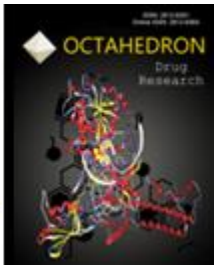
Octahedron Drug Research 2 (2023) 36-43 ISSN: 2812-6351
Online ISSN: 2812-636X

OCTAHEDRON Drug Research Vol. 2

Review Article



Review article on instrumental analysis of molnupiravir, favipiravir, and ritonavir in different matrices

Roshdy E. Saraya [1], Monzer I. Elgamal[1], Hany A. Batakoushy[2], Baher I.Salman[3]

[1] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Port said University, Egypt.

[2] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Menoufia University, Egypt.

[3] Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy-Al-Azhar University-Assiut branch, Egypt

*Correspondence: Roshdy E. Saraya Email: drsaraya@yahoo.com, Roshdy.elsayed@pharm.psu.edu.eg Tel:0201006911004

ARTICLE INFO

Article history:
Received 28 December 2022
Received in revised form
15 January 2023
Accepted 19 January 2023
Available online 19 January 2023

Keywords:

Molnupiravir; Favipiravir; Ritonavir; Corona virus.

© 2023 by the authors; licensee Port Said University, Egypt. This article is an open access article distributed under the terms and conditions of the Creative Commons by Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).

ABSTRACT

Ever since the emergence of the COVID-19 outbreak, there have been so many casualties worldwide. According to WHO, more than half a billion people were infected by the virus, of which 6.5 million deaths were counted. However, some already existing antivirals were repositioned and repurposed as anti-COVID-19 therapeutics such as molnupiravir, favipiravir, and ritonavir. The emergency needs to develop effective anti-viral drugs for the treatment of COVID-19 infection Consequently, there arose a need for effective, rapid, accurate, and reliable techniques for the determination of these antivirals. Here in this review, the different reported analytical methods for the quantitative determination of the studied anti-viral drugs were discussed. These reported methods include spectrophotometric methods, spectroflurometric methods, electrochemical methods, and different chromatographic methods, wither the reported method used for the quantitative determination of the studied anti-viral drugs in a single dosage form or in a co-formulated mixture also in different biological fluids and samples.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a member of the novel coronaviruses, which is caused by the SARS-CoV-2 virus. It's one of the coronaviruses of the family *Coronaviridae* [1] which have been around for quite a time, causing serious symptoms of fever and other respiratory illnesses such as dyspnea and pneumonia [2]. Some of the remarkable traits that distinguish this family of viruses are their extensive ability to recombine and mutate, in addition to their

ability to infect a variety of species and cell types. Because of this, they keep evolving and re-emerging, causing a lot of deaths [3, 4]. Often, outbreaks of coronaviruses start from animal hosts owing to their ability to jump between species. Examples of this are the outbreaks of SARS in 2002, MERS in 2012, and COVID-19 in 2019 which all started from animal hosts like bats and camels [3, 5-7]. According to WHO, there have been 628,694,934 cases of COVID-19 worldwide, of which 6,576,088 deaths were reported [8]. Hence, there was an urgent need for a treatment. For this sake, various antiviral drugs have been repurposed for the treatment of COVID-19, which were previously used for the treatment of other viral infections such as hepatitis C and HIV. The most important of such drugs are remdesivir, favipiravir, hydroxychloroquine, ritonavir [2, 9], and molnupiravir [10] of which only molnupiravir (MLP), favipiravir (FVR) and ritonavir (RTV) will be discussed here.

Molnupiravir

MLP (**Fig:1**) is an isopropyl ester prodrug that is converted inside the body into the active form, β-d-N4-hydroxycytidine [11]. It has a broad-spectrum antiviral activity against RNA viruses like influenza, SARS, MERS, and Ebola. Due to this, it was repurposed to be used against mild-to-moderate COVID-19 cases [12, 13]. It's a nucleoside analog that targets the RNA-dependent RNA-polymerase (RdRp) enzyme, which lies in the core of coronaviruses replication machinery [14], inducing errors in the RNA sequence, producing a fatally mutated viral RNA, and even inhibiting the RdRp enzyme. This consequently inhibits viral replication and pathogenesis [10-12].

Favipiravir

FVR (**Fig:1**) is also a nucleotide analog (guanine) [15] and was initially used for the treatment of influenza, but later was repositioned as an anti-COVID-19 drug due to its wide antiviral activity spectrum [1, 16, 17]. Like molnupiravir and all nucleoside analogs, favipiravir also inhibits the viral RdRp enzyme and can cause fatal mutations when incorporated into the viral RNA, resulting in alleviated disease severity [14, 15].

Ritonavir

RTV (**Fig:1**) is one of the few antivirals used for the treatment of HIV; it's a potent HIV protease inhibitor [18] that's usually used in combination with other synergetic antivirals [19, 20]. For this, it was repositioned as a co-administered drug for the treatment of COVID-19. The literature included co-administration of These antivirals demonstrated some treatment efficacy; however, there is a need to develop accurate and reliable methods for the determination of these drugs. In the following section of this article, the most recent literature concerning the determination of MLP, FVR, and RTV will be review.

Review of the analytical methods:

Different analytical methods were proposed for determination of MLP, FAR, and RTV in different matrices this method of analysis will be summarized as follows:

Spectrophotometric methods:

A few techniques were reported for the spectrophotometric determination of MLP, FVR, and RTV in bulk form and in pharmaceutical formulations, and they are summarized in **Table 1**.

Spectrofluorimetric methods:

A few techniques were reported for the spectrofluorimetric determination of MLP, FVR, and RTV as summarized in **Table 2**.

Chromatographic methods:

Most of the reported techniques in the literature were chromatographic. **Table 3** summarized the most recently published methods of determination of MLP, FVR, and RTV in a variety of matrices such as human and rat plasma, pharmaceutical formulations, and environmental water.

Electrochemical methods:

Some electrochemical approaches to the determination of MLP, FVR, and RTV were published (**Table 4**)

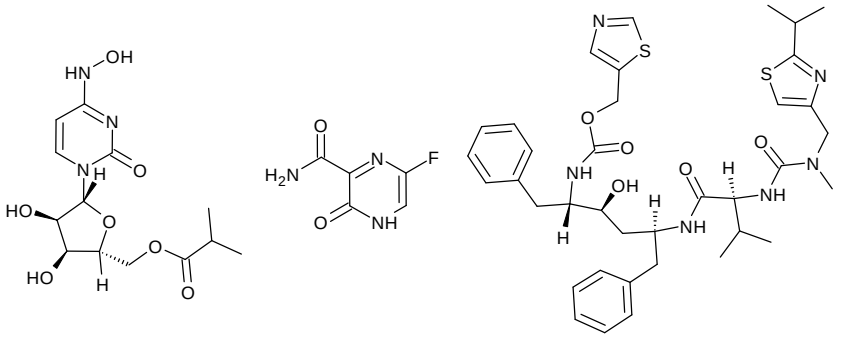


Figure 1: Chemical structures of molnupiravir, favipiravir and ritonavir.

Table 1: Spectrophotometric methods for determination of MLP, FVR, & RTV.

Drug(s)	Matrix	Method or reagent	λ_{max}	Ref.
FVR	Bulk & tablets	Zero order & first order derivative	322 nm (pH 4) 361 nm (pH 6.4) 237 nm (pH 9)	[21]
FVR	Bulk & tablets	Methyl orange- (MO) & Methyl red- (MR) based colorimetry	477 nm (MO) 521.6 nm (MR)	[22]
MLP	Pure form & capsules	Diazo coupling-based spectrophotometry	515 nm	[23]
RTV	Pure form & tablets	Ethanol (solvent)	260 nm	[24]

Table 2. Spectrofluorometric methods for determination of MLP, FVR, & RTV.

Drug(s)	Matrix	Method	$\lambda_{Excitation}$	$\lambda_{Emission}$	Ref.
FVR/ Remdesivir	Synthetic mixtures & Human plasma	First derivative order	195 nm	335 nm	[25]
FVR	Tablets & Human plasma	Relative synchronous fluorescence intensity	312 nm	372 nm	[26]
FVR	Human plasma	Synchronous spectrofluorimetry	363 nm	423 nm	[27]
MLP	Human plasma	PA@CQDs-based spectrofluorimetry	440 nm	504 nm	[28]

Table 3. Chromatographic methods for determination of MLP, FVR, & RTV.

Drug(s)	Matrix	Column	Mobile phase	System	Ref.
FVR	Human plasma	RP-BEH C18 column	Methanol:ACN:water 15:35:50 (acidified with orthophosphate, pH 4)	UPLC–DAD	[29]
FVR	Tablets & Human	Pre-coated silica gel 60	Ethyl acetate:methanol: ammonia (8:2:0.2, v/v)	Normal phase TLC	[30]

	plasma	F254 aluminum plates			
FVR	Bulk & Tablets	Poroshell 120EC-C18 Column	0.1% formic acid in water & 0.1% formic acid in ACN (90:10, v/v)	HPLC–DAD	[31]
FVR	Human plasma	Acquity UPLCr BEH HILIC column	ACN & 0.005% ammonia in water (75:25, v/v)	UPLC–MS/MS	[32]
FVR	Tablets	Zorbax C18 column	25 mM phosphate buffer (pH 3.5 ± 0.05) & 0.1% (w/v) heptane sulphonic acid sodium salt–methanol–acetonitrile (62:28:10, v/v)	HPLC–DAD	[33]
FVR	Human plasma	Hypersil ODS C18 column	50 mM phosphate buffer (pH = 2.5) & ACN (60:40, v/v)	Gadolinium-based MIL microextraction–HPLC–UV	[34]
FVR	Human plasma	Hypersil ODS C18 column	50 mM phosphate buffer (pH = 2.5) & ACN (60:40, v/v)	Menthol-assisted microextraction–HPLC–UV	[35]
FVR	Rat plasma	Shim-pack GISS C18 column	Gradient elution; water:ACN (80:20 to 0:100) + 0.1% v/v formic acid	UHPLC–MS/MS	[36]
FVR, MLP, & RTV	Pure form & capsules	Silica gel 60F254 TLC plates	Methylene chloride: ethyl acetate: methanol: 25% ammonia (6:3:4:1, v/v/v/v)	HPTLC–Densitometric scanning	[37]
FVR	Rat plasma	Poroshell 120 EC-C18 column	methanol: 0.1% formic acid (95:5, v/v)	UPLC–MS/MS	[38]
MLP & FVR	Tablets & capsules	RP-C18 core-shell column	0.1M SDS, 0.01M Brij-35, and 0.02M monobasic potassium phosphate	HPLC–UV/DAD	[39]
NHC, the active metabolite of MLP	Human plasma	Agilent Zorbax Eclipse plus C18 column	0.2% Methanol: acetic acid (5:95, v/v)	HPLC–MS/MS	[40]
MLP	Bulk	Phenomenex C18 column	10mM phosphate buffer (pH 7): ACN (80:20, v/v)	HPLC–DAD	[41]
MLP	Tablet	Agilent C18 column	Orthophopoaricacid: ACN (60:40, v/v)	RP-HPLC–DAD	[42]
RTV/	Human	Thermo BDS	Gradient elution; Deionized	HPLC–MS/MS	[43]

Nirmatrelvir	plasma	Hypersil C18 column	water (solvent A) & methanol (solvent B), each with 0.1% v/v formic acid		
RTV	Pure form & tablets	ODS C18 column	20 mM KH_2PO_4 (pH 3) & ACN (45:55, v/v)	HPLC–UV/Vis	[24]
RTV/ Ombitasvir/ Paritaprevir	Tablets	Inertsil ODS-C18 column	0.02 M phosphate buffer (pH 4.5): ACN: methanol (50:30:20, v/v)	RP-HPLC–UV/Vis	[44]
RTV	Environmental water	Inertsil ODS C18 35C	Acidifed water (pH 3.5): ACN (40:60, v/v)	SPE–HPLC–UV/Vis	[45]
RTV/ Lopinavir	Human plasma	analytical column	Gradient elution; 5 mM methanol & ammonium acetate (85:15, v/v)	UPLC–MS/MS	[46]
RTV/ Darunavir	Tablet	C18 column	0.01N KH_2PO_4: ACN (45:55, v/v)	RP-HPLC–DAD	[47]
RTV	Yellow catfish	Alltima C8 column	Gradient elution; ACN & 0.1% formic acid	PT-SPE–UPLC–MS/MS	[48]
RTV	Lipid nanocarriers	Inertsil ODS-3V C18 column	Orthophosphoric acid (OPA) in water (pH 3) & CAN	SPE–RP-HPLC–UV/Vis	[49]
RTV/ Lopinavir	Tablet	Kromasil C18 column	Phosphate buffer:ACN (30:70, v/v)	RP-HPLC–UV/Vis	[50]
FVR	Film-coated tablets	Inert sustain AQ-C18	Gradient elution; KH_2PO_4 buffer:ACN (98:2, v/v) & water:ACN (50:50, v/v)	HPLC–DAD	[51]
RTV/ Nirmatrelvir	Human plasma	Zorbax XDB-C18	Gradient elution; aq. ammonium formate/formic acid buffer (pH 3.5): ACN (9:1, v/v)	HPLC–MS/MS	[52]
MLP	Rat plasma	X-bridge phenyl columns	Methanol:ACN (60:40, v/v)	HPLC–MS/MS	[53]
RTV/ Lopinavir	Rat plasma	Agilent ZORBAX eclipse plus C18 columns	Gradient elution; ACN: 0.1% formic acid	UHPLC-MS/MS	[54]
FVR	Pharmaceutical dosage forms	Nucleosil C18 column	ACN: methanol: water (50:40:10, v/v)	HPLC–DAD	[55]

Table 4. Electrochemical methods for determination of MLP, FVR, & RTV.

Drug(s)	Matrix	Method/Technique	Electrode/sensor	LOD	Ref.
FVR	Tablets & Serum Samples	AdSDPV AdSSWV	Diamond NPs-C paste (modified Carbon paste electrode)	4.83×10^{-9} M (Tab) 5.18×10^{-8} M (Ser) 2.44×10^{-7} M (Tab) 4.38×10^{-8} M (Ser)	[56]
FVR	Tablets & Serum Samples	CV & DPV	Au NPs/NiS_2 NS/BC/GCE/MIP	0.13 nM	[57]
FVR	River water, human plasma, & urine	CV, DPV, EIS, & CA	MIP-Co/Ni@MOF/SPE	7.5×10^{-11} M	[58]
FVR	Plasma & urine	CV, DPV, EIS	MoS_2@MIP core-shell nanocomposite	0.002 nM	[59]
MLP	Capsules	CV, EIS, & SWV	GCE modified with rGO	0.03 μM	[60]
FVR	Tablets,human urine, & artificial blood	DPV	Pencil graphite electrode (PGE)	0.35 μM	[61]

Conclusion

This review includes the most recent methods of determination of molnupiravir, favipiravir, and ritonavir, which were reported in 2022. There were a relatively small number of reported spectroscopic and electrochemical techniques. Meanwhile, on the other hand, most of the reported literature was chromatographic. The techniques included the determination of MLP, FVR, and RTV in bulk form, tablets, capsules, human and rat plasma, urine samples, combined with other antivirals, and in the form of their degradation products.

Conflict of Interest

The authors declare and state that this research was conducted in the absence of any potential or source for conflict of interest.

References

1. Frediansyah, A., et al., *Antivirals for COVID-19: A critical review.* Clinical Epidemiology and Global Health, 2021. **9**: p. 90-98.
2. Malinis, M., et al., *An overview on the use of antivirals for the treatment of patients with COVID19 disease.* Expert Opinion on Investigational Drugs, 2021. **30**(1): p. 45-59.
3. Platto, S., T. Xue, and E. Carafoli, *COVID19: an announced pandemic.* Cell Death & Disease, 2020. **11**(9): p. 799.
4. Saraya, R.E. and B.I. Salman, *Sensitive spectrofluorimetric determination of metoclopramide, itopride, mosapride, and trimebutine by Fluorescence Quenching Reaction with Eosin Y in Pharmaceutical Formulations and Spiked Human Plasma.* Octahedron Drug Research, 2022: p. 13-25.
5. de Wit, E., et al., *SARS and MERS: recent insights into emerging coronaviruses.* Nature Reviews Microbiology, 2016. **14**(8): p. 523-534.
6. Roshdy ES, Magda E, and Hanaa S, *Development of a highly sensitive high-performance thin-layer chromatography method for the screening and simultaneous determination of sofosbuvir, daclatasvir, and ledipasvir in their pure forms and their different pharmaceutical formulations.* J. Sep. Sci., 2018. **41**(18): p. 3553-3560.
7. Adel EI, et al., *Development and validation of eco-friendly micellar-HPLC and HPTLC-densitometry methods for the simultaneous determination of paritaprevir, ritonavir and ombitasvir in pharmaceutical dosage forms.* Heliyon, 2019. **5**(4): p. e01518.
8. Organization, W.H. *WHO Coronavirus (COVID-19) Dashboard*. 2022 5 November 2022]; Available from: https://covid19.who.int/.
9. Simsek Yavuz, S. and S. Unal, *Antiviral treatment of COVID-19.* Turk J Med Sci, 2020. **50**(SI-1): p. 611-619.
10. Pourkarim, F., S. Pourtaghi-Anvarian, and H. Rezaee, *Molnupiravir: A new candidate for COVID-19 treatment.* 2022. **10**(1): p. e00909.
11. Singh, A.K., et al., *Molnupiravir in COVID-19: A systematic review of literature.* Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2021. **15**(6): p. 102329.
12. Tian, L., et al., *Molnupiravir and Its Antiviral Activity Against COVID-19.* 2022. **13**.
13. Yip, A.J.W., et al., *Repurposing Molnupiravir for COVID-19: The Mechanisms of Antiviral Activity.* 2022. **14**(6): p. 1345.

14. Joshi, S., et al., *Role of favipiravir in the treatment of COVID-19.* International Journal of Infectious Diseases, 2021. **102**: p. 501-508.
15. Ghasemnejad-Berenji, M. and S. Pashapour, *Favipiravir and COVID-19: A Simplified Summary.* Drug Res (Stuttg), 2020. **71**(03): p. 166-170.
16. Qomara, W.F., et al., *Effectiveness of Remdesivir, Lopinavir/Ritonavir, and Favipiravir for COVID-19 Treatment: A Systematic Review.* Int J Gen Med, 2021. **14**: p. 8557-8571.
17. Agrawal, U., R. Raju, and Z.F. Udwadia, *Favipiravir: A new and emerging antiviral option in COVID-19.* Medical Journal Armed Forces India, 2020. **76**(4): p. 370-376.
18. Hsu, A., G.R. Granneman, and R.J. Bertz, *Ritonavir.* Clinical Pharmacokinetics, 1998. **35**(4): p. 275-291.
19. Amani, B., et al., *Lopinavir/Ritonavir for COVID-19: a Systematic Review and Meta-Analysis.* Journal of Pharmacy & Pharmaceutical Sciences, 2021. **24**: p. 246-257.
20. Roshdy ES, Magda E, and Hanaa S, *Development of a high-performance thin-layer chromatographic method for the simultaneous determination of newly co-formulated antiviral drugs sofosbuvir and velpatasvir in their pure forms and tablet dosage form.* JPC, 2019. **32**(2): p. 141-147.
21. Gummadi, S., et al., *AN ECONOMICAL ASSAY METHOD FOR THE SPECTROSCOPIC QUANTIFICATION OF AN ANTIVIRAL DRUG.* YMER, 2022. **21**(9): p. 672–684.
22. Wrushali, A.P., et al., *Development of visible spectrophotometric methods for the analysis of favipiravir in pure drug and tablet formulation.* GSC Biological and Pharmaceutical Sciences, 2022. **20**(2): p. 184-195.
23. Abdelazim, A.H., et al., *Green adherent spectrophotometric determination of molnupiravir based on computational calculations; application to a recently FDA-approved pharmaceutical dosage form.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2023. **285**: p. 121911.
24. Akbel, E., *Analytical methods for the quantification of ritonavir in pharmaceuticals, a comparative evaluation.* Bulletin of the Chemical Society of Ethiopia, 2022. **36**(4): p. 737-747.
25. El-Awady, M., et al., *Insights on the Quantitative Concurrent Fluorescence-Based Analysis of Anti-COVID-19 Drugs Remdesivir and Favipiravir.* Journal of Fluorescence, 2022. **32**(5): p. 1941-1948.
26. El Sharkasy, M.E., et al., *Quantitative analysis of favipiravir and hydroxychloroquine as FDA-approved drugs for treatment of COVID-19 using synchronous spectrofluorimetry: application to pharmaceutical formulations and biological fluids.* 2022. **37**(6): p. 953-964.
27. Ramzy, S., et al., *Spectrofluorimetric quantitative analysis of favipiravir, remdesivir and hydroxychloroquine in spiked human plasma.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2022. **281**: p. 121625.
28. Salman, B.I., et al., *Fabrication of novel quantum dots for the estimation of COVID-19 antiviral drug using green chemistry: application to real human plasma.* RSC Advances, 2022. **12**(26): p. 16624-16631.
29. Emam, A.A., et al., *Rapid and ecofriendly UPLC quantification of Remdesivir, Favipiravir and Dexamethasone for accurate therapeutic drug monitoring in Covid-19 Patient's plasma.* Microchemical Journal, 2022. **179**: p. 107580.
30. Noureldeen, D.A.M., et al., *Novel environment friendly TLC-densitometric method for the determination of anti-coronavirus drugs "Remdesivir and Favipiravir": Green assessment with application to pharmaceutical formulations and human plasma.* Microchemical Journal, 2022. **174**: p. 107101.
31. TaŞKin, D., *Development and Validation of a Rapid HPLC-DAD Method for Determination of Favipiravir in Pharmaceutical Formulation.* Clinical and Experimental Health Sciences, 2021.
32. Abd Allah, F.I., et al., *Fully validated UPLC–MS/MS method for quantifying Favipiravir in human plasma boosted lean six sigma: An application for a bioequivalence study.* 2022. **36**(9): p. e5381.
33. Marzouk, H.M., et al., *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.* Microchemical Journal, 2022. **172**: p. 106917.
34. Abdallah, I.A., et al., *A gadolinium-based magnetic ionic liquid for supramolecular dispersive liquid–liquid microextraction followed by HPLC/UV for the determination of favipiravir in human plasma.* 2022. **36**(6): p. e5365.
35. Abdallah, I.A., et al., *Menthol-assisted homogenous liquid-liquid microextraction for HPLC/UV determination of favipiravir as an antiviral for COVID-19 in human plasma.* Journal of Chromatography B, 2022. **1189**: p. 123087.
36. El Azab, N.F., *A validated UHPLC-MS/MS method for simultaneous quantification of some repurposed COVID-19 drugs in rat plasma: Application to a pharmacokinetic study.* Microchemical Journal, 2022. **178**: p. 107321.
37. Saraya, R.E., et al., *Highly sensitive high-performance thin-layer chromatography method for the simultaneous determination of molnupiravir, favipiravir, and ritonavir in pure forms and pharmaceutical formulations.* 2022. **45**(14): p. 2582-2590.
38. Tarek Mahmoud, S., et al., *Core shell stationary phase for a novel separation of some COVID-19 used drugs by UPLC-MS/MS Method: Study of grapefruit consumption impact on their pharmacokinetics in rats.* Microchemical Journal, 2022. **181**: p. 107769.
39. Sharaf, Y.A., et al., *Two Green Micellar HPLC and Mathematically Assisted UV Spectroscopic Methods for the Simultaneous Determination of Molnupiravir and Favipiravir as a Novel Combined COVID-19 Antiviral Regimen.* 2022. **27**(7): p. 2330.
40. Gouda, A.S., et al., *A validated LC-MS/MS method for determination of antiviral prodrug molnupiravir in human plasma and its application for a pharmacokinetic modeling study in healthy Egyptian volunteers.* Journal of Chromatography B, 2022. **1206**: p. 123363.
41. Camlik, G., et al., *A Validated High-Pressure Liquid Chromatography (HPLC) Method for Molnupiravir.* 2022. **10**(9).
42. Bindu, M., et al., *A validated stability indicating RP-HPLC method for the determination of molnupiravir in pharmaceutical dosage form.* World Journal of Advanced Research and Reviews, 2022. **15**(1): p. 580-590.
43. Liu, C., et al., *Simultaneous determination of nirmatrelvir and ritonavir in human plasma using LC–MS/MS and its pharmacokinetic application in healthy Chinese volunteers.* 2022. **36**(11): p. e5456.
44. Nagaraju, G., R. Agarwal, and R.R. Nadendla, *Simultaneous Estimation of Ombitasvir, Paritaprevir and Ritonavir in Tablet*

Dosage Form by Reverse Phase High-Performance Liquid Chromatography. International Journal of Life Science and Pharma Research, 2022.

45. Tlili, I., et al., *Cuttlefish bone powder as an efficient solid-phase extraction sorbent of anti-SARS-CoV-2 drugs in environmental water.* Chemical Papers, 2022. **76**(11): p. 6941-6951.
46. Nalini, N.K.S., et al., *New validated LC-MS/MS simultaneous estimation*
of Lopinavir and Ritonavir in human plasma positive
ion mode using Deuterated internal standards. Research Square, 2022.
47. Grace, P.L. and C. Parthiban, *Analytical method development and validation for the simultaneous estimation of Darunavir and Ritonavir by RP-HPLC method.* World Journal of Pharmaceutical Sciences, 2022. **10**(01): p. 32-40.
48. Shen, Q., et al., *Rapid determination of antiviral drugs in yellow catfish (Pelteobagrus fulvidraco) using graphene/silica nanospheres (G/KCC-1) based pipette tip solid-phase extraction with ultra-performance liquid chromatography-tandem mass spectrometry.* Journal of Chromatography B, 2022. **1189**: p. 123097.
49. Jitta, S.R., et al., *Development and Validation of RP-HPLC Method for Quantification of Total, Free and Entrapped Ritonavir in Lipid Nanocarriers and Drug content of Film Coated Fixed Dose Formulation.* Indian Journal of Pharmaceutical Education and Research, 2022. **56**(3s): p. s547-s558.
50. Indira, A., N.Y. Sreedhar, and B. D, *A Stability Indicating Method Development of Lopinavir and Rotinavir in Combined Tablet Dosage Forms by RP-HPLC.* Research Journal of Pharmacy and Technology, 2022: p. 661-664.
51. Vemuri, D.K., et al., *Favipiravir (SARS-CoV-2) degradation impurities: Identification and route of degradation mechanism in the finished solid dosage form using LC/LC–MS method.* 2022. **36**(6): p. e5363.
52. Martens-Lobenhoffer, J., et al., *Simultaneous quantification of nirmatrelvir and ritonavir by LC-MS/MS in patients treated for COVID-19.* Journal of Chromatography B, 2022. **1212**: p. 123510.
53. Konatham Teja Kumar, R. and M.A. Haque, *Develop and validate a highly sensitive method for the estimation of Molnupiravir in rat plasma by high-performance liquid chromatography-tandem mass spectroscopy and its application to pharmacokinetic studies.* Journal of Pharmaceutical Negative Results, 2022: p. 28-34.
54. Li, L., et al., *Influence of traditional Chinese medicines on the in vivo metabolism of lopinavir/ritonavir based on UHPLC-MS/MS analysis.* Journal of Pharmaceutical Analysis, 2022. **12**(2): p. 270-277.
55. Ravisankar, P., et al., *RP-HPLC Method for Determination of Favipiravir (RdRp of RNA Viruses) in Pharmaceutical Dosage Form.* Current Trends in Biotechnology and Pharmacy, 2022. **16**(3s): p. 60 - 69.
56. Kanbeş Dindar, Ç., B. Bozal-Palabiyik, and B. Uslu, *Development of a Diamond Nanoparticles-based Nanosensor for Detection and Determination of Antiviral Drug Favipiravir.* 2022. **34**(7): p. 1174-1186.
57. El-Wekil, M.M., et al., *Nanocomposite of gold nanoparticles@nickel disulfide-plant derived carbon for molecularly imprinted electrochemical determination of favipiravir.* Journal of Electroanalytical Chemistry, 2022. **922**: p. 116745.
58. Erk, N., M. Mehmandoust, and M. Soylak, *Electrochemical Sensing of Favipiravir with an Innovative Water-Dispersible Molecularly Imprinted Polymer Based on the Bimetallic Metal-Organic Framework: Comparison of Morphological Effects.* 2022. **12**(9): p. 769.
59. Wang, S., et al., *Core–shell nanocomposite of flower-like molybdenum disulfide nanospheres and molecularly imprinted polymers for electrochemical detection of anti COVID-19 drug favipiravir in biological samples.* Microchimica Acta, 2022. **189**(3): p. 125.
60. Kablan, S.E., et al., *Voltammetric sensor for COVID-19 drug Molnupiravir on modified glassy carbon electrode with electrochemically reduced graphene oxide.* Journal of Electroanalytical Chemistry, 2022. **920**: p. 116579.
61. Erşan, T., et al., *Voltammetric Determination of Favipiravir used as an antiviral drug for the treatment of Covid-19 at Pencil Graphite Electrode.* **n/a**(n/a).