A Review on Method Development and Validation of Favipiravir Bulk and Their Tablet Dosage Form

Loganathan A[1], Nalla Kumar P[2],Ponnilavarasan I[3],Vignesh S[4], Gowtham D[5]
[1,2,3,4,5]*Department of Pharmaceutical Analysis, KMCH college of pharmacy*

Abstract **-- Favipiravir is an antiviral drug that was initially developed for influenza by Toyama Chemical, which has recently garnered much attention, especially in India, is an anti-viral drug originally designed for influenza, called Favipiravir. In this article, we have tried to provide a complete, evidence-based review of this drug in the perspective of the present pandemic to give further details about its role in the management of COVID-19. Favipiravir is a very widely used pharmaceutical, consequently it has been detected in the water system. The aim of this review is to focus on update of determination of Favipiravir in bulk and in pharmaceutical preparations using chromatographic and spectrophotometric methods. Favipiravir are estimated by RP-HPLC, UV, HPLC, RP-HPLC,UPLC, methods. For subjective and quantitative estimation of Favipiravir these diagnostic techniques can be utilized. This review provides detailed information on separation conditions for Favipiravir in the presence of drug and in presence of its degradation products.**

Index Terms- **RP-HPLC, UV, RP-UPLC, NMR\LC-MS,UPLC**.

I.INTRODUCTION

The coronavirus disease (COVID-19) spread rapidly and became an epidemic, affecting almost all countries and regions around the world. COVID-19 case death rate ranges from 1% to 7% according to the reports of World Health Organization (WHO). It still threatens the entire World [1].Since the outbreak of the COVID-19 began to affect the world, countries have implemented different treatment methods. The alternative Active therapeutis are urgently needed as a rising COVID-19 pandemic and possible effects on global health [2].

Many medications such as chloroquine, remdesivir, and favipiravir are currently undergoing clinical trials in several countries to assess their effectiveness and safety in treating coronavirus disease [3, 4].There is no standard for the treatment of COVID-19 since there is not enough evidence [5]. Favipiravir is an antiviral drug that was initially developed for influenza by Toyama Chemical. The favipiravir selectively inhibits the RNA polymerase of RNA viruses, thus preventing viral reproduction. It displays antiviral activity against alpha-, filo-, bunya-, arena-, flavi-, and noro viruses [6, 7],few LC-MS methods developed and validated for determination of favipiravir .There are numerous drugs become examined and attempted for the treatment of SARS-COV-2.[11-15]

II. CHARACTERISTICS OF SARS-COV-2

SARS-CoV-2 is an enveloped positive-sense virus and belongs to single-stranded RNA beta-coronavirus. Currently, there is not any accepted pattern for nomenclature the growing phylogenetic diversity of SARS-CoV-2 since the rate of genome generation is unprecedented. However, the occurrence of the genetic variants and lineages of SARS-CoV-2 has been studied in some geographical regions [16-18].

Genome of the virus encodes three protein types including structural, non-structural and accessory proteins. Four non-structural proteins including three-chymotrypsin-like protease, papain-like protease, helicase, and RdRp are important in the virus life cycle [19]. Spike glycoprotein is a structural protein essential for interactions between the virus and host cell receptor [20]. Three-chymotrypsin-like and papain-like proteases, helicase, RdRp, and spike glycoprotein are interesting targets for drug development against SARS and MERS coronaviruses [19,20].

III.FAVIPIRAVIR

The agent was discovered using phenotypic screening and manufactured by Japanese pharmaceutical company Fujifilm Toyama Chemical Co., Ltd. Favipiravir was initially detected to be active against influenza virus in vitro [21]. Favipiravir was approved for stockpiling for pandemic purpose only in Japan in 2014, not yet for the treatment of seasonal influenza,

and marketed in China as a second-line treatment of novel or reemerging influenza outbreaks [21,22].Evidences from in vitro, in vivo, and clinical studies strongly recommend that the safety profile and mechanism of action of favipiravir make it a hopeful drug against a board-spectrum of RNA viruses [23-26].

IV. MECHANISM OF ACTION

Favipiravir is a pro-drug that shows its antiviral activity after incorporation into infected human cells [28,29]. With entrance to the infected cells, favipiravir undergoes the phosphoribosylation and further phosphorylation to form an active structure naming favipiravir ribofuranosyl-5′-triphosphate (favipiravir-RTP) [27] .*In vitro* and *in vivo* studies suggested the lethal mutagenesis as the most probable favipiravir mechanism of action [30-33]. However, two distinct studies support the chain termination as the responsible mechanism of action [34,35].

V. REPORTED METHODS

S.NO	TITLE/METHOD	DISCRIPTION	RF.NO
1.	HPLC-UV method for quantification of favipiravir in pharmaceutical formulations.	Model: Shimadzu 1800 UV Visible spectrophotometer Solvent: 50 mM potassium dihydrogen phosphate (pH 2.3) and acetonitrile (90:10 v/v) Wavelength (nm): 323 nm Linearity: 10–100mg/mL RetentionTime:7.696 min. Flow rate:1 ml/min	37
2.	Bio analytical method development and validation for the determination of Favipiravir in spiked human plasma by using RP-HPLC.	Column: cromasil C18 (250mm x 4.6ID, 5 micron). Solvent:water in the ratio(35:65 %v/v) at pH 3.0.Flow rate: 0.8ml/min Wavelength (nm):225 nm Linearity : 0.2- 3.2µg/ml Retention time : 6.62 min	38
3.	Analytical method development and validation and forced degradation stability-indicating studies of Favipiravir by RP-HPLC and UV in bulk and pharmaceutical dosage form .	Model: Shimadzu HPLC system Shimadzu – 1800 UV Visible Spectrophotometer Solvent: buffer pH 3.5: acetonitrile [90:10] Wavelength (nm):358 nm Linearity :2-10µg/ml Retention Time:5.0 min	39
4.	Comparison of HPLC and UV Spectrophotometric Methods for Quantification of Favipiravir in Pharmaceutical Formulations	Column: C_{18} column (250 mm x 4.5 mm, 5 µm) Mobile Phase: Sodium acetate solution (pH 3.0 with glacial acetic acid) and acetonitrile (85:15, v/v) Flow rate:1 ml/min. Wavelength:227 nm Linearity:10-60µg/ml	40
5.	Method development and validation of Favipiravir by RP-HPLC.	Column: Cosmosil C_{18} (250 mm × 4.6ID, Particle size: 5 micron) Mobile Phase: Methanol: Water (75:25, v/v). pH 3 orthophosporic acid Flow rate: 0.8ml/min. Wavelength: 227nm Linearity: 10-50mg/ml Retention Time: 4 min..	41
6.	RP-HPLC method for determination of Favipiravir(RdRp of RNA Viruses) in pharmaceutical dosage Form	Column : NucleosilC18 column 4.6 mm x 250 mm., 5 µm. Mobile Phase: Acetonitrile: methanol: HPLC Grade water(50:40:10 % v/v) Flow Rate: 1ml/min. Wavelength: 365nm Linearity: 10-50 mg/ml Retention Time: 2.794min.	42
7.	Stability indicative and cost effective analytical method development and validation of favipiravir and peramivir in bulk and	Column : Inertsil ODS column of dimensions 250x4.6 mm, 5µm Mobile Phase: Acetonitrile and 0.1 % Orthophosphoric acid (70:30)	43

	pharmaceutical dosage form by using RP-HPLC	Flow Rate: 1ml/min. Wavelength: 260nm Linearity: 10-150 mg/ml Retention Time: Favipiravir and Peramivir were about 3.003 and 7.271 min.	
8.	Development and validation of a rapid HPLC-DAD method for determination of Favipiravir in pharmaceutical formulation .	Column: Poroshell 120EC-C_{18} column (4.6 x 50 mm, 2.7 μm) Mobile Phase: 0.1% formic acid in water and 0.1% formic acid in acetonitrile (90:10, v/v). Flow rate :0.5ml/min Wavelength :323 nm Linearity : 10-100 μg/ml Retention Time: 2.40min	44
9..	Development and validation of novel method for the determination of favipiravir and peramivir using Reverse Phase Ultra Performance Liquid Chromatography	Stationary Phase: Inertsil C18 ODS 2.1x 50 mm, 1.8 mm Mobile Phase: Phosphate buffer (pH 3.0), Methanol in proportion 45: 55 v/v Flow rate: 0.3 ml/min Wavelength : 254nm Linearity:0.67-24mg/ml Retention time: 7.288 min	45
10.	Development and validation of UPLC-MS / MS method for obtaining Favipiravir tablet dosage form and evaluation of its behavior under forced conditions	Column : C_{18}(4.6 mm *50 mm, 2.7 μm) Mobile Phase: water-methanol (80-20 v/v) Wavelength : 222nm Flow Rate: 0.8 mL/min Linearity: 1-10 μg /ml Retention Time: 1.115 min.	46
11.	A novel stability-indicating HPLC-DAD method for determination of favipiravir, a potential antiviral drug for COVID-19 treatment; application to degradation kinetic studies and in-vitro dissolution profiling	Column :Zorbax C_{18} column MobilePhase:25.0 mM phosphate buffer (pH 3.5 ± 0.05) containing 0.1% (w/v) heptane sulphonic acid sodium salt-methanol–acetonitrile (62:28:10)v/v Wavelength : 321nm Flow Rate: 1 mL/min Linearity: 6.25–250.00 μg/mL Retention Time: 1.115 min.	47
12.	The anti-COVID-19 drug Favipiravir: Degradation, Method development, Validation, NMR/LC–MS characterization, and *In-vitro* safety evaluation	Column : Thermo Fischer Hypersil C18 column (4.6 . 150 mm,*5 m) MobilePhase: Acetonitrile-5 mM potassium dihydrogen phosphate (pH 2.5) (50:50, v/v) Wavelength : 332nm Flow Rate: 1 mL/min Linearity: 0.5–100 μg/mL Retention Time: 2.765 min.	48
13.	Development and Validation of HPLC-DADMethod for the Determination of Favipiravir and Studying the Impact of Vitamin C on the Pharmacokinetics of COVID-19 AntiviralDrug Favipiravir	Column: ZORBAX Eclipse XDB-C18 (4.6 * 150mm* 5.0m, MobilePhase: 50% Acetonitrile and 50% water (with 0.25% trifluoroacetic acid) Wavelength : 289nm Flow Rate: 1 ml/min Linearity: 10–2500 ng/mL. Retention Time: 6.464 and 5.441 min.	49

VI.CONCLUSION

The presented review provides information about the various methods available in the literature for the determination of Favipiravir. The different analytical methods are reported for this drug like UV spectroscopy, HPLC, LC-MS, NMR/LC-MS. This review will assist the upcoming analytical method to develop and it gives the evidence about its characteristics of this drugs. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

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