In Vitro Biopharmaceutical Equivalence of 5-mg Glibenclamide Tablets in Simulated Intestinal Fluid Without Enzymes

Angel T. Alvarado1*, Ana Maria Muñoz2, María Bendezú3, Jorge A. García3, Juan J. Palomino-Jhong3, Gaby Ochoa-Pachas4, Andres Chonn-Chang4, Luis Sullon-Dextre4, Berta Loja-Herrera4, and Mario Pineda-Perez4,5

1International Research Network in Pharmacology and Precision Medicine, Human Medicine School, San Ignacio de Loyola University, Lima, Peru.
2Research Unit in Nutrition, Health, Functional Foods and Nutraceuticals, Universidad San Ignacio de Loyola (UNUSAN-USIL), Lima, Peru.
3Faculty of Pharmacy and Biochemistry, National University San Luis Gonzaga, Ica, Peru.
4Peruvian Association of Immunogenomics and Personalized Medicine, Lima, Peru.
5Departmental Pharmaceutical Chemical College of Lima, Peru.

e-mail: eaa.alvarado@hotmail.com

ABSTRACT

This research evaluated the biopharmaceutical equivalence in vitro of three brands of glibenclamide 5-mg tablets (reference, brand name, and generic drugs) from Lima, Peru following the guidelines of the Biopharmaceutical Classification System (BCS). Glibenclamide is a BCS class 2 drug. Quality control parameters were evaluated including hardness, weight, friability, and drug content (hardness: 2.6–2.8 kg-f; weight [mean ± SD]: 103.3–109.8 mg ± 0.27–0.53; friability: 0.19–0.55%; content: 100.65–103.3%). To assess dissolution, apparatus 2 was used at 75 rpm, 900 mL of dissolution medium (37 ± 0.5 °C) at pH 6.8; simulated intestinal fluid without enzymes was used as the dissolution medium. Samples (5 mL) were withdrawn at 5, 10, 15, 30, 45, 60, and 90 min and analyzed at 300 nm in a UV spectrophotometer. Dissolution percentages were 52.79–59.78% at 15 minutes, 59.78–64.54% at 30 mins, 79.64–85.13% at 60 min, and 98.33–99.92% at 90 min. Based on the similarity factor (f2), the dissolution profiles of the brand name (66.61) and generic (70.10) drugs were considered similar to the reference drug (i.e., f2 50–100). Dissolution efficiency was greater than 70% and mean dissolution time exceeded 30 min (p > 0.05). According to the similarity factor and dissolution efficiency, the brand name and generic drugs are biopharmaceutical equivalents in vitro with the reference drug at pH 6.8, with a percentage difference < 5%. However, glibenclamide tablets cannot be exempt from relative bioavailability studies because they did not release at least 85% of the drug within 30 minutes.

KEYWORDS: Glibenclamide, dissolution, generic drug, innovative drug, in vitro biopharmaceutical equivalence

INTRODUCTION

In emerging economy countries, such as Latin American countries, the use of generic drugs from multiple origins (multisource) is promoted. In Peru, the Supreme Decree on the interchangeability of drugs and the Ministerial Resolution of the list of drugs have been promulgated (1). Essential generic drugs have international non-proprietary names to allow for wide distribution of generic drugs from private and public pharmaceutical establishments (2–4). It is essential to have generic drugs to ensure access and availability of medicine in our country, but they must meet quality standards and be bioequivalent and

*Corresponding author
interchangeable (4–6).

Bioequivalence studies for multisource drugs are essential to ensure that the active pharmaceutical ingredient (API) is available at the site of action (4). In vivo bioequivalence studies assess relative bioavailability (pharmacokinetic), pharmacodynamics, or therapeutic effectiveness and are performed for class 2 and 4 high health-risk drugs; in vitro bioequivalence studies are carried out for class 1 and 3 highly soluble drugs, according to the Biopharmaceutical Classification System (BCS) (7–10). Because glibenclamide is a class 2 drug with low aqueous solubility and high membrane permeability, it must be evaluated very rigorously through in vitro biopharmaceutical equivalence studies, including tests of weight, hardness, friability, content, disintegration, and dissolution (11–15).

To establish in vitro bioequivalence, various statistical models are applied, such as the difference factor \( f_1 \), which measures the percentage of error between two dissolution profiles at pre-established sampling times; if the result is zero, then the two profiles are considered equal, if \( f_1 \) is 0–15, then the two profiles are similar, and if the \( f_1 \) is greater than 15, then the profiles are different (10, 16, 17). The similarity factor \( f_2 \), proposed by Moore and Flanner, measures the similarity between two dissolution curves (17–19). This factor is calculated from the mean percentage of dissolution at each sampling time (9, 10, 17). If the result is 100, the two dissolution profiles are identical, if \( f_2 \) is 50–100, then the two profiles are considered to be similar, with some differences. For example, an \( f_2 \) value of 83.5 means that there is a difference of 2%, 65 means the difference is 5%, 50 means the difference is 10%, 41 indicates a difference of 15%, and 36 is a difference of 20% (8, 20). Another parameter used to measure bioequivalence is dissolution efficiency (DE%), which is the area under the dissolution curve at a predetermined time, expressed as a percentage of the rectangle described for 100% dissolution at the same time; the resulting value should optimally be 90% for immediate-release drugs, which indicates that rapid dissolution of the API occurs in the early stages of the dissolution profile (9, 10). Additionally, mean dissolution time (MDT) determines how fast the drug (solid form) dissolves in the dissolution medium (9, 10).

Glibenclamide is a second-generation sulfonylurea, used to treat type 2 diabetes. The chemical name is 5-Chloro-N-[2-[4-(cyclohexylcarbamoylsulfamoyl) phenyl]ethyl]-2-methoxybenzamide, and due to the sulfonamide group, it has a pK\(_a\) of 5.3 (14, 21, 22). Its low aqueous solubility is a limiting factor in dissolution, thus affecting its bioavailability, so the pharmacokinetic parameters are dependent on the formulation (11, 23, 24). Glibenclamide is absorbed from the intestinal mucosa, observing a maximum plasma concentration \( (C_{\text{max}}) \) of 177 ± 75 ng/mL, the same that is reached in a maximum time \( (t_{\text{max}}) \) of 2–6 hours after ingestion of a single dose and fasting (11, 21, 25). Food does not alter the rate of absorption in healthy volunteers (11). It is 99.8% bound to plasma proteins, especially albumin (11, 21). The drug’s volume of distribution \( (V_d) \) is 9–10 L, and its half-life time \( (t^{1/2}) \) is 4–11 hours (11). Glibenclamide is metabolized by phase I by the action of CYP2C9 and to a lesser extent by CYP3A4, transforming into two main active metabolites called 4-trans-hydroxycyclohexyl glibenclamide and 4-cis-hydroxycyclohexyl glibenclamide; the allelic variants CYP2C9*2, CYP2C9*3, and others should be considered in relative bioavailability studies, as they influence the therapeutic level and efficacy of glibenclamide (21, 26, 27).

In Peru, counterfeit generic and brand-name drugs of dubious origin are marketed, as is the case in other low-income countries (28). Counterfeit drugs can have insufficient amounts or
no API and counterfeit packaging, and generic drugs are questioned for low quality (29). This is a global public health problem, which is why the WHO has documented and analyzed that there are counterfeit drugs, substandard drugs, and unregistered or unlicensed medical products (30). It has been established that the largest production of bulk APIs for counterfeit drugs in the world are produced in China and India (31).

In Peru, quality control parameters of pharmaceutical products are regularly tested for compliance with specifications of the official pharmacopoeias, but there is still a need to analyze in vitro biopharmaceutical equivalence via in vitro and in vivo bioequivalence studies. Therefore, it was decided to evaluate the glibenclamide tablets, which is a BCS class 2 drug included in the Ministry of Health’s list of essential drugs, because they are available in the Peruvian pharmaceutical market and are considered low-quality drugs. The results of this study will form part of the scientific evidence to promote the implementation of bioequivalence studies, and with it, guarantee quality and interchangeable multisource drugs for the Peruvian population.

The objective of this research was to evaluate the in vitro biopharmaceutical equivalence between three glibenclamide (5 mg) tablets prescribed in Lima, Peru (brand name, reference, and generic).

METHODS AND MATERIALS

Chemicals and Reagents

The reagents were analytical grade and American Chemical Society (ACS) quality, including 36% hydrochloric acid, sodium hydroxide, monobasic potassium phosphate, 50 mg propylthiouracil tablets, and 96% ethanol. A United States Pharmacopeial (USP) glibenclamide standard was used. Chromafil syringe filters with a size of 25 mm and 0.45-μm pores were used. All substances and reagents were purchased from Mercantil SAC (Lima, Peru).

Sample

The sample size consisted of 200 glibenclamide 5-mg tablets from the brand name, reference, and one generic product. The brand name product, “Glibemlip-5” was assigned the letter “M” (lot 183122039, RS No. EE-05288, expiration date 05/2021, Reyoun Pharmaceutical, Lipharma). The reference product, “5 mg Glidiabet,” was assigned the letter “R” (lot 1010209, RS No. N-12347, expiration date 01/2022; Albis, Ferrer International SA). The generic “glibenclamide 5 mg” was assigned the letter “A” (lot 20297260, RS No. EN-04934, expiration date 08/2023; Farmindustria). All samples were acquired from the same pharmacy in Lima, Peru.

Equipment Calibration and Technique Validation

The dissolution method was validated with 50-mg propylthiouracil tablets by spectrophotometry at a wavelength of 300 nm to evaluate the parameters of specificity, linearity, precision, and influence of filtration. Specificity indicates that there is no interference from tablet excipients in the determination of the API (i.e., no absorbance of placebo is observed in the maximum absorbance zone of API). Linearity was carried out in the range of 1.60–7.75 μg/mL with an $R^2$ 0.9998. Precision was studied with six tablets on two different days, with no significant differences observed ($p = 0.064$). The test for influence of filtration showed that filtration does not adsorb the API and there is no interference ($p = 0.32$), so it is possible to use it in the experimental process.
INTRODUCTION

The dissolution equipment was calibrated, the same as performed once a year with USP prednisone tablets (disintegrating dissolution calibrator) and with USP salicylic acid tablets (non-disintegrating dissolution calibrator), in degassed purified water and in phosphate buffer 0.05 M pH 7.40 ± 0.05 (degassed) at 37 ± 0.5 °C for 30 min. The isothermal medium (water bath) was classified in two stages: operation and performance. In the operation stage, the operation of the switched on was verified; the temperature selector of the equipment was set at 37 °C to check the performance of the water bath, observing the distribution of heat from the water bath that heats distilled water in the external container and degassed purified water inside the glass until reaching and keeping the optimum temperature constant at 37 ± 0.5 °C. The water bath equipment heated homogeneously by thermal convection of the water.

According to the internal calibration sheet of the UV/Vis spectrophotometer (Varian 5000), the equipment passed the diagnosis of photometric accuracy, linearity, noise, stability, diffuse light, and resolution.

Hardness Test

The hardness of each tablet was determined by selecting 20 tablets of each product at random using a durometer, with an acceptance limit of 6 ± 2 kgf (29, 32).

Weight Variation

Twenty tablets of each product were selected at random, then each tablet was weighed individually on an analytical balance. The tablet complies with the test if not more than two individual weights deviate from the average weight by more than the 5% (29, 33).

Friability Test

A Erweka TADR friabilizer was used for this test. Twenty tablets of each of each product were weighed and placed in the friabilizer drum at 25 rpm for 4 min (100 times), then the tablets were dusted and weighed. The difference in the two weights was used to calculate the friability, using the following formula: friability = [(Iw - Fw) / Iw] × 100% where Iw is the total initial weight of the tablets and Fw is the total final weight of the tablets. The tablet complies with the test according to USP-NF if the tablets loss less than 1% of their initial weight (33, 34).

Assay

The average weight of 20 glibenclamide 5-mg tablets was determined, then they were crushed to fine powder to weigh the equivalent of 3.5 mg of glibenclamide. Next, the powder was transferred to a 50-mL volumetric flask, and 30 mL of 96% ethanol was added. The flask was mixed and subjected to the action of ultrasound (UCP-10, Lab Companion) for 30 min and allowed to cool to room temperature. Then the volume was made up to 50 mL with 96% ethanol, obtaining a final concentration of 0.07 mg/mL. Finally, it was filtered to read the absorbance in triplicate at a wavelength of 300 nm using ethanol as a blank.

Dissolution Test

To perform the dissolution test, 12 tablets of each glibenclamide formulation were placed in a USP dissolution apparatus 2 (paddle) for 90 minutes at 75 rpm with 900 mL volume of dissolution medium (simulated intestinal fluid without enzymes, SIF) pH 6.8 at 37 ± 0.5 °C.

The SIF dissolution medium was prepared by dissolving 27.22 g of monobasic potassium...
phosphate (KH₂PO₄) in 250 mL of water, then diluting with water to 1000 mL. The pH was adjusted to pH 6.8 ± 0.1 with a 0.2 N sodium hydroxide solution or 0.2 N hydrochloric acid (33).

Deaeration of the dissolution medium was carried out under vacuum, passing the liquid through a 0.45-µm membrane filter while sonicating with an ultrasound water bath (UCP-10). The dissolver was programmed so that the dissolution medium took the optimum temperature. Each tablet was weighed and subsequently placed in each of the six containers containing 900 mL of dissolution medium.

The 5-mL samples were extracted through syringes with 0.45-µm chromafil filters at 5, 10, 15, 30, 45, 60, and 90 minutes, without replacement of medium. These samples were covered with aluminum foil until analysis.

The absorbances were determined by UV/Vis spectrophotometry at a wavelength of 300 nm, and dissolution medium pH 6.8 was used as a blank. A calibration curve with an $R^2$ value of 0.9978 was made to calculate the concentration and percentage of content (4).

**Statistical Analysis**

SPSS 23 and Microsoft Office Excel 2007 were used for statistical analysis. As a statistical indicator of the in vitro biopharmaceutical equivalence, $f_2$, DE%, and MDT were used (10, 35). DE% was determined with the formula: $DE\% = \frac{AUC_{tot} \times 100}{Q_{\infty} \times t_{\infty}}$, where $AUC_{tot}$ is the area under the release curve from the initial time to the final time of the experiment; $Q_{\infty}$ is the mean amount of drug obtained at the end time ($t_{\infty}$) of the experiment. MDT was estimated with the formula: $MDT = \frac{\sum t_i \Delta Q_{ti}}{Q_{\infty}}$, where $\sum t_i \Delta Q_{ti}$ is the sum of the intermediate times ($t_i$) and the increase in the dissolved amounts of dissolved drug ($\Delta Q_{ti}$) (9, 10, 35). A one-way analysis of variance (ANOVA) was performed, and Tukey and Dunnett were determined as a multiple comparison test (reference versus the brand name and generic products). A value of $p < 0.05$ was considered significant (9, 35).

**RESULTS**

The results showed that the investigated brands had a hardness value within the acceptable range of 6 ± 2 kgf (2.6–2.8 kgf); mean weights had a standard deviation of less than 5% (103.3–109.8 mg, SD ± 0.27–0.53). Similarly, the percentage of weight loss of the tablets after the friability test was acceptable (0.19–0.55%), and the percentage of drug content was within the declared amount (100.65–103.30%) (Table 1).

The investigated drugs did not meet the dissolution criteria at 15, 30, and 45 min. At 60 min, only the reference product dissolved more than 85% in the SIF dissolution medium. There were no statistically significant differences ($p > 0.05$) (Table 2).

Table 3 shows the dissolution percentages of the 5-mg glibenclamide tablets, previously studied in other countries such as Ethiopia, Cuba, and Guatemala, observing dissolution percentages lower than 85% up to 120 min, except for generic drugs in Guatemala, which reached 85% dissolution after 60 min, but standard deviation values were not reported. These studies indicate that the first phase of the dissolution process is slow and variable.

Figure 1 shows the dissolution profiles of 5-mg glibenclamide for the brand name and generic products, indicating a slow curve up to 30 min and more than 75% dissolving after 45 min. When compared to the reference, similarity factor values ($f_2$) were 66.61 for the brand name and 70.10 for the generic product.
Because drug-surfactant interactions are specific, careful choice of surfactant media is required to develop dissolution similarity for drug products. This study investigated the effects of cationic hexadecyltrimethylammonium bromide (CTAB) and nonionic surfactants (polysorbate 80) on the dissolution of tamoxifen (TMX), a selective estrogen receptor modulator in breast cancer (WHO). The objective of this study was to test the in vitro dissolution profile similarity of tamoxifen (TMX) in five dissolution media compositions for quality control (QC) purposes and drug product development, as well as to determine the most suitable surfactant medium for dissolution testing to reflect the formulation effects of TMX. All test products were investigated to make a comparison and to identify the most suitable surfactant medium for dissolution testing to reflect the formulation differences and in vivo dissolution of the drug. Being a BCS Class II weak base, TMX (2-[4-[(Z)-1,2-diphenylbut-1-enyl]phenoxy]-N,N dimethylethanamine; 2-hydroxypropane-1,2,3-tricarboxylic acid) (CAS 54965-24-1) was chosen for this study.

**INTRODUCTION**

Dissolution, solubility, surfactant, tamoxifen, BCS class II

**ABSTRACT**

The purpose of this study was to investigate the effects of CTAB and polysorbate 80 on the dissolution behavior of tamoxifen. Currently, the U.S. Food and Drug Administration (FDA) waives the regulatory requirement for in vivo testing for drugs based on their aqueous solubility and intestinal permeability, which has been an important tool for drug development. The World Health Organization (WHO) further considers dissolution test for BCS Class II drug products for quality control (QC) purposes. Hence, a mechanistic understanding of the correlation between in vitro dissolution profile similarity of a drug product and its in vivo performance during drug development is crucial.

**RESULTS**

At pH 6.8, the effects of 0.5% (w/v) CTAB and 0.5% (w/v) polysorbate 80 on dissolution rates were evaluated. Overall, none of the surfactant media reflected the bioequivalence of test products to the reference; however, polysorbate 80 in independent approaches, test products were found to be different from the reference in all surfactant media. Overall, 6.8 with and without surfactant. At pH 6.8, the effects of 0.5% (w/v) CTAB and 0.5% (w/v) polysorbate 80 on dissolution rates were evaluated. Overall, none of the surfactant media reflected the bioequivalence of test products to the reference; however, polysorbate 80 in independent approaches, test products were found to be different from the reference in all surfactant media. Overall, none of the surfactant media reflected the bioequivalence of test products to the reference; however, polysorbate 80 in independent approaches, test products were found to be different from the reference in all surfactant media. Overall, none of the surfactant media reflected the bioequivalence of test products to the reference; however, polysorbate 80 in independent approaches, test products were found to be different from the reference in all surfactant media.

**DISCUSSION**

The results of this study indicate that surfactant media have a significant impact on the dissolution process of poorly soluble drugs and may provide a discriminative test for certain formulation changes. It is physiologically meaningful to mimic in vitro dissolution profiles in order to predict in vivo performance. Further studies are needed to establish the most suitable surfactant medium for dissolution testing to reflect the formulation effects of tamoxifen.

**REFERENCE**

Ref: Reference (Lot no. 1010209, expires 01/22, Albis); Gen M: Lot no. 183122039, expires 05/21, Reyoung); Gen A: Lot no. 20297260, expires 08.23, Farmindustria; SD: standard deviation; CV%: coefficient of variation.

**TABLE 1. Quality Control Characteristics of Glibenclamide 5-mg Tablets**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Reference</th>
<th>Gen M</th>
<th>Gen A</th>
<th>ANOVA</th>
<th>Dunnett / Tukey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>CV%</td>
<td>Mean ± SD</td>
<td>CV%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>5</td>
<td>32.3 ± 8.7</td>
<td>14.65</td>
<td>40.9 ± 0.2</td>
<td>0.50</td>
<td>30.0 ± 0.64</td>
</tr>
<tr>
<td>10</td>
<td>48.5 ± 1.6</td>
<td>3.36</td>
<td>46.9 ± 0.96</td>
<td>2.04</td>
<td>49.5 ± 0.28</td>
</tr>
<tr>
<td>15</td>
<td>59.8 ± 1.8</td>
<td>2.76</td>
<td>54.3 ± 0.25</td>
<td>9.0</td>
<td>52.7 ± 0.27</td>
</tr>
<tr>
<td>30</td>
<td>64.5 ± 0.23</td>
<td>3.5</td>
<td>61.5 ± 0.31</td>
<td>0.51</td>
<td>59.7 ± 1.05</td>
</tr>
<tr>
<td>45</td>
<td>75.4 ± 0.21</td>
<td>2.76</td>
<td>77.1 ± 0.92</td>
<td>1.19</td>
<td>75.4 ± 0.20</td>
</tr>
<tr>
<td>60</td>
<td>85.1 ± 0.11</td>
<td>0.13</td>
<td>79.6 ± 0.00</td>
<td>0.00</td>
<td>79.7 ± 0.52</td>
</tr>
<tr>
<td>90</td>
<td>99.9 ± 0.63</td>
<td>0.63</td>
<td>98.6 ± 0.41</td>
<td>0.41</td>
<td>98.3 ± 0.17</td>
</tr>
</tbody>
</table>

**TABLE 2. Dissolution Test Results for Glibenclamide 5-mg Tablets in SIF**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Reference</th>
<th>Gen M</th>
<th>Gen A</th>
<th>ANOVA</th>
<th>Dunnett / Tukey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>CV%</td>
<td>Mean ± SD</td>
<td>CV%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>5</td>
<td>32.3 ± 8.7</td>
<td>14.65</td>
<td>40.9 ± 0.2</td>
<td>0.50</td>
<td>30.0 ± 0.64</td>
</tr>
<tr>
<td>10</td>
<td>48.5 ± 1.6</td>
<td>3.36</td>
<td>46.9 ± 0.96</td>
<td>2.04</td>
<td>49.5 ± 0.28</td>
</tr>
<tr>
<td>15</td>
<td>59.8 ± 1.8</td>
<td>2.76</td>
<td>54.3 ± 0.25</td>
<td>9.0</td>
<td>52.7 ± 0.27</td>
</tr>
<tr>
<td>30</td>
<td>64.5 ± 0.23</td>
<td>3.5</td>
<td>61.5 ± 0.31</td>
<td>0.51</td>
<td>59.7 ± 1.05</td>
</tr>
<tr>
<td>45</td>
<td>75.4 ± 0.21</td>
<td>2.76</td>
<td>77.1 ± 0.92</td>
<td>1.19</td>
<td>75.4 ± 0.20</td>
</tr>
<tr>
<td>60</td>
<td>85.1 ± 0.11</td>
<td>0.13</td>
<td>79.6 ± 0.00</td>
<td>0.00</td>
<td>79.7 ± 0.52</td>
</tr>
<tr>
<td>90</td>
<td>99.9 ± 0.63</td>
<td>0.63</td>
<td>98.6 ± 0.41</td>
<td>0.41</td>
<td>98.3 ± 0.17</td>
</tr>
</tbody>
</table>

SIF: Simulated intestinal fluid without enzymes; Gen: generic; SD: standard deviation; CV%: coefficient of variation; ANOVA: analysis of variance.

**TABLE 3. Dissolution Test Results for Glibenclamide 5-mg Tablets from Previous Studies**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Peru</th>
<th>Ethiopia</th>
<th>Cuba</th>
<th>Guatemala</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glidiabet</td>
<td>Daonil</td>
<td>Melix</td>
<td>Gen (Lot 8124)</td>
</tr>
<tr>
<td>5</td>
<td>32.3 ± 4.73</td>
<td>51.89 ± 0.028</td>
<td>44.94 ± 0.04</td>
<td>25.0 ± 1.5</td>
</tr>
<tr>
<td>10</td>
<td>48.5 ± 1.63</td>
<td>56.79 ± 0.06</td>
<td>67.5 ± 0.067</td>
<td>33.1 ± 0.8</td>
</tr>
<tr>
<td>15</td>
<td>59.78 ± 1.05</td>
<td>64.54 ± 0.23</td>
<td>67.5 ± 0.067</td>
<td>33.1 ± 0.8</td>
</tr>
<tr>
<td>20</td>
<td>53.64 ± 0.012</td>
<td>54.85 ± 0.006</td>
<td>43.3 ± 1.5</td>
<td>26.7 ± 1.3</td>
</tr>
<tr>
<td>30</td>
<td>53.64 ± 0.012</td>
<td>54.85 ± 0.006</td>
<td>43.3 ± 1.5</td>
<td>26.7 ± 1.3</td>
</tr>
<tr>
<td>45</td>
<td>75.47 ± 0.20</td>
<td>60.69 ± 0.02</td>
<td>70.13 ± 0.04</td>
<td>57.2 ± 1.5</td>
</tr>
<tr>
<td>60</td>
<td>85.13 ± 0.11</td>
<td>61.57 ± 0.072</td>
<td>73.16 ± 0.035</td>
<td>65.2 ± 1.7</td>
</tr>
<tr>
<td>90</td>
<td>99.92 ± 0.63</td>
<td>74.8 ± 1.7</td>
<td>54.5 ± 1.9</td>
<td>54.5 ± 1.0</td>
</tr>
</tbody>
</table>

Data are mean dissolution % with standard deviation in parentheses. Ref: reference; Gen: generic product.
The AUC value for the reference drug was 6516.6 min%, followed by the brand name (6333.8 min%) and generic (6224.3 min%) drugs. All products had MDT values greater than 30 min (30.4–32.9 min), and DE% values were similar (70.33–72.47%) (Table 4).

![Dissolution profiles of 5-mg glibenclamide formulations in SIF.](image)

**Table 4. Parameters of the Drug Release Curve for Glibenclamide 5-mg Tablets at pH 6.8**

<table>
<thead>
<tr>
<th></th>
<th>Similarity factor ($f_2$)</th>
<th>AUC (min%)</th>
<th>MDT (min)</th>
<th>DE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovator</td>
<td>Ref</td>
<td>6516.6</td>
<td>30.4</td>
<td>72.47</td>
</tr>
<tr>
<td>Generic M</td>
<td>66.61</td>
<td>6333.8</td>
<td>32.0</td>
<td>71.37</td>
</tr>
<tr>
<td>Generic A</td>
<td>70.10</td>
<td>6224.3</td>
<td>32.9</td>
<td>70.33</td>
</tr>
</tbody>
</table>

AUC: area under the release curve; MDT: mean dissolution time; DE: dissolution efficiency.

**DISCUSSION**

To demonstrate the bioequivalence of BCS class 2 drugs such as glibenclamide, the WHO and European Medicines Agency indicates to perform in vivo bioavailability studies (7, 8). Therefore, we conducted an in vitro biopharmaceutical equivalence study to evaluate the biopharmaceutical or drug release phase (disintegration, dissolution, and diffusion to the absorption site) of oral pharmaceutical forms based on the guidelines of the BCS that applies for class 1 and 3 (15). Our analyses included the hardness test, and results were below 6 ± 2 kgf, which is the requirement of satisfactory hardness of a tablet (29, 32, 34). Mean weights of the tablets had an SD less than 5%, which ensures reproducibility within and between batches (36). Through the friability test, the resistance capacity of the tablets to abrasion was established. The results indicated that the surfaces of the tablets are fragile, but there were no cracked or broken tablets after performing the test. The content assay was within acceptable values (90–110%) per USP specifications, which ensures the amount of API and is indicative of the efficacy and stability of the product (9, 33). The study confirmed that all three products of glibenclamide 5 mg tablets investigated (reference, brand name, and generic) met the official quality control specifications.

The drug release phase was evaluated by the dissolution profile at seven sampling points, applying the same requirement criteria of class 1, which indicates that very fast-acting
Role of Surfactants on Dissolution Behavior of Tamoxifen

Tuba Incecayir*,... and
e-mail: tincecayir@gazi.edu.tr

ABSTRACT

Because drug-surfactant interactions are specific, careful choice of surfactant media is required to develop dissolution profiles, as in our research, are slow. Kassahun et al. evaluated the quality and physicochemical bioequivalence of various brands of glibenclamide tablets marketed in Addis Ababa, Ethiopia using a dissolution medium at pH 7.4 and reported f2 values greater than 50 for all glibenclamide products (4). In contrast, Pereda and Martínez studied several batches of glibenclamide from the Medsol laboratory in Habana, Cuba in a dissolution medium at pH 7.6 and reported f2 values below 50 (i.e., similarity condition not met) (38). In Guatemala, Mansilla compared the dissolution profiles of generic glibenclamide in a dissolution medium at pH 7.5 and reported three formulations with an f2 greater than 50, but four others were not bioequivalent in vitro (39). In another investigation carried out by El-Sabawi et al. in Jordan, five generic glibenclamide tablets were studied in a dissolution medium at pH 6.8 and reported f2 values below 50 (they did not publish dissolution percentages) (40).

In our research, rates of dissolution were slow in the first 30 min, whereas in previously published studies, dissolution was slow up to 45 min; this difference might be attributed to the drug’s poor solubility in water, pH of the medium dissolution, technological process, and excipients. Silva Filho et al. and Mah et al. investigated various technological strategies to increase their solubility, proposing the use of molecular dispersion, micronization, and inclusion complexes with cyclodextrin and polymorphs (14, 41). Markopoulos et al. and Dressman et al. demonstrated that pH of the dissolution medium influences dissolution profiles (16, 42). Battu et al. demonstrated that technological processes (mixing time, compression force, and formulation) and the amount of disintegrant and lubricant influence the dissolution profile (43). All these factors can contribute to irregular and delayed absorption in vivo.

In the present study, the similarity factor indicated that the drug release curves of the brand name and generic drugs are similar to the reference at pH 6.8 as evidenced f2 values in the range of 50–100), with a less than 5% difference for the brand name (f2: 66.61) and
Because drug-surfactant interactions are specific, careful choice of surfactant media is required to develop dissolution

The authors disclosed no conflicts of interest related to this article.

REFERENCES


Because drug-surfactant interactions are specific, careful choice of surfactant media is required to develop dissolution
Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Ankara, Turkey
Tuba Incecayir*, Seval Olgac, Duygu Yilmaz Usta, and Zeynep Safak Teksin
Role of Surfactants on Dissolution Behavior of Tamoxifen
Tuba Incecayir*, ... and
test products were investigated to make a comparison
dx.doi.org/10.14227/DT280221P6
e-mail: tincecayir@gazi.edu.tr

For BCS Class II drugs, dissolution can be the rate-limiting step for waiving the regulatory requirement for in vivo testing for immediate release (IR) solid dosage forms


Wei, H.; Löbenberg, R. Biorelevant dissolution media as a predictive tool for glyburide a class II drug. Eur J Pharm Sci. 2006, 29, 45–52. DOI: 10.1016/j.ejps.2006.05.004.


Costa, P.; Sousa Lobo, J. M. Influence of dissolution medium agitation on release profiles
34. Uddin, M. S.; Mamun, A. A.; Tasnu, T.; Asaduzzaman, M. In-process and finished
Because drug-surfactant interactions are specific, careful choice of surfactant media is required to develop dissolution
vivo solubilization and sink conditions due to continuous intestinal absorption of TMX. may provide a discriminative test for certain formulation changes, and it may be physiologically meaningful to mimic in
none of the surfactant media reflected the bioequivalence of test products to the reference; however, polysorbate 80
independent approaches, test products were found to be different from the reference in all surfactant media. Overall,
of the formulations were much more pronounced compared to pH 1.2. Based on model-dependent and model-
6.8 with and without surfactant. At pH 6.8, the effects of 0.5% (w/v) CTAB and 0.5% (w/v) polysorbate 80 on dissolution
drug. Dissolution behaviors of the reference and test products were studied using USP apparatus II at pH 1.2, 4.5, and

For BCS Class II drugs, dissolution can be the rate-limiting step of drug absorption (10). Therefore, a mechanistic
increase drug solubility and dissolution and provide sink 