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Original Research Article

Quantitative estimation of hydroxychloroquine sulphate in pharmaceutical dosage form by FT-IR spectroscopy

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ABSTRACT

Background: A novel, cost-effective infrared spectroscopic method has been developed for the quantitative estimation of hydroxychloroquine sulphate in bulk and tablet dosage forms.

Materials and Methods: The analysis was performed using attenuated total reflectance (ATR) sampling method in FTIR.

Results: The linearity range of the proposed methods were determined to be in the range of 5-45 μg. The percent assay by proposed methods were found to be 100.01±0.0008. Te recoveries from the proposed methods were found to be 99.90 ± 0.008 (by area method) and 100.09 ± 0.007 (by absorption intensity method). The proposed methods were successfully applied for the determination of hydroxychloroquine sulphate in pharmaceutical tablets The proposed methods were validated according to the guidelines set by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Conclusion: The results demonstrated that the proposed methods are accurate, precise, and reproducible (with a relative standard deviation of less than 2 %). Additionally, these methods are simple, cost-effective, and requires less time compared to other available methods. They can be effectively utilized for the estimation of hydroxychloroquine sulphate in various dosage forms.

1. Introduction

In the field of pharmaceutical sciences, Fourier Transform Infrared Spectroscopy (FTIR) has emerged as a powerful analytical technique. The IR region (4000 cm^{-1} to 400 cm^{-1}) of the FTIR spectrum provides valuable insights into the structural characteristics of functional groups present in the analyte, making it a well-established method for analyzing organic compounds.[1–7] The absorption of energy at specific wavelengths is directly proportional to the number of bonds absorbing the corresponding energy quanta, enabling quantitative analysis using FTIR. Consequently, higher analyte concentrations result in increased energy absorption.[8–12]

FTIR technology enables simultaneous examination of multiple elements within a single sample through continuous monitoring of the spectral baseline. Both qualitative and quantitative analyses can be performed using FTIR. The objective of this study was to develop, validate, and apply a reliable, cost-effective, and straightforward infrared spectroscopy method for routine quantitative determination of hydroxychloroquine sulphate in pharmaceutical products.[13–15]

The global spread of the novel beta coronavirus SARS-CoV-2, leading to the outbreak of Coronavirus Disease

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2019 (COVID-19), has prompted the search for effective treatments.[16,17] One approach has been the repurposing of approved drugs originally developed for different diseases. Among the options explored, the anti-malarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) have emerged as potential treatments for COVID-19. These drugs have gained attention due to their long-standing usage, established dosages, known safety profiles, adverse effects, and drug interactions. Under pressure to provide antiviral treatment options during the pandemic, the FDA approved the use of CQ and HCQS for treating COVID-19.[17,18] Due to the renewed interest in hydroxychloroquine sulphate during the COVID-19 era, we selected this drug for further investigation.

Hydroxychloroquine sulphate[19–21] (HCQS), with the chemical formula $C_{18}H_{26}ClN_3O.H_2SO_4$, is a solid, crystalline compound with CAS No. 747-36-4 (Figure 1). The first synthesis of this compound occurred in 1946 by introducing a hydroxy group to the parent compound, chloroquine, to reduce toxicity. HCQS belongs to the larger class of 4-amino quinolones and possesses antimalarial activity.[22–25] While HCQS was primarily developed as an antimalarial drug, it also exhibits various pharmacological properties. Its well-known anti-inflammatory effects have made it effective in treating conditions such as lupus erythematosus and rheumatoid arthritis. HCQS is an analogue of CQ, with one of the N-ethyl substituents being hydroxylated. Due to its lower ocular toxicity compared to CQ, HCQS is preferred when higher dosages of medication are required for malaria treatment. The present study aimed to contribute to the quality control analysis of this drug.[26–33]

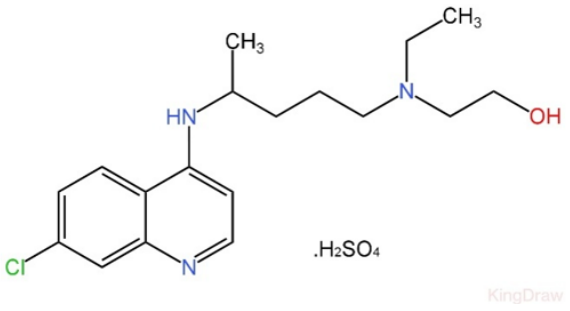

Figure 1: Chemical structure of Hydroxychloroquine Sulphate

The development of effective analytical techniques plays a critical role in ensuring the quality of pharmaceuticals available in the market by providing precise information about the composition and characteristics of the materials under investigation.

Infrared (IR) spectroscopy is a rapid, cost-effective, and non-destructive method for obtaining qualitative and quantitative data. It eliminates the need for hazardous chemicals and can be utilized by minimally trained personnel. The introduction of Fourier transform (FT) instruments and sensors has significantly enhanced the repeatability of IR spectroscopy. In particular, IR spectroscopy is highly sensitive in detecting specific functional groups in polymers. Functional groups such as hydroxy, amine, and carbonyl can be readily identified, especially in hydrocarbon polymers like polystyrenes and polyenes. IR spectroscopy is also valuable in studying reactions that modify the functional groups of polymers, allowing for quick assessment of reaction efficiency. Moreover, these procedures are advantageous over chromatographic methods found in literature and pharmacopoeias as they avoid interference from excipient matrices. Furthermore, they eliminate the need for laborious processes such as chemometric analysis, multivariate analysis, or internal standards. As a result, IR spectroscopy holds great potential for routine quantitative analysis of pharmaceuticals in the pharmaceutical industry.[34–41].

Based on the review of existing literature, no method utilizing infrared spectroscopy has been reported for the determination of related substances in specific drugs. Therefore, it is deemed necessary to develop a precise, accurate, and straightforward validation method for the quantification of related substances in the specific drug. The objective of this research was to design, validate, and apply a quantitative routine infrared (IR) spectroscopic method for the determination of hydroxychloroquine sulphate in pharmaceutical products. In this study, two methods, namely the area under curve method (Method I) and the absorptive intensity method (Method II), were developed for the analysis of hydroxychloroquine sulphate drug. The method aimed to be accurate, cost-effective, rapid, and simple in its implementation.

2. Experimental Section

An ALPHA-II E FT-IR Spectrometer (Bruker) connected to a computer was employed for the experimental measurements. The spectrometer was equipped with a spectral band for data acquisition. All sample weights were measured using an electronic balance.

3. Materials and Methods

3.1. Chemicals and reagents

Pharmaceutical grade Hydroxychloroquine Sulphate standard was obtained as generous gift from Wallace Pharmaceuticals Pvt Ltd, Mumbai, Maharashtra, India.

3.2. Instruments

Opus/IR, FT-IR Spectroscopy Software Package Version 8.0 with the ATR accessory capable of handling solids, liquids, semi-solid, paste, powder, viscous sqample without sample

preparation, ECO-ATR and with the crystal ZnSe.

Weighing balance: Shimadzu AUX220 and Analytical Balance.

3.3. Analysis of solid samples (using IR Grade KBr)

3.3.1. Sample preparation

To prepare the samples, 5 different concentrations of 5, 15, 25, 35, and 45 μg% of API Hydroxychloroquine Sulphate were created. This was achieved by adding 5, 15, 25, 35, and 45 mg of API Hydroxychloroquine Sulphate to 95, 85, 75, 65, and 55 mg of KBr powder, respectively, in a glazed mortar. The mixture was thoroughly mixed with a pestle to ensure homogeneity. Subsequently, the samples were dried in a hot air oven at 60 °C for 15 minutes to obtain a dried, fine powder mixture. These samples were used for quantitative measurements. Each mixture, containing 5 μg, 15 μg, 25 μg, 35 μg, and 45 μg of API Hydroxychloroquine Sulphate, was subjected to FT-IR analysis. The standard curve was constructed by plotting the area values and absorptive values of API Hydroxychloroquine Sulphate, calculated using the baseline technique, against the corresponding concentrations. Figure 2 shows the spectra for plain Hydroxychloroquine, laboratory mixture of hydroxychloroquine and marketed mixture of hydroxychloroquine.

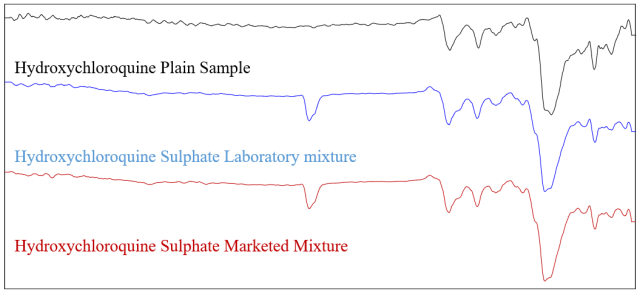

Figure 2: IR Spectra for Hydroxychloroquine sulphate

4. IR Spectroscopic Method Development

A tablet formulation containing hydroxychloroquine sulphate (HCQS) was obtained from the market for the purpose of this study.

5. Selection of Wavenumber and Absorption intensity

The working standard of hydroxychloroquine sulphate API (25 μg) was prepared according to the previously mentioned procedure. The API was scanned using infrared spectroscopy in the wavelength range of 4000-600 $cm^{-1}$with a spectral resolution of 2 cm^{-1}, and the resulting spectrum was recorded. The analysis of the spectra revealed the presence of characteristic peaks corresponding to hydroxychloroquine sulphate at wave numbers of 1660.23 cm^{-1}, 1444.54 cm^{-1}, 1138.21 cm^{-1}, and 2360.22 cm^{-1} in the functional group region of the pure drug spectrum.

6. Method I- Area Under Curve

The working standard of hydroxychloroquine sulphate API (25 μg) was subjected to scanning in the range of 4000-600 cm^{-1}, and the resulting spectra were recorded for the area under curve method. The wave numbers within the range of 2398.60-2258.60 cm^{-1}were selected for the estimation of hydroxychloroquine sulphate based on the area under the curve (Figure 3).

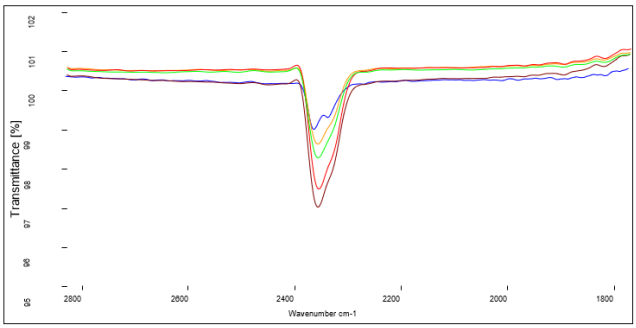

Figure 3: Overlay of selected peak area atdifferent concentration of Hydroxychloroquine sulphate.

7. Method II- Absorptive Intensity

The working standard of hydroxychloroquine sulphate API (25 μg) was scanned in the range of 4000-667 cm-1, and the resulting spectra were recorded for the absorptive intensity method. The wave numbers within the range of 2398.60-2258.60 cm-1 were selected for the estimation of hydroxychloroquine sulphate based on the absorptive intensity. At a wave number of 2361.216 cm-1, an absorptive intensity in the range of 0.998-0.999 was observed, as shown in

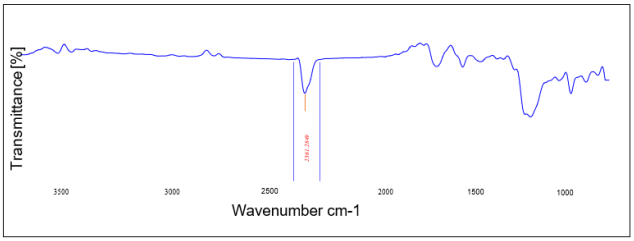

Figure 4: Peak of Hydroxychloroquine sulphateby Method II.

8. Assay of Pharmaceutical Products

The validated IR spectroscopy method was utilized for the quantitation of hydroxychloroquine sulphate in tablets (HCQS IP tablets 200 mg). The results were obtained by

comparing the spectroscopy measurements of the marketed sample with those obtained from API hydroxychloroquine sulphate standard mixtures at the same concentration levels, using both the area and absorptive intensity. The recorded spectra of the marketed sample are shown in Figure 5. The results for the marketed sample are shown in Table 1 .

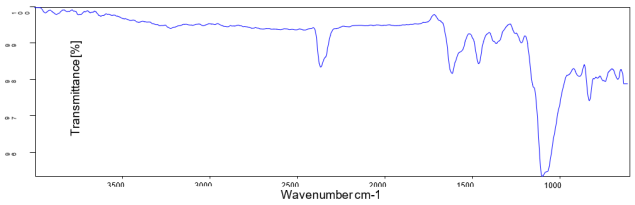

Figure 5: Recorded IR spectra of marketed mixture

8.1. Marketed sample

8.1.1. Method I and II

8.2. Method validation

8.2.1. Linearity

The linearity of the proposed method was assessed by analyzing five individual samples of the drug in the concentration range of 5-45 μg. The obtained data was subjected to regression analysis to determine the linearity characteristics of the proposed methods. The plot of area Vs Concentration and Absorption intensity Vs concentration are shown in Figure 5a and 5b respectively.

8.2.2. Accuracy

Accuracy was evaluated by calculating the percentage relative standard deviation (%RSD) and mean percentage recovery. To further validate the accuracy of the developed assay method, a standard addition method was performed. In this study, pre-analyzed marketed sample equivalent to 25mg hydroxychloroquine sulphate powder was weighed, to it different amount of pure drug 8 mg, 10mg, and 12 mg of API Hydroxychloroquine Sulphate were added and the percent recovery determined. Results of recoveries study are shown in Table 2.

8.2.3. Method I and Method II

8.3. Precision

Repeatability was assessed by preparing and analyzing the same drug concentration from the marketed sample that content equivalent 25 mg of API hydroxychloroquine sulphate, which was obtained from a marketed mixture. Inter-day and intra-day variations were considered to determine the precision of the proposed method. The drug concentrations equivalent to 25 mg API hydroxychloroquine sulphate sample were prepared and studied at three different time points within a day to

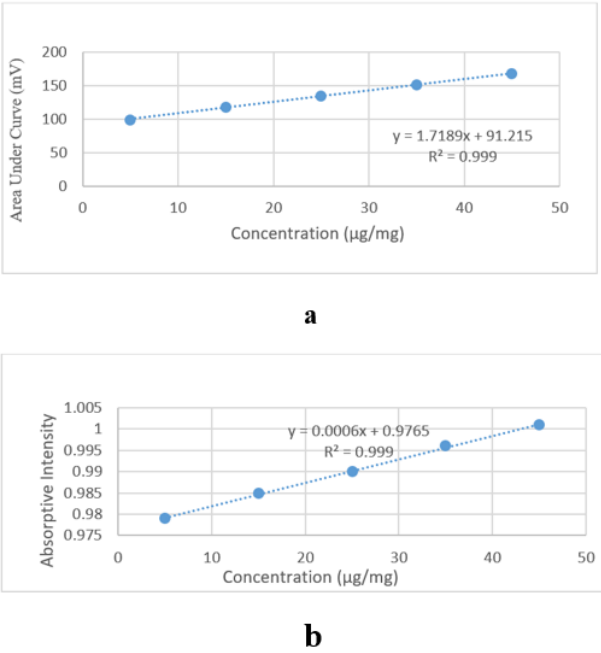

Figure 6: a: Calibration curve of Hydroxychloroquine sulphate for Method I. **b:** Calibration curve of Hydroxychloroquine sulphate for Method II

evaluate intra-day variation. The samples were then studied again on the following day to assess inter-day variation, following the same protocol (n = 15). The analysis was performed for both the area and absorptive intensity of the samples. The relative standard deviation (%RSD) of the concentrations, obtained from the regression equation, was used as a measure of precision. The results of intraday and inter day study are shown in Table 6

8.4. Limit of detection (LOD and limit of quantification LOQ)

The LOD and LOQ of marketed hydroxychloroquine sulphate by the proposed method were determined using calibration standards. LOD and LOQ were calculated as 3.3σ/S and 10σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of y-intercept of regression equation.

9. Discussion 1 Method Development

Existing methods for the determination of hydroxychloroquine sulphate are associated with drawbacks such as the need for expensive equipment, the use of multiple solvents, and time-consuming procedures. In this research, we aimed to develop a cost-effective, simple, and environmentally friendly method using infrared spectroscopy for the quantification of hydroxychloroquine sulphate in tablets. The H-SO4- stretching band between

Table 1: Observation and results of assay of marketed sample

Sr. no.	Wt. of marketed sample taken (mg)	Method I (Peak Area) (mV)	Method II (Peak Intensity)	Amount of drug estimated in weighed marketed sample (mg)		Percent Assay	
				Method I (Peak Area)	Method II (Peak Intensity)	Method I (Peak Area)	Method II (Peak Intensity)
1	38.64	139.98	0.999	25.03	25.09	100.09	100.03
2	38.60	139.883	0.997	25.01	25.04	100.01	100.10
3	38.67	139.751	0.995	25.9	24.98	99.92	99.89
					Mean	100.01	100.01
					±SD	0.0007	0.0008
					%RSD	0.0850	0.1069

Table 2: Observation and results of recovery study of sample

Sr. no.	Wt. of marketed sample taken (mg) + amount of pure drug added (mg)	Method I (Peak Area) (mV)	Method II (Peak Intensity)	Amount of pure drug recovered (mg)		Percent Recovery	
				Method I (Peak Area)	Method II (Peak Intensity)	Method I (Peak Area)	Method II (Peak Intensity)
1	38.64+8	146.76	0.995	7.91	8.09	98.88	101.12
2	38.60+10	156.43	0.998	10.09	9.99	100.9	99.9
3	38.67+12	165.92	1.001	11.99	11.91	99.92	99.25
					Mean	99.9	100.09
					±SD	0.0083	0.0077
					%RSD	1.0112	0.9485

Table 3: Observation and results of LOD and LOQ of sample

Sr. No.	Limit od Detection and Limit of Quantitation study	μg/mg	
		By Area	By Absorptive intensity
1	LOD	5.67	6.26
2	LOQ	17.17	18.97

Table 4: Complied results of validation study

Sr. No.	Study Carried Out		% Drug Estimation Mean		±SD		%RSD	
	Area	Absorptive intensity	Area	Absorptive intensity	Area	Absorptive intensity	Area	Absorptive intensity
1	% Assay	Laboratory Mixture	100.49	100.50	0.0007	0.0017	0.0846	0.2040
		Laboratory Mixture	100.01	100.01	0.0007	0.0008	0.0850	0.1069
2	Intra-day Precision		99.91	99.88	0.1143	0.0020	0.1279	0.2248
3	Inter-day Precision		99.51	99.25	0.0099	0.0036	0.1115	0.4004
4	Accuracy		99.9	100.09	0.0083	0.0077	10.0112	0.9485
5	Robustness		99.98	99.88	0.0017	0.0011	0.2056	0.1381

2398.60 – 2258.60 cm-1 in the obtained spectra was analyzed, and its absorbance values were determined. No interference from tablet excipients was observed in this specific region, making it suitable for the determination of hydroxychloroquine sulphate in tablets.

9.1. Method validation

The developed analytical method was validated according to the International Council for Harmonization (ICH) guidelines.

1. *Accuracy:* The accuracy of the method was assessed by performing the standard addition method and calculating the average recoveries from the samples. The mean percentage recoveries of the HCQS® 200 mg tablets (Table 16) fell within the accepted range of 98.0 to 102.0%, demonstrating the suitability of the method for quantifying the concentration of hydroxychloroquine sulphate in pharmaceutical

tablets.

2. *Precision:* The repeatability (intra-day precision) of the method was evaluated by analyzing multiple samples within the same day, and the intermediate precision (inter-day precision) was assessed by two analysts on different days. The %R.S.D. values were below 2%, indicating reliable precision of the method (Table 6).
3. *Limits of Detection and Quantification:* The LOD values were determined to be 5.6655 and 17.1682 μg/mg for peak area and peak intensity, respectively. The LOQ values were found to be 6.2613 and 18.9737 μg/mg for peak area and peak intensity, respectively, for HCQS® tablets 200 mg in the 2398.60 – 2258.60 cm-1 region (Table 5).

9.2. Assay of pharmaceutical products

The validated method was successfully applied to determine the hydroxychloroquine sulphate content in tablets. Samples from HCQS® tablets 200 mg were analyzed, and the results, expressed as percentage drug related, are presented in Table 6.

10. Conclusion

The recent literature review focused on analytical methods employed in the quality control of active pharmaceutical ingredients (APIs). Among these methods, FTIR spectrometry has emerged as a valuable tool for the quantification of pharmaceutical products. The proposed methods utilizing FTIR are characterized by their simplicity, precision, and time efficiency compared to other methods described in the literature. The quantification process, including sample preparation and spectral acquisition, can be completed within approximately 10-15 minutes.

IR spectroscopy offers several advantages in terms of gathering qualitative and quantitative data, including its rapidity, cost-effectiveness, and non-destructive nature. Recent advancements in analytical instrumentation and signal processing techniques have further expanded the applications of IR spectroscopy in various industrial sectors, particularly in the pharmaceutical industry.

Although imaging spectra obtained from IR spectroscopy have limitations in terms of the wavenumber range and signal-to-noise ratio, comparative results have been achieved for the calibration models of active ingredients when compared to calibration models based on single-element diffuse reflection spectra.

The minimal sample preparation required, absence of expensive, toxic, and volatile solvents, and the speed of analysis make IR spectroscopy an attractive technique for industries conducting a large number of analyses annually.

11. Authors' Contributions

All authors have read and approved the manuscript. TM contributed in preparation primary content. She performed extensive literature survey and compile the content. TM contributed in preparation of figures and table. SR contributed in checking of manuscript and correction of grammatical mistake. SR contributed in preparation of figure. SR contributed in finalization of manuscript and in its correction. KR contributed in finalization of content, preparation of concrete manuscript and in schematic presentation of content.

12. Source of Funding

None.

13. Conflict of Interest

None.

14. Acknowledgement

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Author's biography

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