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Review

A Comprehensive Review On Analytical Methods For The Quantification Of Favipiravir In The Drug Product, Drug Substance And In Biological Samples

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Abstract

Advanced Pharmaceutical analysis plays an important role in the quantitative estimation of drugs in the drug formulations and in biological samples. The Present review highlights the different methods used for the estimation of Favipiravir. Favipiravir is one of the drug used in the management of COVID-19 infection. Favipiravir acts by selectively inhibiting the RNA dependent RNA polymerase, an enzyme required for RNA viral replication inside human cells. It shows a broad spectrum of activity against different RNA viruses including influenza virus. The current review article provides the data for the quantification of favipiravir by using UV, HPLC and LCMS/MS methods. In this review the estimation of favipiravir in the drug substance and product can be done by using HPLC methods and in the plasma sample the drug quantification can be done by using LC MS/MS methods. This data can be used for the verification of listed methods briefly for the development of new methods for the research and development.

Keywords: Favipiravir, COVID-19, RNA Polymerase, HPLC, LCMS/MS, Influenza virus.

INTRODUCTION

Favipiravir (Avigan) was developed by the Fujifilm Toyama Chemical Company in Japan. It selectively inhibits RNA dependant RNA polymerase (RdRP), an enzyme required for RNA viral replication inside human cells. It functions as a purine analogue and is incorporated instead of guanine and adenine. The incorporation of a single molecule of FAV into nascent viral RNA by error prone viral Rdrp leads to chain termination and viral mutagenesis and inhibits the elongation of viral RNA. Inside the cell, FAV is converted into its active phosphorylated form and is then recognized as a substrate by viral RNA dependant RNA polymerase. It shows a broad spectrum of activity against different RNA viruses including influenza virus. Favipiravir is effective against

a wide range of influenza virus types and subtypes, including strains resistant to existing influenza drugs [1]. Of note, Favipiravir exhibits antiviral activity against other RNA viruses such as arenavirus, bunyavirus, and filovirus, all of which are known to cause fatal haemorrhagic fever. These unique antiviral profiles will make Favipiravir a potentially promising drug for specifically intractable viral RNA infections [2]. In December 2019, the first cases infected with COVID-19 virus (also known as SARS-Cov-2) were reported in Wuhan, China. Now this virus becomes pandemic all over the world. SARS-Cov-2 is a beta coronavirus which is enveloped positive strand RNA viruses like MERS (Middle East respiratory syndrome)-Cov and SARS (severe acute respiratory syndrome)-Cov. For SARS-Cov-2, the viral genome codes for sixteen non-structural proteins (Nsps) required for virus replication and pathogenesis and four structural proteins. Unfortunately, specific therapeutic agent has been approved for the treatment of SARS-Cov-2 till now. However, a number of already existing antiviral drugs which have been proved to be safe and effective against other viruses are tested for their activity against the SARS-Cov-2. Special concern is given to RNA dependent RNA polymerase (RdRp) inhibitors. One of these drugs is favipiravir (FAV) which is known as T-705.Chemically it is, 6-Fluoro-3-hydroxy-pyrazine-2-carboxamide as shown in Fig1 [1]. Its molecular formula is $C_5H_4FN_3O_2$ and its molecular weight is 157.104g/mol. Elimination half-life of favipiravir is 2-5.5 hrs.

Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidelines state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factor. Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generates degradation products that can be studied to determine the stability of the molecule. The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used [2]

Table 1: Physical Characteristics of Favipiravir [3]

Parameters	Description
Molecular Formula	$C_5H_4FN_3O_2$
Molecular Weight	157.104g/mol
Appearance	Crystalline Solid Form
Colour	White to Pale Yellow
Melting point	187-193ºC
Solubility	Slightly soluble in water Completely soluble in Acetonitrile, Methanol
Synonyms	Fapilavir, Favilavir
Drug Type	Approved

Pharmacokinetic parameters

Absorption

It is well absorbed after oral administration. Bioavailability of favipiravir is almost complete up to 97.6%.

Distribution

Favipiravir Distribution depends on the plasma protein Binding. Approximately 54% of Favipiravir is plasma protein bound in this 54%, 65% is serum albumin-bound and 6.5%is alpha-1 acid glycoprotein bound. The apparent volume of distribution (V_d) of favipiravir is 15-20 L.

Metabolism

Favipiravir extensively metabolised in kidneys. It primarily undergoes metabolism through hydroxylation by aldehyde oxidase and partially by Xanthine oxidase, produces an inactive oxidative metabolite. The inactive metabolite of Favipiravir Produced by metabolism includes T705 and M2 (Favipiravir Glucuronide conjugate).

Elimination

Inactive metabolites of Favipiravir are excreted through renal route. It possess a short half-life i.e.,2 to 5.5 hrs.

Analytical methods for determination of favipiravir

The physical and chemical properties of the drug favipiravir was identified in terms of qualitative and quantitative methods.

High performance liquid chromatography

High-Performance Liquid Chromatography (HPLC) is a powerful analytical technique used for separating, identifying, and quantifying components in a mixture. It relies on the principle of liquid chromatography, where a sample is injected into a liquid mobile phase that carries it through a chromatographic column. The components in the sample interact differently with the stationary phase in the column, leading to their separation based on various physical and chemical properties. HPLC is widely employed in pharmaceuticals, food analysis, environmental monitoring, and other fields due to its high sensitivity, precision, and ability to handle a variety of sample types.

Liquid chromatography- mass spectrometry

Liquid chromatography-mass spectrometry (LC-MS) is a powerful analytical technique that combines the separation capabilities of liquid chromatography with the detection and identification capabilities of mass spectrometry. This hybrid technique is widely used in various scientific disciplines, including chemistry, biochemistry, pharmacology, environmental science, and clinical research. LC-MS has become a cornerstone in analytical laboratories for its ability to provide detailed information about the composition of complex samples.

Liquid Chromatography (LC)

LC is a chromatographic technique that separates components of a mixture based on their interactions with a liquid mobile phase and a stationary phase. The sample is dissolved in a liquid and injected into a chromatographic column, where the separation occurs. The stationary phase can be composed of various materials, and different types of LC, such as reversed-phase or normal-phase chromatography, are chosen based on the characteristics of the analytes of interest.

Mass Spectrometry (MS)

Mass spectrometry is a technique used to measure the mass-to-charge ratio of ions. In MS, analytes are ionized, and the resulting ions are accelerated in an electric or magnetic field. The ions are then separated based on their mass-to-charge ratio, and a detector records the abundance of ions at each mass-to-charge ratio. The resulting mass spectrum provides information about the molecular weight and structural characteristics of the analytes.

LC-MS Integration

The combination of LC and MS creates a powerful analytical tool. LC-MS allows for the separation of complex mixtures by liquid chromatography followed by mass spectrometric detection of the separated components. The liquid chromatography step enhances the selectivity of the analysis by separating compounds based on their chemical properties, and the mass spectrometry step provides high sensitivity and specificity for the identification and quantification of the separated compounds.

UV- visible spectroscopy

Ultraviolet-Visible (UV-Vis) Spectroscopy is a powerful analytical technique that explores the absorption of light by molecules. Operating within the UV and visible regions of the electromagnetic spectrum, typically between 190 and 800 nanometers, UV-Vis spectroscopy is widely employed in chemistry, biochemistry, and various scientific disciplines. The fundamental principle of UV-Vis spectroscopy involves the interaction of molecules with light. When a molecule absorbs UV or visible light, electrons are excited to higher energy levels. The extent and nature of this absorption provide valuable information about the molecule's structure, concentration, and electronic transitions. UV-Vis spectroscopy is particularly useful for analyzing conjugated organic compounds, as these compounds often exhibit strong absorption in the UV-Vis range due to π-electron transitions. The resulting spectrum, known as an absorption spectrum, illustrates the absorption maxima and minima at specific wavelengths. In practical terms, a UV-Vis spectrophotometer is employed to measure the intensity of light before and after it passes through a sample. The absorption spectrum is generated by plotting the absorbance values against the corresponding wavelengths. The Beer-Lambert law is then utilized to relate absorbance to concentration, providing a quantitative measure of the analyte. UV-Vis spectroscopy finds extensive applications in various fields. In biochemistry, it is employed for the quantification of nucleic acids and proteins, relying on their characteristic absorption at specific wavelengths. In pharmaceuticals, UV-Vis spectroscopy aids in assessing the purity of drugs and analyzing reaction kinetics. Furthermore, environmental monitoring and industrial quality control benefit from UV-Vis spectroscopy's ability to detect and quantify pollutants and impurities. The technique's simplicity, speed, and accuracy make it an indispensable tool in laboratories worldwide. UV-Vis spectroscopy stands as a cornerstone in analytical chemistry, providing valuable insights into the electronic structure and concentration of molecules. Its versatility and applicability across diverse scientific domains underscore its significance in advancing research, quality control, and the understanding of molecular interactions.

Chemical taxonomy

Favipiravir is an organic compound belongs to Pyrazine carboxamide Class. It possesses Pyrazine nucleus and an amide group substituted on Pyrazine nucleus.

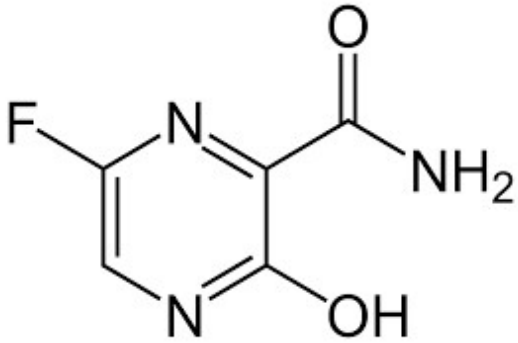

Fig 1: Structure of Favipiravir

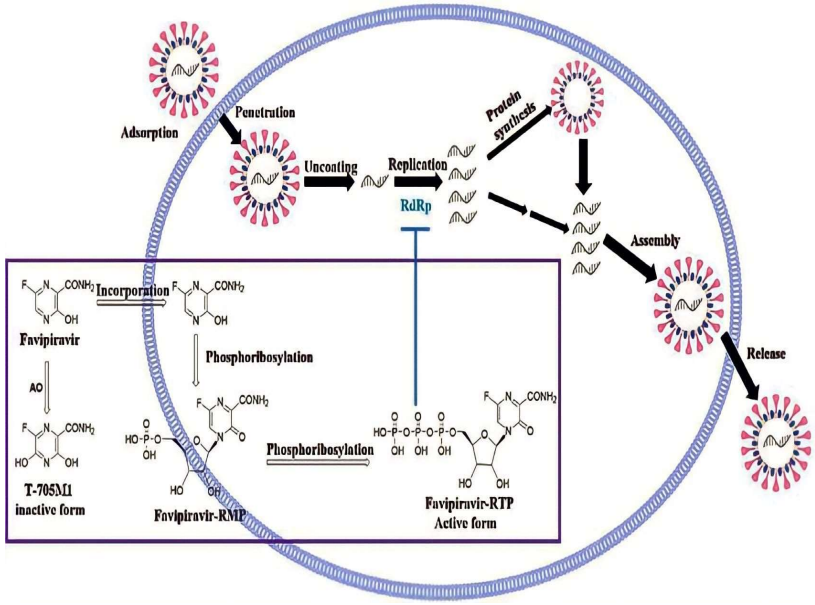

Fig 2: Mechanism of Favipiravir [4]

Table 2: Marketed Formulations of Favipiravir (from 1mg)

S. No	Trade name	Company name	Formulation	Dosage form
1	Avigan	Glenmark pharmaceuticals	Tablets	200mg
2	Fabi Flu	Glenmark pharmaceuticals	Tablets	200 mg,400 mg, 800mg
3	Favikast	Nulead pharmaceuticals Pvt Ltd	Tablets	200mg & 400 mg
4	Favijaj	Bajaj pharmaceuticals	Tablets	200 mg
5	Fevifast	Best biotech	Tablets	400 mg
6	Covihalt	Lupin Pvt Ltd	Tablets	200 mg
7	Fevilab	Chemross life sciences	Tablets	400 mg
8	Favtris	Mylan pharmaceuticals Pvt Ltd	Tablets	200 mg &800 mg
9	Fabikind	Mankind Pharma Ltd	Tablets	800mg
10	Faviour	Abott	Tablets	200mg
11	Fluguard	Sun Pharmaceutical Industries Ltd	Tablets	200mg,400mg,800mg

Table 3: List of HPLC methods for the quantification of Favipiravir

S. No	Column type	Mobile phase	Run time (min)	Retention time (min)	Flow Rate (mL/min)	Wavelength (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Correlation coefficient	References
1	C18 (250×4.6mm,5µm)	Methanol: Water (35:65 % v/v)	10.0	6.62	0.8	225.0	0.2-3.2	0.23	0.72	0.999	5
2	C18 (100×4.6mm,5µm)	Methanol: Water (70:30%v/v)	20.0	2.34	0.8	360.0	20-100	1.73	5.26	0.999	1
3	C18 (250×4.6mm ×5µm)	Acetonitrile: Methanol: Water (50:40:10%v/v)	10.0	2.79	1.0	365.0	10-15	1.04	3.16	0.999	6
4	C18 (150×4.6mm×5µm)	Acetonitrile: water (80:20%v/v)	30.0	2.70	1.0	323.0	10-90	104.44	316.5	0.998	7
5	C18 (300×3.9mm,5µm)	Water: Methanol (50:50%v/v)	6.0	3.28	1.0	221.0	20-100	0.15	0.44	0.999	8
6	C18 (15cm×4.6mm×5µm)	Methanol: Phosphate buffer 0.02m P^H 3.6 (45:55%v/v)	7.0	3.29	1.0	255.0	0-28	5.00	15.1	0.999	9
7	C18 (250×4.6mm×5µm)	Methanol: Phosphate buffer (35:65%v/v)	8.0	2.27	1.0	235.0	6.0-14	0.95	2.9	0.999	10
8	C18 (150×4.6mm×3µm)	Methanol: Ethanol: Water (25:35:40 v/v/v)	10.0	7.21	0.8	236.0	20-60	0.52	1.56	0.999	11
9	C18 Inertsil (150×4.6mm× 5µm)	Potassium dihydrogen phosphate 50 mM Buffer pH 3.5: acetonitrile 90:10%v/v)	10.0	5.0	1.0	358.0	50- 250	2.186	6.626	0.997	2
10	C18 (100 × 4.6 mm×5µm)	Acetonitrile Ammonium acetate buffer pH 4 (20:80v/v)	10.0	3.40	0.5	323.0	0.062 – 4	0.021	0.053	0.997	12
11	Zorbax C18 (250×4.6mm×5µm)	25.0 mM phosphate buffer (pH 3.5 ± 0.05): 0.1% (w/v) heptane sulphonic	10.0	3.54	1.0	321.0	6.25– 250.0	1.02	3.10	0.999	13

		acid sodium salt-methanol-acetonitrile (62:28:10 v/v/v)									
12	Poroshell 120EC-C18 (50×4.6mm×2.7µm)	0.1% Formic acid in water and 0.1% formic acid in acetonitrile (90:10) v/v	5.0	2.40	0.5	323.0	10-100	0.58	2.03	0.999	14
13	C18 (250×4.6 mm×5µm)	10 mM Potassium dihydrogen ortho phosphate buffer pH 4.0 and acetonitrile in the ratio of (90:10 v/v)	8.0	4.622	1.0	315.0	10-60	0.18	0.53	0.999	15
14	C18 (250 cm×4.6 mm×5µm)	methanol: acetonitrile: 20 mM phosphate buffer pH 3.1 (30:10:60 % v/v/v)	8.0	7.40	1.0	242.0	3.1–60.0	-	3	0.997	16
15	C18 core-shell (150×4.6 mm×5µm)	0.1 M Sodium Dodecyl Sulphate, 0.01 M Brij-35: 0.02 M monobasic potassium phosphate pH 3.1	5.0	1.87±1.23	1.0	230.0	0.5–50.0	0.04	0.12	0.999	17
16	Thermo Fischer Hypersil C18 (150×4.6 mm×5mm)	Acetonitrile: 5 mM potassium dihydrogen phosphate pH 2.5 (50:50 % v/v)	10.0	5.0	1.0	332.0	0.5 – 100	0.037	0.122	0.999	18
17	C18 (100×4.6mm×3.5µm)	0.1% phosphoric acid solution: Isopropanol (98:2 % v/v)	2.4	3.75	0.8	361.0	20-240 ng/ml	2.01 ng/ml	6.11 ng/ml	0.999	19
18	C18 (250×4.6mm×5.0mm)	50 mM Potassium dihydrogen phosphate pH 2.3: acetonitrile (90:10, v/v)	15.0	7.696	1.0	323.0	10-100	1.20	3.60	0.999	20

19	C18 (150×4.6 mm×5µm)	50 mM Phosphate buffer pH 2.5: acetonitrile (60: 40) v/v	1.0	5	1.0	323.0	0.1–100	-	3.09	0.999	21
20	C18 (250×4.6 mm×5.0mm)	0.02 M Brij-35, 0.15 M SDS : 0.02 M disodium hydrogen phosphate pH 5.0	4.0	3.81	1.0	323.0	10–100	0.985	2.986	0.999	22

Table 4: List of LC-MS methods for the quantification of Favipiravir

S. No	M/Z Value	Capillary temperature (^{0} C)	Ionization voltage (V)	Column type	Solvent mixture	Mass spectroscopy used	Run time (min)	Retention time (min)	References
1	Negative Mode: 557.0/278.2 Positive Mode: 559.0/250.2	400	4500	Phenomenex C18 (50 x 4.6) mm, 5µm	A) 0.1% v/v Formic acid in water B) 0.1% v/v Formic acid in Methanol	API 3200 Triple quadrupole Mass spectrometer	3.5	2.21	23
2	156.00-113.00	600	4000	Eclipse Plus C18 (50 x 4.6) mm, 3.5µm	Acetonitrile-Water, (80:20) v/v.	TQD Spectrometry API 4500	3.0	2.10	24
3	90-500	400	5000	Inert sustain AQ C-18 C18 (250 x 4.6) mm, 5µm	A) 0.01 M Ammonium acetate (pH 2.5): Acetonitrile (98:2) v/v B) Acetonitrile: Water (1:1) v/v	TQD Triple quadrupole Mass spectrometer	70.0	23.40	25
4	158.0-141.0	450	5500	Synergy Polar RP C18 (150 x 2.1) mm, 4µm	A) 0.2% v/v Formic acid in water B) 0.2%v/v Formic acid in methanol.	AB Sciex 6500 triple quadrupole system (AB Sciex, Macclesfield, UK) interfaced with a heated-electro-spray ionization (ESI) source.	6.0	1.62	26
5	84.95, 113.05, 141.1	150	6000	Shim Pak GISS	A) 10.0 mM ammonium acetate pH 6.5	TQD Triple quadrupole Mass spectrometer	5.0	1.90	27

	C18 (100 x 2.1) mm, 1.9 µm	B) Methanol	MS-8045

Table 5: List of **UV methods** for the estimation of Favipiravir

S. No	Wavelength (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Correlation coefficient	References
1	223	4-24	0.679	2.05	0.999	**28**
2	323	1-25	0.47	1.43	0.999	**29**
3	236	2-12	0.18	0.55	0.996	**11**
4	358	2-10	0.0723	0.22	0.990	**2**
5	234	0–10	0.095	0.29	0.999	**30**

CONCLUSION

Favipiravir is one of the newly developed anti-viral drug which acts against a wide range of influenza virus types and subtypes, including strains resistant to existing influenza drugs and SARS Cov-2 virus, which is a RNA Virus. In the recent years during the period of covid-19 it is one of the major drug which is used in the management of covid-19 along with other drugs like remdesivir and other steroidal medications to treat the infection. During the last few years majority of pharmaceutical companies were developing the favipiravir formulations in the form of tablets with the strength of 200mg,400mg and 800mg. The current review article provides various precise and consistent analytical methods for the quantification of favipiravir in the drug formulations and in biological samples which is useful for the in-vivo and in-vitro studies for the production of generic formulations as per FDA guidelines. Furthermore, the drug quantification in drug substance and formulations can be done by using UV-Visible Spectrophotometer and HPLC and in biological samples it can be with the help of LCMS/MS and other sophisticated instruments which are sensitive and to detect the compound and its related substances in very minute level (ng/ml) concentrations. This article can be useful for the scientists who are going to develop the drug formulations and in bio-analytical method development to save the time for development studies along with the drug information and its pharmacokinetics.

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CONFLICTS AND INTER STATEMENT

All authors declare that there do not have any conflicts of interest.

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