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Development and Validation of an ICH-Compliant Optimized RP-HPLC Method for Quantitative Analysis of Favipiravir

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Abstract: Favipiravir (FAV) has emerged as a promising antiviral agent. It is particularly effective against influenza and other RNA virus infections. The aim and objective of the present study was developing and optimizing chromatographic conditions for faster analysis of FAV and demonstrating its applicability for tablet assay. The chromatographic separation was obtained using mobile phase with 90:10 % v/v ratio of ammonium acetate buffer (pH 4.5) and methanol on a Waters C18 column (250 x 4.6 mm, 5 µ). A flow rate of 1.4 mL/min was optimized. Chromatographic detection was perform at a wavelength of 323 nm. The FAV retention time was 6.46 min, indicating the efficiency and speed of the method. The developed method was rigorously validated according to ICH guidelines. A strong linear correlation (r^2 = 0.9995) was established in the 5–60 µg/mL range, indicating adequacy for quantitative analysis. The method demonstrated high accuracy, with FAV recovery ranging from 98.77 % to 100.89 %. The % RSD results of less than 2% for intermediate precision and repeatability showed that the method exhibited high precision. The developed HPLC method reduces the Rt. Notably, this method complies with regulatory standards, establishing it as a valuable tool for quality assurance, pharmacological evaluation, and clinical monitoring of FAV. Thus, this validated RP-HPLC method provides a robust and sensitive method for routine FAV quantification, with high accuracy, precision, and compliance results, supporting its potential use in the clinical pharmaceutical industry.

Introduction

Favipiravir (FAV), an antiviral drug, was developed to prevent influenza. Its potential activity against a wide range of RNA viruses has received considerable attention, including its use in the treatment of COVID-19 epidemics caused by SARS-CoV-2 virus FAV mode of action About RNA-dependent inhibition of RNA polymerase (RdRp), which cleaves viral RNA. Known chemically as 6-fluoro-3-hydroxypyrazine-2-carboxamide, an enzyme important for morphology (Agarwal et al., 2020; Furuta et al., 2013), FAV (Figure 1) has gained considerable popularity in the context of related in global health problem.

The literature highlights a diverse array of analytical techniques employed for the analysis of FAV. UV spectrophotometric methods have been extensively studied for their sensitivity and cost-effectiveness in quantitative and chemical quantitative determination (Ali et al., 2021a; Ali et al., 2021b; Chakraborty & Charan, 2023; Karthikeyan et al., 2023; El-Awady et al., 2022; Nithila et al., 2022; Sri et al., 2023; Bhavar et al., 2023). However, these methods often lack specificity and can be easily interfered with by other factors.

The literature study shows that many High-performance liquefied chromatography HPLC methods are suitable for analysing FAV (Abdallah et al., 2016a; Abdallah et al., 2016b; Ali et al., 2021a; Ali et al., 2021b; Apostolidi et al., 2022; Bulduk and Tezcan, 2020; Bulduk, 2021; Chakraborty & Charan, 2023; Ghune & Tapkir, 2022; Kalshetti and Adlinge, 2022; Lingabathula

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& Jain, 2021; Nadendla and Abhinandana, 2021; Taşkın, 2022; Abdallah et al., 2022; Bekegnran et al., 2021). These methods have been extensively developed and validated for quantifying FAV in bulk drugs and pharmaceutic formulations. Additionally, single bioanalytical HPLC methods have been reported for determining FAV in plasm and other natural samples for assisting pharmacokinetic and bioavailability studies (Das et al., 2018; Ding et al., 2021; Habler et al., 2021; Koganti et al., 2023; Vemuri et al., 2022; Curley et al., 2021). A unique Fourier-transform infrared (FTIR) spectroscopy has also been studied as a complementary technique for the quantitative analysis of FAV (Nithila et al., 2022). Furthermore, literature has shown that some analytical methods for simultaneous analysis of FAV along with other antiviral agents, such as remdesivir and nirmatrelvir/ ritonavir (Imam et al., 2023; Gosavi et al., 2023). LC-MS/MS has proven to be a powerful technique for the sensitive and selective quantification of FAV in complex matrices (Habler et al., 2021; Koganti et al., 2023; Eryavuz Onmaz et al., 2021; Bouchet et al., 2021; Harahap et al., 2023; Patel et al., 2022). These methods have been particularly valuable in bioanalytical studies, allowing for the precise measurement of FAV concentrations in biological fluids, such as plasma and serum. Some analytical techniques for FAV determination are found in the literature. These studies have reviewed the antiviral properties of FAV (Agrawal et al., 2020; Furuta et al., 2013) for spiked plasma samples (Hailat et al., 2021), conducted meta-analyses on the efficacy and safety of FAV in COVID-19 patients (Hung et al., 2022).

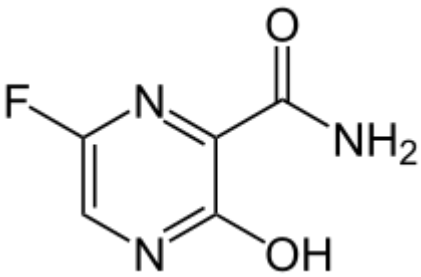

Figure 1. Structure of Favipiravir

The development of a new, robust and sensitive RP-HPLC method for FAV quantification remains an active area of research. No specific and quick method is available in the literature for routine analysis of FAV in pharmaceutical dosage forms, especially tablets. This study aimed to develop and validate a simple, rapid, and robust RP-HPLC method for routine quantitative analysis of FAV in pharmaceutical formulations, addressing the need for efficient quality control procedures in drug manufacturing. The objectives included optimizing chromatographic conditions for faster analysis, validating the method according to ICH guidelines, and demonstrating its applicability for tablet assay for this important antiviral medication. The developed HPLC method reduces the Rt. The present work describes the simple, quick, accurate and precise RP-HPLC method for estimation of FAV in bulk and pharmaceutical tablets.

Materials and Methods

Instrumentation:

Waters e2695 alliance HPLC system equipped with a thermostated column compartment, autosampler, degasser, and quaternary pump and a 2998 PDA-detector was used for analysis. Data were processed by the use of Empower 3 software

Chemicals and reagents

A sample of the working standard grade of FAV was obtained from Glenmark Pharmaceuticals, Nashik, India. HPLC-grade methanol was obtained from the Merck. All other solvents used in the analysis were either AR grade or HPLC grade. The FAV tablets, Favidac® 400 mg from Ikon Remedies Pvt Ltd, Mumbai, Batch no. 21S1GTA371, was obtained from the local market.

Preparation of buffer

Ammonium acetate (0.385 g) was poured into a 500 ml volumetric flask. After adding about 75% of the intended final amount of water to the flask, the ammonium acetate was thoroughly dissolved by stirring. The buffer's pH was brought to 4.5 by the addition of glacial acetic acid. Prior to use, the solution was filtered through a 0.45 µm membrane filter and degassed.

Preparation of standard stock solution:

In methanol, 0.2 g of the FAV standard was dissolved. Using the same solvent, the volume was made up to 100 mL, yielding a solution that contained 2000 µg/mL of FAV. To get a solution with a concentration of 200 µg/mL, from this solution, an aliquot of 1 mL was obtained, moved to a 10 mL volumetric flask, and diluted with methanol.

Chromatographic conditions

By carefully choosing the analytical conditions and evaluating several parameters such as buffer types, buffer concentrations, and other aspects, we were able to develop an accurate and efficient method for quantifying FAV. After testing various mobile phase and buffer solutions compositions, the selected mobile phase was made up of ammonium acetate buffer [pH 4.5] and methanol in a 90:10 (% v/v) ratio to flow at a rate of 1.4 mL per minute. A C_{18} Waters column measuring 250 x 4.6 mm was employed. While detection was examined at several wavelengths, 323 nm was shown to be the drug's

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maximum absorption. The retention time for FAV was 6.46 minutes.

Assay of FAV in Tablet

The active ingredient on the tablets was listed as 400 mg of FAV. Ten tablets were precisely weighed and ground into powder. The powder corresponding to 0.2 g (200 mg) of FAV was added to a 100 mL volumetric flask. After adding 50 mL of methanol to the flask, it was sonicated for 15 minutes. Methanol was added further to get make the volume to 100 mL. A 0.45 µm nylon filter was used to filter the mixture. A 10 mL volumetric flask was filled with 1 mL of this filtrate, which was then diluted with 10 mL of methanol. The 0.5 mL aliquot from this solution was further diluted to 10 mL using methanol. The optimized mobile phase was used to record the chromatogram at 323 nm. This process was carried out six times.

Method validation

Validation of the methodology was conducted to demonstrate that the approach is appropriate for the intended use and complies with ICH regulations. In accordance with ICH requirements, the parameters of the developed method were validated.

System suitability

This was done to make sure the analytical technique created for the quantification of FAV was reliable and reproducible. To prepare the system suitability solution, an aliquot of 0.5 mL from standard stock solution was diluted to 10 mL with methanol. Six replicate injections of system suitability solution were injected. The retention time, areas, theoretical plates, peak asymmetry, and resolution were calculated for the standard solution.

Specificity

A comparison was made between the chromatogram obtained from tablet solutions and the standard solution, which had an equivalent concentration of FAV.

Linearity and range

This method elucidates its capacity to yield results within a predetermined range that exhibits a direct correlation with the drug's concentration in the sample, ensuring data reliability and integrity. Plotting the area against the FAV concentration produced a linear calibration graph.

Accuracy

An analysis of percent recovery was used to assess the procedure's accuracy. The preanalyzed sample was subjected to experiments using the standard addition procedure at 80%, 100%, and 120% levels. The resulting solutions were then reanalyzed. Three determinations were made at every stage. % Mean and % Individual recovery were quantified.

Repeatability

An analytical method's precision indicates how closely measurements agree when the same sample is tested repeatedly. The method's repeatability was assessed by examining six samples with identical drug concentrations. The percentage (RSD) was then determined.

Intermediate precision

In order to assess the consistency of our assay procedure and ascertain intraday precision, the three concentrations of the sample solution were examined in triplicate on the same day. The process was carried out three consecutive days in a row to find the interday precision.

Limit of detection and limit of quantitation

The formulas LOD = 3.3σ/S and LOQ = 10σ/S are used to compute the limits of detection (LOD / detection limit) and quantitation (LOQ / quantitation limit). The slope of the calibration curve is denoted by S, while the standard deviation of the regression line's y-intercept is represented by σ.

Result and Discussion

Our goal was to develop an accurate, reliable, and simple-to-use HPLC method for measuring FAV by utilizing both a photodiode array and UV-visible detector. By evaluating the validation parameters of the method in accordance with ICH criteria, we were able to verify and test its reliability and accuracy.

Assay of FAV in Tablet:

The chromatogram of the sample solution was recorded at 323 nm. This procedure was repeated six times. The amount of FAV present in the formulation was calculated by comparison with the standard solution. The results are shown in Table 1.

Table 1. Results of Assay of Favidac® 400 mg in Tablet.

Labelled claim (mg)	Amount found (mg) Mean ± SD n=6	% Assay Mean ± SD n=6	% RSD n=6
400	396.06 ± 7.32	99.02 ± 1.83	1.85
n= number of repetitions			

System Suitability Parameters

Specifications for system suitability are given in Table 2.

Table 2. System Suitability Parameters.

Parameter	Average	% RSD (n)
Retention time	6.50 minute	0.74
Peak Area	186509.14	0.83
HETP	7249	
Tailing Factor	1.78	
n= 6=number of repetitions		

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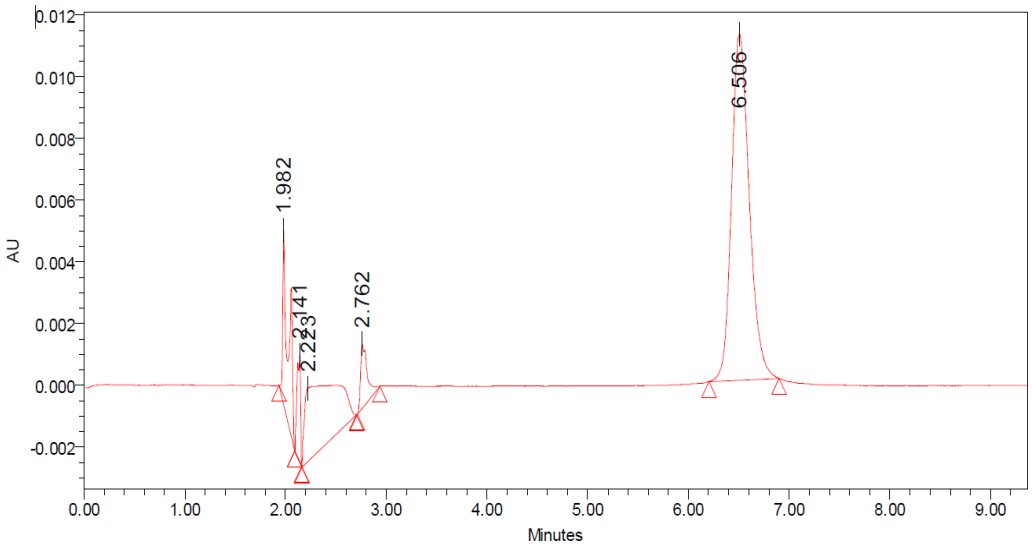

Figure 2. Typical chromatogram of standard FAV.

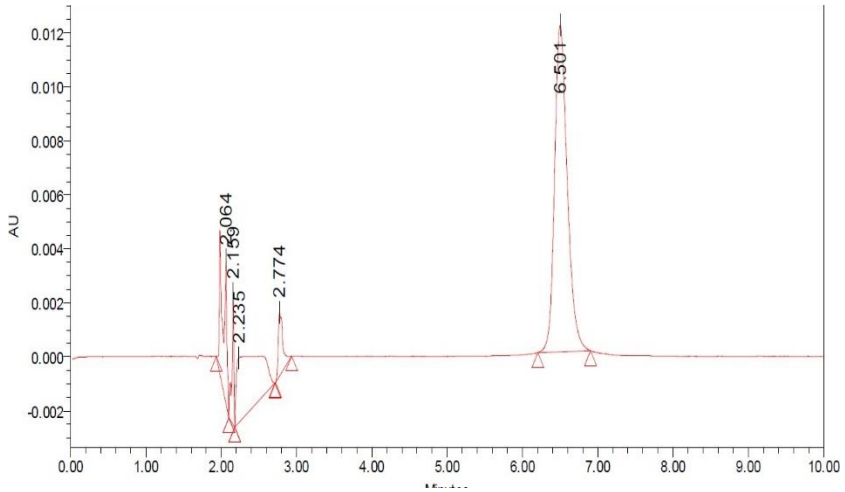

Figure 3. Chromatogram of FAV tablet sample (Favidac® 400 mg Tablet).

Table 3. Linear regression data.

Parameter	Result
Wavelength of analysis (nm)	323 nm
Linearity range (µg/mL)	5-60 µg/mL
Correlation coefficient (r^2)	0.9995
Regression equation	y = 19228x + 1882
Slope (m)	19228
Intercept (c)	1882

Specificity:

The chromatogram obtained from tablet solutions was the same as that obtained from the FAV standard solution. No peak other than FAV was discernible under the same chromatographic conditions. This demonstrated that excipients had not caused any disruption. As a result, the created method might be considered highly specific.

Linearity:

FAV had a linear response within the 5–60µg/mL concentration range. Table 3 presents data from linear regression.

Accuracy:

The developed method was found to be accurate, with a mean percentage between 98 and 102%. Results are illustrated in Table 4.

Method Precision (Repeatability) & Intermediate Precision.

The procedure's accuracy was evaluated by examining the degree of consistency between the findings obtained from six testing. They all fell within the accepted range of being close to each other, which is less than or equal to 2%. Tables 5 and 6 provide an overview of the findings.

Limit of detection and limit of quantitation

The limit of detection (LOD) and limit of quantification (LOQ) were determined to be 1.13 µg/mL and 3.43 µg/mL.

The developed RP-HPLC method for FAV analysis had good performance for the key validation parameters: it was highly specific, with good linearity (r^2 = 0.9995) in the range of 5-60µg/mL,and accuracy within the recovery

Table 4. Result of Recovery studies.

Level (%)	Sample concentration (µg/ml)	Standard drug added (µg/mL)	% Recovery Mean ± SD n=3	Amount recovered (µg/mL) Mean ± SD n=3	% RSD n=3
80	10	8	100.89 ± 0.86	8.15 ± 0.10	1.26
100	10	10	100.44 ± 0.78	10.04 ± 0.08	0.77
120	10	12	98.77 ± 0.19	11.85 ± 0.02	0.19
n= number of repetitions					

Table 5: Results of Repeatability studies.

Concentration (µg/mL)	Concentration found (µg/mL) Mean ± SD	% RSD n=6
10	9.99 ± 0.14	1.40

n= number of repetitions

Table 6: Results of Intermediate precision.

Concentration (µg/mL)	Intraday precision		Interday precision	
	Concentration found (µg/mL) Mean ± SD n=3	% RSD n=3	Concentration found (µg/mL) Mean ± SD n=3	% RSD n=3
5	5.38 ± 0.05	0.87	5.40 ± 0.10	1.77
10	9.72 ± 0.09	0.89	9.70 ± 0.09	0.94
15	15.18 ± 0.22	1.48	15.18 ± 0.25	1.68

range of 98.77 to 100.89%. Intermediary precision was very high, as represented by repeatability and intermediate precision, which were all below 2% RSD. It is sufficiently sensitive (LOD = 1.13 µg/mL and LOQ = 3.43 µg/mL), and the successful application to commercial tablets (label claim 99.02% ± 1.83%) proves its practical utility. Other key strengths are the short run time, wide linear range, and simple mobile phase composition. In the broader context of FAV analysis, the proposed method offers a robust avenue for routine pharmaceutical quality control that is within reach of laboratories that are not equipped with advanced LC-MS/MS capabilities, with potential stability-indicating properties. Its practical applications include high-throughput manufacturing quality control, regulatory compliance thanks to ICH-validated parameters, and possible adaptability for therapeutic drug monitoring. Such methodology will help move the field forward, balancing speed, simplicity, and performance toward more efficient operations, contributing to FAV's quality monitoring process throughout shelf life. Comparison of parameters such as run time, sensitivity, linear range, and mobile-phase composition with existing methods to help further underline its value. The proposed method can be effectively used for routine FAV analysis in pharmaceuticals compared to the more complex methods that are available. This approach presents a very useful complement to options in the analysis of FAV, particularly when pharmaceutical quality control situations require speed, simplicity, and robustness (Bhavar G. 2015, 2016, 2022).

Conclusion

The developed RP-HPLC method demonstrated excellent specificity, linearity, accuracy, and precision, making it suitable for quantitatively determining the antiviral drug Favipiravir in pharmaceutical formulations. This study presents a novel RP-HPLC method for favipiravir analysis that significantly improves existing techniques. Key innovations include the optimized mobile phase composition that reduces analysis time to 6.46 minutes while maintaining excellent resolution. Sensitivity was increased with an LOD of 1.13 and LOQ of 3.43 µg/mL. The validation results gave very high accuracy, evidenced by recoveries from 98.77% to 100.89%, and very high precision, expressed by an RSD below 2% for the wide linear range from 5 to 60 µg/mL. Its successful application to commercial tablet formulations demonstrates the practicality of routine quality control.

These advancements make the developed method particularly suitable for high-throughput analysis in pharmaceutical quality control settings, addressing the growing demand for efficient analytical techniques for antiviral medications. Including these elements would strengthen the manuscript by more clearly demonstrating how the new method compares to and improves upon existing techniques and highlighting its unique contributions to the field. The absence of interfering peaks confirmed the method's specificity, while linearity

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was established over a wide concentration range. Accuracy was validated through recovery studies within acceptable limits. Repeatability and intermediate precision assessments highlight the method's reproducibility and reliability across different testing conditions. In conclusion, this thoroughly validated RP-HPLC method offers a robust and reproducible approach for analyzing Favipiravir, adhering to ICH guidelines. Its implementation in quality control laboratories enables accurate quantification of Favipiravir in various matrices, contributing to this antiviral agent's safe and effective use in pharmaceutical formulations and clinical settings.

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Conflict of interest

None

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