

In -Vitro Study of Favipiravir Marketed 200 mg Tablets

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ABSTRACT: The aim of work to evaluate the marketed tablets of favipiravir of Glenmark which is used for the treatment of covid-19 infection. Dose also varies according to company and firstly designed 200mg favipiravir for the treatment of influenza infection in Japan. Favipiravir is a modified pyrazine analogue and repurposed drug that targets RNA polymerase enzymes. At present, only the oral route is available in the form of tablets in higher doses. They were evaluated in the current studies, i.e., *in-vitro* drug release studies.

Keywords: Favipiravir, In- vitro release, Disintegration, Marketed tablets.

INTRODUCTION

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide; T-705) is a nucleoside analogue that is phosphorylated within cells, resulting in a tri-phosphate analogues, the active metabolite. As with other nucleoside analogues, studies suggest that favipiravir interferes with viral RNA replication.

Favipiravir has been approved in Japan since March 2014 for an outbreak of novel or re-emerging influenza virus infections and its use is limited to cases in which other anti influenza virus agents are either ineffective or insufficiently effective. The approved posology is 1,600 mg orally twice daily for 1 day followed by 600 mg twice daily for 4 days.

Favipiravir is currently being tested for treating uncomplicated influenza infection at a differential dosing regimen (taking into account differential pharmacokinetic parameters between Japanese and non-Japanese subjects): 1800 mg twice daily at day 1 then 800 mg twice daily from day 2 to 5[1-3].

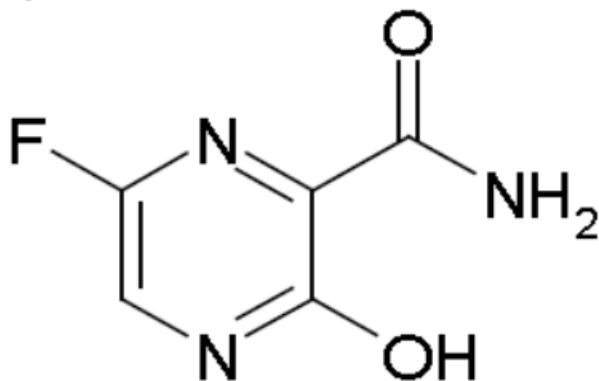


Figure.1: Structure of favipiravir

Favipiravir is rapidly absorbed, with a median $t_{\max \frac{1}{2}}$ of 2 hours following multiple doses. The oral bioavailability of favipiravir in patients with symptomatic EBOV infection is unknown. The compound has a terminal $t_{1/2}$ of 2 to 4 hours. The main elimination pathway of favipiravir is likely via metabolism. *In vitro* data have indicated that CYP isoenzymes are not involved, and that the major metabolite (M1) may be formed by aldehyde oxidase. A glucuronide metabolite has also been detected in plasma and urine[4,5].

Following single doses of 30 mg to 1,200 mg, favipiravir exposure increases in an almost dose-proportional manner. However, non-linear pharmacokinetics have been suggested in studies with multiple doses of favipiravir: the $t_{1/2}$ of the compound increases to some extent, favipiravir plasma levels accumulate in some studies, and the relative metabolite-to-parent ratio of metabolite M1 has been shown to be reduced (from 43% at day 1 to 6% at day 5). The underlying cause of the non-linearity is suggested to be the saturation of aldehyde oxydase[6].

COVID-19 which is originated in Wuhan, China in 2019 and was declared a pandemic by WHO on March 12th, 2020 [9]. The virus which is causing influenza in patients was identified to be Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)[7-10]. The constant research is going on repurposing of drugs such as hydroxychloroquine, remdesivir, lopinavir, ritonavir, and some drugs that previously existing against COVID-19 treatment. The previously existing drug favipiravir is showing effectiveness in SARS-CoV and MERS (Middle East Respiratory Syndrome) which are having similarities in the genome sequence of SARS CoV-2. Hence, favipiravir is studied for its effectiveness in the treatment of SARS-CoV-2 [10]. The dosage for adults is varying from 600- 800mg, whereas in children 100mg to 200mg, still data on favipiravir use in children is very limited, extensive clinical trails are needed to recommend the use of favipiravir in children in COVID-19 situation [11].

IN-VITRO DISINTEGRATION TIME:

The test was performed using the disintegration apparatus. A tablet was placed in each of the six tubes of the apparatus the basket with the bottom surface made of a stainless-steel screen was immersed in a water bath at 37°C and one perforated disc was placed on each of the tubes. The time in seconds was recorded for the completed disintegration of the tablet with no remnants of the palpable mass in the apparatus [12-13].

Table:1 Disintegration time of Tablets of favipiravir

Tablet No.	Disintegration time
T1	75.16
T2	66.10
T3	60.13
T4	74.12
T5	70.15
T6	68.17

IN-VITRO DRUG RELEASE STUDIES:

The release rate of favipiravir from the fast-dissolving tablet was determined by using the USP dissolution testing apparatus II[14,15]. The dissolution test was performed using 900ml of phosphate buffer pH-6.8 as dissolution medium at 50rpm and temperature 37±0.5°C. At predetermined time intervals, 5ml of the sample was withdrawn using the syringe fitted to a free filter, the volume withdrawn at each interval was replaced with the same quantity of fresh medium. The resultant samples were filtered through Whatman filter paper No.41 and analyzed for the presence of the drug release by measuring the absorbance at 235 nm using UV visible spectrophotometer after suitable dilutions[16,17].

Table: 2 Cumulative % drug release of Tablets of Favipiravir

Time in minutes	0	2	4	6	8	10	12	14
T1	0.00	25.02	42.31	62.13	76.23	81.25	89.25	97.98
T2	0.00	25.45	42.56	63.01	76.45	81.23	89.46	97.15
T3	0.00	24.99	42.85	62.58	76.58	81.56	90.12	97.12
T4	0.00	25.98	41.98	62.48	75.85	81.97	90.89	97.45
T5	0.00	24.78	42.12	61.99	76.12	80.65	89.45	98.45
T6	0.00	25.06	42.78	62.45	76.51	81.47	89.99	97.89

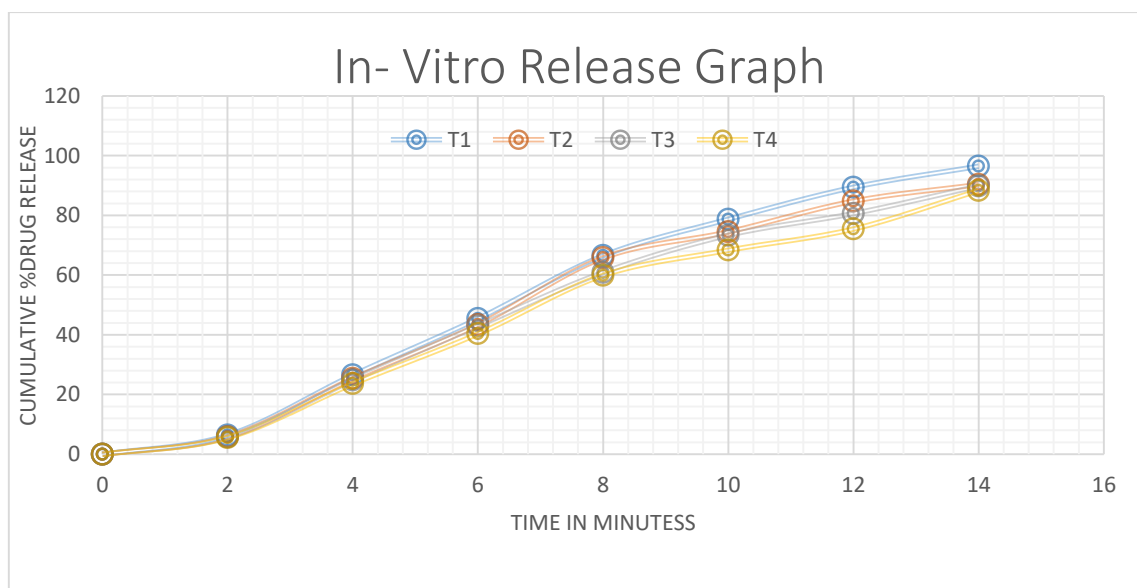


Figure.2 : Cumulative % drug release of Tablets of Favipiravir (T1-T4)

RESULT AND CONCLUSION:

Favipiravir marketed tablets passed the disintegration and in-vitro release tests properly which is used to treatment of covid-19. Cumulative percentage drug release was found to be 97.12% to 98.45%.

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Nil

AUTHOR CONTRIBUTION:

Navdeep Kaur conducted the practical work and wrote the manuscript draft

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