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A review of analytical methods for the estimation of favipiravir in pharmaceutical dosage forms

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Abstract

This review article aimed to provide detailed information on developed analytical methods for the estimation of favipiravir in pharmaceutical dosage forms. This review article was prepared by gathering various analytical methods available in the literature for the determination of favipiravir. The various analytical methods available included spectroscopic methods such as UV spectroscopic methods, visible spectrophotometric methods, Fourier transform infrared spectroscopic (FTIR) method, spectrofluorimetric method, chromatographic methods such as reverse-phase high-performance liquid chromatographic (RP-HPLC) methods, thin layer chromatography (TLC) and hyphenated techniques such as ultra-performance liquid chromatography-tandem mass spectrometric (UPLC-MS/MS) methods, liquid chromatography-tandem mass spectrometric (LC-MS/MS) methods and electrical methods such as voltammetric methods. This article contains the information necessary to carry out the research work for the estimation of favipiravir in pharmaceutical dosage forms using analytical techniques. The present review article can be effectively investigated to conduct future analytical research for the estimation of favipiravir.

1. Introduction

Favipiravir is an antiviral drug developed for the treatment of various viral infections like influenza, and COVID-19 (Nupur, 2020; Khan *et al*., 2020; Shiraki and Daikoku, 2020). Chemically it is designated as 6-fluoro-3-hydroxypyrazine-2-carboxamide, with molecular formula $C_5H_4FN_3O_2$ and molecular weight 157.104 g/mol. It is a colorless powder, soluble in organic solvents and slightly soluble in water, and has a pKa value of 5.1. It is an organic compound belonging to the pyrazine carboxamides class (Du and Chen, 2020). Favipiravir belongs to the antiviral category where it acts by inhibiting RNA-dependent RNA polymerase enzyme which prevents viral transcription and replication (Sandip *et al*., 2021; Yuva *et al*., 2020; Pilkington *et al*., 2020; Hayden and Shindo, 2019) (Figure 1).

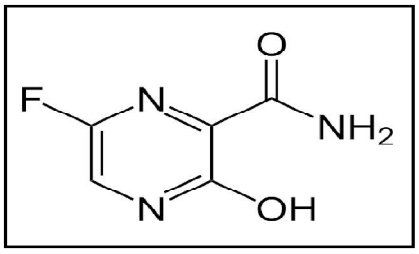

Figure 1: Chemical Structure of Favipiravir.

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The main aim of this review article is to describe the developed analytical methods for the estimation of favipiravir in pharmaceutical dosage forms. The developed methods for the estimation of favipiravir included spectroscopic methods such as UV spectroscopic methods, visible spectrophotometric methods, fourier transform infrared spectroscopic (FTIR) method (Chandan *et al*., 2022), spectrofluorimetric method, chromatographic methods such as reverse-phase high-performance liquid chromatographic (RP-HPLC) methods, thin layer chromatography (TLC) and hyphenated techniques such as ultra-performance liquid chromatography-tandem mass spectrometric (UPLC-MS/MS) methods, liquid chromatography-tandem mass spectrometric (LC-MS/MS) methods and electrical methods such as voltammetric methods.

1.1 Spectroscopic methods

Pritee and Mirza (2022), developed and validated an analytical method for the determination of favipiravir in bulk and tablet formulation using UV spectroscopy. In this method, the sample solutions were prepared using ethanol as solvent, and absorption maxima was found to be 323 nm. This method showed good linearity in the concentration range of 0.5-2.5 µg/ml with a correlation coefficient of 0.999. The developed method was also validated, for other parameters like accuracy, precision, specificity, and sensitivity. In this method, based on the values obtained authors concluded that the developed method could be suitable for the analysis of commercial samples.

Ibrahim (2021), developed a UV spectrophotometric method for the quantification of favipiravir in pharmaceutical formulations. In this article, the method was developed by dissolving the drug in deionized water and measuring the absorbance at 227 nm. The method obeyed Beer's law in the concentration range of 10-60 µg/ml with a correlation

coefficient of 0.9996. The method was also found to be accurate, precise, robust, and specific.

Sayyed Nazifa Sabir Ali *et al*. (2021), developed a UV spectrophotometric method and validated it for the estimation of favipiravir in bulk and pharmaceutical dosage form. In this article, the method was developed for the estimation of favipiravir by choosing the solvent as water. The maximum absorbance was observed at 358 nm. At this wavelength, the calibration curve was determined with concentrations ranging from 2-10 µg/ml. The % recovery was found to be 100.50-100.76%, indicating the method to be accurate. The method was found to be precise as the % RSD value falls in the acceptance limits, *i.e*., 0.51-1.37 for intraday and 0.77-1.78 for interday, respectively. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.072 µg/ml and 0.219 µg/ml, respectively.

Santosh and Hanmant (2022), developed and validated a UV spectrophotometric method for the estimation of favipiravir in bulk and pharmaceutical dosage form. In this method, maximum absorbance was observed at a wavelength of 323 nm when scanned in the range of 200-400 nm. The sample solutions were prepared by using 0.1N hydrochloric acid as solvent. This method obeyed Beer's law in the concentration range of 5-30 µg/ml with a regression coefficient of 0.997. This method was validated according to ICH guidelines concerning linearity, range, precision, accuracy, robustness, LOD, and LOQ. LOD and LOQ were found to be 1.49 µg/ml and 4.53 µg/ml, respectively. As the results were found within the prescribed limits, the authors concluded that this method could be suitable for the analysis of commercial samples.

Jeevana Jyothi and Venkata Kavya (2021), developed an ultraviolet spectrophotometric method for the estimation of new antiviral repurposing drug favipiravir. This method was developed using ethanol and water as solvents and the drug showed maximum absorbance at 234 nm. The developed method showed a linear response in the range of 0-10 µg/ml with a correlation coefficient of 0.9995% recovery for the drug was found to be 99.30-99.91%, indicating the method to be accurate. The method was also found to be precise, reproducible, and sensitive to the obtained results.

Itigimatha *et al*. (2023), developed new analytical method UV spectroscopy for the determination of a new antiviral drug favipiravir: A potential therapeutic drug against the COVID-19 virus in bulk and dosage forms. In this method, the drug solutions were prepared by using ethanol and scanned in the range of 250 to 400 nm. The maximum absorbance was observed at 323 nm and it was fixed for the whole process of validation in both techniques. The method showed linearity in the range of 20-60 µg/ml with LOD 3.5 µg/ml and LOQ 12 µg/ml. The developed method was validated for accuracy, precision, ruggedness, and robustness.

Wrushali *et al*. (2022), developed a visible spectrophotometric method for the analysis of favipiravir in pure drug and tablet formulation. In this method, colored complexes of the drug are produced by using acidic dyes; namely, methyl orange and methyl red as ion pairing agents. These complexes obeyed Beer's law in the concentration range of 10-50 µg/ml with acceptable correlation coefficients. This method was demonstrated to be accurate, precise, reproducible, sensitive, and specific for the determination of drugs in bulk and formulation with satisfactory results. This developed method can be successfully applied to determine favipiravir in tablet formulation (Wrushali *et al.*, 2022).

Nithila *et al*. (2022), developed a new FTIR method for the quantitative analysis of favipiravir in bulk and pharmaceutical dosage forms using a solid pellet technique and validated it. The samples for this method were prepared by mixing the drug favipiravir with potassium bromide to obtain the required concentrations. Results were found to be linear in the concentration range of 20-100 µg/mg with correlation values exceeding 0.999. The developed method was validated as per the ICH guidelines with results falling the acceptable levels of accuracy, precision, selectivity, robustness, and linearity. Finally, the authors concluded that the newly developed method was significantly distinct in comparison to HPLC. It proves to be applicable as a substitute for the official procedures.

Safa *et al*. (2021), developed a rapid, robust, sensitive, and green spectrofluorimetric method for the determination of favipiravir, a potential therapeutic agent against COVID-19. In this study, different factors affecting fluorescence were carefully studied and Box Behnken Design was applied to optimize experimental parameters. This proposed method was based on measuring the native fluorescence of favipiravir in 0.2 M borate buffer (pH 8.0) at 432 nm after excitation at 361 nm. A good linear relationship was observed in the concentration range of 40-280 ng/ml. The method was found to be sensitive with LOD 9.44 ng/ml and LOQ 28.60 ng/ml. The mean % recovery for favipiravir was found to be 99.26 ± 0.87. This proposed spectrofluorimetric method was proved to be eco-friendly according to the analytical eco-scale.

Ibraam *et al*. (2021), developed a spectrofluorimetric method for the determination of favipiravir as one of the COVID-19 antiviral regimens. In this study, for the improvement of favipiravir native fluorescence, several factors were studied which included solvent type, buffering, pH, and added surfactants. The best sensitivity for favipiravir fluorescence was obtained in Britton-Robinson buffer (pH maintained at 4) at 436 nm after excitation at 323 nm within a concentration range of 20-350 ng/ml. The developed method was validated per FDA guidelines and could be successfully applied for the determination of favipiravir in its marketed tablet formulations.

1.2 Chromatographic methods

Ibrahim (2021), developed a reverse-phase HPLC method for the quantification of favipiravir in pharmaceutical formulations. In this technique, the favipiravir was analyzed at a flow rate of 1 ml/min using a mobile phase composed of sodium acetate solution 50 mM (pH adjusted to 3.0 using glacial acetic acid) and acetonitrile in the ratio 85:15% v/v. Inertsil ODS-3 C18 (4.6 mm × 250 mm, 5 µm) column was utilized by operating it at 30°C and the detection wavelength of 227 nm was used for the analysis in this method. The drug was eluted at a retention time of 5.72 min with a capacity factor of 4.62, a tailing factor of 0.776, and some theoretical plates of 11798. This method obeyed Beer's law in the concentration range of 10-60 µg/ml. The developed method was found to be accurate, precise, robust, and specific and can be used for the routine analysis of the estimation of favipiravir in pharmaceutical formulations.

Pallavi and Kamalkishor (2021), developed and validated a bioanalytical method for the determination of favipiravir in spiked human plasma by using RP-HPLC. In this method, favipiravir was determined using carbamazepine as an internal standard in spiked human plasma. The chromatographic separation was accomplished with cromasil C18 (250 mm × 4.6 ID, 5µ) column using mobile phase methanol and water in the ratio 35:65% v/v at pH 3.0 under

gradient mode at a flow rate of 0.8 ml/min. A detection wavelength of 225 nm was used for this analysis and extraction was performed using ethyl acetate as extracting solvent. The retention time for favipiravir was found to be 6.62 min. The method was found to be linear in the concentration range of 0.2-3.2 µg/ml. The intraday precision, interday precision, and accuracy lie within the specified range. The authors concluded that the proposed RP-HPLC method was highly accurate and rapid for the determination of favipiravir in human plasma and can be applied for pharmacokinetic studies and therapeutic drug monitoring.

Duygu (2022), developed and validated a rapid HPLC-DAD method for the determination of favipiravir in pharmaceutical formulation. In this method, the analysis was done at 30°C with a Poroshell 120 EC-C18 (4.6 mm × 50 mm, 2.7µ) column consisting of a mobile phase of 0.1% formic acid in water and 0.1% formic acid in acetonitrile in the ratio 90:10% v/v run at a flow rate of 0.5 ml/min. The developed method was successfully validated in terms of precision, accuracy, linearity, robustness, LOD, and LOQ parameters. The method obeyed Beer's law in the concentration range of 10-100 µg/ml. LOD was found to be 0.58 µg/ml and LOQ was found to be 2.03 µg/ml. The author concluded that the developed method can be used for the estimation of favipiravir in pharmaceutical preparations.

Sayyed Nazifa Sabir Ali *et al*. (2021), developed an RP-HPLC method and validated it for the estimation of favipiravir in bulk and pharmaceutical dosage form. The optimized chromatographic conditions for this method included inertsil ODS-3V C18 (150 mm × 4.6 mm, 5 µ) column, buffer pH 3.5, and acetonitrile (90:10%v/v) as mobile phase at a flow rate of 1 ml/min and PDA detection at 358 nm. The developed method showed a linear response in the concentration range of 50-250 µg/ml. The LOD and LOQ were found to be 2.19 µg/ml and 6.63 µg/ml, respectively. The method was found to be precise with a % RSD value of 0.25-1.53 for intraday and 0.86-1.68 for interday. The authors mentioned that the main features of the proposed method are economical and eco-friendly with less retention time of around 5.0 min.

Komarov *et al*. (2022), developed and validated a HPLC method with UV detection for the determination of favipiravir in human plasma for pharmacokinetic studies. The samples were prepared by protein precipitation technique using methanol as solvent. Raltegravir was used as an internal standard in this method. 0.1% formic acid in water with 0.08% aqueous ammonia (eluent A) and 0.1% formic acid in acetonitrile with 0.08% aqueous ammonia (eluent B) was used as mobile phase at a flow rate of 1ml/min under gradient mode with Phenomenex Kinetex R C18 (150 × 4.6 mm, 5 µ) column. 323nm was used as the detection wavelength and the column temperature was maintained at 40°C. This method gave a linear response in the analytical range of 0.25-200.00 µg/ml. This developed method was validated by selectivity, calibration curve, accuracy, precision, spike recovery, the lower limit of quantification, carry-over effect, and stability.

Hailat *et al*. (2022), developed and validated a novel sensitive and low-cost HPLC-DAD method for the rapid determination of favipiravir in rat plasma. Oxcarbazepine was used as the internal standard and favipiravir was separated using a mobile phase of 50% acetonitrile and 50% water (with 0.25% trifluoroacetic acid) at 1ml/min flow rate and detected at λmax 289 nm. Zorbax Eclipse XDB-C18 (4.6 × 150 mm, 5 µm) column was used and maintained at a temperature of 38°C. The intraday and interday values for favipiravir in plasma were less than 15% with low, medium, and high QC levels for the relative recovery rate, according to ICH guidelines.

Hailat *et al*. (2021), developed and validated a method for quantification of favipiravir as COVID-19 management in spiked human plasma using HPLC. Acyclovir was used as an internal standard in this method. Both the drug and internal standard are separated using Symmetry C18 (250 mm × 4.6 mm, 5 µ) column with methanol, acetonitrile, and 20 mM phosphate buffer (pH 3.1) as mobile phase in the ratio 30:10:60% v/v/v under isocratic mode at a flow rate of 1ml/min. All eluents were detected at 242 nm. The retention time for favipiravir was found to be 7.40 min. Maximum recovery of favipiravir and acyclovir from plasma was obtained with dichloromethane as extracting solvent. The calibration curve was found to be linear in the range of 3.1-60.0 µg/ml with a regression coefficient of 0.9976. The method was validated concerning sensitivity, accuracy, precision, recovery (89.99%, 89.09%, and 90.81% for LQC, MQC, and HQC, respectively), stability (% RSD for 30-day were 3.04and 1.71 for LQC and HQC, respectively at -20°C) and carry-over effect.

Vishal and Amit (2022), developed and validated a RP-HPLC method for the estimation of favipiravir in pharmaceutical formulation. Analysis was carried out by Cosmosil C18 (250 mm × 4.6 ID, 5 µ) column using methanol and water (75:25% v/v) as mobile phase pumped at a flow rate of 0.8 ml/min. 227 nm was used as the detection wavelength and column temperature was maintained at 30°C. The retention time for favipiravir was found to be 227 nm. The method obeyed Beer's law in the range of 10-50 ppm with a correlation coefficient of 0.9995. The % recovery was found to be 98.94-99.12%, while the mean % RSD was 0.23. The developed method was found to be sensitive with LOD 0.2236 ppm and LOQ 0.6776 ppm. This proposed method can be successfully applied for method development and validation of favipiravir in pharmaceutical formulations.

Ibrahim (2021), developed the HPLC method with UV detection for the quantification of favipiravir in pharmaceutical formulations. In this method, Inertsil ODS-3V C18 (4.6 mm × 250 mm, 5 µm) column and 50 mM potassium dihydrogen phosphate (pH adjusted to 2.3) and acetonitrile (90:10% v/v) mobile phase composition were used for the analysis. The mobile phase was pumped at a flow rate of 1 ml/min and the column has been thermostated at 30°C. The eluate was monitored using a UV detector set at 323 nm. Favipiravir was eluted at 7.69 min as the retention time. An excellent linear relationship was observed in the range of 10-100 mg/ml with the correlation coefficient being 0.9999. The developed method is sensitive with LOD being 1.2 mg/ml and LOQ being 3.6 mg/ml, precise with a % RSD value of 0.4 for interday studies and 0.2 for intraday studies, accurate with 99.19-100.17% recovery, specific and robust with %RSD less than 1. The authors concluded that the proposed method can be successfully applied for the quantification of favipiravir in pharmaceutical formulations.

Jyoti *et al*. (2022), developed and validated an RP-HPLC method for the estimation of favipiravir API and its tablet dosage form using a quality-by-design approach. In this approach, C18 (150 mm × 4.6 mm, 5 µ) column was maintained at ambient temperature, and acetonitrile and water in the ratio 80:20% v/v as mobile phase pumped at 1ml/min flow rate with detection wavelength 323 nm were used for the analysis. The drug was eluted with a retention time of 2.7 min and a peak area of 51248. Favipiravir showed a good

linear response in the concentration range of 10-90 µg/ml with a correlation coefficient of 0.9985. The %RSD for precision was found to be less than 2. The method validation parameters were within the prescribed limits as per ICH guidelines.

Nadendla and Patchala (2021), developed a validated HPLC method for the quantification of favipiravir in pharmaceutical formulations. The elution was done by using Shim-Pack GIST C18 (250 × 4.6 mm, 5 µ) column with 10 mM potassium dihydrogen orthophosphate buffer (pH 4) and acetonitrile in the ratio 90:10% v/v as mobile phase pumped at 1 ml/min flow rate. The UV detection was done at the wavelength of 315 nm by maintaining column temperature at 30°C. The calibration plot showed the best regression over the concentration range of 10-60 µg/ml of favipiravir standard solutions. The LOD and LOQ were found to be 0.18 µg/ml and 0.53 µg/ml, respectively. The proposed method was found to be accurate and precise as the results were within the prescribed limits.

Kalshetti and Sagar (2022), developed and validated an HPLC method for the quantification of favipiravir in tablet formulation. The chromatographic separation was achieved by using Luna Phenomenex C8 (150 × 4.6 mm, 5 µ) column with a mobile phase comprising of water and methanol (95:5% v/v) pumped at 1 ml/min flow rate and detected at 229 nm. The retention time of favipiravir was found to be 4.3 min in this method. The method showed a good linear relationship within the concentration range of 10-50 µg/ml. The method was successfully validated under the ICH guidelines and the method was found to be sensitive, accurate, precise, and reproducible.

Shimadzu (2020), developed an HPLC method for the quantitative analysis of favipiravir spiked in plasma. The analysis was performed on Shim pack Scepter C18-120 (150 mm × 4.6 mm, 5.0 µm) column using 10 mM sodium phosphate buffer (pH 6.9) and methanol as mobile phase run under gradient mode at a flow rate of 1 ml/min. The column was maintained at 30°C and the eluents were detected using a fluorescence detector. The developed method was validated as per ICH guidelines. The developed method was found to be accurate, precise, linear, specific, and robust.

Yamani and Annapurna (2022), developed a stability-indicating RP-HPLC method for the estimation of favipiravir in API and pharmaceutical dosage forms, especially tablets. In this chromatographic study, Hypersil BDS C18 (250 mm × 4.6 mm, 5 µm) column and methanol and a mixture of tetra butyl ammonium hydrogen sulfate with ammonium dihydrogen phosphate (pH maintained at 5) as mobile phase were used for the separation purpose. The mobile phase was pumped at a 1 ml/min flow rate and eluents were detected at 230 nm. Linearity was observed in the range of 1-300 µg/ml with a regression coefficient of 0.9998 and the method was also found to be precise, accurate, and robust. In this study, stress degradation studies were performed and the method was found to be selective and specific.

Ibraam *et al*. (2021), developed a green micellar solvent-free HPLC method for the determination of favipiravir as one of the COVID-19 antiviral regimens. This method was validated using C18-RP (5 µm, 250 × 4.6 mm) stationary phase and solvent-free mobile phase comprising of 0.02 M Brij-35, 0.15 M SDS, and 0.02 M disodium hydrogen phosphate, pH 5.0 under isocratic mode pumped at 1ml/min flow rate and eluents detected at 323 nm. This method was validated for the linearity in the range of 10-100 µg/ml and the drug was eluted at 3.8 min. This method was validated following FDA guidelines and could be applied successfully for the determination of favipiravir in marketed tablet dosage forms and spiked human plasma samples. This method was considered as eco-friendly as it utilized biodegradable reagents in aqueous solvent-free phases.

Safa *et al*.(2021), developed a green HPLC method for the determination of an anti-coronavirus drug; favipiravir in bulk and spiked human plasma through a chemometric approach based on factorial and Box-Behnken designs. In this study, the fractional factorial design was implemented for screening different factors affecting chromatographic responses, and the Box-Behnken design was applied to study and optimize the most critical method parameters. The optimized chromatographic conditions in this method are Eclipse plus C18 (100 mm × 4.6 mm, 3.5 µm) column maintained at 35°C and a mixture of 0.1% phosphoric acid solution and isopropanol (98:2% v/v) as mobile phase pumped at 0.8ml/min flow rate. The eluents were detected using a fluorescence detector set at 361 nm and 432 nm for excitation and emission, respectively. This method obeyed Beer's law in the concentration range of 20-240 ng/ml with LOD 2.01 ng/ml and LOQ 6.11 ng/ml. This method was validated for accuracy, precision, specificity, and robustness. This study proved that the combined application of green chemistry and quality by design leads to the development of a robust green method.

Jadhav *et al*. (2022), developed a simple validated HPLC method for the estimation of favipiravir. The plasma samples were extracted using ethyl acetate as extracting solvent. The separation was performed using Inertsil ODS-3V C18 (250 mm × 4.6 mm, 5 µ) column with 50 mM potassium dihydrogen phosphate (pH 2.3) and acetonitrile (90:10%v/v) as mobile phase pumped at 1 ml/min flow rate. The retention time for favipiravir was found to be 6.62 min. A good linear response was observed in the range of 0.2-3.2 µg/ml. This method was validated for accuracy, precision, robustness and specificity using the samples spiked from human plasma. The authors concluded that the proposed RP-HPLC technique was highly correct and rapid for the determination of favipiravir in human plasma and could be applied for pharmacokinetic research and therapeutic drug monitoring.

Sonu and Priyanka (2021), developed and validated a stability-indicating HPLC method for the estimation of favipiravir in pharmaceutical dosage form. In this method, chromatographic analysis was performed on stainless steel Inertsil ODS 3V C18 (250 mm × 4.6 mm, 5 µm) column and a mixture of 0.1% ortho-phosphoric acid and acetonitrile (77:23) as mobile phase under isocratic mode with flow rate 1 ml/min. The eluents were detected at 225 nm with a UV detector and the column was maintained at 30°C. This method showed better linearity in the concentration range of 10-30 µg/ml with a regression coefficient of 0.9989. This method was validated as per the ICH guidelines and the results were found to be within the prescribed limits. In this study, the samples were subjected to different stress conditions to study the sensitivity of the method.

Patil and Mahaparale(2021),developed and validated a stability-indicating RP-HPLC method for the estimation of favipiravir in bulk and pharmaceutical dosage form. The optimized chromatographic conditions of this method included a mixture of methanol and water (0.05% triethylamine) in the ratio 70:30% v/v as mobile phase with 0.8ml/min flow rate. The Cosmosil C18 column was used and the detection wavelength of 360 nm. The 20-100 µg/ml concentration

range showed good linearity with a 0.9997 correlation coefficient. This method was validated using precision, accuracy, robustness, specificity, and selectivity parameters. The samples in this method were exposed to different stress conditions to study the stability of the drug. The authors concluded that this developed method could be used for routine analysis of favipiravir in bulk and pharmaceutical dosage form.

Abdallah *et al*. (2022), determined favipiravir in human plasma using homogeneous liquid-liquid microextraction followed by the HPLC method. The optimized extraction conditions included were 500 µl tetrahydrofuran as extractant and 1400 mg fructose as phase separating agent. The developed method was validated by USFDA bioanalytical guidelines and results were found within the limits. A linear response was found in the range of 25-80000 ng/ml with a correlation coefficient of 0.999. These results showed that the developed method was simple, easy, valid, and adequately sensitive for the determination of favipiravir in plasma for bioequivalence studies.

Abdallah *et al*. (2022), developed the HPLC method for the determination of favipiravir an antiviral drug in human plasma using menthol-assisted homogenous liquid-liquid microextraction. The optimized extraction efficiency was achieved using 300 µl of tetrahydrofuran, 30 mg of methanol, and vortexed for 1 min before centrifuging the sample for 5 min at 3467 g. In this study, the highly polar favipiravir molecules would be incorporated into the hydrophilic core of the formed reverse micelle to be extracted by a non-polar organic extractant. This method was validated according to USFDA bioanalytical method guidelines. A good linear response was observed in the concentration range of 0.1-100 µg/ml with a correlation coefficient of 0.9992. The method was also found to be accurate and precise. The authors concluded that the developed method was simple, cheap, more eco-friendly, and sufficiently sensitive for biomedical applications.

Abdallah *et al*. (2022),developed an HPLC method for the determination of favipiravir in human plasma. In this work, gadolinium (Gd) based magnetic ionic liquid was prepared and used as an extractant in dispersive liquid-liquid microextraction (DLLME) of favipiravir in human plasma. The high enriching ability of DLLME allowed the determination of favipiravir in real samples using HPLC with UV detection. Different factors such as type of extractant, amount of extractant, type of disperser, and disperser volume affecting extraction efficiency were investigated. The maximum enrichment was attained using 50 mg of Gd-magnetic ionic liquid and 150 µl of tetrahydrofuran. The developed method was validated according to USFDA bioanalytical method validation guidelines. 0.9999 correlation coefficient was obtained in the concentration range of 25-100000 ng/ml. This method was also found to be accurate and precise. The developed method was simple, selective, and sensitive for the determination of favipiravir in real human plasma.

Itigimatha *et al*. (2023), developed a new analytical method RP-HPLC for the determination of new antiviral drug favipiravir: A potential therapeutic drug against COVID-19 virus in bulk and dosage forms. In this study, a mixture of ammonium acetate buffer (pH adjusted to 6.5) and methanol was used as mobile phase with Sunfire C18 (5 µ, 4.6 mm × 250 mm) column, and the detection wavelength was set at 323 nm. The drug was eluted at a sharp peak at 2.65 min with a total run time of 10 min. The method showed linearity in the range of 10-50 µg/ml with LOD 1.0 µg/ml and LOQ 3.5 µg/ml. The developed method was validated for accuracy, precision, ruggedness, and robustness.

Vemuri *et al*. (2022), developed and validated a liquid chromatographic method for the determination of favipiravir and its degradation impurities in finished solid dosage form. The separation of drug and all impurities were performed using inert sustain AQ-C18, 250 × 4.6 mm, 5 µm stationary phase maintained at 33°C, mixture of potassium dihydrogen phosphate buffer (pH 2.5) and acetonitrile in the ratio 98:2%v/v as mobile phase A and mixture of water and acetonitrile in the ratio 50:50% v/v as mobile phase B pumped at 0.7 ml/min flow rate and detected at 210 nm. The developed method was validated per ICH guidelines and was found to be accurate, linear, precise, and specific. As per the authors, the developed method was found suitable for routine analysis of research and development and quality control.

Jain *et al*. (2023), developed a green, fast, high sample throughput, a non-instrumental and affordable analytical method based on surfactant-assisted dispersive liquid-liquid microextraction combined with thin layer chromatography-digital image colorimetry for the determination of favipiravir in biological and pharmaceutical samples. Triton X-100 was used as a disperser and dichloromethane as an extraction solvent in this analysis. The extract obtained after the extraction process was spotted on a TLC plate and developed using chloroform and methanol (8:2% v/v) as the mobile phase. After the development, the spots were observed under UV irradiation at 254 nm using a smartphone. Under the optimized conditions, the method was found to be linear in the range of 5-100 µg/spot. The developed method was successfully applied for the estimation of favipiravir in biological and pharmaceutical samples.

1.3 Hyphenated techniques

Suleyman *et al.* (2021), developed and validated the ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for obtaining favipiravir tablet dosage form and evaluation of its behavior under forced conditions. In this study, the analysis was performed on 120 EC-C18 (4.6 mm × 50 mm, 2.7 µm) columns using methanol and water with 0.1% formic acid (20:80% v/v) as mobile phase pumped at 0.8 ml/min flow rate. The column temperature has been set to 40°C and eluents were detected at 222 nm. The retention time of favipiravir was found to be 1.155 min in this method. The electrospray jet stream ionization source was analyzed using mass spectrometry in negative ion mode. The molecular peak for favipiravir was [M-1] 155.9 and the daughter ion was determined 112.6. The stability test method was carried out per the ICH procedure. Reaction and degradation rates of the active substance under forced conditions were observed and the degradation products produced during this reaction were analyzed by mass spectrometry. This validated method was selective, robust, simple, and applicable for tablet analysis.

Eryavuz *et al.*, (2021), aimed to develop a validated LC-MS/MS method for the measurement of favipiravir levels in positive and negative electrospray ionization mode and to perform a pilot study in patients with COVID-19 receiving favipiravir to demonstrate the applicability of this method in biological samples. In this study, simple protein precipitation was used for the extraction of favipiravir from the desired matrix. Later the drug levels were quantified using tandem mass spectrometry with an electrospray ionization source

in positive and negative multiple reaction monitoring (MRM) modes. The optimized chromatographic conditions included Phenomenex C18 (50 mm × 4.6 mm, 5 µm, 100 Å) column, 0.1% formic acid in water, and 0.1% formic acid in methanol as mobile phase under gradient mode of elution. The method showed a good linear response in the concentration range of 0.048-50 µg/ml (in negative ionization mode) and 0.062-50 µg/ml (in positive ionization mode) with a 0.998 correlation coefficient. The intra-assay and inter-assay % CV values were less than 7.2% and 8.0%, respectively. The authors finally concluded that a simple, rapid, and robust LC-MS/MS method was developed and validated for the measurement of favipiravir and this method can be successfully applied for drug level measurement in COVID-19 patients receiving favipiravir.

Rezk *et al.* (2021),developed a novel, rapid, and simple UPLC-MS/MS method for the quantification of favipiravir in human plasma and its application to a bioequivalence study. In this method, lamivudine was utilized as an internal standard. The instrument utilized for this study was Xevo TQD LC-MS/MS operated under the MRM mode using electrospray ionization. Samples for the analysis were prepared by precipitating with acetonitrile as it gives relatively cleaner plasma samples. The prepared samples were analyzed using an Acquity UPLC HSS C18 (100 mm × 2.1 mm, 1.8 µ) column with a mixture of ammonium formate and methanol as mobile phase in gradient mode pumped at 0.35 ml/min flow rate. The developed method was validated as per the ICH guidelines and linearity was in the range of 0.25-16 µg/ml. The precision and accuracy results were found to be within the prescribed limits. The authors concluded that a run time of 4.5 min and a low quantification limit of favipiravir allowed the application of the developed method for the determination of favipiravir in bioequivalence study in healthy human volunteers.

Itigimatha *et al*. (2022), developed and validated an LC-MS/MS method for the determination of favipiravir in pure and tablet dosage forms. The stationary phase utilized was Shim pack GISS, C18 (100 mm × 2.1 mm, 1.9 µm) column, and mobile phase comprised of 10 mM ammonium acetate and methanol pump at 0.4 ml/min flow rate under gradient mode. The total run time for this analysis was 5.0 min. The developed method was validated according to ICH guidelines. A linear response was found in the range of 50-200 ng/ml with a 1.0 correlation coefficient. The method was found to be accurate, precise, robust, and sensitive with LOD 4.044 ng/ml and LOQ 12.253 ng/ml. Finally, the authors concluded that this developed novel method could be adopted in the formulation industry.

Mosaad *et al*. (2021), developed a novel LC-MS/MS method for the determination of potential antiviral candidate favipiravir for the emergency treatment of SARS-CoV-2 virus in human plasma and its application to a bioequivalence study in Egyptian human volunteers. In this method, pyrazinamide was used as an internal standard. Plasma samples to be analyzed by this technique were prepared by simple protein precipitation method using methanol. Chromatographic separation was achieved by Eclipse plus C18 (50 × 4.6 mm, 3.5 µm) column with mobile phase comprising of methanol and 0.2% acetic acid in the ratio 20:80%v/v pumped at 0.6 ml/min flow rate and operated under isocratic elution mode. The eluents were passed on to API 4500 triple quadrupole tandem mass spectrometer operated with MRM in negative electrospray ionization interface for the drug and positive electrospray ionization interface for internal standard analysis. The MRM function was used for quantification with the transitions set at m/z 156.00'!113.00 for the drug and m/z 124.80'!81.00 for the internal standard. This method was optimized and fully validated under US FDA guidelines. The developed method acquired linearity over a concentration range of 100.0-20000.0 ng/ml. The authors concluded that the proposed method could be effectively applied for the pharmacokinetic evaluation of favipiravir and to demonstrate the bioequivalence of new favipiravir formulation and reference product in healthy Egyptian human volunteers.

Dominic *et al*. (2020), developed the LC-MS/MS method for the analysis of small molecule antiviral and anti-inflammatory drugs in plasma in clinical research. In this article, the authors performed the analysis for the determination of various antiviral and anti-inflammatory drugs of which one of the drugs was favipiravir. The samples were prepared by simple protein precipitation with methanol and 0.1 M zinc sulfate (30:70%v/v). In this method, separation was achieved by Cortecs T3 (2.1 mm × 50 mm, 2.7 µm) column maintained at 45°C using 10 mM ammonium formate, 0.2% formic acid in water, and methanol as mobile phase under gradient program. The eluents were passed on to the Xevo TQ-S micro mass spectrometer operated with positive electrospray ionization with MRM mode. The developed method was validated and found to be linear, specific, accurate, and precise.

Curley *et al*. (2021), developed a highly sensitive, robust bioanalytical liquid chromatography-tandem mass spectrometry assay for the quantification of favipiravir. The developed method was found to be linear in the range of 0.78-200 ng/ml. The method was validated and found to be accurate, precise, robust, and sensitive. The authors concluded that this study will have applications in both pre-clinical and clinical research.

1.4 Electrical methods

Ersan *et al*. (2022), developed a sensitive voltammetric method for the determination of favipiravir used as an antiviral drug for the treatment of COVID-19 at pencil graphite electrode. Differential pulse voltammograms recorded in 0.5 M sulfuric acid used for the reduction of favipiravir showed that peak currents were increased linearly in the range of 1-600 µM with LOD 0.35 µM. The acceptable recovery values observed from pharmaceutical tablets, real human urine, and artificial blood serum samples spiked with favipiravir confirmed that the developed method was accurate.

Mehmandoust *et al*. (2021), developed a novel and sensitive voltammetric nanosensor for the trace-level monitoring of favipiravir based on gold/silver core-shell nanoparticles prepared with conductive polymer poly (3,4-ethylene dioxythiophene) polystyrene sulfonate and functionalized multicarbon nanotubes on a glassy carbon electrode. The prepared favipiravir nanoparticles showed linearity in the concentration range of 0.005-0.009 and 0.009-1.95 µM with LOD 0.46 nM. The developed method was found to be accurate, reproducible, precise, stable, and specific. The authors concluded that the developed assay method had promising applications in diagnosing favipiravir in clinical samples.

Akca *et al.*(2022), developed a voltammetric method for the quantification of antiviral drug favipiravir in the pharmaceutical formulation and biological sample, *i.e.*, urine sample using glassy carbon electrode in anionic surfactant media. The developed method was found to be linear in the concentration range of 1-100 µg/ml with

LOD 0.26 µg/ml. The proposed method can be used successfully to determine favipiravir in pharmaceutical formulations and model human urine samples.

2. Conclusion

In recent years, various analytical methods were developed and validated for the estimation of favipiravir in bulk, pharmaceutical dosage forms, and in biological matrices such as blood plasma, and urine samples. Various analytical methods consist of spectroscopy, chromatography, hyphenated techniques, and electrical methods. From this survey, it was revealed that very few analytical techniques were developed using spectroscopic methods and electrical methods, a handful of analytical techniques were developed using RP-HPLC and a few methods were developed using hyphenated techniques. All the developed methods were validated following ICH guidelines and the methods met its acceptance criteria. Finally, it can be concluded that there is a scope for the development and validation of favipiravir using spectroscopic and chromatographic methods in the future.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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