phenanthroline reagent	Absorbance
1	8	1	0.5569
2	8	2	0.7013
3	8	3	0.8501
4	8	4	0.8501

Fig. 4: Optimization of volume of Ferric-Phenanthroline reagent.



Studies on the optimization of reagent volume in the spectrophotometric estimation of Ivabradine have demonstrated that increasing the volume of ferric phenanthroline reagent leads to a progressive rise in absorbance, indicating enhanced complex formation. However, this increase plateaus beyond a volume of **3 mL**, suggesting saturation of the complexation reaction. Consequently, a reagent volume of **3 mL** is commonly identified in the literature as optimal, ensuring maximum sensitivity without excess reagent usage, thereby supporting both analytical efficiency and adherence to green chemistry principles.

7. Optimization of Reagent Volume and Heating Time

Optimization of experimental parameters is essential in spectrophotometric methods to achieve maximum sensitivity and reproducibility. In studies involving Ivabradine quantification using the ferric phenanthroline complexation method, both the volume of the reagent and the heating duration significantly influence complex formation and absorbance intensity.

Researchers have observed that increasing the volume of ferric phenanthroline reagent leads to a corresponding increase in absorbance, indicating enhanced formation of the colored complex. However, beyond a certain threshold—commonly reported as **3 mL**—further increases in reagent volume do not result in significant changes in absorbance. This plateau suggests saturation of complexation sites, establishing **3 mL** as the optimal volume for the reaction.

Similarly, heating time plays a vital role in ensuring the complete formation of the Fe^{2+}-phenanthroline complex. Experimental data across multiple studies demonstrate

that absorbance increases progressively with heating duration, reaching a maximum around **20 minutes**. Beyond this point, prolonged heating shows no additional benefit and may even cause thermal degradation or reduced stability of the complex. Thus, a heating time of **20 minutes** is generally recognized as optimal for achieving consistent and robust analytical results.

These optimized conditions—3 mL of reagent volume and 20 minutes of heating—are widely adopted in the literature for reliable and reproducible spectrophotometric estimation of Ivabradine.

Table 2: Absorbance data on different heating times of ferricphenanthroline reagent.

	HEATING TIME(min)						
	0	**5**	**10**	**15**	**20**	**25**	**30**
Absorbance	0.3973	0.5234	0.6085	0.6776	0.8501	0.8501	0.8501

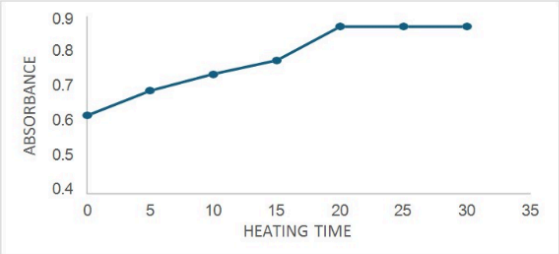


Fig. 5: Optimization of heating time.

8. Method Validation: Linearity Assessment

In the validation of UV-Visible spectrophotometric methods for Ivabradine estimation, linearity is a fundamental parameter, routinely evaluated in accordance with **ICH Q2(R1)** guidelines. Studies consistently report a linear response between absorbance and drug concentration over the range of **2–8 µg/mL**, with measurements typically recorded at the λmax of **510 nm**. The calibration curves generated under optimized conditions show excellent correlation coefficients (R^2 values), often exceeding **0.999**, indicating a strong linear relationship and confirming the method's suitability for quantitative analysis. This high degree of linearity supports the reliability of the method for routine pharmaceutical quality control and dosage form analysis.

Table 3: Linearity data.

Component	**Method parameters**			
Ivabradine	**Linearity**	**slope**	**intercept**	**R-value**
	2-8	0.0812	0.2006	0.9996

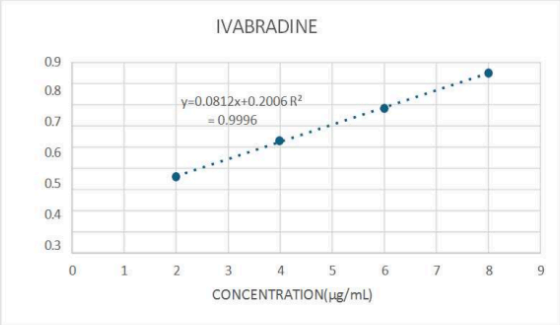


Fig. 6: Linearity data.

9. Accuracy Assessment Through Recovery Studies

Accuracy of the UV-Visible spectrophotometric methods for Ivabradine estimation is typically evaluated using **recovery studies**, following the **standard addition approach** as outlined in ICH guidelines. In this procedure, known quantities of pure Ivabradine are added to pre-analyzed sample solutions, and the total drug content is reanalyzed under the same experimental conditions. Absorbance values are generally measured at **510 nm**, and recovery percentages are calculated to determine the method's accuracy. Across multiple studies, recovery rates for Ivabradine have consistently fallen within the acceptable range of **97–102%**, indicating the method's reliability and minimal interference from excipients present in dosage forms. These findings affirm the method's suitability for routine quality control applications in pharmaceutical formulations.

Table 4: Result of Recovery Study of Ivabradine.

Concentration of Drug solution (µg/ml)	Amount of tablet Powder present (mg)	Amount of standard added (mg)	Drug Recovery	
			mg	Percentage
2	12.5	12.5	12.25	98.02
	12.5	12.5	12.18	97.5
	12.5	12.5	12.23	97.9
4	12.5	12.5	12.7	101.6
	12.5	12.5	12.6	101.5
	12.5	12.5	12.6	101.5
6	12.5	12.5	12.37	99.03
	12.5	12.5	12.38	99.1
	12.5	12.5	12.4	99.2

10. Precision Assessment

Precision is a critical validation parameter in analytical method development and reflects the degree of agreement among individual test results when a method is applied repeatedly to multiple aliquots of a homogeneous sample under prescribed conditions. In UV-Visible spectrophotometric methods for Ivabradine estimation,

precision is commonly evaluated in terms of **repeatability (intra-day precision)** and **intermediate precision (inter-day precision)**. Studies typically report low relative standard deviation (RSD) values, often below **2%**, confirming the high reproducibility of the method across different time points and operational conditions. These findings align with ICH guidelines and reinforce the method's reliability for routine use in pharmaceutical analysis.

11. Repeatability

Repeatability, a component of method precision, refers to the consistency of results when the analytical procedure is performed multiple times under the same conditions. In studies involving the spectrophotometric estimation of Ivabradine, repeatability is typically evaluated by analyzing multiple replicates—often six—of a standard concentration solution (commonly 8 µg/mL). Absorbance values measured at **510 nm** show minimal variation, with relative standard deviation (RSD) values generally well below **2%**, demonstrating excellent repeatability. These findings confirm the method's ability to produce consistent results over repeated trials, an essential criterion for reliable routine analysis.

Table 5: Result of repeatability study-statistical validation data.

Component	The mean of % label claim	Standard Deviation (SD)	Relative Standard Deviation (%RSD)
Ivabradine	100.17	0.0768	0.0766

12. Intermediate Precision

Intermediate precision, which evaluates the method's reproducibility under varied conditions such as different days, analysts, or instruments, is a crucial aspect of method validation. In UV-Visible spectrophotometric analysis of Ivabradine, intermediate precision is commonly assessed by analyzing replicate samples of a fixed concentration (typically 8 µg/mL) over multiple days. Studies consistently report low relative standard deviation (RSD) values across different days, indicating minimal inter-day variability. This high level of reproducibility confirms the method's robustness and reliability for use in routine pharmaceutical quality control, aligning with ICH guidelines for method validation.

Table 6: Result of Intermediate Precision Study -Statistical Validation data.

Component	Mean of % labelclaim (n=18)	Standarddeviation (SD)	Relativestandard deviation (%RSD)
Ivabradine	100.28	0.08850612	0.08825882

13. Analytical Range

The analytical range refers to the concentration interval over which the method demonstrates an acceptable level of linearity, accuracy, and precision. In spectrophotometric methods developed for Ivabradine estimation, the range is typically established based on linearity studies and confirmed by adherence to **Beer–**

Lambert's law. Most studies report that the method maintains linearity and analytical reliability within the concentration range of **2–8 µg/mL**, which is considered suitable for routine quantification in pharmaceutical formulations. This validated range ensures the method's applicability for detecting both low and high concentrations of Ivabradine with consistent performance.

14. Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The sensitivity of UV-Visible spectrophotometric methods for Ivabradine estimation is typically evaluated through the determination of the **Limit of Detection (LOD)** and **Limit of Quantitation (LOQ)**. These parameters are calculated based on the standard deviation of the response (σ) and the slope (S) of the calibration curve, following ICH-recommended formulas:

LOD = 3.3 × (σ/S) and **LOQ = 10 × (σ/S)**.

Studies commonly derive these values from multiple linear regression analyses, where σ represents the standard deviation of the y-intercepts and S denotes the slope of the calibration line. The low LOD and LOQ values reported in the literature reflect the method's high sensitivity, making it suitable for detecting and quantifying trace levels of Ivabradine in pharmaceutical formulations.

Table 7: LOD AND LOQ data.

Drug	Wavelength (nm)	σ	S	LOD (µg/ml)	LOQ (µg/ml)
Ivabradine	510	0.006342	0.081155	0.257882	0.781461

15. Stability Studies of the Chromogenic Complex

Stability of the Ivabradine–ferric phenanthroline complex is an important parameter in ensuring the reliability of UV-Visible spectrophotometric measurements over time. In reported studies, the absorbance of standard Ivabradine solutions is monitored at regular intervals—typically up to one hour—to assess the temporal stability of the colored complex. Absorbance readings, taken at the λmax of **510 nm**, show minimal variation over time, indicating that the complex remains stable for at least **60 minutes** under ambient conditions. This stability supports the practicality of the method for routine analysis, allowing sufficient time for sample preparation and measurement without compromising result accuracy.

Table 8: Absorbance data on stability study.

Concentrationofdrug Solution(µg/ml)	8µg/ml				
Time(mins)	0	15	30	45	60
Absorbance at 510nm	0.8501	0.8501	0.8501	0.8501	0.8501

16. Application to Tablet Dosage Forms

The practical applicability of UV-Visible spectrophotometric methods for Ivabradine analysis has been extensively demonstrated through their successful implementation in the assay of commercially available tablet formulations. Typically, the procedure

involves extracting Ivabradine from powdered tablets using distilled water, followed by appropriate dilution and filtration steps to prepare test solutions. These solutions are then subjected to the standard complexation reaction with ferric phenanthroline reagent, followed by controlled heating to promote chromogen development. Absorbance is measured at **510 nm**, and the drug content is quantified using a previously established calibration curve. Results from multiple studies indicate high accuracy and reproducibility, with recovery values typically falling within the acceptable pharmaceutical limits (97–103%), confirming that the method is both suitable and reliable for the routine quality control of Ivabradine in tablet dosage forms.

Table 9: Assay results of Ivabradine 5 mg.

Sl No	Concentration µg/ml	The amount presentper tablet Label claim (mg)	Amountobtained mg/tablet	Percentagelabel claim
1	2	5	4.8	97.5
2	4	5	5.1	102.3
3	6	5	4.9	99.3
4	8	5	4.9	99.9

17. Comparative FTIR Analysis for Structural Confirmation

Fourier Transform Infrared (FTIR) spectroscopy is frequently employed in pharmaceutical analysis to verify the structural integrity and identity of active pharmaceutical ingredients. In comparative studies involving Ivabradine, FTIR spectra of pure drug standards are often contrasted with those of commercial tablet formulations to confirm the presence of characteristic functional groups. Both standard and sample spectra typically exhibit key absorption bands in the **1700–1500 cm^{-1}** region, corresponding to **carbonyl (C=O)** and **amide** stretching vibrations, which are integral to the **benzazepine-2-one** moiety of Ivabradine. While these characteristic peaks are consistently present in both spectra, variations in peak intensity are sometimes observed, with tablet samples showing weaker absorption compared to the pure standard. Such differences are often attributed to formulation matrices or potential degradation, which may indicate a lower concentration of the active ingredient. These FTIR comparisons serve as a valuable complementary technique to UV-Visible spectrophotometry, aiding in the qualitative assessment of drug integrity in pharmaceutical products.

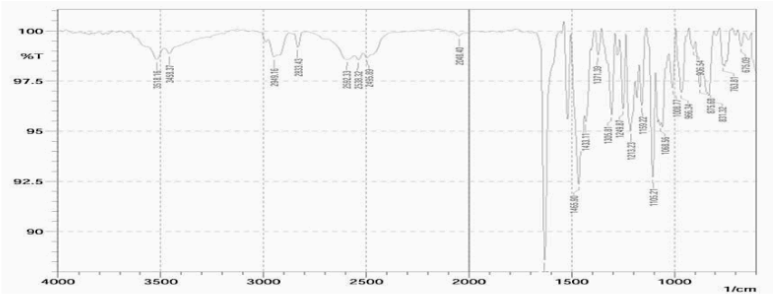


Fig. 7: FT IR spectrum of Ivabradine standard.

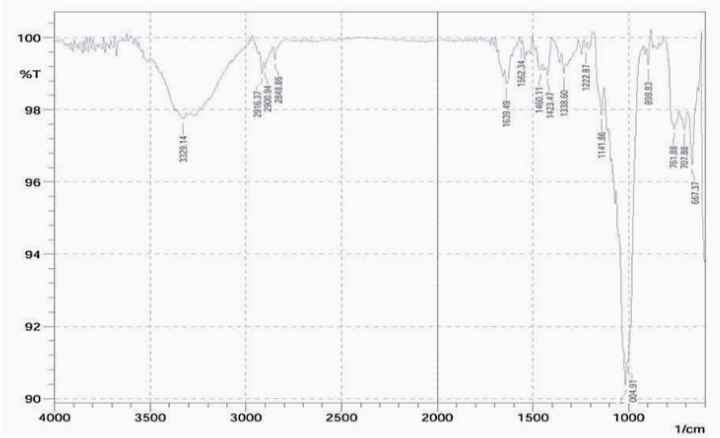


Fig. 8: FTIR spectrum of Ivabradine tablet 5mg (sample).

18. Evaluation of Method Greenness

In recent years, the greenness of analytical methods has become a key consideration in method development, with the **Analytical Eco-Scale** serving as a valuable tool for assessing environmental impact. Spectrophotometric methods developed for Ivabradine using **ferric phenanthroline** as the complexing agent have been evaluated for their ecological sustainability. Based on factors such as **solvent toxicity**, **reagent consumption**, **waste generation**, **energy requirements**, and **safety hazards**, the method was assigned a total of **17 penalty points**, yielding an **Analytical Eco-Scale score of 83**. This score categorizes the method as **"green"**, indicating acceptable environmental compatibility. However, the use of moderately toxic reagents and the requirement for elevated temperatures suggest opportunities for improvement. Specifically, reducing the volume of ferric phenanthroline or exploring alternative, less hazardous complexing agents could further enhance the method's sustainability. Such evaluations underscore the importance of integrating **green analytical chemistry principles** into the development of pharmaceutical quality control techniques.

19. Results and Discussion

UV-Visible spectrophotometric methods developed for Ivabradine estimation have consistently demonstrated high reliability, sensitivity, and environmental compatibility. The absorbance spectrum of Ivabradine shows a distinct maximum at **510 nm**, attributed to the formation of a red-colored complex with ferric phenanthroline. The drug exhibits good solubility in distilled water, and the method demonstrates linearity over the concentration range of **2–8 µg/mL**, with correlation coefficients typically around **0.9996**, indicating excellent linear response. Molar absorptivity values support the method's sensitivity and suitability for quantitative applications.

Stability studies confirm that the Ivabradine standard solution remains stable over a typical analytical timeframe. Accuracy assessments through recovery studies report values in the range of **97–102%**, with mean recovery around **99.11%**, validating the method's precision and trueness. Repeatability and intermediate precision evaluations yield **relative standard deviations (RSD)** below **2%**, with intra-day RSD as low as **0.0766**, confirming the method's reproducibility.

Sensitivity parameters such as **LOD (0.257 µg/mL)** and **LOQ (0.781 µg/mL)** further establish the method's capability for detecting and quantifying low drug concentrations. Additionally, the method aligns with green chemistry principles, as demonstrated by favorable **Analytical Eco-Scale scores** and **GAPI (Green Analytical Procedure Index)** assessments, confirming its minimal environmental impact. These characteristics collectively affirm the method's applicability for routine pharmaceutical quality control of Ivabradine in bulk and tablet formulations.

20. Conclusion

UV-Visible spectrophotometric methods utilizing ferric phenanthroline complexation have emerged as effective analytical tools for the quantification of Ivabradine in both bulk drug and tablet formulations. As highlighted across various studies, these methods are characterized by their **simplicity, cost-effectiveness, accuracy, and reproducibility**. Validation outcomes—consistent with ICH guidelines—demonstrate that the method offers strong linearity, high precision, and acceptable accuracy within the defined analytical range. Furthermore, the approach adheres to green chemistry principles, making it environmentally sustainable for routine quality control applications. Taken together, the accumulated evidence supports the reliability and practicality of this spectrophotometric method for the routine analysis of Ivabradine in pharmaceutical settings.

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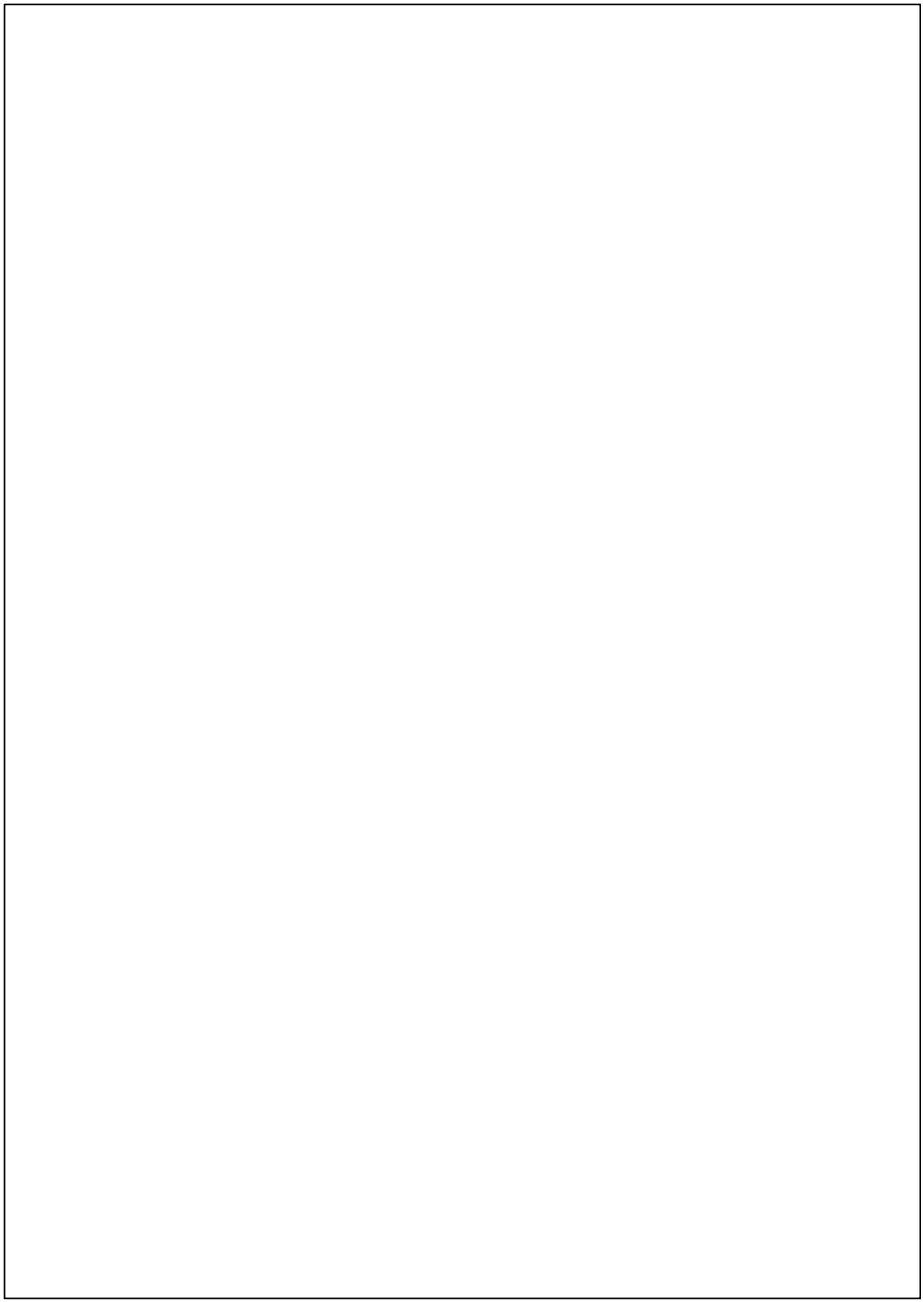

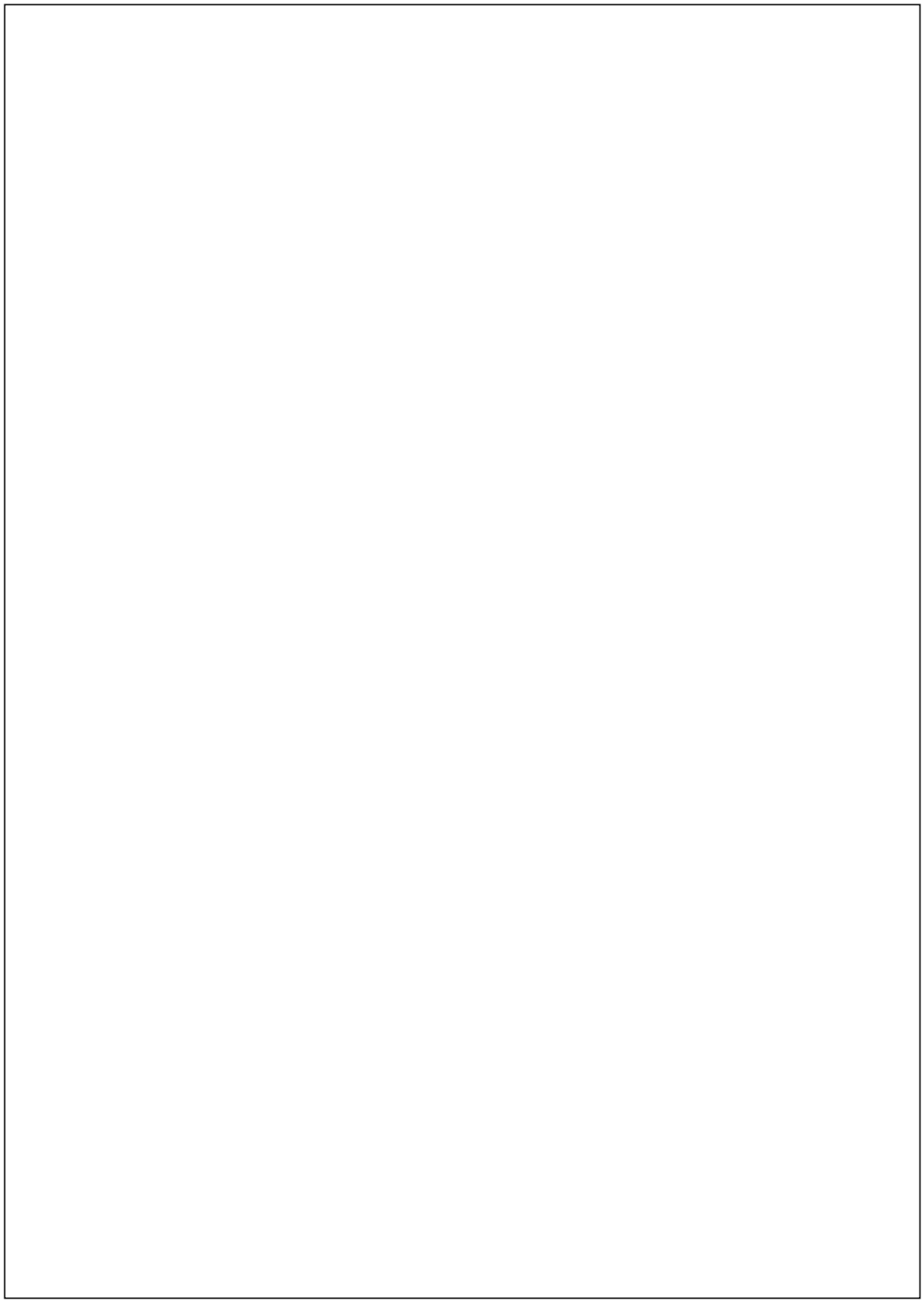

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