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In Vitro Dissolution Similarity as a Surrogate for In Vivo Bioavailability and Therapeutic Equivalence

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ABSTRACT

Generic immediate-release solid oral dosage forms containing BCS Class I and III drugs that have similar in vitro dissolution profiles might receive market authorization without in vivo bioequivalence testing. The objective was to investigate whether the different immediate-release generic products containing BCS Class I drugs (fluoxetine and linezolid) and a Class III drug (fluconazole) fulfill the requirements of 85% or more drug release in 15 or 30 min in all three buffers (pH 1.2, pH 4.5, and pH 6.8) using in vitro dissolution testing in accordance with WHO requirements. The dissolution profiles were compared statistically to the relevant reference product by calculating the fit factors (f_1 and f_2), dissolution efficiencies, and mean dissolution time. The amount of drug dissolved in all dissolution media was determined by a validated UV spectrophotometric method. All investigated products of fluoxetine and linezolid met the biowaiver criteria for BCS Class I drugs and would be considered in vitro equivalent. Only one product of the BCS Class III drug fluconazole did not pass the WHO guideline for in vitro equivalence; however, all the products released fluconazole satisfactorily, with at least 80% dissolved within 30 min. Pharmaceutical equivalence together with in vitro dissolution similarity could be considered suitable to ensure in vivo bioequivalence and, hence, therapeutic equivalence of BCS Class I and III drugs. Not all generic products containing the same drug (BCS Class I or III) in similar strengths and dosage forms are in vitro equivalent.

KEYWORDS: BCS; generic drug; in vitro dissolution similarity; immediate-release solid oral dosage forms; therapeutic equivalence; dissolution.

INTRODUCTION

Generic drugs should be pharmaceutically, biologically, and therapeutically equivalent to the reference drug to guarantee interchangeability for pharmacotherapy (*1*). Drug products are considered therapeutically equivalent if they meet the regulatory criteria of pharmaceutical equivalence and bioequivalence (*2–6*). Generic pharmaceutical equivalents should contain the same active ingredient(s) manufactured in the same dosage form and administered in the same pathway. Additionally, they should meet the same compendial or other applicable standards and be similar in strength or concentration (*1*). However, they may differ in shape, excipients, release mechanisms, packaging, scoring configuration, and expiration time (*7*). Bioequivalence of pharmaceutically equivalent products also implies their therapeutic equivalence (*8*). In accordance with WHO recommendations (*1, 7*), bioequivalence can be determined by in vivo pharmacokinetic methods and, in some cases, by in vitro dissolution test. A biowaiver is a simplification and reduction of time required for product approval, thus releasing new qualified products to the market at lower costs (*5, 9*). According to the WHO (*3*) and the EMA (*2*), a biowaiver implies that in vivo bioequivalence studies may be substituted by performing in vitro dissolution testing to compare the test product against a reference product.

The Biopharmaceutics Classification System (BCS) differentiates active pharmaceutical ingredients (API) into four different classes according to their solubility and permeability (*10*). In a science-based approach, BCS allows waiver of in vivo bioavailability and bioequivalence testing for immediate-release solid dosage forms for Class I and III compounds when they exhibit rapid or very rapid dissolution (2–4). Class I includes drugs with high solubility and high permeability, whereas, Class III includes drugs with high solubility and low permeability. Class I drugs may receive a waiver if 85% or more of drug content is released in 15 min (very rapid release) in three different buffer solutions or may need to be compared using f_2 statistics when greater than 85% is released in 30 min (rapid release) (*4, 7*). Whereas, Class III drugs may receive a waiver only if 85% or more of drug content is released in 15 min (very rapid release) in three different buffer solutions (*4, 7*). The diagram in Figure 1 shows the steps

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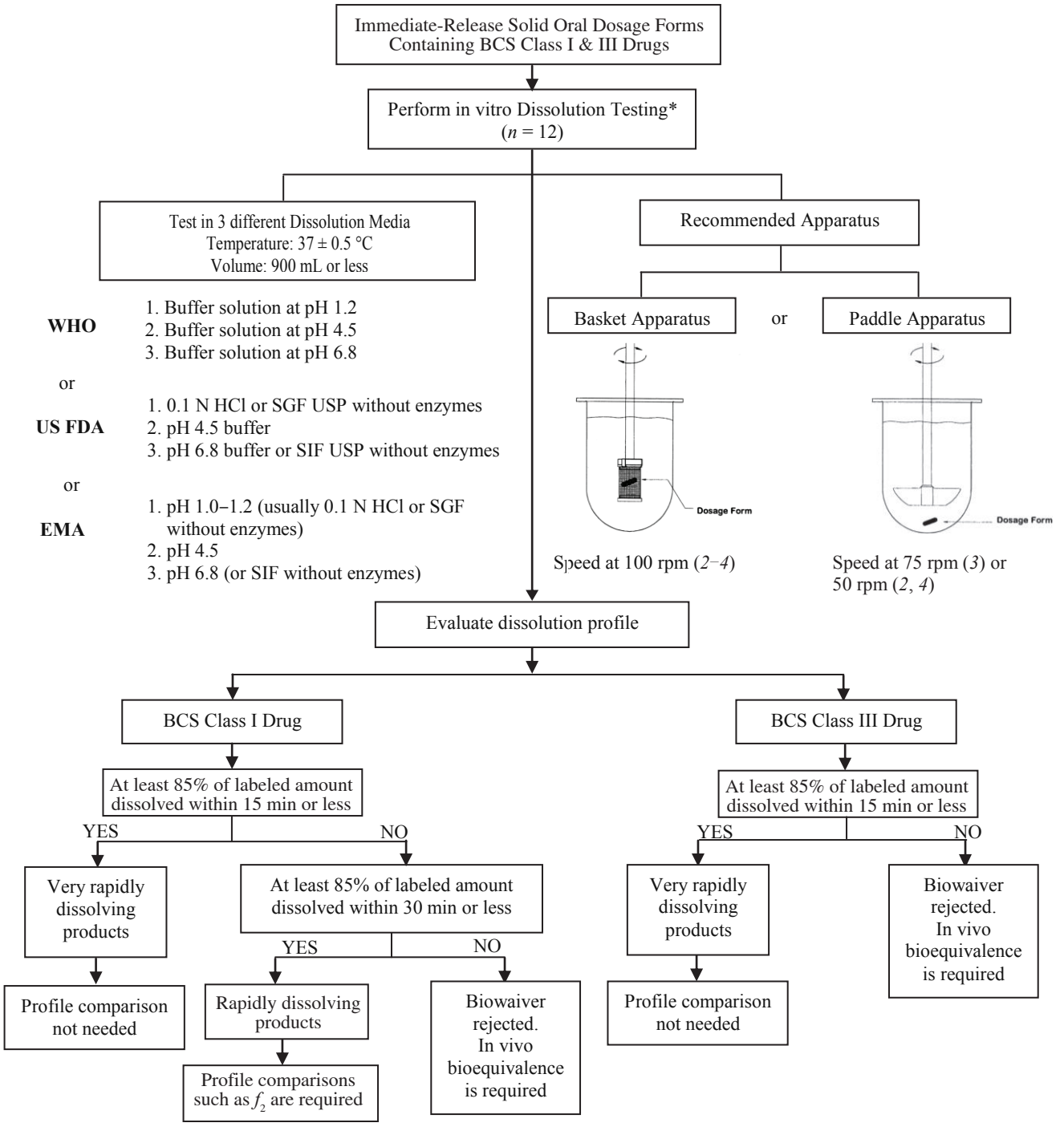
for obtaining a biowaiver for immediate-release solid oral dosage forms containing BCS Class I and III drugs.

This study compares the dissolution results for different generic products containing BCS Class I drugs (fluoxetine and linezolid) and a Class III drug (fluconazole) marketed in Egypt with those of the innovator products. The objective was to investigate whether the different immediate-release oral formulations of fluoxetine, linezolid, and fluconazole fulfill the requirements of 85% or more drug release in 15 or 30 min in all three buffers (pH 1.2, pH 4.5 and pH 6.8) using in vitro dissolution testing. Drug release was assessed for bioequivalence in accordance with the WHO requirements (*3*) for biowaivers for immediate-release solid oral dosage forms containing BCS Class I and III drugs.



***Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product**
SIF simulated intestinal fluid, SGF simulated gastric fluid

Figure 1. Flowchart for obtaining a biowaiver for immediate-release solid oral dosage forms containing BCS Class I and III Drugs (2–6).

MATERIALS AND METHODS

Reagents and Materials

Fluoxetine HCl (purity 99%), linezolid (purity 99%), and fluconazole (purity 99%) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Generic and innovator products were purchased from local pharmacies in Egypt. Buffer media for dissolution testing were prepared as per USP specifications at pH 1.2, 4.5, and 6.8 (*11*).

Instrumentation and Equipment

The pH of the prepared buffers was checked using a pH meter (Orion 520A, Waltham, MA, USA). A dissolution apparatus (Copley Scientific, Nottingham, UK) was used for dissolution testing of dosage forms. An ultrasonic bath (UltraSonik 57X, Elmsford, U.S.A) was used to dissolve the reference standards during preparation of standard solutions.

Dissolution Testing

Dissolution testing was performed at pH 1.2, 4.5, and 6.8 using a USP Apparatus 2 (paddle) dissolution apparatus (Copley Scientific, Nottingham, UK). The paddle speed was set at 75 rpm, and 900 mL of dissolution medium was used to test all samples. Prior to testing, the dissolution medium was preheated and degassed to prevent air bubble formation during transfer into the vessels. Dissolution testing was started after a temperature of 37 ± 0.5 °C was confirmed in all vessels. Five-milliliter samples of the dissolution medium were withdrawn at appropriate time intervals (1, 2, 3, 4, 5, 10, 15, 30, 45, 60, 90, and 120 min). Each sample was filtered through a 0.45-µm Millipore filter (Merck KGaA, Darmstadt, Germany), and fresh dissolution medium preheated to 37 °C was added to compensate for the withdrawn volume. Drug content was determined spectrophotometrically (Thermo Scientific Evolution 300 UV–vis Spectrophotometer, Madison, WI, USA). Each result represented an average of twelve measurements, and the error was expressed as standard deviation (SD). The cumulative amount and percentage of drug release at each sampling time was computed, and release profiles were plotted as the cumulative percentage of drug released versus time.

Analytical Quantification

Drug content was determined at 230 nm, 254 nm, and 210 nm for fluoxetine, linezolid, and fluconazole, respectively, in the three dissolution media with reference to a standard curve constructed for each dissolution medium. Prior to sample testing, the spectrophotometric method was validated for its suitability in all three dissolution media for linearity, precision, and accuracy according to the USP General Chapter <1225> Validation of Compendial Procedures (*12*). The linear range was selected based on an expected highest release concentration of 120% of drug content dissolved in 900 mL of each dissolution medium at pH 1.2, 4.5, and 6.8 for all the studied drugs. The lowest release concentrations were 1.2%, 2.3%, and 6.5% for fluoxetine, linezolid, and fluconazole, respectively. The observed correlation coefficient was r^2 = 0.999 for all the studied products. The precision and accuracy of the assay method in all the three media were 1.3–8.1% and 97.9–103%, respectively, for fluoxetine; 0.9–4.3% and 98.6–104%, respectively, for linezolid; and 1.1–9.1% and 99.3–104%, respectively, for fluconazole.

Comparison of Release Profiles

Fit Factors

A simple model-independent approach that uses fit factors was applied to compare the dissolution profiles of the selected drugs (*13*). Fit factors were adopted by the FDA Center for Drug Evaluation and Research (CDER), and the similarity factor was adopted by the European Medicines Evaluation Agency (EMA) Committee for Proprietary Medicinal Products (CPMP) as an assessment criterion of similarity between two in vitro dissolution profiles (*3, 14, 15*). They include a difference factor (f_1) and a similarity factor (f_2).

The difference factor, f_1, shows the percentage error between the two curves at all time points. The similarity factor, f_2, as defined by and EMA (*14*) and FDA (*15*) is the logarithmic transform of the sum of the squares of the errors calculated from the difference between the test and the standard samples at all time points. The values of f_1 and f_2 for the generic products versus the reference were calculated from the means of the percentage of drug dissolved at each time point using:

$$f_1 = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} R_j} \times 100$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{j=1}^{n} \left(R_j - T_j \right)^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of time points and R_j and T_j are the percentages of reference and test product, respectively, released into the dissolution medium at time j.

According to the FDA guidance (*4*), dissolution profiles are similar if f_1 values are between 0 and 15 and f_2 values are between 50 and 100.

Additionally, the dissolution data of each product were used to calculate the model-independent parameters of mean dissolution time (*MDT*) (*16*) and dissolution efficiency (*DE*) (*17*).

Dissolution Efficiency

DE was employed to compare drug release from various brands (*18*). DE is the area under the dissolution curve (*AUC*) between times t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time (*17, 19*). *DE* can be calculated with:

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

where *y* is the percentage of dissolved product.

The integral of the numerator (i.e., *AUC*) is calculated by trapezoidal method (*20*). *AUC* is the sum of all the trapezoids and calculated by:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2}$$

where t_i is the i^{th} time point and y_i is the percentage of dissolved product at time t_i (*20*). The reference and the test product are equivalent if the difference between their *DE* values are within appropriate limits (±10%).

Moments of the Dissolution Profiles

MDT has been used to test the equivalence of two dissolution profiles (*16, 21*) or to compare different profiles statistically. *MDT* is calculated from the amount of drug released to the total cumulative drug (*16, 18, 22*). Dissolution rate is expressed by *MDT*. The value of *MDT* decreases with an increase in the release rate and is calculated from:

$$MDT = \frac{\sum_{j=1}^{n} t_{j\,mid} \times \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where *j* is the dissolution sample number, *n* is the number of dissolution sample times, $t_{j\ mid}$ is the time at the midpoint between t_j and t_{j-1} (calculated as t_j+t_{j-1}/2), and ΔM_j is the additional amount of drug dissolved between *t* and t_{j-1} (calculated as M_t-M_{t-1}). *MDT* calculations were carried out using the Excel add-in DDSolver (*23*).

Statistical Analysis

Comparisons among the generic products and the reference were made by the Student's *t*-test at the 95% confidence interval using Microsoft Office Excel 2007. Differences were considered significant if $p < 0.05$.

RESULTS AND DISCUSSION

In vitro dissolution studies are sometimes used as an alternative to in vivo studies in assessing bioequivalence of immediate-release solid oral dosage forms containing BCS Class I and III drugs for both cost reduction and ethical considerations (*24*). In vitro tests embrace the principle that "No unnecessary human testing should be performed." The aim of this study was to evaluate the use of in vitro dissolution testing as a biowaiver procedure to assess the interchangeability of generics based on WHO recommendations (*3*). The dissolution process can be used as a surrogate for absorption (*25, 26*). Not all generic products containing the same drug in similar strengths and dosage forms are equivalent. Class I drugs with rapid dissolution and Class III drugs with very rapid dissolution may possess the same active ingredient and amount of drug but may show significant differences to in vitro equivalence requirements (*26*). Comparative in vitro dissolution should ensure the similarity of the test and comparator product in three different pH media considered relevant for absorption in the gastrointestinal tract (*3*).

The equivalence of the dissolution profiles of fluoxetine, linezolid, and fluconazole was assessed in terms of the fit factors (f_1 and f_2), which were evaluated in accordance with the WHO requirements (*3*). Additionally, *DE* and *MDT* were also applied.

Fluoxetine

Fluoxetine belongs to BCS Class I (*10*). To establish bioequivalence using the in vitro method (*3, 27*), fluoxetine products should meet the biowaiver requirements presented in Figure 1. The dissolution profiles of fluoxetine marketed products versus the reference product are shown in Figure 2. The reference product (R) and generic products (T1–T3) dissolved rapidly (85% or more in 30 min) in pH 1.2, 4.5, and 6.8. The three generic products met the f_1 and f_2 requirements (Table 1).

Dissolution profiles of all generic products were similar to dissolution profile of the reference product.

Fluoxetine release from the reference and generics was also assessed through *DE* and *MDT*. If a drug has high *DE*, the API remains in contact with physiologic membranes for a long time and thus has high bioavailability in the assessed concentration range (*28*). *MDT* reflects the time for a drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release profile. The mean values of *MDT* and *DE* for the products under study are shown in Table 2. The *MDT* and *DE* values for all generic

products were similar to that of the reference product. The regulatory authorities (EMA, FDA, and WHO) accept rapidly dissolving (>85% dissolved in 30 min) BCS Class I drug products for biowaiver candidates. Accordingly, all the fluoxetine products would be considered in vitro equivalent in accordance with the biowaiver criteria.

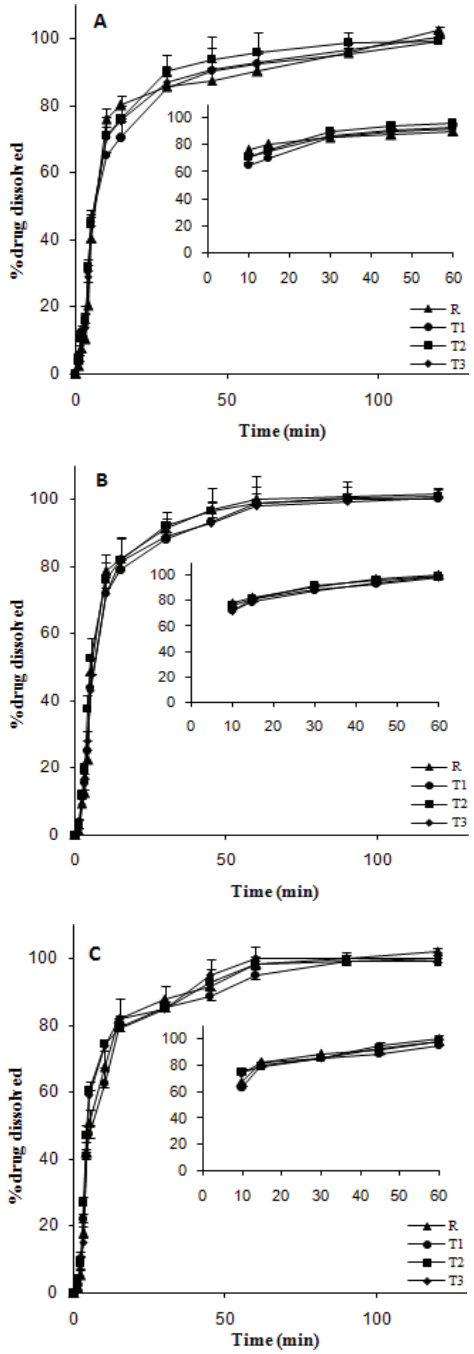


Figure 2. Dissolution profiles of various generic fluoxetine products in (A) pH 1.2, (B) pH 4.5, and (C) pH 6.8.

Table 1. Comparison of Generic Fluoxetine, Linezolid, and Fluconazole Products

Product	pH 1.2			pH 4.5			pH 6.8		
	% diss.	f_1	f_2	% diss.	f_1	f_2	% diss.	f_1	f_2
Fluoxetine									
R	+			+			+		
T1	+	1.2	78.6	+	1.1	78.6	+	2.2	65.1
T2	+	4.6	51.0	+	4.3	51.4	+	3.6	54.8
T3	+	2.3	65.4	+	1.1	79.1	+	1.9	67.9
Linezolid									
R	++			++			++		
T1	++	0.3	93.3	++	0.4	91.7	++	0.5	90.1
T2	++	2.2	57.9	++	2.1	61.0	++	2.0	64.6
Fluconaole									
R	++			+			++		
T1	++	3.3	50.9	+	3.5	54.3	++	2.8	59.0
T2	++	2.3	58.0	+	0.9	81.2	++	1.8	67.9
T3	++	3.4	54.0	-	3.6	50.1	-	4.2	49.2*

(+) At least 85% released within 30 min or less (rapidly dissolving)
(++) At least 85% released within 15 min or less (very rapidly dissolving)
(-) Less than 85% released in more than 30 min
(*) fails f_2
f_1 of 0–15 ensures minor difference
f_2 > 50 represents similarity while <50 represent dissimilarity

Table 2. MDT and DE of Fluoxetine Products

Product	pH 1.2		pH 4.5		pH 6.8	
	MDT (min)	DE (%)	MDT (min)	DE (%)	MDT (min)	DE (%)
Fluoxetine						
R	6.2	86.8	5.6	92.3	6.0	90.5
T1	6.2	86.1	5.9	90.2	6.1	89.2
T2	5.8	89.3	5.4	92.2	5.4	90.0
T3	6.0	87.4	5.9	90.1	5.5	90.9
Linezolid						
R	1.7	98.8	2.9	96.8	4.2	94.7
T1	1.7	98.3	2.8	96.0	4.1	93.7
T2	2.2	98.7	3.3	95.8	4.5	92.9
Fluconaole						
R	2.2	97.7	5.3	92.1	5.1	90.8
T1	2.6	97.6	4.7	91.5	4.9	92.0
T2	2.5	96.4	5.7	92.9	5.4	89.4
T3	2.7	96.3	6.1[a]	88.6	5.9a	87.7

[a] Significant difference from R at P < 0.05

Linezolid

All of the products (R, T1, and T2) of linezolid (BCS Class I) dissolved very rapidly in pH 1.2, 4.5, and 6.8, with a release of >85% in 15 min in all three media. The dissolution

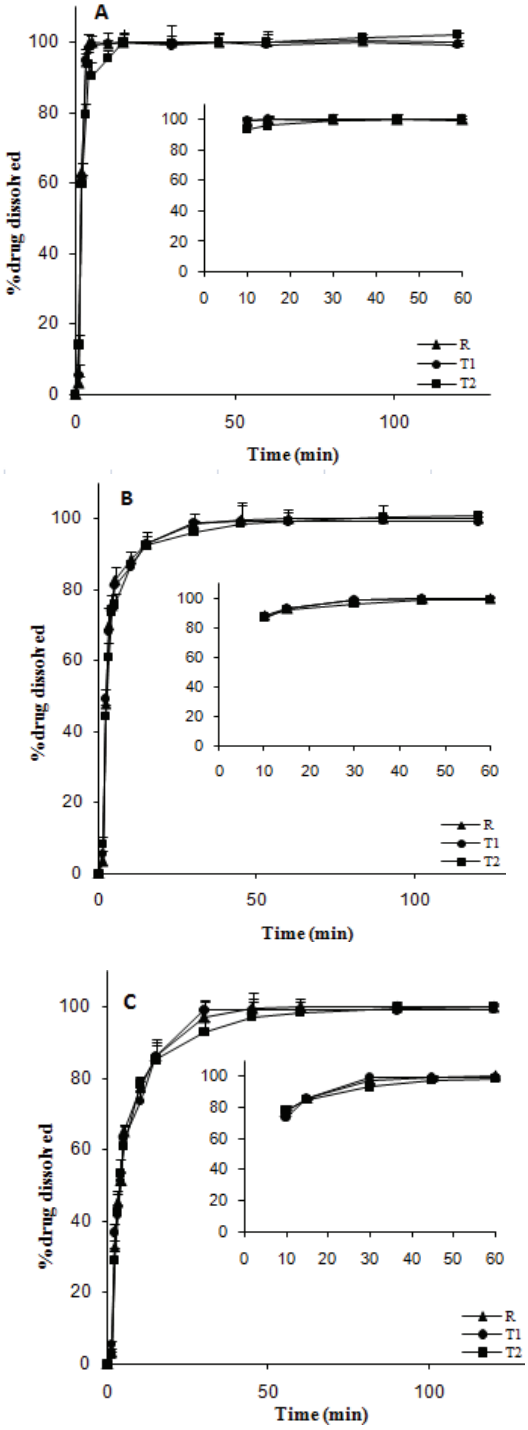


Figure 3. Dissolution profiles of various generic linezolid products in (A) pH 1.2, (B) pH 4.5, and (C) pH 6.8.

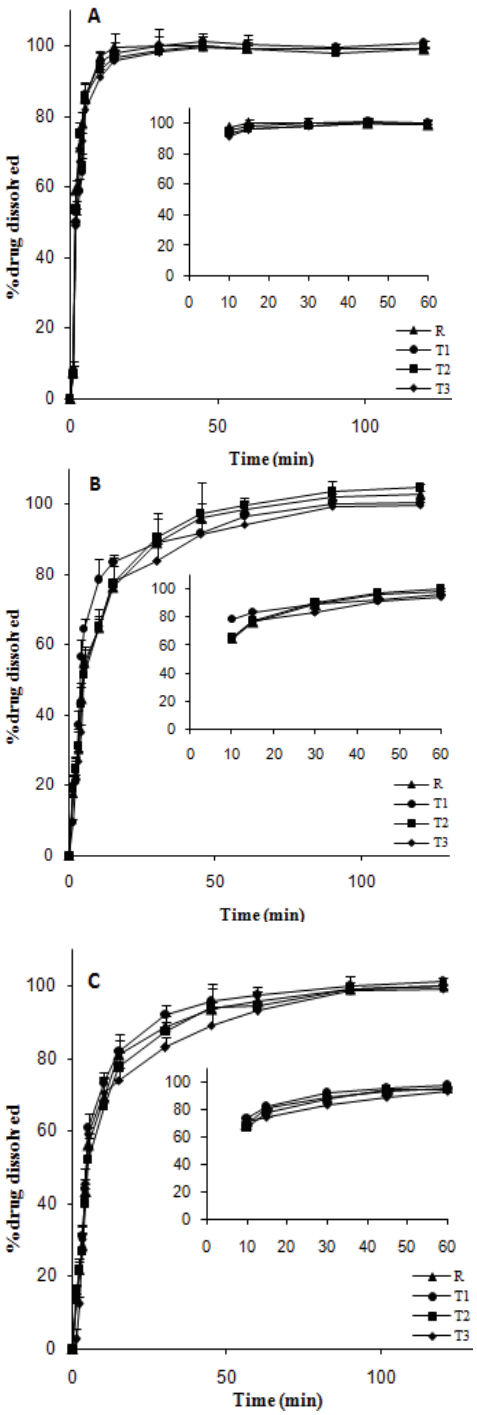


Figure 4. Dissolution profiles of various generic fluconazole products in (A) pH 1.2, (B) pH 4.5, and (C) pH 6.8.

profiles of marketed linezolid products versus the reference product are shown in Figure 3. The dissolution parameters shown in Tables 1 and 2 indicate the similarity of the studied generics to the reference product. None of the tested drugs exhibited f_2 outside of the established limits. Additionally, the results of *DE* and *MDT* support the conclusions drawn from the f_2 analysis. Therefore, all the linezolid products met the biowaiver criteria and would be considered in vitro equivalent.

Fluconazole

Fluconazole belongs to BCS Class III (*10*). To establish bioequivalence using the in vitro method (*27*), fluconazole products should be very rapidly dissolving (i.e., at least 85% of labeled amount dissolved within 15 min or less). The dissolution profiles of fluconazole generic products versus the reference product are shown in Figure 4. The dissolution parameters including f_1, f_2, *MDT*, and *DE* are shown in Tables 1 and 2.

The reference and generic products (T1–T3) dissolved very rapidly in pH 1.2 and met the requirement by exceeding a release of 85% fluconazole in 15 min. In addition, they passed the f_2 requirement of ≥50. In the case of pH 4.5, all the products dissolved rapidly (85% or more in 30 min) except T3, for which more than 30 min was required to release 83.7% of fluconazole. On the other hand, T1 and T2 dissolved very rapidly in pH 6.8 and thus met the requirement by exceeding a release of 85% in 15 min. However, T3 required more than 30 min in pH 6.8 to release 81.1% of fluconazole, and the f_2 value in pH 6.8 was just below the acceptance value of 50 (49.2). Thus, T3 did not meet the biowaiver requirements for Class III drugs. The dissolution rate of T3 at pH 4.5 and 6.8 was slower than that of the reference product, which is evidenced by the increased MDT values in pH 4.5 (6.1 vs. 5.3 min) and pH 6.8 (5.9 vs. 5.1 min). The reason for the poor dissolution of T3 at pH 4.5 and 6.8 could be the variation of excipients or the manufacturing process. As a result, for generic products containing Class III drugs, the quality of excipients and the manufacturing process must allow full and timely release of the drug in the same way as the reference product at predefined conditions (*29*). Therefore, in vivo bioequivalence studies are required to ascertain the therapeutic equivalence.

CONCLUSION

In accordance with WHO recommendations for biowaivers for immediate-release solid oral dosage forms containing BCS Class I and III drugs, the interchangeability assessment of generics using in vitro dissolution similarity as a surrogate for in vivo bioavailability is a very simple approach and does not require the involvement of healthy volunteers in the study. This study used biowaiver conditions to assess the in vitro equivalence of some generic products containing BCS Class I and III drugs. All the BCS Class I generic products studied (fluoxetine and linezolid) met the biowaiver criteria and would be considered in vitro equivalent. For the BCS III drug (fluconazole), only one product (T3) did not meet the biowaiver requirements. However, all the products released fluconazole satisfactorily, with at least 80% of fluconazole dissolved within 30 min. Pharmaceutical equivalence together with in vitro dissolution similarity could be considered a suitable surrogate to ensure the in vivo bioequivalence and hence the therapeutic equivalence of BCS Class I and III drugs.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interest with respect to the research, authorship, or publication of this article.

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