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An Overview on Analytical Estimation of Favipiravir

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ABSTRACT
Favipiravir, sold under the brand name Avigan among others, is an antiviral medication used to treat influenza in Japan. It is also being studied to treat a number of other viral infections, including SARS-CoV-2. The plethora subscribed in this work is directed towards the collection of various important methods used for the estimation of Favipiravir, from its bulk and formulations. As the newer guidelines from ICH had been directed towards the qualitative estimation of drugs from its bulk and formulations are made significant as it directly related towards the effectiveness of the drugs.

Key-words: Analytical, Method, Estimation, Techniques, Favipiravir.

I. INTRODUCTION

Favipiravir, sold under the brand name Avigan among others,is an antiviral medication used to treat influenza in Japan.[1] It is also being studied to treat a number of other viral infections, including SARS-CoV-2.[2] Like the experimental antiviral drugs T-1105 and T-1106, it is a pyrazinecarboxamide derivative.It is being developed and manufactured by Toyama Chemical (a subsidiary of Fujifilm) and was approved for medical use in Japan in 2014. In 2016, Fujifilm licensed it to Zhejiang Hisun Pharmaceutical Co. It became a generic drug in 2019. Chinese-borne coronavirus disease (COVID-19) spread rapidly and became an epidemic,affecting almost all countries and regions around the world. COVID-19 case death rateranges from 1% to 7% according to the reports of World Health Organization (WHO). Itcaused all people in the world to change their lifestyle. It still threatens the entire World [3].Since the outbreak of the COVID-19 began to affect the world, countries have implementeddifferent treatment methods.

Active therapeutic alternatives are urgently needed as a rising COVID-19 pandemic andpossible effects on global health [5]. Many medications such as chloroquine, arbidol,remdesivir, and favipiravir are currently undergoing clinical trials in several countries toassess their effectiveness and safety in treating coronavirus disease [6]. So far, there is nogold standard for the treatment of COVID-19 since there is not enough evidence [7].Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide) is an analog of pyrazine (Fig. 1).Favipiravir (FVP) is an antiviral drug that was initially developed for influenza by ToyamaChemical. It selectively inhibits the RNA polymerase of RNA viruses, thus preventing viralreproduction. It displays antiviral activity against alpha-, filo-, bunya-, arena-, flavi-, andnoroviruses [6, 7], as well as being active against the influenza virus.After a pilot trial by Zhongnan Hospital of Wuhan University has found a better recoveryrate in COVID-19 patients in the favipiravir group compared to the arbidol group , FVP isconsidered to be worth further investigation as a potential candidate drug for this disease.[8]

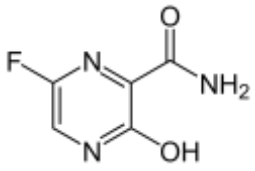

Fig. no. 01: Structure of Favipiravir

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III. ANALYTICAL METHODS USED FOR THE ESTIMATION OF FAVIPIRAVIR

Sr. no.	Author & Year	Description of method
1	**Ibrahim Bulduk (2020)**	A rapid, simple, precise, accurate, and isocratic high performance liquid chromatography (HPLC) method has been developed for routine quality control of 314avipiravir in pharmaceutical formulations. Separation was carried out by C18 column. The mobile phase was a mixture of 50 mM potassium dihydrogen phosphate (pH 2.3) and acetonitrile (90:10, v/v) at a flow rate of 1 mL min [9]
2	**Dr. SHREERANG JOSHI (2021)**	A Simple accurate, precise, and reproducible stability-indicating high-performance liquid chromatography (RP-HPLC) method has been developed for the determination of Favipiravir, its known impurities, and degradationproducts. The method was validated according to the current International Council for Harmonizationrequirements. The proposed method shows excellent linearity, accuracy, precision, specificity, robustness, LOD,LOQ, and system suitability results within the acceptance criteria. The calibration plot gave a linear relationshipfor all known analytes over the concentration range from LOQ to 200 % of specification level. LOD and LOQ forall known analytes were found in the field of 0.02-0.16 µg mL-1 and 0.06-0.40 µg mL-1, respectively. Theaccuracy of the proposed method was determined by a recovery study. The results of robustness and solutionstability studies were within the permissible limits. The developed method is suitable for routine analysis.[10]
3	**Safa M. Megahed (2019)**	The present work describes the development of a robust, sensitive, and green HPLC method with fluorescence detection for the determination ofFavipiravir (FAV). A fractional factorial design was implemented for the screening of different factors affecting chromatographic responses. TheBox-Behnken design was applied to study and optimize the most critical method parameters. The optimum chromatographic conditions obtainedinvolved the use of 0.1% phosphoric acid solution and isopropanol in the ratio 98:2 % v/v as mobile phase at a flow rate of 0.8 mL/min and columnoven temperature of 35°C. Chromatographic analysis was performed on Eclipse plus® C18 (100 mm × 4.6 mm × 3.5 µm) column with fluorescencedetector set at 361 nm and 432 nm for excitation and emission,

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		respectively. A linear response was obtained over the range of 20 - 240 ng/mL witha limit of detection of 2.01 ng/mL and a quantitation limit of 6.11 ng/mL. The method was successfully implemented for the determination of FAVin its pharmaceutical formulation with a mean % recovery ± SD of 99.42 ± 0.59. Moreover, the sensitivity of the method allowed the determinationof FAV in spiked human plasma over a range of 40-240 ng/mL. The combined application of green chemistry and quality by design leads to thedevelopment of a robust green method.[11]
4	**Paul Curley (2021)**	Here, a liquid chromatography tandem mass spectrometry assay is presented which was linear from 0.78-200 ng/mL Accuracy and precision ranged between 89% and 110%, 101% and 106%, respectively [12]
5	**Sonu A. Varma (2021)**	Favipiravir {FVP}, is an antiviral drug C5H4FN3O2 that is administered orally or interavenously also and the drug inhibitits viral replication of RNA viruses by interfering with viral RNA polymerase function. The officially Method are not available in any pharmacopeia. The ultraviolet (UV) detection 323nm and 225nm, Scanning between 200 and 800 nm.[13]
6	**Shyamala (2021)**	Forced degradation studies and stability indicating method were developed for the estimation of Favipiravir by reverse phase High performance liquid chromatography in active Pharmaceutical ingredient and its tablet dosage form. The method was achieved by using C18 column (250 X 4.6mm X 4µm) with mobile phase mixture ortho phosphoric acid and acetonitrile in the ratio 60:40. The mobile phase was allowed to pump with the flow rate 1ml/min by maintaining detection wavelength at 324nm using ultra-violet detector. Favipiravir drug was subjected to various stress conditions according to International Conference of Harmonization Q1A(R2) guidelines to establish stability indicating method. Favipiravir drug was found to be sensitive at peroxide degradation. The impurity peak was characterized by mass spectral studies. The method was validated for analytical standards such as linearity, accuracy, Precision, sensitivity and robustness. A rapid and sensitive method was developed for the estimation of favipiravir which indicates its stability indicating behavior.[14]

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7	**Dr. Sandip D Firke (2021)**	A novel, simple and accurate UV-Spectrophotometry method have been develop and validate for the analysis offavipiravir in bulk and tablet formulation. Favipiravir, also known as 6-Fluoro-3-hydroxypyrazine-2-carboxamide,is an antiviral medication. It is a modified pyrazine analogue. The quantitative determination of the drug wascarried out using the zero order derivative values measured at 323 nm. Linearity plot was constructed andlinearity was followed in the concentration range of 4-20 µg/ml with coefficient correlation (r^2) 0.9997 for zeroorder spectrophotometry method. The LOD and LOQ were found to be 0.08 µg and 0.26 µg, respectively. All theproposed methods have been extensively validated as per ICH guidelines. Developed spectrophotometrymethods in this study are simple, accurate, precise and sensitive for Favipiravir in bulk and Tablet formulation.[15]
8	**Sayyed Nazifa Sabir Ali (2022)**	UV-Spectroscopic method was developed for the estimation of Favipiravir in the bulk and pharmaceutical dosage form. The solvent selected for the Favipiravir UV analysis was water, the solution in a range of 2-10µg/ml was scanned in the UV region from 200-400 nm and the λmax value was determined. The RP-HPLC method was developed on inertsil ODS-3V C18 150 mm x 4.6mm x 5µ column using buffer pH 3.5: acetonitrile [90:10] as mobile phase at flow rate 1.0 ml/min and PDA detection at 358 nm. [16]
9	**Rele Rajan V. (2021)**	Simple sensitive and accurate extractive colorimetric method was developed for the estimation of favipiravir in Pharmaceutical dosage forms. The method was based on the formation of colored ion pair complexes by the drugs with thiocynate ions. These ion pair complexes were quantitatively extracted under the experimental condition in chloroform. The absorbance values were measured at 618 respectively. The proposed method was validated statistically. A recovery of method was carried out by standard addition methods. The Beer's law ranges were found to be 1-12µg/ml, respectively. The low values of standard deviation and percentage RSD indicate high precision of method. Hence the method is useful for routine estimation of favipiravir in tablets respectively.[17]
10	**Rambabu Gundla (2021)**	Favipiravir finished dosage was approved for emergency use in many countries to treatSARS-CoV-2 patients. A specific, accurate, linear, robust, simple and stability-indicatingHPLC method was

		developed and validated for the determination of degradation impuritiespresent in the Favipiravir film coated tablets. All impurities were separation achieved fromthe stationary phase (Inert sustain AQ-C18, 250 x 4.6 mm, 5 □ m particle) and mobile phase.The mobile phase – A contains KH2PO4 buffer (pH 2.5±0.05) and acetonitrile in the ratio of98:2 v/v and mobile phase – B contains water and acetonitrile in the ratio of 50:50 v/vrespectively.[18]
11	**Srinivas Lingabathula (2021)**	A simple, selective, validated and well-defined stability that shows gradient RP-HPLC methodology for the quantitative determination of Favipiravir and Peramivir. The chromatographic strategy utilized Inertsil ODS column of dimensions 250x4.6 mm, 5 micron, using isocratic elution with a mobile phase of acetonitrile and 0.1 percent orthophosphoric acid (70:30). A flow rate of 1 ml/min and a detector wavelength of 260 nm utilizing the PDA detector was given in the instrumental settings. Using the impurity-spiked solution, the chromatographic approach was streamlined.[19]
12	**Alessandro Di Michele (2020)**	For the achiral method based on the use of a water/acetonitrile [70:30, v/v; with 0.1% (v) formic acid] eluent, All the system suitability parameters were within the acceptance criteria: tailing factor, between 1.7 and 2.0; retention factor, 2.2; number of theoretical plates, >9000. The linearity curve showed R2 = 0.99 (Rxv 2 = 0.99), while trueness (expressed as recovery) was between 96.3 and 106.3%. Coefficient of variations (CVs) (repeatability: CVw and intermediate precision: CVIP) did not exceed 1.3% and 2.9%, respectively. [20]
13	**China patent (CN104914185B)**	A kind of Favipiravir has the HPLC assay method of related substance.The invention discloses the relevant substance detecting method of a kind of Favipiravir, specifically use diode array detector, with acetonitrile (mobile phase A) phosphate solution (Mobile phase B) for flowing phase.Take Favipiravir and the related preparations containing Favipiravir is appropriate, add flowing and be configured to the mg solution Han Favipiravir 0.2 in every 1 ml mutually, as need testing solution.And become containing about 2 g solution in every 1 ml with flowing phase dilution, as contrast solution. Respectively sample introduction, in need testing solution chromatogram each impurity peak area and the main peak area that cannot be greater than contrast

		solution.[21]
14	**China patent (CN104914185A)**	The invention discloses an HPLC method for measuring related substances in Favipiravir. According to the HPLC method for measuring related substances in Favipiravir, disclosed by the invention, specifically, a diode array detector is adopted, and acetonitrile (mobile phase A)-phosphate solution (mobile phase B) serves as a mobile phase [21]

IV. CONCLUSION

The analytical chemist mainly directs his research towards the development and validation of analytical methods for the estimation of Drugs from its bulk and formulations. In the view of this fact here a details about the various methods used for the estimation of Favipiravir form bulk and formulations had been studied expensively for its application in further research

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