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Evaluation of Different Methods for Dissolution Profile Similarity Comparison of Montelukast Tablets in Türkiye

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ABSTRACT

This study aimed to evaluate the highly variable in vitro dissolution profiles of generics and innovator montelukast products in the Turkish drug market by comparing model-dependent and model-independent analysis methods. Seven generic montelukast sodium products were tested, labeled G1–G7, and compared with the innovator. Dissolution tests were carried out with United States Pharmacopeia (USP) apparatus 2 (paddle) in 900 mL of distilled water containing 0.5% sodium dodecyl sulfate (SDS), fasted state simulated intestinal fluid (FaSSIF), or fed state simulated intestinal fluid (FeSSIF). The most accepted and used model for dissolution profile comparison of regulations in the world is the model-independent similarity factor (f_2); however, in this study, the bootstrap f_2 confidence interval method was also used due to highly variable dissolution data. The values of f_2, $\hat{f}_{2,exp}$, and $\hat{f}_{2,bc}$ were calculated with DDSolver, Bootf2BCA, and PhEq_bootstrap software. DDSolver was also used for model-dependent calculations. Two generic products showed similarity with the innovator ($f_2 > 50$) in biorelevant media (G4 in FeSSIF and G7 in FaSSIF); however, satisfactory results were not obtained in 0.5% SDS. The observed differences may be due to the dissolution method or nature of montelukast sodium (i.e., pH-dependent, poorly water-soluble, first-pass metabolism-exposed drug).

KEYWORDS: montelukast, DDSolver, Bootf2BCA, PhEq_bootstrap, f_2 bootstrap methods, dissolution

INTRODUCTION

Asthma is a chronic inflammatory respiratory disease characterized by inflammation of the airways, which causes swelling and narrowing of the airways. The disease pathogenesis mostly involves interactions between inflammatory mediators such as cytokines, cysteinyl leukotrienes, and environmental factors (*1*). Montelukast is a selective leukotriene receptor agonist that inhibits the cysteinyl leukotriene receptor 1, and it has been approved by many national authorities, including the United States Food and Drug Administration (FDA) and the Turkish Medicines and Medical Devices Agency (TITCK), for treatment and prophylaxis of diseases such as seasonal allergies and bronchospasm (*2*).

Montelukast is an acidic and lipophilic substance with solubility in water of 0.2–0.5 µg/mL at 25 °C (*3*). Montelukast is classified as a class IIa compound according to the Biopharmaceutics Classification System (BCS) due to low solubility, high permeability, and weak acid structure (*4*). Because of the low water solubility of montelukast, the salt form, montelukast sodium (MS), is generally used. MS undergoes hepatic first-pass metabolism (*3*, *5*). Commercially available dosage forms of MS include film-coated tablets, chewable tablets, and powders containing granules. For solid dosage forms, dissolution is important in optimizing the drug manufacturing process, maintaining the same quality in production across all batches, evaluating pre- and post-approval changes, predicting in vivo drug behavior, and determining bioequivalence and therapeutic equivalence between innovator and generic products. The most used approach to examine the effect of dissolution on all these processes is to perform in vitro dissolution studies under conditions determined by various guidelines and pharmacopeia (*6*, *7*).

The dissolution test and dissolution profile comparison are important tools for drug development and regulatory approval. The most common method used to compare dissolution profiles is the similarity factor (f_2). Because it is easy to use and calculate, it has been accepted by many

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regulatory authorities in the world in a short time for comparison of dissolution profiles (*7–9*). Although it is a simple method, some conditions must be met for the use of f_2. The profile should contain at least three dissolution time points other than 0; 12 units should be tested for each innovator and generic; the total cumulative percentage of dissolved drug should be above 85%; and the coefficient of variation for the dissolution points being compared should be less than 20% at the first time point and less than 10% at the other time points (*6*). Disadvantages of f_2 include unknown sample distribution, not reflecting the location of change, being easily affected by a change in the number of time points, and not considering high variability (*7*).

In recent years, different methods have been evaluated for comparison of variable dissolution profiles. Among these, a 90% confidence interval (CI) of f_2 has been proposed as a possible approach for profile comparison based on bootstrap methodology, where f_2 is not a point estimator, to assesses the similarity of dissolution profiles with high variation (*10, 11*). The f_2 bootstrap method is generally preferred by the US FDA and European Medicines Agency (EMA) (*6, 7, 10*).

This study aimed to compare dissolution profiles with high variability at early time points for innovator and generic MS tablets available in the Turkish drug market using model-independent (f_2 similarity and f_2 bootstrap methods) and model-dependent approaches.

MATERIALS AND METHODS

Materials

MS was provided by Enaltec (India). Innovator (Singulair 10 mg film-coated tablet) and generic MS tablets were bought from different pharmacies in the Turkish drug market. The chemicals and reagents used to perform the experiments included sodium dodecyl sulfate (SDS, Tekkim, Türkiye), sodium hydroxide pellets (NaOH, Sigma Aldrich, USA), monobasic sodium phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$, Merck, Germany), sodium chloride (NaCl, Merck, Denmark), hydrochloric acid (HCl, Isolab, Germany), glacial acetic acid (CH_3COOH, Sigma Aldrich, USA), and simulated intestinal fluids (SIF) powder (Biorelevant, UK).

In Vitro Dissolution Studies

In vitro dissolution studies were carried out using United States Pharmacopeia (USP) apparatus 2 (paddle) (Sotax Unit-AT 7 Smart, Switzerland) at 50 rpm and 37 ± 0.5 °C. The dissolution apparatus was wrapped with aluminum foil during the studies to protect MS from light. The dissolution studies were conducted using 900 mL distilled water containing 0.5% SDS, which is the FDA-recommended dissolution media, fasted state SIF (FaSSIF), or fed state SIF (FeSSIF) because the FDA recommended that bioequivalence studies of film-coated tablets containing montelukast be performed under fasting or fed conditions (*12*). FaSSIF and FeSSIF are biorelevant media that contain different amounts of sodium taurocholate and phospholipids to simulate the in vivo fasted and fed states. These media were prepared according to the protocols of Biorelevant.com. Samples were withdrawn at predetermined times (5, 10, 20, and 30 min). An equal volume of fresh medium was added to maintain sink conditions. The samples were filtered using a 0.45-µm membrane filter, and the concentration of MS in samples was determined by UV spectrophotometry (Thermo Scientific Multiskan GO Microplate Spectrophotometer, Finland) at 359 nm. The dissolution profiles were evaluated by the cumulative percentage of drug dissolved over time, reported as mean ± standard deviation (SD) (n = 3).

Data Analysis

Three software programs were used to evaluate similarity of the dissolution profiles: DDSolver for model-dependent evaluation (f_2); DDSolver, Bootf2BCA_v1.3, and PhEq_bootstrap v 1.2 for model-independent evaluation (f_1 [difference factor], f_2, and f_2 bootstrap).

DDSolver is an easy-to-use Microsoft Excel add-in program that is often used for the comparison of dissolution profiles.

Bootf2BCA_v 1.3 is an open-source software developed with the R statistics environment. Statistical analysis and graphical evaluation were performed using R (V 4.1.3) and RStudio (V 2022.02.1). This program includes four different types of confidence intervals when determining the expected parameters (i.e., the normal approximation interval, base bootstrap interval, percentile interval, and bias-corrected and accelerated [BCa] interval). The program includes advanced parameters such as dissolved amount (Q) ≥ 85% auto cut-off rule options, sampling mode (individual values, whole profiles), boot package simulation type (ordinary and balanced), statistic (selection of statistic to be bootstrapped), and seed (setting the value of seed for pseudorandom numbers).

PhEq_bootstrap v 1.2 was developed in the Lazarus environment, it is a program coded in Pascal (*13*). The program consists of three parts (main, graph, and about). It has two options for sampling (individual values and whole profiles), and each dissolution profile has options for a default rule of Q above 85% and bootstrap of 5000.

PhEq_bootstrap calculates f_2, expected f_2 ($\hat{f}_{2,exp}$), and bias-corrected f_2 ($\hat{f}_{2,bc}$), and gives a 90% CI for $\hat{f}_{2,exp}$, although the type of CI is not explicitly specified.

Suitability of the dissolution profiles to fit kinetic models was determined by the adjusted coefficient of determination (R^2_{adj}), Akaike information criterion (AIC), and model selection criterion (MSC). The model with the highest R^2_{adj} and MSC and the lowest AIC were determined as the most suitable model (*14*). In addition, different f_2 estimators and various bootstrap CIs (calculated based on 5000 bootstraps) were evaluated.

Tablet Characterization Studies for Quality Control

Within the scope of quality control, the appearance, weight variation, content uniformity, hardness, and disintegration time were analyzed according to USP guidelines.

Validation Studies

The validation and analytical studies were performed according to the USP and ICH Q2 guidelines (*15*). Results were within acceptable limits for all parameters.

RESULTS

In Vitro Dissolution Profiles

Dissolution studies are used to predict the in vivo behavior and therapeutic efficacy of active substances such as MS prior to conducting in vivo bioequivalence studies. MS is a weakly acidic active substance with pH-dependent solubility. Although MS has low solubility at pH 1.2–4.5, its solubility increases as pH increases, there is no significant difference in solubility between pH 5 and 7.5 (*3*, *4*). This situation is similar to the results of the current study. Namely, no pH-dependent increase in dissolution was observed in 0.5% SDS, FaSSIF, or FeSSIF media with pH values of 7, 6.5, and 5, respectively. More than 85% of MS was dissolved within 30 minutes in 0.5% SDS for all products except G1; however, this differed for biorelevant media. More than 85% of MS dissolved within 30 minutes in FaSSIF for the innovator, G1, G6, and G7 tablets and in FeSSIF for the innovator, G1, G3, G4, G5, and G7 tablets (Figure 1). High variability was observed at the early time points (i.e., coefficient of variation was > 20 for the first time points and > 10 for subsequent time points).

Results of the profiles evaluated with DDSolver, DDSolver bootstrap, Bootf2BCA and PhEq_bootstrap are presented in Tables 1–3 (data for DDSolver evaluation are not shown). When all results were compared, f_2, and f_2 bootstrap values calculated using DDSolver, Bootf2BCA, and PhEq_bootstrap differed in all dissolution media. For MS release in 0.5% SDS, similarity with the innovator (f_2 > 50) was demonstrated by DDSolver for G4, G5, and G7 but by DDSolver bootstrap for G5 only. In FaSSIF,

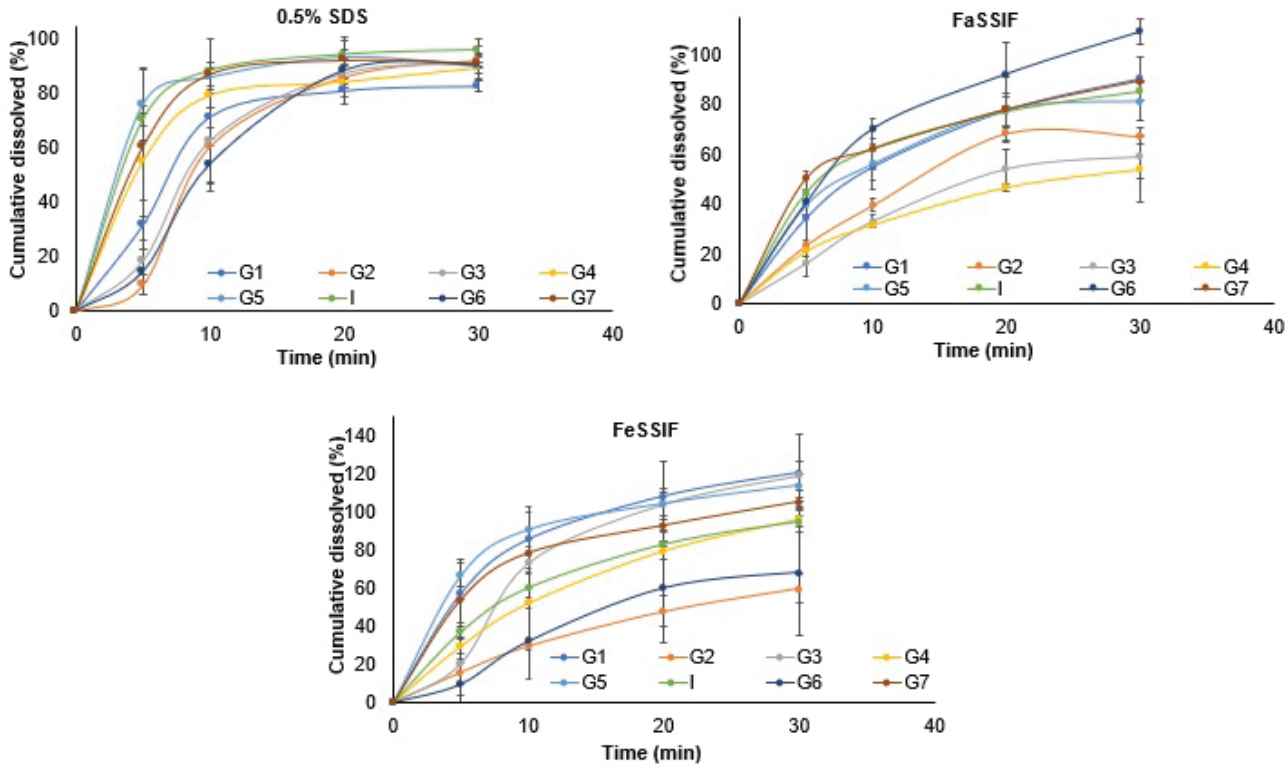

Figure 1. In vitro dissolution profiles of innovator and generic tablets in 0.5% SDS, FaSSIF, and FeSSIF. SDS: sodium dodecyl sulfate; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid.

similarity was demonstrated by DDSolver for G1, G5, and G7, by DDSolver bootstrap for G7, and by Bootf2BCA and PhEq_bootstrap for G5 and G7. The only generic product that had an f_2 value higher than 50 according to all calculation methods was G7; only $\hat{f}_{2,bc}$ obtained from PhEq_bootstrap was not greater than 50 (Table 3).

Kinetic release parameters showed that the innovator MS tablet fit the Gompertz 1, Probit 1, and Weibull 2 models for 0.5% SDS, FaSSIF, and FeSSIF, respectively. The generic MS tablet parameters also fit different models in each media, with most of them fitting the Gompertz and Weibull models (Table 4).

Tablet Characterization

Tablet shapes or colors differed. Four of the seven generic products were square and similar to the innovator product, and three were round. All tablets were light pink except G4, which was yellowish. Diameter and thickness SD values were 5% or less except the innovator and G7 (6%) and G1 and G4 (7%).

According to the USP, the weight can exceed the limit of 7.5% deviation for a maximum of two out of 20 tablets (10%), but none can exceed 15% deviation from the average weight. For G2, G4, and G7, one tablet each exceeded the 15% deviation limit. Tablet weights of the other products were within the acceptable limit.

For content uniformity, the acceptable limit is within 15% of the label claim. All products were within this limit. Therefore, the out-of-limit tablet weights for G4 and G7 did not adversely affected content uniformity. Content uniformity must be assessed to ensure dosing accuracy in tablets with an active substance content below 25% or 25 mg.

Hardness values of the innovator and all generic products were higher than 50 N; however, a linear relationship between the tablet hardness and disintegration time could not be established. For example, despite G2 having the lowest tablet hardness, its disintegration time was the highest.

Table 1. Similarity Assessment by f_2 Bootstrap Method with DDSolver

Comparison	Observed Similarity Factor (f_2)	Bootstrap (Mean)	5000 Bootstrap (5th percentile)	5000 Bootstrap (95th percentile)	Similarity Assessment
0.5% SDS					
I-G1	32.7	32.8	29.2	36.9	No
I-G2	23.7	23.6	21.5	25.6	No
I-G3	26.6	26.7	23.0	30.5	No
I-G4	48.3	49.7	36.3	68.9	No
I-G5	68.1	63.6	53.6	73.7	Yes
I-G6	24.1	24.1	21.7	26.7	No
I-G7	63.0	57.3	40.1	78.1	No
FaSSIF					
I-G1	58.0	54.6	43.0	70.9	No
I-G2	36.5	36.2	33.8	39.0	No
I-G3	28.5	28.2	26.2	30.4	No
I-G4	26.6	26.4	23.6	29.2	No
I-G5	66.5	59.5	49.6	67.7	No
I-G6	41.5	41.0	34.8	47.1	No
I-G7	72.1	63.4	51.0	77.0	Yes
FeSSIF					
I-G1	30.5	32.1	21.4	46.1	No
I-G2	25.4	25.4	22.1	28.8	No
I-G3	35.7	35.6	29.8	41.9	No
I-G4	62.1	61.3	51.3	72.2	Yes
I-G5	29.6	29.8	25.5	35.0	No
I-G6	30.3	30.1	18.5	46.0	No
I-G7	42.0	41.8	36.8	49.0	No

I: innovator, G: generic (G1–G7); SDS: sodium dodecyl sulfate; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid.

Table 2. Similarity Assessment by f_2 Bootstrap Method with Bootf2BCA

		G1		G2		G3		G4		G5*		G6		G7*	
0.5% SDS															
f_2 Type	**CI Type**	**f_2: 32.7**		**f_2: 21.4**		**f_2: 24.0**		**f_2: 43.6**		**f_2: -**		**f_2: 21.1**		**f_2: -**	
		L	U	L	U	L	U	L	U	L	U	L	U	L	U
$\hat{f}_2$	Normal	28.7	36.8	18.4	21.2	18.9	27.5	43.0	63.3	-	-	18.2	23.8	-	-
	Basic	29.0	36.3	18.7	21.1	19.7	27.0	44.1	65.5	-	-	18.2	23.5	-	-
	PI	29.2	36.5	20.1	22.5	20.3	27.6	31.3	52.7	-	-	18.5	23.8	-	-
	Bca	27.3	36.2	19.8	21.9	20.0	27.1	39.1	53.3	-	-	18.7	24.9	-	-
		f_2: 32.5		**f_2: 21.3**		**f_2: 23.7**		**f_2: 40.5**		**f_2: -**		**f_2: 21.0**		**f_2: -**	
$\hat{f}_{2,exp}$	Normal	28.2	36.4	18.1	21.0	18.6	26.7	40.6	55.0	-	-	18.1	23.6	-	-
	Basic	28.4	35.8	18.3	20.8	19.3	26.1	42.2	57.0	-	-	18.1	23.3	-	-
	PI	29.0	36.4	20.0	22.5	20.2	27.0	31.3	46.1	-	-	18.5	23.7	-	-
	Bca	27.2	36.1	19.7	21.7	20.0	26.5	35.9	46.6	-	-	18.7	24.9	-	-
FaSSIF															
f_2 Type	**CI Type**	**f_2: 54.7**		**f_2: 36.3**		**f_2: 28.3**		**f_2: 26.5**		**f_2: 59.6**		**f_2: 41.0**		**f_2: 63.5**	
		L	U	L	U	L	U	L	U	L	U	L	U	L	U
$\hat{f}_2$	Normal	47.6	75.1	34.2	39.3	26.5	30.8	24.0	29.5	63.7	83.4	35.7	48.2	67.0	94.6
	Basic	45.2	73.2	34.1	39.3	26.5	30.8	24.0	29.6	65.4	83.5	35.8	48.4	67.2	94.4
	PI	42.8	70.9	33.8	39.0	26.2	30.4	23.7	29.2	49.6	67.7	34.6	47.1	49.9	77.1
	Bca	47.4	78.3	34.1	39.3	26.4	31.0	23.7	29.2	60.9	71.2	34.3	47.1	61.3	79.3
		f_2: 48.9		**f_2: 35.9**		**f_2: 28.0**		**f_2: 26.2**		**f_2: 53.5**		**f_2: 39.9**		**f_2: 56.0**	
$\hat{f}_{2,exp}$	Normal	43.3	57.9	33.5	38.6	26.0	30.2	23.5	29.0	52.5	61.4	33.9	45.6	50.0	66.9
	Basic	43.3	58.1	33.3	38.4	25.9	30.2	23.4	28.9	53.4	61.8	33.9	45.3	49.8	65.3
	PI	41.4	56.2	33.5	38.6	25.9	30.2	23.5	29.0	48.7	57.1	34.3	45.7	49.1	64.7
	Bca	42.6	57.0	33.6	38.7	26.3	30.7	23.4	29.0	51.6	60.1	33.1	45.3	49.3	66.5
FeSSIF															
f_2 Type	**CI Type**	**f_2: 32.1**		**f_2: 25.5**		**f_2: 35.7**		**f_2: 61.3**		**f_2: 29.8**		**f_2: 30.1**		**f_2: 41.8**	
		L	U	L	U	L	U	L	U	L	U	L	U	L	U
$\hat{f}_2$	Normal	13.5	44.5	21.9	28.8	29.4	42.3	51.9	74.1	24.3	34.7	13.8	42.6	35.9	48.3
	Basic	15.0	39.7	22.0	28.7	29.3	41.7	52.0	73.0	23.8	33.7	11.8	39.8	34.9	47.5
	PI	21.4	46.1	22.1	28.8	29.8	42.2	51.3	72.3	25.5	35.4	18.4	46.5	36.5	49.0
	Bca	21.7	59.1	21.4	28.4	30.1	42.9	53.4	78.7	25.6	36.8	18.7	46.5	37.3	50.3
		f_2: 30.3		**f_2: 25.3**		**f_2: 34.8**		**f_2: 58.5**		**f_2: 29.5**		**f_2: 27.4**		**f_2: 41.1**	
$\hat{f}_{2,exp}$	Normal	12.9	41.0	21.6	28.5	28.5	40.4	49.6	66.6	23.9	33.9	12.9	37.0	35.0	46.5
	Basic	15.6	36.0	21.6	28.3	28.6	39.6	49.4	66.3	23.5	33.0	11.7	34.2	34.2	45.4
	PI	21.2	41.7	22.0	28.7	29.6	40.7	50.3	67.2	25.4	34.9	18.2	40.7	36.4	47.6
	Bca	21.5	46.1	21.1	28.2	29.6	40.7	50.3	66.9	25.5	36.5	18.2	40.7	36.6	48.0

**Could not be calculated.*
$\hat{f}_{2,exp}$: expected similarity factor; CI: confidence interval; G: generic product (G1–G7); L: lower limit of 90% CI; U: upper limit of the 90% CI; PI: percentile; BCa: bias-corrected and accelerated; SDS: sodium dodecyl sulfate; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid.

DISCUSSION

Compared to the innovator product, f_1 and f_2 for generic products are expected to be less than 15% and greater than 50%, respectively. The results were within the limit values for G4, G5, and G7 in 0.5% SDS; G1, G5, and G7 in FaSSIF; and G4 in FeSSIF. Thus, none of the generic tablets had similar dissolution profiles with the innovator in all three media. There are studies showing that the oral bioavailability of montelukast is affected by food (*5*); however, the FDA recommends that in vivo bioequivalence studies can be performed under fasting or fed conditions, and the product monograph states that the product can be taken with or without food (*12*). Therefore, the observed variability may be due to the pH-dependent dissolution of montelukast, differences in formulation ingredients and production methods, tablet

Table 3. Similarity Assessment by f_2 Bootstrap Method with PhEq_bootstrap

Product	f_2		$\hat{f}_{2,average}$	$\hat{f}_{2,bc}$	$\hat{f}_{2,exp}$
	L	U			
0.5% SDS					
G1	29.0	36.4	32.7	32.9	32.4
G2	20.0	22.5	21.4	21.5	21.2
G3	20.2	27.0	24.1	24.4	23.7
G4	35.5	63.9	51.0	46.8	46.1
G5*	-	-	-	-	-
G6	18.6	23.7	21.1	21.2	21.0
G7	36.2	48.9	53.6	13.1	41.9
FaSSIF					
G1	41.4	56.2	54.8	38.8	48.9
G2	33.5	38.6	36.2	36.6	35.9
G3	25.9	32.2	28.2	28.5	27.9
G4	23.4	29.0	26.4	26.7	26.2
G5	48.4	57.1	59.3	38.7	53.3
G6	33.8	45.6	40.9	42.2	39.8
G7	49.1	66.5	63.7	41.2	56.2
FeSSIF					
G1	21.5	41.7	32.4	35.1	30.5
G2	22.0	28.7	25.4	25.6	25.3
G3	29.6	40.7	35.5	36.4	34.7
G4	50.6	67.2	61.4	62.6	58.5
G5	25.4	34.9	29.8	30.2	29.5
G6	18.2	39.9	29.8	33.9	27.1
G7	36.5	47.2	41.7	42.6	41.0

**Could not be calculated.*
$\hat{f}_{2,bc}$: bias-corrected f_2; $\hat{f}_{2,exp}$: expected f_2; G: generic product (G1–G7); L: lower limit of 90% confidence interval (CI); U: upper limit of the 90% CI; SDS: sodium dodecyl sulfate; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid.

shape, the presence of surfactants that increase solubility at different rates, and/or different viscosities and buffering capacity of the media (*4*, *16*). However, these differences do not have an exact equivalent in vivo because of the inappropriate dissolution method (*17*). For example, Prieto-Escolar et al. observed that the dissolution profiles of two film-coated tablets containing montelukast were similar, but they were not bioequivalent in vivo, so a new dissolution method was developed to establish the in vitro-in vivo correlation (IVIVC) (*4*).

Dissolution profiles of all generic tablets showed high variability at the early time points. This variability may be associated with variations in tablet placement and tablet-to-tablet variability (*18*). This situation may prohibit observation of the effect of formulation or manufacturing changes on drug release properties and create a major handicap in generic product development (*19*). The similarity factor analysis is insufficient for statistical comparison of dissolution profiles because it does not contain a mathematical formula for statistical distribution in the calculation of f_2 (*20*). Moreover, it is difficult to evaluate type I (consumer's risk) and type II (manufacturer's risk) errors because f_2 is insensitive to the shape of the profiles (*21*). Therefore, regulatory authorities may recommend using an alternative statistical method, such as a 90% CI of f_2 based on the bootstrap methodology to compare dissolution profiles (*7*, *9*). For example, Health Canada and the US FDA suggested the use of the $\hat{f}_2$ and BCa range (*22*). Compared to f_2, the bootstrap-based f_2 approach is more sensitive in comparing dissolution profiles and is especially important when f_2 is less than 60. Among these approaches, Bootf2BCA and PhEq_bootstrap methods are based on a bootstrap percentile, and lower and upper limits are used. To support similarity, both limits should be above the cut-off value (≥ 50). On the other hand, DDSolver is solely based on the lower bound of the CI of bootstrap f_2, and it is not recommended for comparing dissolution profiles with high variability as it cannot calculate parameters such as $\hat{f}_{2,exp}$ and $\hat{f}_{2,bc}$ (*7*). Because $\hat{f}_{2,exp}$ is the most prudent unbiased estimate of f_2 and is always defined, it should be used to conclude about the similarity of highly variable dissolution profiles (*8*). In the current study, f_2 was calculation with all approaches, and the bootstrap approach was more sensitive to detect similarity. Three tablets (G4, G5 and G7) were similar to the innovator in 0.5% SDS according to f_2, but only one tablet (G4) was similar in the bootstrap approaches. When the f_2 values for the G4 in FeSSIF media were calculated with all methods (f_2, $\hat{f}_{2,exp}$, $\hat{f}_{2,bc}$), similarity was higher than 50. Evaluation could not be performed for G5 and G7 with Bootf2BCA and for G5 with PhEq_bootstrap in 0.5% SDS because the last two time points in the dissolution study were mathematically higher at the 20th minute than at the 30th minute.

When choosing the most suitable model and comparing models with different numbers of parameters, R^2_{adj} should be used instead of the coefficient of determination (R^2). R^2 will always increase as more parameters are included, whereas R^2_{adj} may decrease during the model fit. Therefore, the best model should be the one with the highest R^2_{adj} rather than R^2 (*23*). AIC is a parameter that depends on the size of the data and the number of data points. If the two models have a different number of parameters, it can be said that the model with the lower AIC value is better (*24*). MSC is a criterion for choosing a statistical model. MSC is modified from AIC and normalized to be independent of the scaling of data

Table 4. Parameters for Mathematical Models and Descriptive Statistics for Dissolution of MS Innovator (I) and Generic (G1–G7) Tablets

	Model parameters	I Gompertz 1	G1 Gompertz 2	G2 Gompertz 2	G3 Gompertz 2	G4 Gompertz 2	G5 Peppas-Sahlin 1	G6 Logistic 2	G7 Logistic 2
0.5% SDS		α: 2.10	α: 16.6	α: 67.9	α: 41.5	α: 3.61	k_1: 51.0	α: -6.53	α: -1.63
		β: 2.69	β: 3.93	β: 4.91	β: 4.64	β: 2.86	k_2: -6.93	β: 6.94	β: 3.15
			F_{max}: 88.9	F_{max}: 96.9	F_{max}: 95.3	F_{max}: 93.8	*m*: 0.43	F_{max}: 94.4	F_{max}: 98.5
	R^2_{adj}	0.998	0.979	0.999	0.999	0.993	0.998	0.997	0.982
	AIC	14.0	26.1	14.3	11.2	20.4	14.1	18.2	26.2
	MSC	4.58	2.57	5.62	6.06	3.32	4.41	4.75	2.24
		Probit 1	Weibull 2	Quadratic	Weibull 3	Logistic 1	Logistic 1	Weibull 3	Korsmeyer-Peppas
FaSSIF		α: -1.19	α: 11.0	k_1: -0.001	α: 27.0	α: -2.69	α: -2.24	α: 12.1	k_{KP}: 29.8
		β: 1.51	β: 0.95	k_2: 0.052	β: 1.31	β: 1.94	β: 2.57	β: 1.04	*n*: 0.322
					F_{max}: 61.9			F_{max}: 115	
	R^2_{adj}	1.00	1.00	0.992	0.998	0.999	0.995	0.993	1.00
	AIC	1.13	6.20	19.2	10.1	4.17	17.6	22.3	0.630
	MSC	7.20	6.58	3.69	5.26	5.96	3.98	3.72	7.30
		Weibull 2	Weibull 3	Logistic 1	Gompertz 2	Hixson-Crowell	Weibull 3	Weibull 4	Peppas-Sahlin 2
FeSSIF		α: 11.2	α: 6.93	α: -3.51	α: 44.0	k_{HC}: 0.022	α: 3.79	α: 27.1	k_1: 29.6
		β: 1.01	β: 0.885	β: 2.63	β: 4.44		β: 0.71	β: 1.38	k_2: -1.92
			F_{max}: 126		F_{max}: 125		F_{max}: 119	*Ti*: 2.16	
								F_{max}: 69.3	
	R^2_{adj}	0.999	0.999	1.00	0.993	0.999	0.998	0.999	0.995
	AIC	9.95	14.2	-4.52	24.2	9.77	17.1	6.76	19.9
	MSC	5.91	5.37	8.11	3.96	6.14	4.47	6.44	3.86

F_{max}: maximum fraction of drug released at infinite time; k_{KP}: release constant incorporating structural and geometric characteristics of drug-dosage form; m,n: diffusional exponent; Ti: location parameter that represents lag time; k_1: constant related to Fickian kinetics and denotes relative contribution of $t^{0.5}$-dependent drug diffusion to drug release; k_2: constant related to Case-II relaxation kinetics and denotes relative contribution of t-dependent polymer relaxation to drug release in Peppas–Sahlin 2; Φ: standard normal distribution; α: scale factor; β: shape factor.

points. Among the different models, the model with the highest MSC value is the most suitable criterion. Considering these parameters, all generic tablets fit different dissolution models than the innovator, and most of them fit Gompertz and Weibull models. These results are similar to other studies, which reported that both Weibull and Gompertz frequently provide a good fit for different types of dissolution profiles (*25*). Considering the models that the generic tablets fit, it was determined that α (scale factor) and β (shape factors), which characterize the type of dissolution profile parameters, affected the dissolution behavior of MS. The effect of changes in these parameters on in vitro dissolution is evident. Therefore, no single method can be recommended as the best-fitting dissolution model, as others have pointed out (*26*). In addition, model-dependent methods have disadvantages such as the low number of time points for fast-dissolving immediate-release products and the fact that the most appropriate model selection is directly related to the product (*22*).

The shape of some generic tablets (G1, G3, and G4) differed from the innovator. The difference in tablet shape can affect both patient recognizability and in vitro dissolution results and may lead to errors in treatment (*16*). The observed weight deviation is related to poor powder flow properties. To improve powder flowability, granulation is performed, and lubricants are added to the formulation. Even though the same lubricant was used in the innovator and all generic products, high granule size or excessive use of lubricant may cause an increase in weight deviation. The diameter-thickness determination, which is an important parameter for packaging, is not a required test in the pharmacopeia. However, the general approach to evaluating the results is that the SD should not be more than 5% (*27*). Homogeneity of the coating influences deviations in diameter thickness of the film-coated tablets, especially due to the tablet shape. Tablet hardness is also not a required test in pharmacopeia; however, it is stated in various sources that hardness values should be at least 50 N (5 kg) to have sufficient

mechanical strength. On the other hand, if the tablet hardness is high, the disintegration time of the tablets may be delayed, which delays the onset of therapeutic effects especially for immediate-release tablets (*28*). All generic products had a longer disintegration time than the innovator. This may be because the disintegrant agents in the tablet formulations are different. Details of the production method of the innovator are confidential, but differences in production can affect tablet hardness, disintegration time, and dissolution (e.g., granule size, binder solution used during granulation, and the method of adding the disintegrant to the granule phase) (*29*).

A generic drug is the same as the innovator in terms of dosage form, administration route, and active ingredient, with similar efficacy, quality, and safety profiles within certain limits. However, generic products are produced by different companies and might contain different contents. According to Türkiye guidelines, for drugs/products that do not have a biowaiver, in vivo bioequivalence must be established (IVIVC), and comparative in vitro dissolution results should be presented with in vivo results. Additionally, the similarity of bioseries (series used for in vivo studies) should be demonstrated in vitro (*30*). However, recent studies have reported marked differences in therapeutic efficacy of marketed products containing the same amount of active ingredient, indicating that some generic products are not interchangeable with the innovator and/or each other (*31*). These differences may be because two-point dissolution analyses are considered sufficient instead of the full profile in batch-release studies, especially for immediate-release tablets, and the commercial lots are not analyzed despite the products being analyzed during the registration process (*32, 33*). Therefore, it is important to obtain a dissolution profile that demonstrates similarity with bioseries in batch-release studies.

In the current study, despite in vivo bioequivalence being established for the generic MS tablets in 0.5% SDS, similarity with the innovator product could not be established based on dissolution profiles using Bootf2BCA and PhEq_bootstrap methods. Possible reasons for the observed differences are that the dissolution medium might not be sufficient to show differences or similarities in the drug release profile, and/or the dissolution method (with USP apparatus 2) may not fully reflect the in vivo conditions for pH-dependent, poorly water-soluble, first-pass metabolism-exposed drugs such as MS (*34*, *35*).

CONCLUSION

The similarity factor f_2 is still the most common and accepted tool for dissolution profile comparisons; however, the bootstrap f_2 approach, which has a 90% CI of expected f_2, seems to be a more conservative way to assess the similarity of dissolution profiles, especially when the profiles show high variability. When comparing model-dependent and independent analysis methods, the dissolution profiles of generic products with proven in vivo bioequivalence in FDA-recommended media were different, especially in FaSSIF and FeSSIF media. The differences may be due to the weak acid structure of MS changing with the pH of media with a low buffer capacity, such as distilled water, or it may also be because the dissolution method cannot fully reflect the in vivo conditions due to the first-pass effect of MS. Therefore, dissolution methods should be developed that can better reflect in vivo conditions for pH-dependent and low-soluble drugs such as MS. Moreover, the use of PhEq_bootstrap and/or Bootf2BCA methods instead of the f_2 should be accepted by the guidelines.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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DISCLOSURES

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