Does the Ethnic Difference Affect the Pharmacokinetics of Favipiravir? A Pharmacokinetic Study in Healthy Egyptian Volunteers and Development of Level C In-vitro In-vivo Correlation

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ABSTRACT

Favipiravir is an antiviral drug used to treat influenza and is also being investigated for the treatment of SARS-CoV-2. Its pharmacokinetic profile varies depending on ethnic group. The present research examines the pharmacokinetic features of favipiravir in healthy male Egyptian volunteers. Another goal of this research is to determine the optimum dissolution testing conditions for immediate release tablets. In vitro dissolution testing was investigated for favipiravir tablets in three different pH media. The pharmacokinetic features of favipiravir were examined in 27 healthy male Egyptian volunteers. The parameter "AUC0-t" vs. percent dissolved was used to develop level C in vitro in vivo correlation (IVIVC) to set the optimum dissolution medium to achieve accurate dissolution profile for favipiravir (IR) tablets. The in vitro release results revealed significant difference among the three different dissolution media. The Pk parameters of twenty-seven human subjects showed mean value of Cpmax of 5966.45 ng/mL at median tmax of 0.75 h with AUC0-∞ equals 13325.54 ng.h/mL, showing half-life of 1.25 h. Level C IVIVC was developed successfully. It was concluded that Egyptian volunteers had comparable Pk values to American and Caucasian volunteers, however they were considerably different from Japanese subjects. AUC0-t vs. % dissolved was used to develop level C IVIVC to set the optimum dissolution medium. Phosphate buffer medium (pH 6.8) was found to be the optimum dissolution medium for in vitro dissolution testing for Favipiravir IR tablets.

Introduction

Viruses, unlike bacteria and other free-living microbes, cannot grow in culture. Viruses must reproduce in a living cell. A virus includes genetic information in the form of DNA or RNA [1]. These genetic materials are surrounded by a protein coat called a capsid or an outer lipid envelope [2]. A broad variety of diseases are caused by viruses which may be simple acute disorders or life threatening infections [3]. One of these highly contagious and pathogenic viruses is SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) which have appeared in late 2019 caused a pandemic of high mortality respiratory disease, named COVID-19 (coronavirus disease 2019) [4]. This necessitates fast invention of vaccines and drugs. There are major platforms for vaccine developments as nucleic acid (DNA and RNA), live attenuated or inactivated virus, subunit (protein, recombinant proteins or polysaccharide) and viral vectors (replicating or non-replicating) approaches [5]. These vaccines may vary in their effectiveness at reducing the incidence and

severity of SARS-CoV-2 infection [6]. Despite the effectiveness of vaccines, no particular drugs have been approved for COVID-19 as of yet [7]. Many drugs are demonstrating their antiviral activity against SARS-CoV-2 by inhibiting the fusion process during viral entry into the host cells as baricitinib [8] and umifenovir [9]. Protease inhibitor drug like lopinavir is considered a potential candidate for COVID-19 treatment especially in combination with ritonavir [10]. Remdesivir is a nucleotide analogue prodrug that disturbs viral replication of majority of the single stranded RNA viruses like coronaviruses [11]. Following this family, there is favipiravir, an oral RNA-dependent RNA polymerase (RdRp) inhibitor which already approved for treatment of influenza in Japan [12]. Favipiravir could be administered in a safe therapeutic dose to give effective concentration against the SARS-CoV-2 infection [13]. It has hydrophobic macromolecular structures of low solubility. It is slightly soluble at pH 2.0 to 5.5 and sparingly soluble at pH 5.5 to 6.1. Its log P = 0.8 [14]. For formulation development, its in-vitro dissolution and the efficiency with which a medication is released from the dosage form should be established [15]. Stability testing for favipiravir in its pharmaceutical formulation was investigated by Marzouk et al. [16] Determination of favipiravir in human plasma for bioequivalence studies was reported. [17, 18] Favipiravir pharmacokinetic parameters were estimated in Japanese healthy volunteers and Cp_{max} occurred within 2 hours and it is eliminated mainly via aldehyde oxidase metabolism and partially by xanthine oxidase [19], with an elimination half-life of 2–5.5 hours. Patients in the United States had a plasma concentration levels that was roughly 50 percent lower than those in Japan for the same dose [20]. Due to pharmacokinetic concerns and varying efficacy outcomes [21], our study is needed to calculate the pharmacokinetic parameters in healthy Egyptian volunteers to identify how to dose patients treated with favipiravir. Also to establishing in vitro in vivo correlation (IVIVC) to correlate in vitro drug data to in vivo performance to waive regulatory requirements for the evidence of in vivo bioavailability and to set reliable specifications for in vitro dissolution method.

Materials And Methods

Materials

Favipiravir was kindly supplied by Optrix Laboratories private Limited, India. Lamivudine, used as an internal standard (IS), was bought from LGC GmbH, Germany. Potassium dihydrogen phosphate, sodium dihydrogen phosphate, ortho phosphoric acid, acetic acid, ammonium formate and formic acid were purchased from Scharlau, Spain. Methanol and acetonitrile (HPLC grade), Sigma Aldrich, Germany.

Pharmaceutical product

Avigan 200 mg Tablets, manufactured by Toyama Chemical Co., Ltd., Japan.

Analytical methodology

For in-vitro dissolution testing: HPLC Alliance/e2695S separation module, Waters LC system equipped with photodiode array detector (2998 PDA), (USA) was used. Separation was achieved on Inertsil C_{18} (250 × 4.6 mm, 5 µm) column using acetonitrile: 10 mM phosphate buffer (pH 3) (40:60, v/v) as a mobile phase that was pumped at a flow rate of 1 mL/min. with UV detection at 320 nm.

For in-vivo testing: Waters Acquity UPLC H Class-Xevo TQD system (USA) was used for assay of favipiravir in human plasma. It was equipped with electrospray ionization. Chromatographic separation of analytes was carried out on Acquity UPLC HSS C_{18} (100 × 2.1 mm, 1.8 µm) column using methanol-10 mM ammonium formate + 0.1 % formic acid in gradient mode as a mobile phase at a flow rate of 0.35 mL/minute. Other source dependent parameters were cone gas flow, 50 L/hr; desolvation gas flow, 800 L/hr; capillary voltage, 2.41 kV, source temperature, 120 °C; desolvation temperature, 550 °C. The optimum values for compound dependent parameters like cone voltage and collision energy were set at 33 V and 15 eV for FAV and 20 V and 15 eV for IS, respectively. Detection of the ions was performed in the multiple-reaction monitoring (MRM) mode, by monitoring the transition pairs (precursor to product ion) of m/z 156 to m/z 113 for FAV, m/z 230 to m/z 112 for IS. Mass Lynx software version 4.1 was used to control all parameters of UPLC and MS.

In-vitro dissolution assessment

In vitro dissolution studies were carried out for Avigan 200 mg tablets using USP Apparatus 2 - Rotating Paddle in three different dissolution media, namely, pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. All tests were done in triplicate.

All dissolution media were kept at 37 °C ± 0.5 °C at 50 rpm. Samples of 5 mL were withdrawn from each dissolution medium at time intervals 5, 10, 15, 20 and 30 minutes and were replaced by 5 mL of fresh dissolution medium to keep the volume constant. Membrane filters of 0.45 µm were used to filter the withdrawn samples and the first part of the filtrate was discarded. One mL of the filtrate of each sample was placed in 10 mL volumetric flask and completed to volume with mobile phase (filtered degassed mixture of phosphate buffer (pH 3): acetonitrile (60: 40, v/v). A volume of 20 µL of each sample was injected into HPLC-UV apparatus using a validated method of analysis to detect the percent dissolved of favipiravir at 320 nm.

Study subjects and study design

Twenty-seven male healthy Egyptian volunteers were recruited to participate in this study. Sample size was calculated by SAS software. Demographic data including age, height, weight and body mass index and physical examinations and vital signs were examined. All laboratory tests including biochemical, serological and urine analyses were carried out. One tablet was swallowed by each volunteer under fasting condition for 10 hours pre-dose. This clinical study was done in accordance with the Guideline for Good Clinical Practice of the International Conference on Harmonization [22] and the principles of the World Medical Association's Declaration of Helsinki [23] and was authorized by the ethics committee of Advanced Research Center (ARC), Egypt. Each volunteer signed an informed consent form written in lay language to understand his role and rights in this study and the possible risks [24].

Blood sampling

Blood samples were obtained from the volunteers at 0.00 (predose), 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3, 3.5, 4, 5, 6, 8 and 10 hours after dose administration. The collected blood samples were centrifuged at 3500 rpm for 10 minutes and then transferred directly into 5-mL plastic tubes. The plasma samples were stored at the study site in an ultra-deep freezer at -80 °C until measurement.

Pharmacokinetic analysis

The pharmacokinetic parameters (The maximum concentration in plasma (Cp_{max}), time to reach it (t_{max}), the area under the curve (AUC_{0-t} and $AUC_{0-\infty}$) and the terminal elimination half-life ($t_{1/2}$) were calculated by non-compartmental analysis using Phoenix WinNonlin software (version 8.1; Certara USA, Princeton, NJ, USA). The AUC_{0-t} was calculated by the linear trapezoidal rule. The elimination rate constant (k) was estimated from the slope of the terminal elimination phase of the plasma concentration-time curve and hence the elimination half-life ($t_{1/2}$) was calculated by using the formula: $t_{1/2} = 0.693/k$. The $AUC_{0-\infty}$was calculated using the following formula:

$AUC_{0-\infty} = AUC_{0-t} + Cp^* / k$

Where Cp^* is the last measured concentration.

In vitro in vivo correlation (IVIVC)

The cumulative percent dissolved of favipiravir at 5, 15 and 30 minutes were correlated with partial areas under the curves of the in-vivo plasma concentration – time curves namely, $AUC_{0-0.5}$, $AUC_{0-0.75}$ and AUC_{0-1} till reaching the peak (Cp_{max}). This procedure was done for each dissolution medium (pH 1.2, pH 4.5 and pH 6.8). The % dissolved was depicted on x-axis (independent variable) and the calculated partial areas were depicted on y-axis. The coefficient of determination (r^2) and the slope were calculated by linear regression analysis using Microsoft Excel software to develop level C correlation [25].

Statistical evaluation

The Student t-test was used to determine the significance difference between the means of two sets of data for in vitro dissolution data. Microsoft Excel 365 was used to perform such a calculation. z-test is used to compare between 2 sample means [26]. These calculations were done applying special syntax using SPSS software ver. 16.0 (IBM, Armonk, NY, USA).

Results

Chromatographic conditions and analytical method validation

A simple LC method was developed and validated to separate favipiravir from dissolution medium, additives and/or excipients. Linearity was tested over a concentration range of 2–28 µg/mL with a linear regression equation of: Y = 58797 X + 3081 and r = 0.9998. Where, Y is peak area, X is concentration (µg/mL), and r is coefficient of correlation. Quantitation of favipiravir in human plasma samples was achieved by applying a previously validated UPLC–MS/MS method. The analytical method was validated in terms of specificity and selectivity, linearity, precision and accuracy, recovery, matrix effect, dilution accuracy and stability [18].

In Vitro Dissolution of Favipiravir

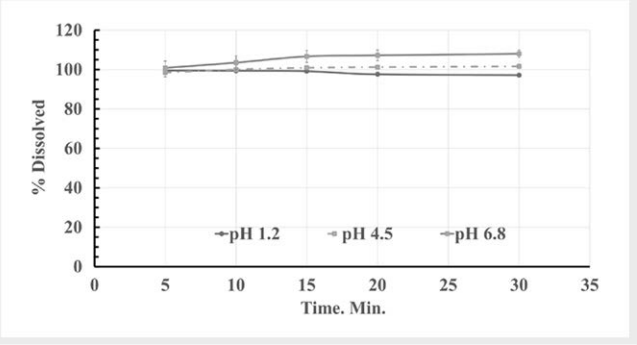
The individual dissolution profiles of favipiravir at three different dissolution media are presented in ▶ **Fig. 1**. It was observed that > 97 % was dissolved after 5 minutes in all dissolution media and ~ 100 % was dissolved after 30 minutes in both acetate buffer pH 4.5 and phosphate buffer pH 6.8 while 97.19 % was dissolved after 30 minutes in pH 1.2. Statistical analysis by one-way ANOVA showed that there is a significant difference between the dissolution results of the acid medium pH 1.2 and acetate buffer medium pH 4.5 (p = 0.0368) and there is a significant difference between the dissolution results of the acid medium pH 1.2 and phosphate buffer medium pH 6.8 (p = 0.0017). It was found that there is also a significant difference between the dissolution profile of acetate buffer medium pH 4.5 and phosphate buffer medium pH 6.8 (p = 0.0105). The mean dissolution time (MDT) was calculated to be 2.13, 2.80 and 3.16 minutes for acid medium, acetate buffer medium and phosphate buffer respectively.

Demographic data

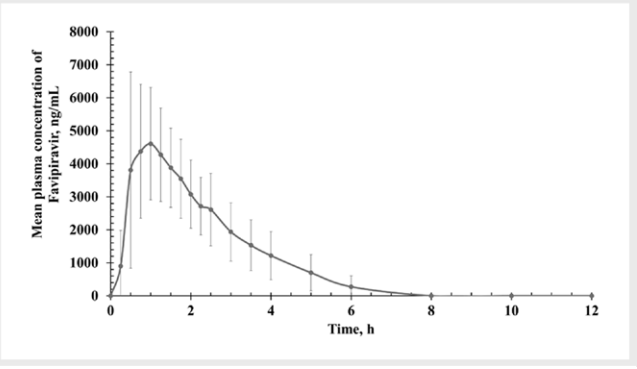
Thirty male subjects were screened but 27 subjects completed the clinical study. All physical examinations and vital signs including blood pressure, pulse and body temperature showed normal results. All lab results were in normal range. The mean age of the volunteers was 33.3 ± 10.14 years (20–53 years), mean weight was 73.31 ± 11.44 kg (49–92 kg), mean height was 172.76 ± 5.41 cm (165.0–187.5 cm) and mean body mass index was 24.61 ± 3.99 (16.37–31.11).

Pharmacokinetic evaluation

Plasma samples of human volunteers were analyzed by a validated LC-MS/MS method [18]. The average plasma concentration-time profiles following a single oral dosing of 200 mg Avigan tablets to 27 healthy Egyptian volunteers is presented in ▶ **Fig. 2**. The estimated median time required to achieve the highest concentration in plasma (T_{max}) was 0.75 h and ranged from 0.5 to 2.5 h. The calculated mean maximum plasma concentration (Cp_{max}) ± Standard deviation (SD) of favipiravir was 5966.45 ± 1767.26 ng/mL



▶ **Fig. 1** In vitro dissolution of favipiravir in different dissolution media (pH 1.2, pH 4.5 and pH 6.8).



▶ **Fig. 2** Plasma concentration of Favipiravir after oral administration of one tablet of Avigan® 200 mg Tablets to 27 healthy Egyptian volunteers.

(3714.66–10793.00 ng/mL). The mean area under the curve ($AUC_{0\text{-}t}$) ± SD was calculated to be 12577.14 ± 4967.23 ng.h/mL (7787.76–29892.55 ng.h/mL) while the mean $AUC_{0\text{-}\infty}$ ± SD was assessed to equal 13325.54 ± 5049.05 ng.h/mL (8136.41–30642.65 ng.h/mL) and the ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}\infty}$ was calculated to be 94.38 %. The volunteers showed elimination half-life ($t_{1/2}$) ranged from 0.87 h to 2.34 h with an estimated average value of 1.25 ± 0.29 h. It was found that the estimated pharmacokinetic parameters Cp_{max} and AUC of favipiravir were higher in healthy adult Japanese than in American subjects as published in the Review Report by "Pharmaceuticals and Medical Devices Agency: Avigan (favipiravir)" [27]. The outcomes of our study were compared to these pharmacokinetic parameters and tabulated in ▶ **Table 1**.

In vitro in vivo correlation

Linear regression models were used to correlate mean $AUC_{0\text{-}t}$ values (*in vivo* data) with the percent dissolved at different time points (*in vitro* data). Understanding the in vitro properties of possible formulations that could predict their in vivo performance is essential in pharmaceutical product development [28].

The level C IVIVC of $AUC_{0-0.5}$, $AUC_{0-0.75}$ and AUC_{0-1} values of favipiravir for the various % dissolved at different dissolution media pH 1.2, pH 4.5 and pH 6.8 at 5, 15 and 30 minutes are shown in ▶ **Fig. 3a–c**. The calculated coefficients of determination (r^2) were 0.8798, 0.8926 and 0.9501 for dissolution media pH 1.2, pH 4.5 and pH 6.8 respectively.

Discussion

Most people infected with SARS-CoV-2 virus will suffer from mild to moderate respiratory infection symptoms and recover without the need for additional therapy. Some, though, will get very ill and require medical treatment. Many antiviral drugs and monoclonal antibodies were authorized for COVID-19 in persons who are more prone to get severely ill. The efficacy of favipiravir against several viral infections has emerged as possible therapy for COVID-19 [29]. The pharmacokinetic profile of favipiravir is quite complex [30]. Inconsistency in the efficacy outcomes of favipiravir treatment in many clinical studies can be attributed to a variety of factors, including research design, demographic, and ethnicity [31]. These findings urge to investigate the pharmacokinetic characteristics of favipiravir in various ethnic groups. Our work focuses on the examination of Pk profile in healthy Egyptian volunteers and compares the results of Pk parameters with published data in other ethnic groups. After completing the screening phase and exhibiting normal vital signs, blood and urine tests, twenty-seven male healthy Egyptian participants were chosen for the study.

The pharmacokinetic results revealed considerable similarities between American and Egyptian volunteers if the values are corrected with respect to the dose. z-test was used to demonstrates how far one sample data point is far from another known sample mean using either a known population standard deviation or a sample standard deviation [32, 33]. It was found that there is no significant difference between Cp_{max} of Egyptian and American volunteers (p = 0.620), while there is significant difference between Egyptian and Japanese volunteers (p = 0.0001). It was also observed that there is no significant difference between $AUC_{0\text{-}\infty}$ of Egyptian and American volunteers (p = 0.924), while there is significant difference between Egyptian and Japanese volunteers (p = 0.0001). In another study to evaluate the bioequivalence of two favipiravir oral tablet formulations (200 mg) in Caucasian adult males under fasting conditions, the observed Cp_{max} of the reference product was 5002.171 ± 1231.177 ng/mL and $AUC_{0\text{-}\infty}$ was 10152.115 ± 2507.694 ng.h/mL. T_{max} was 0.75 h while $t_{1/2}$ was 1.319 h [34]. The results showed substantial comparisons between Caucasian and Egyptian volunteers. According to Michael G. and Marc H., favipiravir has a highly complex pharmacokinetic profile [21]. Physiologic condition can also influence medication pharmacokinetic characteristics and dosage recommendations [35]. Due to limited number of participants, more clinical pharmacokinetic studies in different ethnic groups are required to adjust dosing of favipiravir in different patients.

In vitro dissolution is a critical test used in formulation development to evaluate a drug's characteristics. It is often used as a predictor of in vivo performance and is routinely used in quality control to evaluate the performance of solid dosage forms and to examine the batch-to-batch variation.

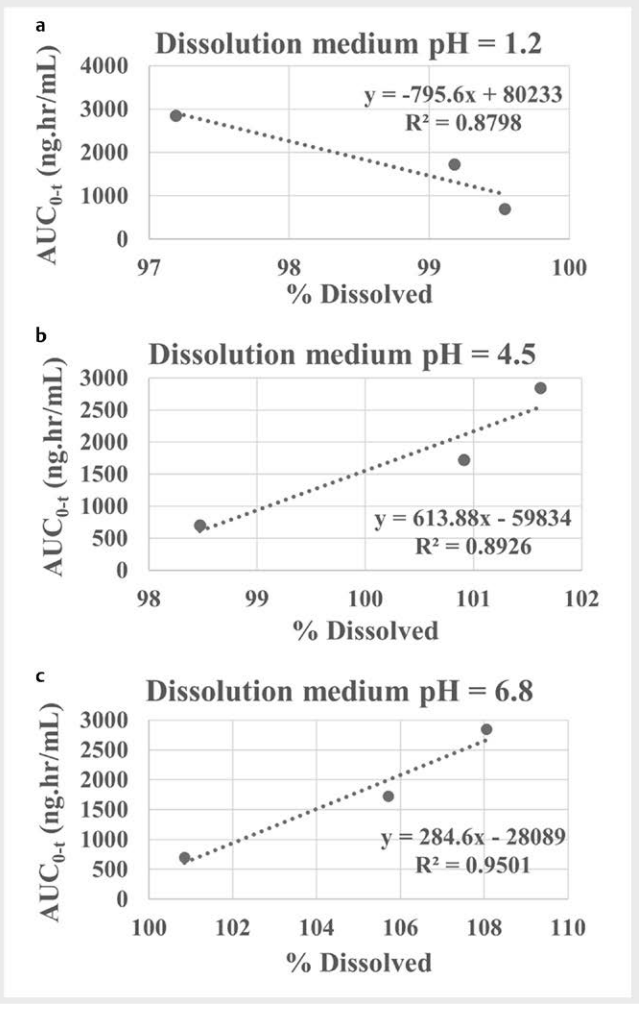
There is no official monograph for *in vitro* dissolution of favipiravir. As a result, the purpose of this research is to develop an optimum *in vitro* dissolution test for favipiravir IR tablets. A novel HPLC method was developed and validated for in vitro assay of favipiravir. It was realized that there is a considerable disparity in the dissolution profiles of all dissolution media.

The Level C IVIVC was created by correlating certain Pk parameter as $AUC_{0\text{-}t}$ to the percentage of drug dissolved in three distinct dissolving media at various times. Because the results showed a better fit [36], phosphate buffer medium (pH 6.8) is recommended as the optimal dissolution medium for level C IVIVC. These findings were consistent with results obtained by Göktuğ et al. [37] who concluded that 900 mL of phosphate buffer (pH 6.8) maintained at 37.0 ± 0.5°C is considered as proper dissolution medium for favipiravir tablets if using USP (apparatus II) at 50 rpm for 30 min. In vitro-in vivo correlations (IVIVCs) are generally practiced for modified-release (MR) formulations. Consequently, there are few publications regarding Level C IVIVC for immediate release (IR) preparations which might be helpful in product development and setting dissolution specifications [38]. Filippos Kesisoglou et al.

▶ **Table 1** Pharmacokinetic parameters of single oral dose of 400 mg of favipiravir in healthy adult Japanese and American subjects Vs. Pharmacokinetic parameters of single oral dose of 200 mg in healthy adult Egyptian volunteers.

Pharmacokinetic parameter	Japanese subjects * (400 mg)	American subjects * (400 mg)	Egyptian subjects (200 mg)
Median T_{max}, h	0.5	0.6	0.75
Cp_{max}, ng/mL (CV)**	16590 (6.0)	12170 (20.4)	5966.45 (29.62)
$AUC_{0-\infty}$, ng.h/mL (CV)**	39410.00 (16.0)	26740.00 (18.2)	13325.54 (37.89)
$t_{1/2}$, h ± SD***	1.60 ± 0.20	1.40 ± 0.10	1.25 ± 0.29

* Data was retrieved from reference 27.; ** CV is the coefficient of variation.; *** SD is the standard deviation.



▶ **Fig. 3** Level C IVIVC models for favipiravir for mean AUCs vs. percent dissolved at different dissolution media (**a**) pH 1.2, (**b**) pH 4.5 and (**c**) pH 6.8.

demonstrated level C correlation for the disintegration versus Cp_{max} of suvorexant immediate release tablets formulated using solid dispersion methodology. They came to the conclusion that disintegration time might be used as a substitute for dissolution in the establishment of IVIVC [39]. Dissolution data at certain times versus in vitro mean dissolution time, were used to create highly predictive level C IVIVC models for IR metformin tablets [40]. Cp_{max} vs. numerous in vitro dissolution parameters were successfully used to attain level C IVIVC for carbamazepine IR products [41, 42].

Conclusion

This study was performed on healthy Egyptian volunteers to assess the probable ethnic or regional variations in pharmacokinetics of favipiravir. It was concluded that there are similarities in the pharmacokinetic profile of favipiravir in healthy Egyptian, Caucasian, and American volunteers but there is a considerable difference between Egyptian and Japanese volunteers. In the future, clinical pharmacokinetic studies will be conducted on COVID-19 Egyptian patients to compare their pharmacokinetic parameters with other ethnic groups. Also, in this study, level C IVIVC model was implemented to select the recommended dissolution medium for favipiravir IR tablets as crucial preference for drug dissolution testing.

Data availability statement

The data are available as preprint on Research Square.

Conflict of Interests

The authors declare that there is no conflict of interests in this study.

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