iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 9 **Issue:** VIII **Month of publication:** August 2021

DOI: https://doi.org/10.22214/ijraset.2021.37739

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VIII Aug 2021- Available at www.ijraset.com

Favipiravir: A Critical Review of Pharmacology, Pre-Clinical Data, and Emerging Clinical Uses in COVID-19

Anuja S. Motule[1], Sumit P. Isane[2], Minakshee G. Nimbalwar[3], Rahul D. Jawarkar[4], Ravindra L. Bakal[5], Jagdish V. Manwar[6]

[1, 2, 3, 4, 5]*IBSS's Dr. Rajendra Gode Institute of Pharmacy, Mardi road, Amravati-444 602, MS, India*

[6]*IBSS's Dr. Rajendra Gode College of Pharmacy, Mardi road, Amravati-444 602, MS, India*

Abstract: ***Since last two years, whole world is going through the pandemic situation of Corona Virus Disease-19 (COVID-19). It caused more than 43 lakhs deaths worldwide. COVID-19 outbreak all over the world has led the researchers and Scientists to develop drugs or vaccines to prevent the spreading of this virus. Due to the unavailabity of proper drug treatment, various veterinary drugs are trying in humans. It is one of such type of antiviral drug which was previously used in treatment of viral infection in animals and birds. In this article, we have tried to provide a comprehensive, evidence-based review of this drug in the context of the present pandemic to elucidate its role in the management of COVID-19.***

Keywords: Favipiravir; Pharmacology; COVID-19; Antiviral; Clinical trials.

I. INTRODUCTION

Favipiravir (5-fluoro-2-oxo1H-pyrazine-3-carboxamide) **(Fig. 1)**, an antiviral drug that was initially introduced in the treatment of treat influenza in Japan. In Feb., 2020 post the outbreak of novel corona virus (covid-19). Favipiravir was studied in China and several other countries as an experimental treatment of Covid-19. In late December 2019, Chinese health authorities reported an outbreak of pneumonia of unknown origin in Wuhan, Hubei Province [1].

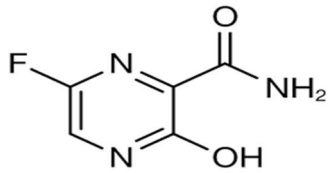


Fig. 1: Chemical structure of favipiravir.

As COVID-19 incidence and mortality rapidly climb, treatment options are limited. Repurposing existing pharmaceuticals provides an immediate treatment opportunity. While there is no licensed treatment that specifically acts against COVID-19, medications such as broad-spectrum antiviral are being employed as experimental adjuncts to supportive care. Potential drugs that may be repurposed include antimalarial hydroxychloroquine, antiretrovirals lopinavir/ritonavir and darunavir/ritonavir, and influenza drugs oseltamivir, remdesivir and favipiravir (FP). These drugs are now being trialed globally in different combinations for the treatment of COVID-19 [2-4].

II. INVENTION OF NEWER DRUGS

Invention of a new and specific antiviral agent against the SARS-CoV-2 would involve a long and arduous timeline. Hence, by default, repurposed drugs, already in use against other viral infections, have been pressed into quick service. One such drug is favipiravir, initially marketed as an anti-influenza agent in Japan. It is derived by chemical modification of the pyrazine moiety of T-1105. This drug has just received emergency approval by the *Drug Controller General of India* and hence this comprehensive review of favipiravir comes at a timely juncture [5]. Hydroxychloroquine, remdesivir, ritonavir, Favipiravir, etc are some existing drugs being explored for treatment. The results of repurposing prevailing antiviral were not acceptable level in COVID-19 patients especially with diabetes mellitus, hypertension, CVS, renal failure, liver cirrhosis, stroke, etc [6-7].

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VIII Aug 2021- Available at www.ijraset.com

III. MECHANISM OF ACTION

Favipiravir is acts as a substrate for the RNA-dependent RNA- polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, thus inhibiting its activity leading to termination of viral protein synthesis. It gets incorporated in the viral RNA strand, preventing further extension [8].

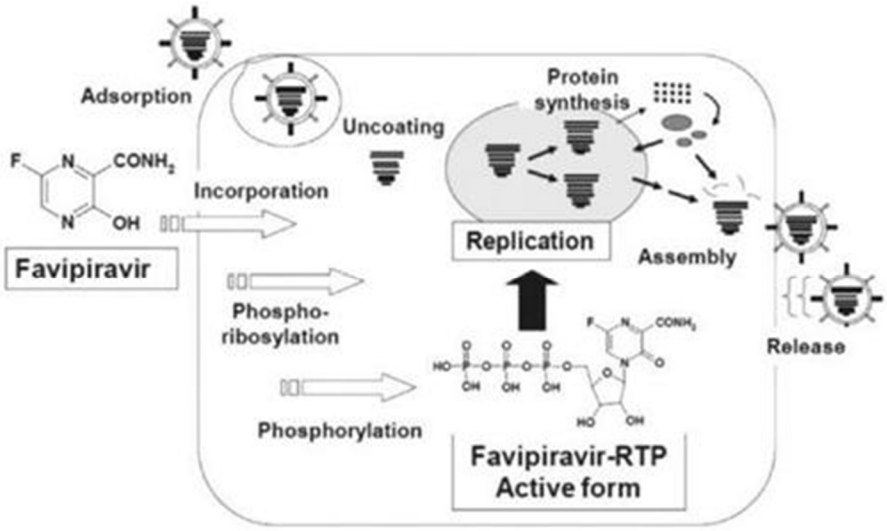


Fig. 2: Mechanism of anti-viral action (www.google.com).

IV. PHARMACOKINETICS STUDY

Favipiravir is administered orally as a prodrug. It has an excellent bioavailability (~94%) plasma protein binding 54%. It has a short half-life (2.5-5h) leading to rapid renal elimination in the hydroxylated form. Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Prophylaxis 1600 mg orally twice daily on day 1 followed by 800 mg orally twice a day on days 2–25. It exhibits both, dose-dependent and time dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system but inhibits one of its components (CYP2C8) [9-10].

V. SPECTRUM OF ACTIVITY

RNA viruses, including West Nile virus, yellow fever virus, foot-and- mouth disease virus, enterovirus, and rift valley fever [11].

VI. SAFETY PROFILE

Favipiravir has an established and well-characterized safety profile from 4000+ patients (Pilkington et al., 2020). The common adverse events (AEs) include gastrointestinal AEs, uric acid elevations, decrease of neutrophil count, increase of aspartate aminotransferase (SGOT), increase of alanine transaminase (SGPT), psychiatric symptom reactions, and increase in blood triglycerides. The proportion of serious AEs was 0.4% and 1.1% discontinuation due to AEs (Fabiflu Prescribing Information). Similar proportions of AEs were reported between low and high doses of favipiravir. It demonstrates a favorable safety profile with respect to total and serious AEs [12-15].

VII. PRECAUTIONS & CONTRAINDICATIONS

Precautions and contraindications are discussed bellow [16]

A. It is contraindicated in pregnant and lactating women. Due to its teratogenic potential, it is contraindicated in pregnant and suspected pregnant women.
B. It is distributed in sperms; hence, it is advised to use effective contraceptive methods by both women and men of reproductive age during the course and 7 days post-therapy.
C. It is contraindicated in patients with hypersensitivity, severe hepatic impairment, and severe renal impairment.
D. It should be administered with care in patients with gout or a history of gout, with hyperuricemia.

VIII. CLINICAL TRIALS

Various clinical trials studies are carried out for the drugs in various countries. The details of study are discussed bellow.

A. Japan

Japan hospitalized COVID-19 patients in Japan to assess the safety and efficacy of favipiravir.18 From February to May 2020, a total of 2158 cases were registered from 407 hospitals. In more than 90 percent of cases, favipiravir was administered at a dose of 1800 mg orally on day 1 followed by 800 mg twice daily on subsequent days. The median duration of therapy was 11 days. Rates of clinical improvement at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and % for mild, moderate, and severe disease, respectively [17]. Favipiravir in combination with nafomostat (transmembrane protease serine 2 inhibitor, previously used successfully in MERS-CoV-2 infection, acute pancreatitis and DIC) was found to be useful in a small case series consisting of 11 serious patients with COVID-19 in Japan [18].

B. Russia

The Russian Government approved favipiravir for the treatment of COVID-19, on the basis of encouraging early readouts from ongoing open-label randomized adaptive design clinical trial [COVID-FPR-01] in a 390-patient population. Results from 60 patients (40 on favipiravir and 20 on SOC) showed faster fever resolution (3 days vs. 6 days), rapid viral elimination (4 days vs. 9 days), and RT-PCR negativity up to 87.5% by day 10 [19].

C. China

An open-label control study in Chinese (N = 80) patients with mild to moderate COVID-19 was conducted to examine the effects of favipiravir vs. LPV/RTV for the treatment of COVID-19. It also showed a significant improvement rate in chest imaging (CT) (91.43% vs. 62.22%; p = 0.004) and higher improvement rates of chest CT in the group with viral clearance within 7 days of treatment were observed.

Multivariate logistic regression showed that the antiviral therapy independently affected the CT changes. Multivariable Cox regression showed that favipiravir was significantly (p = 0.026) associated with faster viral clearance, additionally the timing of antiviral therapy reached near significance (p = 0.055). Favipiravir was better (p < 0.001) tolerated than LPV/RTV. The major limitation of this study was that it was not randomized, doubleblinded, and placebo- controlled [20-21].

D. India

Recently, a phase 3, open label, randomized, multicenter study (CTRI/2020/05/025114, Glenmark Pharmaceuticals) was initiated in India to determine the efficacy of favipiravir in patients infected with mild to moderate COVID-19 in line with the global trials ongoing for this drug. The study enrolled patients with both mild (N = 90) and moderate (N = 60) COVID-19 by stratified randomization based on baseline disease severity. The primary objective of this study was to evaluate the clinical efficacy and safety of favipiravir combined with standard supportive care. The primary endpoint was time until the cessation of oral shedding of SARS-CoV-2 virus.

The secondary endpoints included— time from randomization to clinical cure based on clinician assessment, rate of clinical cure at day 4/7/10/14, rate of SARS-CoV2 RT-PCR negativity at day 4/7/10/14, time from randomization to first time use of high flow supplemental oxygen/noninvasive ventilation/ mechanical ventilation/extracorporeal membrane oxygenation, and time from randomization to hospital discharge. The total duration of study participation had been a maximum of 28 days from the day of randomization. The results from this study will be pivotal in the further substantiation of global evidence on the efficacy and safety therapy against COVID-19 [22].

E. Saudi Arabia

An ongoing open-labeled randomized controlled trial from Saudi Arabia is evaluating the efficacy of favipiravir and hydroxychloroquine combination therapy Identifier: NCT04392973] in the management of moderate to severe COVID-19. The experimental arm consists of favipiravir (dose: 1800 mg twice daily on day 1 followed by 800 mg twice daily for a total period of 10 days or till hospital discharge) plus hydroxychloroquine (400 mg twice daily on day 1 followed by 200 mg twice daily for next 4 days). The control arm includes the SOC treatment in COVID 19. The primary endpoint of the trial is time to clinical improvement and time to a negative PCR test.21 Results of this trial are eagerly awaited [23].

F. USA

The research team at Stanford Medicine have recently commenced a double-blind, placebo- controlled trial (favipiravir vs placebo for 10 days) to assess the utility of favipiravir in reducing symptoms and the duration of viral shedding in outpatients with COVID-19.About 120 patients are expected to be enrolled beginning July 6, 2020 [24].

IX. SIDES EFFECTS

The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain, with some pharmacodynamic studies suggesting a positive association, but a Japanese study suggesting otherwise. Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review [25].

A. Hyperuricemia

Favipiravir use results in a dose-dependent increasing trend in the prevalence of hyperuricemia. This is however not associated with clinical manifestations. There has been no evidence that hyperuricemia caused by favipiravir leads to clinical manifestations; however, longer follow-up periods would be required to fully assess this risk [26-27].

B. Teratogenicity

There is evidence that favipiravir has a teratogenic potential and embryotoxicity. The Japanese drug safety bureau approval advises that favipiravir be given a strong warning against use in women of reproductive age and recommends precautionary statements on packaging and prescription alerts. The bureau also recommends that favipiravir should be avoided where alternative drugs could be used [28].

X. DRUG INTERACTIONS

Drug interactions are discussed bellow.

A. Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.
B. Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.
C. Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.
D. Famciclovir, sulindac: Efficacy of these drugs may be reduced when coadministered with favipiravir.
E. Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy [29].

XI. ASSAY OF DRUG

There are many analytical tools that are used for the analysis of various pharmaceutical drugs, formulations, herbal formulations, crude drugs and their extracts [30-54]. These methods includes Uv-spectrophotometry, gas chromatography, HPLC, HPTLC, etc [55- 75].

XII. CONCLUSION

Thus, it is conclude that Favipiravir, can be a best option to remdesivir in the treatment of COVID-19.

XIII. DISCLOSURE OF CONFLICT OF INTEREST

The author declares no conflict of interest.

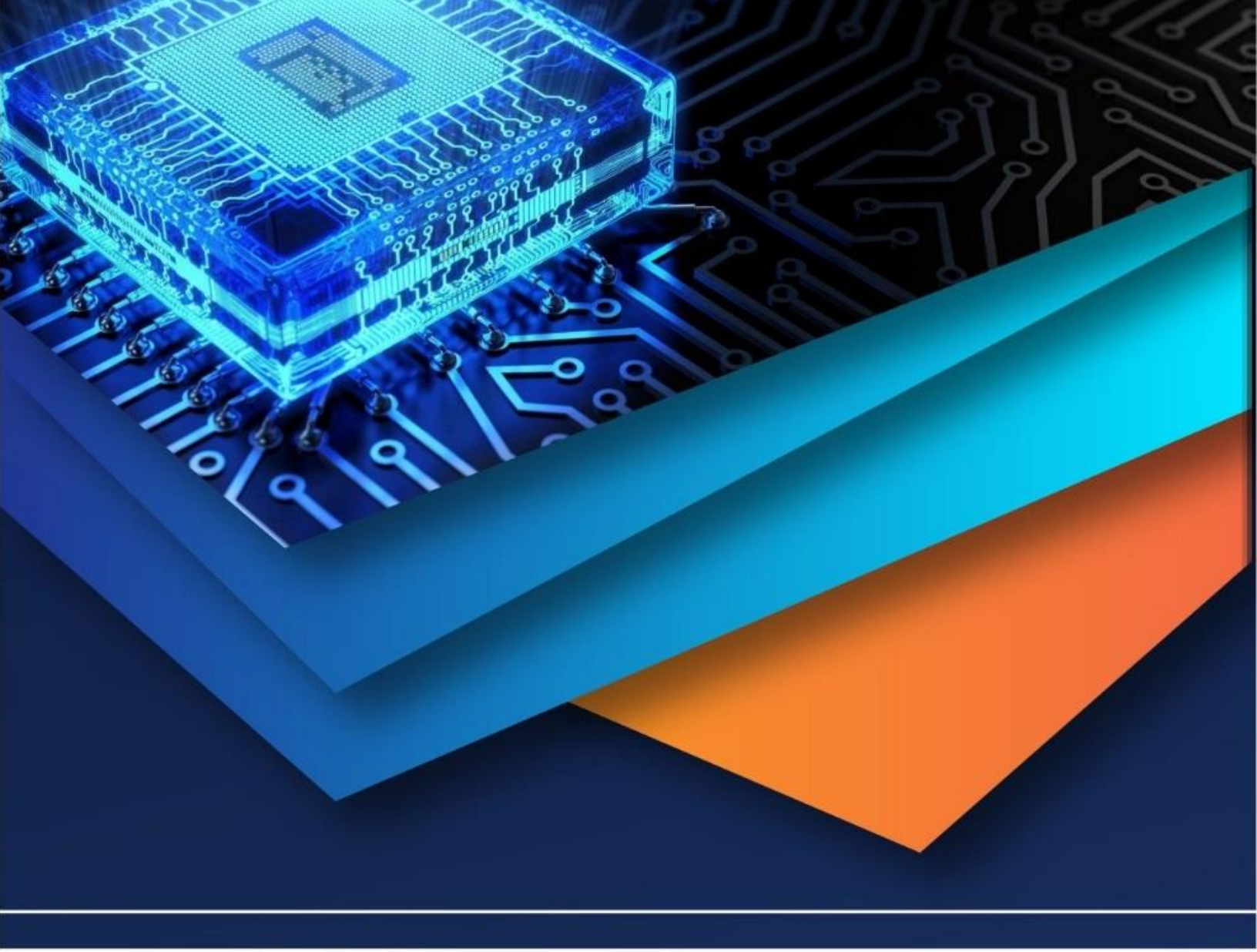
REFERENCES

[1] Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic? J Virus Erad. 2020 Apr 30;6(2):45-51. doi: 10.1016/S2055-6640(20)30016-9. PMID: 32405421; PMCID: PMC7331506.
[2] Kalil AC. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. JAMA. 2020 May 19;323(19):1897-1898. doi: 10.1001/jama.2020.4742. PMID: 32208486.

[3] Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob Health. 2020 May;8(5):e639-e640. doi: 10.1016/S2214-109X(20)30114-5.
[4] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020 Mar;19(3):149-150. doi: 10.1038/d41573-020-00016-0.
[5] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020 Mar 26;382(13):1199-1207. doi: 10.1056/NEJMoa2001316
[6] Ghinai I, McPherson TD, Hunter JC, Kirking HL, Christiansen D, Joshi K, Rubin R, Morales-Estrada S, Black SR, Pacilli M, Fricchione MJ, Chugh RK, Walblay KA, Ahmed NS, Stoecker WC, Hasan NF, Burdsall DP, Reese HE, Wallace M, Wang C, Moeller D, Korpics J, Novosad SA, Benowitz I, Jacobs MW, Dasari VS, Patel MT, Kauerauf J, Charles EM, Ezike NO, Chu V, Midgley CM, Rolfes MA, Gerber SI, Lu X, Lindstrom S, Verani JR, Layden JE; Illinois COVID-19 Investigation Team. First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. Lancet. 2020 Apr 4;395(10230):1137-1144. doi: 10.1016/S0140-6736(20)30607-3.
[7] Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ, Amorosa L, Brunetti L, Kong AN. An Update on Current Therapeutic Drugs Treating COVID-19. Curr Pharmacol Rep. 2020 May 11:1-15. doi: 10.1007/s40495-020-00216-7
[8] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8.
[9] Coomes EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother. 2020 Jul 1;75(7):2013-2014. doi: 10.1093/jac/dkaa171. PMID: 32417899; PMCID: PMC7239147.
[10] Castillo AE, Parra B, Tapia P, et al. Geographical distribution of genetic variants and lineages of SARS-CoV-2 in Chile. Front Public Health. 2020;8:525.
[11] Rambaut A, Holmes EC, O'Toole Á, Hill V, McCrone JT, Ruis C, du Plessis L, Pybus OG. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat Microbiol. 2020 Nov;5(11):1403-1407. doi: 10.1038/s41564-020-0770-5.
[12] Boni MF, Lemey P, Jiang X, Lam TT, Perry BW, Castoe TA, Rambaut A, Robertson DL. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. Nat Microbiol. 2020 Nov;5(11):1408-1417. doi: 10.1038/s41564-020-0771-4.
[13] Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181 (2):281–292.e6.
[14] Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Med J Armed Forces India. 2020 Oct;76(4):370-376. doi: 10.1016/j.mjafi.2020.08.004.
[15] Madelain V, Nguyen TH, Olivo A, de Lamballerie X, Guedj J, Taburet AM, Mentré F. Ebola Virus Infection: Review of the Pharmacokinetic and Pharmacodynamic Properties of Drugs Considered for Testing in Human Efficacy Trials. Clin Pharmacokinet. 2016 Aug;55(8):907-23. doi: 10.1007/s40262-015-0364-1.
[16] Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, Patil S, Barkate H. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021 Jan;102:501-508. doi: 10.1016/j.ijid.2020.10.069.
[17] and Concerns About Clinical Trials for 2019-nCoV Infection. Clin. Pharmacol. Ther. 2020 doi: 10.1002/cpt.1844.
[18] Japanese Association for Infectious Diseases. Treatment guidelines for COVID-19, 3rd edition.
[19] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-271.
[20] Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020.
[21] Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020.
[22] Baru RV. Health systems preparedness during COVID-19 pandemic: China and India. Indian J Public Health. 2020 Jun;64(Supplement):S96-S98. doi: 10.4103/ijph.IJPH_501_20. PMID: 32496234.
[23] Matsuyama S, Kawase M, Nao N, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. bioRxiv. 2020. 6) Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
[24] Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020.
[25] Doi K, Ikeda M, Hayase N, Moriya K, Morimura N; COVID-UTH Study Group. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. Crit Care. 2020 Jul 3;24(1):392. doi: 10.1186/s13054-020-03078-z.
[26] Prakash A, Singh H, Kaur H, Semwal A, Sarma P, Bhattacharyya A, Dhibar DP, Medhi B. Systematic review and meta-analysis of effectiveness and safety of favipiravir in the management of novel coronavirus (COVID-19) patients. Indian J Pharmacol. 2020 Sep-Oct;52(5):414-421. doi: 10.4103/ijp.ijp_998_20.
[27] Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020 Oct;6(10):1192-1198. doi: 10.1016/j.eng.2020.03.007
[28] Sisay M. Available Evidence and Ongoing Clinical Trials of Remdesivir: Could It Be a Promising Therapeutic Option for COVID-19? Front Pharmacol. 2020 May 26;11:791. doi: 10.3389/fphar.2020.00791.
[29] Lam S, Lombardi A, Ouanounou A. COVID-19: A review of the proposed pharmacological treatments. Eur J Pharmacol. 2020 Nov 5;886:173451. doi: 10.1016/j.ejphar.2020.173451.
[30]Motule AS, et al. Development and physicochemical evaluation of bilayered transdermal patches of ondansetron hydrochloride Journal of Innovations in Pharmaceutical and Biological Sciences. 2021; 8(3): 17-23.
[31]Chaudhari KD, et al. Floating drug delivery system: An update of preparation and classification of formulation. Ijppr.Human. 2021; 21(1):207-220.

[32]Chaudhari KD, et al. Comprehensive review on characterizations and application of gastro-retentive floating drug delivery system. GSC Advanced Research and Reviews. 2021; 07(01):035-044.
[33]Dhamankar AK, et al. The novel formulation design of O/of ketoprofen for improving transdermal absorption. Int J of Pharm Tech Res. 2009; 4(1Suppl): 1449-1457.
[34]Jain CM, et al.Review on approaches for development and evaluation of extended-release tablets. Review on approaches for development and evaluation of extended-release tablets. World Journal f Pharmacy and Pharmaceutical Sciences. 2021;10(4): 542-554.
[35]Kadam CY, et al. Design and In vitro characterization of phase transition system using rivastigmine tartrate for nasal drug delivery system. World Journal of Pharmaceutical Research. 2018; 8(1): 815-829.
[36]Malode GP, et al.Formulation and evaluation of a novel floating in situ gel system for the treatment of peptic ulcer. World Journal of Pharmacy and Pharmaceutical Sciences. 2021; 10(4):416-1433.
[37] Manwar J, Kumbhar DD, Bakal RL, Baviskar SR, Manmode RS. Response surface based co-optimization of release kinetics and mucoadhesive strength for an oral mucoadhesive tablet of cefixime trihydrate. Bulletin of Faculty of Pharmacy. Cairo University. 2016; 54: 227–235. http://dx.doi.org/10.1016/j.bfopcu.2016.06.004
[38] Manwar JV, et al. Diclofenac Sodium Loaded Nanosized Ethosomes: An Investigation on Z-Average, Polydispersity and Stability. J Pharm Res. 2017; 1(3): 000115.
[39] Nimbalwar MG, et al. A brief review on principle, preparation and properties of proniosomes: A provesicular drug delivery system. World J Pharm Sci. 2021; 9(5): 149-162.
[40] Nimbalwar MG, et al. Fabrication and evaluation of ritonavir proniosomal transdermal gel as a vesicular drug delivery system. Pharmacophore. 2016; 7(2): 82-95.
[41] Patil SS, et al. Ultrasound-Assisted Facile Synthesis of Nanostructured Hybrid Vesicle for the Nasal Delivery of Indomethacin: Response Surface Optimization, Microstructure, and Stability. AAPS PharmSciTech. 2019;20(3):97.
[42] Pophalkar PB, et al. Development and evaluation of ondansetron medicated jelly. World Journal of Pharmaceutical Research. 2018; 7(19): 1252-1263.
[43] Shubham Garibe, et al. Bioequivalence study of test formulations T1 and T2 Nadolol tablets USP with reference formulation in healthy adult, human subjects under fed conditions. Ijppr.Human. 2021; 20(2):20-28.
[44] Suroshe RS, et al. Development and characterization of osmotic drug delivery system of model drug. World Journal of Pharmaceutical Research. 2018; 7(18): 1158-1171.
[45] Nimbalwar MG, et al. An overview of characterizatons and applications of proniosomal drug delivery system. GSC Advanced Research and Reviews. 2021; 07(02): 025-034.
[46] Nimbalwar MG, et al. Pharmacognostic and nootropic aspects of withania somnifera: a potential herbal drug as memory enhancer. International Journal for Research in Applied Science & Engineering Technology (IJRASET).2021;9(VIII):1075-1081.
[47] Vaidya VM, et al. Design and in vitro evaluation of mucoadhesive buccal tablets of terbutaline sulphate. Int J PharmTech Res. 2009; 1(3): 588-597.
[48] Vohra M, et al. Bioethanol production: Feedstock and current technologies. Journal of Environmental Chemical Engineering. 2014; 2 (1):573-584.
[49] Gulhane CA, Motule AS, et al. An Overview On Nail Drug Delivery System: A Promising Application for Various diseases. European Journal of Biomedical and Pharmaceutical Sciences. 2021;8(2):104-110.
[50] Dongare PN, Motule AS, et al. Recent development in novel drug delivery systems for delivery of herbal drugs: An updates. GSC Advanced Research and Reviews. 2021; 8(08):008-018.
[51] Mankar SS, Motule AS, et al. Progress in development of herbal cosmeceuticals: An current status and prospects. International Journal of Medical, Pharmaceutical and Biological Sciences. 2021; 1(2): 1-11.
[52] Motule AS, et al. Ethnopharmacological relevances of herbal plants used in cosmetics and toiletries preparations. GSC Biological and Pharmaceutical Sciences. 2020.
[53] More MP, et al. Pharmacognosy, Phytochemistry, Pharmacology and Clinical Application of Ginkgo Biloba. GSC Biological and Pharmaceutical Sciences. 2020.
[54] Nimbalwar MG, et al. An overview of characterizatons and applications of proniosomal drug delivery system. GSC Advanced Research and Reviews. 2021; 07(02): 025-034.
[55] Bakal RL, et al. Spectrophotometric estimation of amitriptyline HCl and chlordiazepoxide in pharmaceutical dosage form. Indian Journal of Pharmaceutical Education and Research. 2008; 42: 23–26.
[56] Bakal RL, et al. Spectrophotometric estimation of amitriptyline HCL and chlordiazepoxide in tablet dosage form. International Journal of Chemical Sciences. 2007; 5(1):360–364.
[57] Gulhane CA, et al. UV- Visible Spectrophotometric estimation of azithromycin and cefixime from tablet formulation by area under curve method. World Journal of Pharmaceutical Sciences.2021; 9(6): 163-168.
[58] Manwar JV, et al. Development of newer RP-HPLC method for simultaneous estimation of cefiximeand linezolide in bulk drugs and combined dosage form. International Journal of Pharmacy and Life Sciences. 2021;12(1):26-31.
[59] Gulhane CA, et al.Liquid chromatographic method for simultaneous estimation of thiocolchicoside and etoricoxib from tablet formulation. Asian Journal of Pharmaceutical Analysis. 2021;11(2): 118-122.
[60] Manwar JV, et al. Application of simultaneous equation method for the determination of azithromycin and cefixime trihydrate in tablet formulation. Research Journal of Pharmacy and Technology. 2017;10(1):108-112.
[61] Bagade SB, et al. Simultaneous high performance thin layer chromatographic estimation of methocarbamol and nimesulide in combined dose tablet. Journal of Pharmaceutical Research. 2006;5(4):137-140.
[62] Manwar J, Mahadik K, Paradkar A, et al. Gas chromatography method for the determination of non-ethanol volatile compounds in herbal formulation. International Journal of Analytical and Bioanalytical Chemistry. 2013; 3(1):12-17.
[63] Panchale WA, et al. Concurrent analysis of ambroxol HCl and salbutamol sulphate from tablet formulation by RP-HPLC. GSC Biological and Pharmaceutical Sciences. 2020; 13(03):197-202.

[64] Panchale WA, et al. RP-HPLC method for simultaneous determination of escitalopram oxalate and flupentixol HCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(01):169-174.
[65] Panchale WA, et al. RP-HPLC method for simultaneous determination of metformin hydrochloride and linagliptine in pharmaceutical dosage form. World Journal of Pharmaceutical and Medical Research. 2021;7(5):234- 238.
[66] Panchale WA, et al. Simultaneous estimation of salbutamol sulphate and ambroxol HCl from their combined dosage form by UV-Vis spectroscopy using simultaneous equation method. GSC Biological and Pharmaceutical Sciences. 2020;13(03):127-134.
[67] Sabhadinde AF, et al. Novel RP-HPLC method for simultaneous analysis of chlorthalidone and telmisartan from combined dosage form. Ijppr.Human. 2020; 20(1):491-502.
[68] Manwar JV, et al. Experimental design approach for chromatographic determination of ketorolac tromethamine from bulk drug and tablet formulation. Global Journal of Pharmacy & Pharmaceutical Sciences. 2017;3(2):38-47.
[69] Manwar JV, et al. Rapid RP-HPLC method for estimation of zidovudine from tablet dosage form. Der Chemica Sinica.2011; 2(5): 152-156.
[70] Panchale WA, et al. Chromatographic analysis of famotidine, paracetamol and ibuprofen from tablet formulation. Research Journal of Pharmacy and Technology. 2019; 12:231-263.
[71] Manwar JV, et al. Response surface based optimization of system variables for liquid chromatographic analysis of candesartan cilexetil. Journal of Taibah University for Science. 2017; 11:159–172.
[72] Manwar JV, Mahadik KR, Paradkar AR, et al. Determination of withanolides from the roots and herbal formulation of Withania somnifera by HPLC using DAD and ELSD detector. Der Pharmacia Sinica. 2012; 3: 41–46.
[73] Nimbokar SW, et al. Development and validation of RP-HPLC method for determination of zonisamide from tablet formulation. World Journal of Pharmaceutical and Medical Research. 2021;7(2):196-200.
[74] Panchale WA, Bakal RL. First-order derivative spectrophotometric estimation of gemifloxacin mesylate and ambroxol HCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(2):029-036.
[75] Manmode RS, et al. Stability indicating HPLC method for simultaneous determination of methocarbamol and nimesulide from tablet matrix. Der Chemica Sinica.2011;2(4):81-85.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY