FABAD J. Pharm. Sci., 51, 1, 89-104, 2026
Doi: 10.55262/fabadeczacilik.1811982
RESEARCH ARTICLE

Evaluation for Dissolution Profile Similarity of Multisource Generic Products Containing Favipiravir in the Treatment of COVID-19: Model-independent Bootstrap f_2 and Model-dependent Approaches

Duygu YILMAZ USTA[*°]

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SUMMARY

Favipiravir (FAV) has emerged as a potential antiviral drug for treating COVID-19 and has received emergency use approval in many countries, including Türkiye. This study aimed to assess the similarity of the dissolution profiles of FAV products using model-independent bootstrap f_2 and model-dependent approaches, particularly in cases of high variability in dissolution profiles at early time points and cumulative drug release less than 85%. Five generic FAV tablets were tested in pH 4.5 acetate and 6.8 phosphate buffers. The DDSolver®, Bootf2BCA_v1.3, and PhEq_bootstrap v1.2 software were used for similarity evaluation. At pH 4.5, none of the products reached 85% dissolution within 60 minutes. However, F2 and F4 achieved this within 30 minutes at pH 6.8. High variability was observed at early time points. Model-dependent analyses revealed differences in dissolution kinetics that were specific to the product and pH. For bootstrap f_2, DDSolver® identified similarity between F1-F2 at pH 4.5 and F1-F5 at pH 6.8. However, Bootf2BCA and PhEq_bootstrap could only confirm this for F1-F2 at pH 4.5 due to the lower limits of the confidence interval falling below 50. These findings demonstrate the importance of conducting dissolution tests to demonstrate therapeutic equivalence among multisource generic drugs, particularly during public health emergencies such as the COVID-19 pandemic. Bootstrap f_2 has been observed to provide more robust results, particularly when the classical f_2 assessment criteria commonly used are not met. This reliable approach also meets the expectations of regulatory authorities such as the EMA and FDA.

Keywords: *Favipiravir, COVID-19, high variable dissolution profile comparison, bootstrap f_2, model-dependent approach.*

COVID-19 Tedavisinde Favipiravir İçeren Çok Kaynaklı Jenerik Ürünlerin Çözünme Profili Benzerliğinin Değerlendirilmesi: Modelden Bağımsız Bootstrap f_2 ve Modele Bağımlı Yaklaşımlar

ÖZ

Favipiravir (FAV), COVID-19 tedavisi için potansiyel bir antiviral ilaç olarak ortaya çıkmış ve Türkiye dahil birçok ülkede acil kullanım onayı almıştır. Bu çalışma, özellikle erken zaman noktalarında çözünme profillerinde yüksek değişkenlik ve kümülatif ilaç salımının %85'ten az olduğu durumlarda, model bağımsız bootstrap f_2 ve modele bağlı yaklaşımlar kullanarak FAV ürünlerinin çözünme profillerinin benzerliğini değerlendirmeyi amaçlamıştır. Beş jenerik FAV tableti, pH 4,5 asetat ve 6,8 fosfat tamponlarında test edilmiştir. Benzerlik değerlendirmesi için DDSolver®, Bootf2BCA_v1.3 ve PhEq_bootstrap v1.2 yazılımları kullanılmıştır. pH 4,5'te hiçbir ürün 60 dakika içinde %85 çözünme oranına ulaşamadı; ancak pH 6,8'de F2 ve F4 30 dakika içinde bu orana ulaşmıştır. Erken zaman noktalarında yüksek değişkenlik gözlemlenmiştir. Modele bağlı analizler, ürüne ve pH'ya özgü çözünme kinetiğinde farklılıklar olduğunu ortaya koymuştur. Bootsrap f_2 için, DDSolver® pH 4,5'te F1-F2 ile pH 6,8'de F1-F5 arasında benzerlik tespit etti. Ancak Bootf2BCA ve PhEq_bootstrap, güven aralığının alt sınırlarının 50'nin altına düşmesi nedeniyle bunu sadece pH 4,5'te F1-F2 için doğrulayabilmiştir. Bu bulgular, özellikle COVID-19 pandemisi gibi halk sağlığı acil durumlarında, çok kaynaklı jenerik ilaçlar arasında terapötik eşdeğerliği göstermek için çözünme testleri yapmanın önemini ortaya koymaktadır. Bootstrap f_2'nin, özellikle yaygın olarak kullanılan klasik f_2 değerlendirme kriterleri karşılanmadığında daha sağlam sonuçlar sağladığı gözlemlenmiştir. Bu güvenilir yaklaşım, EMA ve FDA gibi düzenleyici kurumların beklentilerini de karşılamaktadır.

Anahtar Kelimeler: *Favipiravir, COVİD-19, yüksek değişkenli çözünme profili karşılaştırması, bootstrap f_2, model bağımlı yaklaşım.*

Recieved: 29.10.2025
Revised: 16.12.2025
Accepted: 20.12.2025

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INTRODUCTION

The coronavirus outbreak was first observed in Wuhan, China, in 2019, when it was identified as an unknown acute respiratory infection. After spreading to many countries, the World Health Organization (WHO) declared it a pandemic on 11 March 2020 (Dousari et al., 2020; Usta & Teksin, 2020). Since the start of the pandemic, countries have implemented different treatment approaches (FDA 2020; Jamshaid et al., 2020; Tsang et al., 2021). In view of the urgency of the situation, it has been deemed preferable to use approved drugs prescribed for other diseases that have an acceptable safety profile. This is because it could take months or even years to develop a drug molecule from scratch and prove its effectiveness in treating the disease (Liu et al., 2020; Pilkington et al., 2020).

One such drug is the antiviral Favipiravir (FAV), which is assumed to be therapeutically effective against the disease. FAV ($C_5H_4FN_3O_2$), also known as 6-fluoro-3-hydroxy-2-pyrazine carboxamide, is a pyrazine carboxamide derivative (Furuta et al., 2013). FAV has a molecular weight of 157.1 g/mol and is a prodrug (T-705). Its elimination half-life is 2–5.5 hours, and its bioavailability is 97.6%. The mean C_{max} is 51.5 μg/mL, the main volume of distribution is 15–20 L, and it is metabolized via the kidney (Joshi et al., 2021). There is no effect of food on FAV bioavailability. FAV was developed by the Japanese company Fujifilm Toyama Chemical in 2002 and approved for the treatment of influenza in 2014 (Dindar et al., 2022). FAV is an oral, broad-spectrum RNA-dependent RNA polymerase inhibitor with a well-defined safety profile (Joshi et al., 2021). It is thought that antiviral drugs administered shortly after the onset of symptoms may shorten the clinical course of the disease and reduce viral shedding when used to treat coronaviruses, thus reducing transmission, and these drugs have been included in treatment protocols. Avigan®, the reference drug for FAV included in the treatment protocol, was not available on the Turkish pharmaceutical market; however, the Ministry of Health has approved and used five generic products as of film-coated tablets (each includes 200 mg of FAV).

When a pharmaceutical product is taken orally, the active ingredient must be dissolved in gastrointestinal fluids before it can be absorbed. Dissolution is crucial for predicting *in vivo* drug behavior, ensuring consistent quality across all production batches and" post-approval adjustments, optimizing the drug manufacturing process, and determining bioequivalence and therapeutic equivalence between generic and reference drugs (McAllister et al., 2020). The most popular method of examining the effect of dissolution on these processes is to conduct *in vitro* dissolution studies in accordance with the relevant guidelines and pharmacopoeias (Muselík et al., 2021).

Dissolution studies enable drug behavior and performance in the gastrointestinal tract to be observed under *in vitro* conditions (Yılmaz Usta & Teksin, 2017). A key aspect of dissolution studies in drug development and regulatory approval is comparing dissolution profiles (Zuo et al., 2014). To this end, regulatory guidelines and legal authorities recommend using different methodologies to compare *in vitro* dissolution profiles based on dissolution data obtained from the dosage forms under study. The similarity factor (f_2) is the most widely used method for this purpose due to its simplicity and ease of calculation (Diaz et al., 2016). Recognized by numerous regulatory agencies worldwide, f_2 has become the standard approach for assessing dissolution profile similarity. However, specific conditions must be met for its application: the dissolution profile must include at least three time points beyond the initial measurement; testing must be conducted on 12 dosage units per formulation; the total dissolved drug percentage must exceed 85%; and the coefficient of variation (CV) must remain within acceptable limits - less than 20% at the first time point and below 10% for subsequent points

(Wang et al., 2016). In addition, the f_2 method has several limitations. These include assumptions about sample distribution and sensitivity to the number of time points. Furthermore, it is unable to pinpoint where variations occur within the dissolution profile. Furthermore, it does not account for high variability in dissolution data effectively.

Given the high variability observed at the start of the study and the fact that the cumulative percentage of the active ingredient dissolved remained below 85% for some products, it is important to determine the most appropriate method for evaluating the similarity of dissolution profiles and assessing generic formulations. Alternative approaches have been explored to address the shortcomings of the similarity factor (f_2). One such method uses a 90% confidence interval (CI) for f_2, applying bootstrap resampling techniques to evaluate similarity without relying on f_2 as a single-point estimator. This approach has attracted considerable interest from regulatory authorities, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in recent years for evaluating dissolution profile similarity, especially when the prerequisites for using classical f_2 are not met (Paixão et al., 2017).

This study aimed to demonstrate the equivalence of generic products containing FAV in the Turkish pharmaceutical market, which have been approved for emergency use in the Ministry of Health's treatment protocol for patients with COVID-19, through dissolution studies. Dissolution profiles exhibiting high variability at early time points and a dissolved FAV amount of less than 85% were evaluated using both model-independent bootstrap f_2 methods and model-dependent approaches. The results obtained from these different approaches were then compared. As there are no dissolution or dissolution profile comparison studies in the literature for generic products containing FAV in the Turkish pharmaceutical market, this study is scientifically innovative.

MATERIALS AND METHODS

Materials

FAV was provided by Atabay Drug Company (İstanbul, Türkiye). Acetic acid ($C_2H_4O_2$), sodium acetate trihydrate ($NaC_2H_3O_2 \cdot 3H_2O$), potassium dihydrogen phosphate (KH_2PO_4), and sodium hydroxide (NaOH) were purchased from Merck, Germany. The batch numbers for generic products are as follows: F1, 204332; F2, 3388006; F3, 20N702; F4, 33927; F5,10100006. The F2 product was requested from the manufacturer, while the other generics are products provided to patients by contact tracing teams for emergency treatment.

Analytical quantification of FAV

pH 4.5 acetate and pH 6.8 phosphate buffers were used as media. A stock solution of FAV was prepared by dissolving 25 mg in 250 mL of buffer to obtain a concentration of 100 µg/mL. Working standard solutions in the concentration range (for pH 4.5, 10-20 µg/mL and pH 6.8, 4–12 µg/mL) were prepared by suitable dilution of the stock solution. All the samples were filtered with a 0.45µm membrane filter. The standard solutions (10 µg/mL) were scanned in the range of 200 -800 nm by a UV-spectrophotometer (Cary 60 UV-Vis, Agilent, Germany). The maximum absorbances were observed at 360 nm for both, and this wavelength was used for all measurements. The methods were validated using FDA guidelines and ICH Q2(R2) (FDA 2018; ICH 2023).

Preparation of buffer media

Preparation of pH 4.5 acetate buffer. The pH 4.5 acetate buffer was prepared by mixing 2.99 g $NaC_2H_3O_2 \cdot 3H_2O$ and 14 mL 2N acetic acid solution, and the required amount of distilled water was added up to 1 L. The pH was checked and adjusted to 4.5, if necessary, by adding small volumes of either acid or base. The solution was filtered through a 0.45 µm membrane filter before use.

Preparation of pH 6.8 phosphate buffer. The pH 6.8 phosphate buffer was prepared by mixing 250 mL of

0.2 M potassium dihydrogen phosphate (KH_2PO_4) with 112 mL of 0.2 M sodium hydroxide (NaOH) solution. Adjust the volume to 1000 mL with distilled water. The pH was checked, and the pH was adjusted to 6.8, if necessary, by adding small volumes of either acid or base. The solution was filtered through a 0.45 µm membrane filter before use.

0.2 M potassium dihydrogen phosphate solution: Dissolve 22.7 g of KH_2PO_4 in distilled water and dilute to 1000 mL.

0.2 M sodium hydroxide solution: Dissolve 2 g of NaOH in distilled water and dilute to 1000 mL.

Dissolution studies

There is no official monograph available for tablet dosage forms containing FAV. In such cases, it is recommended to perform dissolution testing for immediate release (IR) tablets using the basket or paddle method with different rotation speeds in different dissolution media (pH 1.0 to 6.8) (FDA, 1997). The dissolution testing of FAV generic tablets was conducted at 37 ± 0.5°C at 50 rpm using the USP apparatus II. pH 4.5 acetate buffer and pH 6.8 phosphate buffer, with 900 mL, were used as dissolution media. Aliquots of 5 mL were withdrawn at the 5, 10, 15, 20, 30, 45, and 60 min from each dissolution vessel, an equivalent volume of the corresponding fresh media was added. All samples were filtered 0.45µm membrane filter and analyzed by UV analysis at 360 nm. The studies were conducted in 12 parallel studies.

Software used for data analysis

For comparing estimations of the similarity factor (f_2, unbiased f_2 (bc- f_2), or the expected value ($_{2,exp}$)) and their corresponding 90% confidence intervals (CIs), three widely used and freely accessible software tools were selected: DDSolver®, Bootf2BCA (Version 1.3), and PhEq_bootstrap (Version 1.2). The method is implemented in Bootf2BCA, an open-source tool developed in the R statistical environment (Noce et al., 2020). Analyses were conducted in R (Version 4.1.3) and RStudio (Version 2022.02.1) using the bootf2 and bootf2BCa functions. All three compute the conventional f_2 metric, and each of these platforms employs a bootstrap approach to approximate the sampling distribution of the similarity factor. In addition, PhEq_bootstrap is the only platform that provides bc- f_2, while both Bootf2BCA and PhEq_bootstrap can calculate $_{2,exp}$ (Table 1.) (Noce et al., 2020). The primary functionalities and tools offered by these platforms are summarized in Table 2.

Table 1. Equations for different f_2 types calculated by software tools

f_2 types	Equations	Parameters
f_2	$f_2 = 50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{k=1}^{n}(R_k-T_k)^2\right]^{-0.5}.100\right\}$	n: Number of time points R_t and T_t: Mean dissolution amount of reference and test products at time t
Estimated f_2 ($\hat{f}_2$)	$\hat{f}_2 = 100-25\log\left(1+\left(\frac{1}{n}\right)\sum_{k=1}^{n}(\overline{X}_{T,k}-\overline{X}_{R,k})^2\right)$	n: number of time points $\bar{X}_{R,k}$ *and* $\bar{X}_{T,k}$: Mean dissolution data at the k^{th} time point of random samples chosen from the reference and test populations, respectively.
Bias-corrected f_2 ($\hat{f}_{2,bc}$)	$\hat{f}_{2,bc} = 100-25\log\left(1+\left(\frac{1}{n}\right)\left(\sum_{k=1}^{n}(\overline{X}_{T,k}-\overline{X}_{R,k})^2-\left(\frac{1}{n}\right)\sum_{k=1}^{n}(S^2_{T,k}+S^2_{R,k})\right)\right)$	n: sample size $S^2_{R,k}$ and $S^2_{T,k}$: Unbiased estimates of variance at the k^{th} time points of random samples chosen from reference and test population, respectively.
Unbiased f_2	$bc-f_2 = 50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{k=1}^{n}(R_k-T_k)^2-\sum_{k=1}^{n}(S^2_{R,k}+S^2_{T,k})/n\right]^{-0.5}.100\right\}$	$S^2_{R,k}$ and $S^2_{T,k}$: The sample variances at the k^{th} time point of reference and test products
Expected f_2 ($\hat{f}_{2,bc}$)	$E(\hat{f}_2) = 100-25\log(1+(\frac{1}{n})(\sum_{k=1}^{n}(\mu_{T,k}-\mu_{R,k})^2+(\frac{1}{n})\sum_{k=1}^{n}(\sigma^2_{T,k})^2+\sigma^2_{R,k})^2)))$	$\sigma^2_{R,k}$ and $\sigma^2_{T,k}$: Population variance at k^{th} time points of the reference and the test product, respectively.
Types of CI		
Normal interval	$\hat{f}_{2,L} = \hat{f}_{2,S}-E_B-\sqrt{V_B}.Z_{1-\alpha}$ $\quad$ $\hat{f}_{2,U} = \hat{f}_{2,S}-E_B-\sqrt{V_B}.Z_{1-\alpha}$ $E_B = \frac{1}{B}\sum_b^B \hat{f}_{2,b}-\hat{f}_{2,S} = \bar{f}_2-f_{2,S}$ $\quad$ $V_B = \frac{1}{B-1}\sum_b^B(\hat{f}^*_{2,b}-\bar{f}^*_2)^2$	$\hat{f}_{2,L}$ and $\hat{f}_{2,u}$: Lower and upper limit of the confidence interval estimated from bootstrap samples $Z_{1-\alpha}$: The inverse of the standard normal cumulative distribution function with type I error α: E_B and V_B are the resampling estimates of bias and variance B: Number of bootstrap samples $\hat{f}_{2,S}$: f_2 estimate with b^{th} bootstrap sample and $\bar{f}^*_2$: mean value
Basic interval	$\hat{f}_{2,L} = 2\hat{f}_{2,S}-\hat{f}^*_{2,(B+1)(1-\alpha)}$ $\quad$ $\hat{f}_{2,U} = 2\hat{f}_{2,S}-\hat{f}^*_{2,(B+1)\alpha}$ $\hat{f}^*_{2,(B+1)\alpha} = \hat{f}^*_{2,k}+\frac{\Phi^{-1}(\alpha)-\Phi^{-1}(\frac{k}{B+1})}{\Phi^{-1}(\frac{k+1}{B+1})-\Phi^{-1}(\frac{k}{B+1})}(\hat{f}^*_{2,k+1}-\hat{f}^*_{2,k})$	$\hat{f}^*_{2,(B+1)\alpha}$ and $\hat{f}^*_{2,(B+1)(1-\alpha)}$: (B+1)αth and (B+1)(1- α)th ordered resampling estimates of f_2 k: The integer part of (B+1)α, $\hat{f}^*_{2,k+1}$ and $\hat{f}^*_{2,k}$ the (k+1)th and the k^{th} ordered resampling estimates of f_2, respectively.
Bias-corrected and accelerated (BCa) intervals	$\hat{f}_{2,L} = \hat{f}^*_{2,\alpha_1}$ $\quad$ $\hat{f}_{2,U} = \hat{f}^*_{2,\alpha_2}$ $\alpha_1 = \Phi\left(\hat{Z}_0+\frac{\hat{z}_0+\hat{z}_\alpha}{1-\hat{a}(\hat{z}_0+\hat{z}_\alpha)}\right)$ $\quad$ $\alpha_2 = \Phi\left(\hat{Z}_0+\frac{\hat{z}_0+\hat{z}_{1-\alpha}}{1-\hat{a}(\hat{z}_0+\hat{z}_{1-\alpha})}\right)$	$\hat{f}^*_{2,\alpha_1}$ and $\hat{f}^*_{2,\alpha_2}$: The 100α$_1^{th}$ and the 100α$_2^{th}$ percentile of the resampling estimates of f_2 $\hat{z}_0$ and $\hat{a}$: Bias-correction and acceleration

CI: Confidence interval

Table 2. The summary of features, functionality, and parameters of the software tools

	Coding language	Using similarity parameters	Confidence interval	Sampling mode	Key advantages	Limitations
DDSolver[*,**]	Visual basic	*CI* for f_2	Percentile bootstrap	Whole vectors	Free Excel add-in Easy to use	Limited to n<36 No BCa CI
Bootf2BCA[**]	R language	*CI* for $E(f_2)$	Normal Basic Percent BCa (adjusted)	Individual values Whole vectors	Highly flexible Customizable Supports all CI methods	Requires coding skills
PhEq_bootstrap[***]	Lazarus RAD language in Pascal	*CI* for f_2 *CI* for $E(f_2)$	Percentile bootstrap	Individual values Whole vectors	Free Open-source Handles large datasets	No BCa CI Limited f_2 variants for CI

CI: Confidence interval; **BCa:** Bias-corrected and accelerated; **$E(f_2)$:** Expected f_2; **RAD:** Rapid application development
[*] Zhang et al., 2010
[**] Sourceforge.net, 2016
[***] Sourceforge.net, 2014

RESULTS and DISCUSSION

Dissolution studies

The apparatus, dissolution medium, sampling time, and rotation speed must be carefully selected in accordance with the relevant dissolution test conditions before conducting an *in vitro* dissolution test. There is no official monograph for tablet dosage forms containing FAV. In such cases, it is recommended that dissolution testing be performed under various conditions (pH 1 - 6.8) using a basket or paddle at different rotation speeds for IR tablets (FDA, 1997). When reviewing dissolution studies of FAV in the literature, it was found that studies had been conducted at different pH levels (pH 2.0 - 7.2), speeds (25 - 100 rpm), and media volumes (500 - 1000 mL) (Chakraborty & Mondal, 2023; Marzouk et al., 2022). The most important parameter when selecting the dissolution medium and volume is the solubility of the active ingredient. Solubility studies conducted for FAV in the literature show that solubility increases with pH (with the highest solubility occurring at pH 6.8) (Timur et al., 2021).

Considering suitable media volumes for dissolution studies, the theoretical solubility under sink conditions is 1.2 mg/mL for a volume of 500 mL and 0.7 mg/mL for a volume of 900 mL (Göktuğ et al., 2021). However, the solubility of FAV in different pH media (0.526 mg/mL at pH 1.2, 0.818 mg/mL at pH 4.5, and 0.815 mg/mL at pH 6.8) did not meet the sink conditions for a medium volume of 500 mL (as the solubility of FAV at these pH levels was less than 1.2 mg/mL), so the medium volume was increased to 900 mL. The sink condition saturation solubility (C_S)/drug concentration (C_D) ratio was calculated by dividing the dose by the 900 mL dissolution medium (Incecayir et al., 2021). According to the USP, the sink condition is met when the C_S/C_D value is greater than 3 (Hamed et al., 2016). For 200 mg of FAV in 900 mL, the sink condition was found to be 2.37, 3.68, and 3.67 at pH 1.2, 4.5, and 6.8, respectively. As the sink condition was not met at pH 1.2, and larger volumes are generally not favored in dissolution studies, comparisons were made using media at pH 4.5 and 6.8. A rotation speed of 50 rpm was selected, as recommended by the FDA and EMA for new studies (EMA, 2017; FDA, 1997).

Avigan®, the reference product, is unavailable on the Turkish pharmaceutical market; therefore, evaluations were carried out using F1, the first generic product to be launched, as the reference. The dissolution profiles are given in Figure 1 for the studies conducted at pH 4.5 and pH 6.8. The percentage of FAV dissolved at pH 6.8 was higher for F1, F2, and F4 than at pH 4.5, while the results for F3 and F5 were similar at both pH values. At pH 4.5, the percentage of dissolved FAV remained below 85% for all products after 60 minutes. At pH 6.8, however, F2 and F4 reached 85% within 30 minutes. F1, F3, and F5 remained below 85% at the end of the study. Examining the profiles revealed high variation at the early points.

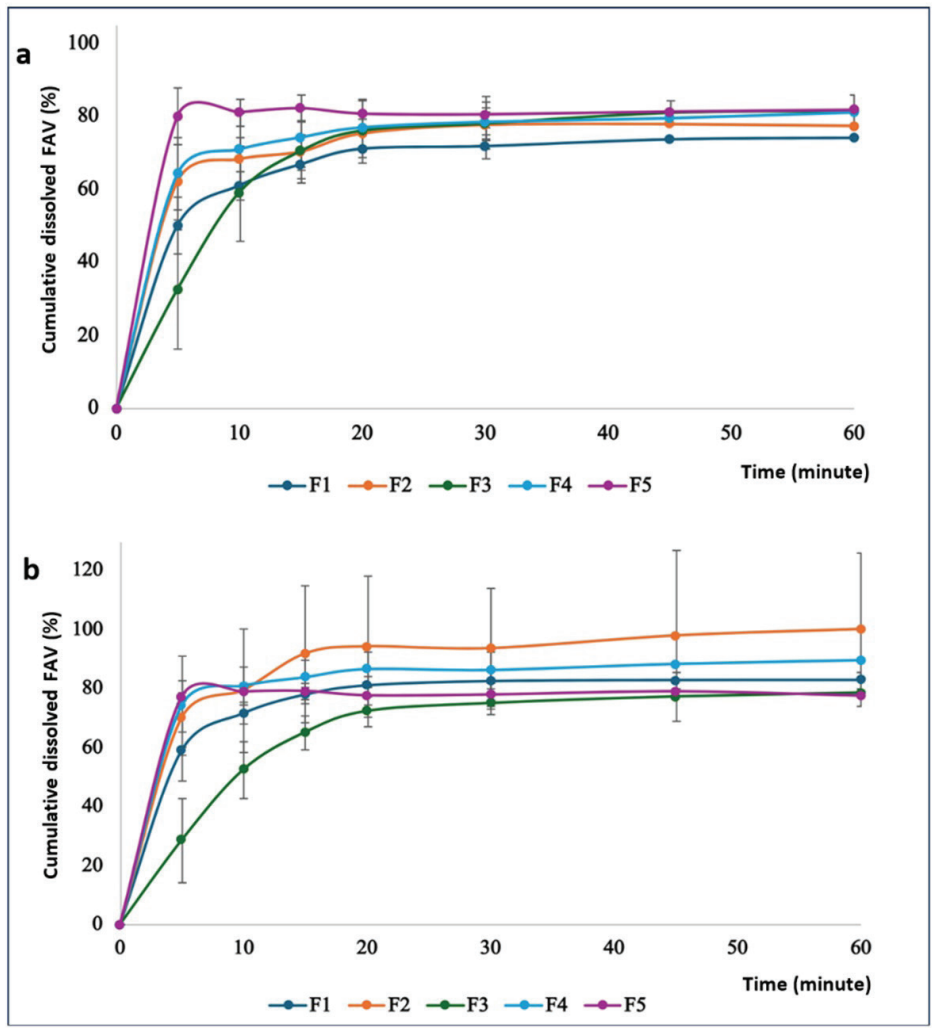

Figure 1. Dissolution profiles of FAV a) at pH 4.5 and b) at pH 6.8 (n=12, mean ± standard deviation)

Results of data analysis

Accurately assessing the similarity between dissolution profiles is important when analyzing dissolution data. Various approaches have therefore been developed to facilitate this comparison. These approaches can be broadly classified as either model-dependent or model-independent methods (Usta & Incecayir, 2022). Model-dependent methods involve fitting dissolution data to a specific mathematical or kinetic model for evaluation. These methods aim to determine the parameters that define the dissolution process and to make comparisons based on these

parameters. In these models, experimental dissolution data are fitted to mathematical equations, and the model parameters are determined. Statistical analyses of these parameters are then performed. Statistical measures such as the coefficient of determination, the root mean square error, corrected determination coefficient (R^2_{adj}), Akaike information criterion (AIC), and/or model selection criterion (MSC) are used to evaluate the model's fit.

DDSolver® is a free, menu-driven, computer-based program developed in Visual Basic for Microsoft Excel. It is designed to simplify the comparison, modelling, and calculation of dissolution profiles (Zhang et al., 2010). It is the first program of its kind to offer a user-friendly interface for analyzing pharmaceutical dissolution data. The software's primary objectives are to facilitate the evaluation of similarity between dissolution profiles, build a library of models that fit dissolution data using non-linear optimization methods, and enable reliable comparison of dissolution profiles. From the model library, the program can quickly determine which model best fits the release data. It can then generate fitted curves for each dataset, complete with error bars and mean dissolution curves (Yılmaz Usta & Teksin, 2017). In addition to profile fitting, DDSolver® provides over 40 built-in mathematical models, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Weibull models. This enables both empirical and mechanistic analyses. The software also includes statistical tools for profile comparison, such as the f_2, the difference factor (f_1), and multivariate CIs. It also provides model selection criteria, such as the AIC and the MSC. By integrating directly into Excel, DDSolver® automates calculations, minimizes the risk of human error, and does not require advanced programming skills. Due to these advantages, it has become a widely used tool in pharmaceutical research, particularly in formulation development, quality control, and regulatory submissions. In addition to the classic f_2 statistic, the similarity of percentile CIs can be assessed using different resampling levels (5000, 10000, and 20000) and sample sizes (n = 12 and n = 24) for dissolution profiles with various levels of variability (10–20%, 40–50%, and 70–80% RSD). One limitation of the interface is that it cannot perform similarity assessments when the sample size is large (≥ 36).

The most suitable model for each product was determined by the lowest AIC value and the highest MSC and R^2_{adj}. The AIC evaluates both the complexity of the model and the quality of the fit, depending on the size of the dataset and the number of parameters. When comparing models with different numbers of parameters, the model with the lower AIC value is considered to provide a better fit. MSC is derived from AIC and normalized so that it is independent of the scaling of the data points. MSC is relatively easier to interpret, with a value above 3 indicating a good fit (Usta et al., 2018). R^2_{adj} is recommended for model selection and for comparing models with different numbers of parameters. As it considers the explanatory power of the included parameters when being calculated, R^2_{adj} more accurately reflects the true performance of the model. It may decrease if unnecessary parameters are added (Çoban et al., 2024). The reliability of model-dependent methods largely depends on the correct selection and statistical validation of the model. Incorrect model selection can lead to dissolution behavior being misinterpreted.

In this study, the AIC, MSC, and R^2_{adj} criteria were used for evaluation. Table 3 shows the models to which tablets containing FAV were fitted. Although different models were observed for different pH levels and generic products, it was determined that the tablet's dissolution behavior of is affected by β (shape factor) and α (scale factor), which characterize the dissolution profile parameters.

Table 3. Results of the evaluation of model-dependent methods using DDSolver® for FAV generic tablets

		F1	F2	F3	F4	F5
pH 4.5	**Model parameters**	**Gompertz 2**	**Probit 2**	**Gompertz 2**	**Logistic 2**	**Gompertz 1**
		α: 1.83	α: 0.05	α: 67.9	α: 41.5	α: 0.22
		β: 2.12	β: 0.963	β: 2.82	β: 1.69	β: 0.048
		F_{max}: 77.8	F_{max}: 81.7	F_{max}: 85.5	F_{max}: 85.1	
	R^2_{adj}	0.998	0.997	0.992	1	0.999
	AIC	21.4	24.5	33.9	5.57	11.5
	MSC	4.17	3.61	3.53	6.01	5.15
pH 6.8	**Model parameters**	**Gompertz 2**	**Weibull 2**	**Gompertz 2**	**Gompertz 2**	**Weibull 2**
		α: 1.36	α: 1.92	α: 7.45	α: 0.606	α: 0.662
		β: 2.04	β: 0.53	β: 2.90	β: 1.40	β: 0.003
		F_{max}: 87.1		F_{max}: 82.5	F_{max}: 94.1	
	R^2_{adj}	0.994	0.995	0.995	0.999	0.999
	AIC	31.3	31.8	30.0	14.7	14.7
	MSC	3.11	3.40	4.04	5.01	4.67

$\boldsymbol{F_{max}}$: Maximum fraction of drug released at infinite time; $\boldsymbol{\beta}$: Shape factor; $\boldsymbol{\alpha}$: Scale factor

Unlike model-dependent methods, model-independent methods are unaffected by errors resulting from incorrect model selection. This characteristic makes them widely preferred for regulatory submissions, bioequivalence assessments, and formulation optimization studies. However, when applying these methods, factors such as sampling design, the number of time points, and variability in dissolution data must be carefully evaluated. The f_2 method proposed by Moore and Flanner is the preferred criterion for this purpose, as it is simple (Muselík et al., 2021). Nevertheless, neither the EMA nor the FDA provides specific instructions for comparing dissolution curves beyond calculating the f_2 similarity factor. Furthermore, since f_2 is insensitive to the shape of the profiles, it is difficult to assess consumer risk (type I) and manufacturer risk (type II) errors (Hoffelder et al., 2022). In recent years, resampling techniques such as bootstrapping have been employed to mitigate the impact of factors such as variability in dissolution data and sample size on statistical reliability. These techniques generate a distribution of f_2 values and multiple simulated datasets from observed dissolution data (Efron 1992; Xu et al., 2021). Among multivariate, model-independent approaches, bootstrap statistics have become a widely used statistical approach for regulatory submissions and determining dissolution similarity (EMA, 2018). Bootstrap is a software-based statistical inference method that enables CIs and standard errors to be calculated for hypothesis testing without making classical statistical assumptions about probability distributions (Jamil & Polli, 2024; Kaity et al., 2023). Including CIs in the bootstrap method proposed by Shah et al. provides an interval estimate for assessing similarity, as opposed to the single point estimate provided by the classical f_2 method (Shah et al., 1998). These approaches strengthen the reliability of statistical inferences and evaluations by considering data variability and uncertainty (Rabelo & Lourenço, 2025).

In this study, due to some CV values exceeding the acceptable maximum (CV > 20 at initial time points and CV > 10 at subsequent time points) and the percentage of the active substance remaining

dissolved being below 85% (see *Dissolution studies,* Figure 1.), comparisons were performed using bootstrap f_2 (with CI), as recommended by EMA guidelines (Mendyk et al., 2013; Muselík et al., 2021). For bootstrap f_2 evaluations of dissolution profiles, the sample size was at least 12 units per batch or product. However, if a higher level of confidence is required, larger sample sizes should be used. The bootstrap f_2 approach is particularly important when f_2 is less than 60. In the bootstrap evaluation, the lower limit of the bootstrap CI is accepted if it is above 50. This meets the EMA guideline requirement that 'the f_2 value should be between 50 and 100' (EMA 2010; 2018). As the guidelines do not explain the details of the estimators or different CI types, this study presents the results obtained from estimators provided by different programs. The CI can be determined based on bootstrap analysis using various methods, including the normal approximation, the percentile method, and the BCa method (Boddu et al., 2023).

Bootf2BCA is a statistical approach designed to evaluate similarity between dissolution profiles by combining the bootstrap method with bias-corrected and accelerated (BCa) CIs. The analysis can be performed with varying numbers of bootstrap replications (5000, 10000, and 20000), different sample sizes (n = 12, 24, and 36), and across a wide range of dissolution profile variabilities (10–20%, 40–50%, and 70–80% RSD). The Bootf2BCA method uses a resampling strategy to generate thousands of bootstrap datasets, randomly sampling the original dissolution data with replacement. The BCa adjustment corrects for bias and skewness in the bootstrap distribution, enabling more accurate estimation of the f_2 of CIs. This allows multiple forms of similarity factors to be calculated, including estimated, expected, bias-corrected, variance-corrected and combined variance, and bias-corrected f_2, along with percentile and BCa CIs for each.

PhEq_bootstrap is freely available open-source statistical software, which was developed to compare the dissolution profiles of test and reference pharmaceutical products, using both conventional and advanced similarity assessment methods. It can calculate the conventional f_2, the bc- f_2, the $_{2,exp}$, and the percentile CI similarity limits through a bootstrap resampling approach (Noce et al., 2020). Unlike traditional methods, which produce only a single point estimate, the bootstrap technique repeatedly resamples dissolution data to generate a distribution of the similarity metric. This distribution can then be used to derive CIs. Previous studies have demonstrated that the conventional f_2 statistics are a biased, yet asymptotically unbiased, estimator of the true population similarity (Shah et al., 1998). This bias arises from the combined within-batch variance of the test and reference products. PhEq_Bootstrap overcomes these limitations by providing $_{2,exp}$, and percentile CI estimates, offering a more probabilistic understanding of similarity. In practical applications, the software enables evaluations under varying conditions, including different numbers of bootstrap resamples and sample sizes, and across profiles with different levels of variability (Table 6.). However, it should be noted that percentile CI limits can only be generated for $_{2,exp}$, and not for conventional f_2 or bc- f_2. This makes this method particularly valuable for cases involving high variability or limited data points, where conventional similarity factors may not fully capture the uncertainty in dissolution profile comparisons.

The results of profiles evaluated using DDSolver®, Bootf2BCA, and PhEq_Bootstrap are presented in Tables 4–6. Bootstrap f_2 values calculated using the software differed for the pH 4.5 and 6.8 media, but similar similarity assessment results were obtained. Comparisons were made using the first generic product (F1 was accepted as the reference), and only the similarity factor was found > 50 for F2 in the pH 4.5 media using all software. For a pH of 6.8, F5 was similar to F1 in the DDSolver® bootstrap assessment (Table 4.). However, similarity could not be achieved using the Bootf2BCA and PhEq_bootstrap methods because the lower limits of the CIs remained below 50 (Tables 5 and 6.).

Table 4. Results and evaluation of the bootstrap f_2 method with DDSolver®

	Observed similarity factor (f_2)	Bootstrap (Mean)	5000 Bootstrap (5^{th} percentile)	5000 Bootstrap (95^{th} percentile)	Similarity
pH 4.5					
F1-F2	60.8	60.7	53.8	68.6	*Yes*
F1-F3	55.1	54.6	49.0	60.4	*No*
F1-F4	54.7	55.2	47.7	67.1	*No*
F1-F5	41.0	40.9	38.8	43.4	*No*
pH 6.8					
F1-F2	45.4	46.4	34.2	68.3	*No*
F1-F3	42.2	42.3	38.0	47.0	*No*
F1-F4	55.5	55.5	48.9	63.5	*No*
F1-F5	55.8	55.7	51.5	61.8	*Yes*

Table 5. Results and evaluation of the bootstrap f_2 method with Bootf2BCA

	f_2 type	CI type	F2		F3		F4		F5	
pH 4.5	$\hat{f}_2$		$f_{2\,avr}$: 60.6		$f_{2\,avr}$: 54.5		$f_{2\,avr}$: 55.1		$f_{2\,avr}$: 41.0	
			L	U	L	U	L	U	L	U
		Normal	53.5	68.4	49.9	61.5	44.1	64.5	38.7	43.3
		Basic	53.0	67.6	49.7	61.3	42.3	61.9	38.6	43.2
		PI	53.9	68.6	48.9	60.5	47.4	67.0	38.8	43.5
		BCa	54.7	70.1	50.3	62.5	49.0	75.9	39.1	43.8
		Similarity	*Yes*		*No*		*No*		*No*	
	$\hat{f}_{2,exp}$		$f_{2\,avr}$: 59.5		$f_{2\,avr}$: 53.3		$f_{2\,avr}$: 53.7		$f_{2\,avr}$: 40.9	
			L	U	L	U	L	U	L	U
		Normal	53.0	66.5	49.3	59.5	45.9	61.3	38.6	43.2
		Basic	52.5	66.0	49.1	59.4	44.6	60.1	38.5	43.0
		PI	53.3	66.7	48.3	58.6	47.2	62.8	38.8	43.3
		BCa	54.0	67.6	49.4	59.9	48.5	66.3	39.0	43.6
		Similarity	*Yes*		*No*		*No*		*No*	
pH 6.8	$\hat{f}_2$		$f_{2\,avr}$: 52.0		$f_{2\,avr}$: 42.2		$f_{2\,avr}$: 53.0		$f_{2\,avr}$: 55.7	
			L	U	L	U	L	U	L	U
		Normal	32.2	65.4	37.7	46.8	43.0	61.9	50.5	61.2
		Basic	28.3	61.1	37.4	46.6	41.9	60.5	49.7	60.1
		PI	39.8	72.6	37.9	47.1	44.9	63.5	51.4	61.8
		BCa	41.3	78.1	38.2	47.4	45.6	65.2	52.4	66.5
		Similarity	*No*		*No*		*No*		*No*	
	$\hat{f}_{2,exp}$		$f_{2\,avr}$: 46.9		$f_{2\,avr}$: 41.9		$f_{2\,avr}$: 52.0		$f_{2\,avr}$: 55.1	
			L	U	L	U	L	U	L	U
		Normal	39.5	55.4	37.4	46.3	43.2	60.1	50.5	60.0
		Basic	39.7	55.2	37.1	46.1	42.4	59.1	49.8	59.2
		PI	39.1	54.7	37.7	46.6	44.5	61.3	51.2	60.5
		BCa	39.8	55.3	37.8	46.8	45.0	62.2	52.1	63.9
		Similarity	*No*		*No*		*No*		*No*	

5000 bootstrap replicates; $f_{2\,avr}$: Avarage f_2; $_2$: Observed similarity factor; $_{2,exp}$: Expected similarity factor; **CI**: Confidence interval; **L**: Lower limit of 90% CI; **U**: Upper limit of the 90% CI; **PI**: Percentile; **BCa**: Bias-corrected and accelerated

Table 6. Results and evaluation of the bootstrap f_2 method with PhEq_bootstrap

	f_2		$_{2,average}$	bc-f_2	$_{2,exp}$	*Similarity*
	L	U				
			pH 4.5			
F2	51.6	65.3	59.2	60.4	58.1	*Yes*
F3	46.8	57.2	53.1	54.4	52.0	*No*
F4	46.0	61.1	53.7	*	52.3	*No*
F5	37.3	42.0	39.5	39.7	39.4	*No*
			pH 6.8			
F2	32.4	50.0	45.2	*	40.8	*No*
F3	36.4	45.1	40.8	41.1	40.4	*No*
F4	46.9	60.4	54.0	55.1	53.1	*No*
F5	49.8	58.9	54.2	54.9	53.6	*No*

* An unbiased estimator for f_2 is not valid because of the large variance of dissolution points. Seek for values "-1" for unbiased f_2; **bc-f_2**: unbiased f_2; $_{2,exp}$: expected f_2; **L**: Lower limit of 90% confidence interval (CI); **U**: Upper limit of the 90% confidence interval (CI)

CONCLUSION

During the pandemic, FAV tablets were included in emergency treatment protocols for off-indication use, and various generic products became available for treatment. The dissolution profiles of the FAV tablets examined in this study were evaluated at pH 4.5 and pH 6.8 according to solubility and sink conditions. Significant differences in dissolution behavior were observed between products, particularly regarding the amount of dissolved substance remaining below 85%, and high intra-batch variation for the same product. These findings suggest that differences in bioavailability between generics may directly impact treatment efficacy. Although model-dependent methods identified parameters affecting the dissolution process (such as F_{max}, β, α), the high variation and the fact that the cumulative percentage of the dissolved substance was below the desired level (i.e., < 85%) for an IR product led to the use of the model-independent, bootstrap-based f_2 method to enable a more reliable comparison. DDSolver®, Bootf2BCA, and PhEq_bootstrap software generally provided consistent results. However, it was observed that similarity findings varied for some products due to program-dependent factors (e.g., changes in CI limits, skewness, and adjusted f_2). In conclusion, including different generic products in treatment, especially during periods of urgent use, suggests that differences in dissolution profiles may impact the clinical response. These findings emphasize the critical importance of dissolution testing when comparing generics, as well as the importance of accurately evaluating these tests, particularly when variation is high, or 85% dissolution cannot be achieved. Bootstrap f_2 approaches provide more robust results than classical f_2 assessments and are considered a reliable method compatible with the expectations of regulatory authorities such as EMA and FDA in bioequivalence assessments and formulation development studies.

ACKNOWLEDGEMENTS

The author thanks Atabay Drug Company (Türkiye) for kindly providing the active pharmaceutical ingredient, favipiravir.

AUTHOR CONTRIBUTION STATEMENT

The author was responsible for developing the hypothesis, conducting literature research, performing experiments, and preparing and reviewing the manuscript (DYU).

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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