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In Vitro Performance of Commercially Available Glimepiride Tablets in Indonesia

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ABSTRACT

Introduction: Glimepiride is a commonly prescribed medication for diabetes mellitus that is available in both generic and innovator products. Although the performance of individual products varies, generics should meet quality standards of bioequivalence with the innovator. This study aimed to evaluate the therapeutic equivalence of eight glimepiride products, including four generic and four branded products sourced from various manufacturers, by assessing in vitro dissolution and pharmacodynamics in rats. **Methods**: The comparative dissolution study was conducted in phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and 0.1 N hydrochloric acid (HCl) (pH 1.2). Pharmacodynamic assessment in rats was carried out by measuring blood glucose levels up to 11 hours after dose administration. **Results**: The in vitro dissolution profile of one generic product was not similar to the innovator at pH 1.2 ($f_2 < 50$) but was similar at pH 4.5 and 6.8 ($f_2 > 50$). In the in vivo pharmacodynamic study, all samples showed the potential to effectively reduce blood glucose levels, without substantial variance compared with the innovator. **Conclusion**: Seven out of eight glimepiride products circulating in the Indonesian market had bioequivalence to innovator and can be used interchangeably for therapeutic purposes.

Keywords: dissolution, generic comparison, glimepiride, in vitro equivalence

INTRODUCTION

Indonesia stands as the biggest market for pharmaceutical products in Southeast Asia, where several pharmaceutical industries compete to market various innovator and generic drug products for degenerative diseases. Although the therapeutic efficacy of the innovator is widely acknowledged, it typically comes at a higher cost. Generic products should achieve bioequivalence (BE) with the corresponding innovator to ensure they contain the same quantitative and qualitative composition of active pharmaceutical ingredients, in comparable strength, dosage form, and the identical route of administration (*1*). Despite some variation in quality and quantity of components used in formulation, generic products are intended to be used interchangeably with innovator (*2*).

The lack of BE among generic products has implications for public health, as evidenced by several studies showing post-marketing inequivalence (*3*). A comprehensive evaluation of levothyroxine and glimepiride in Egypt, including in vitro quality assessment and post-marketing clinical studies, showed that the products were not equivalent to the innovator. This

underscores the importance to carefully consider the implications of replacing products, particularly in cases of chronic disease, such as hypothyroidism and type 2 diabetes mellitus (*4, 5*). In Spain, study of BE and non-bioequivalent (NBE) pravastatin formulations did not establish in vitro equivalence for BE formulations at pH 1.2, 4.5, and 6.8, whereas the NBE formulation was equivalent in vitro at pH 6.8 because the in vitro dissolution method (paddle apparatus, 50 rpm) with 900 mL media was unable to detect the in vivo C_{max} differences. Using 500 mL of media, the BE formulation was equivalent at pH 6.8 but not at pH 1.2 and 4.5 (*6*). A study conducted in Peru showed that 100-mg phenytoin products were equivalent to innovator at pH 1.2 in vitro, but not at pH 4.5 and 6.8 (*7*). Another study in Peru found that one of four moxifloxacin tablet products were not equivalent to the innovator (*8*). Other studies have reported in vitro and in vivo equivalence of generic amlodipine products circulating in Mexico, including furosemide and glibenclamide in Ethiopia (*9*–*11*).

Glimepiride, (1-(p-(2-(3-ethylene-4-methyl-2-oxo-3- pyrroline-1- carboxamide) ethyl) phenyl) sulfonyl)-3-(trans-4-methyl cyclohexyl) urea) or $C_{24}H_{34}N_4O_5S$, is the most recent addition to the class of second-generation sulfonylurea drugs and is frequently prescribed for the management treatment of type 2 diabetes mellitus, with daily doses varying from 1–8 mg (*12*). This compound belongs to class 2 in the Biopharmaceutics Classification System (BCS), characterized by high permeability and low solubility in the gastrointestinal tract (*13*). Its solubility at 37 °C is pH-dependent, being < 0.004 mg/mL at low pH and increasing to 0.02 mg/mL at pH above 7 media, with daily doses varying between 1 and 8 mg (*4, 12, 14*).

The dissolution profiles of generic glimepiride tablets on the Indonesian market vary significantly, impacting their application in clinical practice. A clinical study in Egypt showed that four generic products did not have the same clinical efficacy as the innovator (*4*). Similar studies in the Middle East have shown that generic versions of glimepiride are not interchangeable with the innovator in clinical settings due to observed differences (*15*).The post-marketing performance of glimepiride tablets available in Indonesia has not been evaluated. This study aimed to compare the pharmaceutical quality of the innovator glimepiride product with eight multisource products (including four generic and four branded, hereafter referred to collectively as the generic products) marketed in Indonesia and evaluate their interchangeability through comparative in vitro dissolution testing at the three pH levels that occur in the gastrointestinal tract and in vivo pharmacodynamic assessment using fasted healthy rats.

METHODS

Materials

Glimepiride working standard was obtained from PT Phapros, Tbk., Semarang, Indonesia. Analytical grade chemical reagents from Merck, such as methanol, monopotassium phosphate (KH_2PO_4), sodium hydroxide (NaOH), sodium acetate trihydrate ($NaC_2H_3O_2.3H_2O$), glacial acetic acid, and hydrochloric acid (HCl), were used. Other materials included CMC Na 0.5%, which was used to prepare glimepiride oral suspension and distilled water.

Eight multisource products containing 2 mg of glimepiride (coded A-H) and the innovator (Amaryl, 2-mg tablets) were obtained from local pharmacies in Semarang City, Indonesia. All products were analyzed before expiration dates, and the descriptions are presented in Table 1.

Table 1. Detailed Description of Glimepiride (2 mg) Tablets

Product	Name	Manufacturer	Batch/lot no.	Expiration Date
A	Amadiab	Lapi Laboratories	A6031	September 2023
B	Anpirid	Sanbe Farma	BA2313	July 2023
C	Glamarol	Guardian Pharmatama	2106094.2	June 2023
D	Metrix	Kalbe Farma	KTMTXB14188	July 2024
E	Glimepiride	Kimia Farma	G01970J	July 2024
F	Glimepiride	Dexa Medica	5204165	May 2023
G	Glimepiride	Hexpharm	HTGMPK31295	January 2027
H	Glimepiride	Bernofarm	010077004	April 2023
Innovator	Amaryl	Sanofi-Aventis	1DN024	September 2024

Calibration and Performance Verification of the Instrument

The UV-Vis spectrophotometer (Shimadzu UV-1800 240V) was calibrated annually following laboratory guidelines. The calibration process involved assessing wavelength and absorbance accuracy, noise, fixed light limit, resolution power, photometric linearity, as well as the suitability of baseline and sample cells.

The dissolution tester was installed and qualified by the vendor, followed by annual mechanical calibration and performance verification through an accredited laboratory (certified ISO/IEC 17025: 2017). Routine checks include the dimensions, temperature control, rotation speed, and inclination arrangement for all vessels. Performance verification was carried out with USP Standard Prednisone Tablet (37 ± 0,5 °C, paddle, 50 rpm, in 500 mL purified water for 30 minutes).

Calibration Curve and Range Linearity

A spectrophotometric technique was employed to measure the drug content in each sample, as well as the rate of dissolution in three different dissolution media: phosphate buffer pH 6.8, acetate buffer pH 4.5, and HCl pH 1.2. The analysis method used for developing the assay and studying dissolution profiles underwent validation to assess specificity to detect interference from excipients and the active pharmaceutical ingredient (API) in the tablets, linearity, interday precision, and accuracy; all assessments were conducted with six tablets.

A stock solution of glimepiride working standard at a concentration of 100 µg/mL was prepared in 10 mL of phosphate buffer pH 7.8 for assay purposes as well as pH 6.8, 4.5, and 1.2 for dissolution testing. Aliquots from the stock solution were diluted to concentrations ranging from 2–16 µg/mL, then scanned using a UV/Visible spectrophotometer at a maximum wavelength of 210–240 nm. The absorbance-concentration plot (r^2) was utilized for dissolution and assay testing analysis.

Assay

Ten tablets of each generic product of glimepiride and the reference brand were weighed and crushed. A portion equal to 2 mg of glimepiride powder was transferred to a 100-mL volumetric flask and dissolved in 100 mL of phosphate buffer pH 7.8, followed by sonication in an ultrasonic water bath, then filtration using a syringe filter (0.45 µm). The 2.5-mL aliquots from the filtered solution were diluted to a total volume of 10 mL using phosphate buffer pH 7.8. The absorbance of glimepiride at its maximum wavelength in pH 7.8 was determined utilizing UV spectrophotometry.

The concentration was extrapolated from a standard curve calibration previously established for glimepiride in pH 7.8.

In Vitro Dissolution Testing

The comparative dissolution test was carried out according to the United States Pharmacopeia (USP) using apparatus 2 (Electrolab TDT–08L), with a paddle speed of 75 rpm in 500 mL of each dissolution media, namely phosphate buffer pH 6.8, acetic buffer pH 4.5, and HCl pH 1.2, at 37 ± 0.5 °C. The samples (5 ± 0.1 mL) were withdrawn at 10, 15, 20, 30, 45, and 60 minutes and then replaced with an equal volume of fresh dissolution medium to maintain sink conditions. Each aliquot sample was filtered with a 0.45-µm membrane filter (Whatman Puradisc), followed by measurement of absorbance with a UV/Vis spectrophotometer at 226.5 nm for pH 6.8 and 229 nm for pH 4.5 and pH 1.2. at the maximum wavelength. Absorbance values were matched with the previously established standard curve calibration to determine the concentration of drug released at each time interval. Dissolution testing was conducted with a total of six tablets of each product at each pH level.

Pharmacodynamic Study in Rats

The pharmacodynamic study was carried out using male Wistar rats (*Rattus norvegicus*)**,** in compliance with the protocol approved by the Bioethics Commission for Medical/Health Research at Sultan Agung Islamic University, Semarang, Indonesia (no. 381/IX/2022/Bioethics Commission). The protocol adheres to the principles outlined in the Declaration of Helsinki as well as the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The rats were expected to meet the inclusion criteria, i.e., 6–8 weeks old, body weight of at least 100 g, and healthy conditions with blood glucose levels (BGLs) in the normal range. Exclusion criteria were weight below 120 g or above 200 g, unhealthy conditions shown by low reactivity, and BGLs outside the normal range. Dropout criteria were rats receiving medicinal products but experiencing unhealthy symptoms until death during the sampling period.

The pharmacodynamic study was conducted concurrently, with each sample administered as a single dose to six test subjects. The rats were conditioned for one week before the experiments (*11*). To prepare the doses, a tablet of the test product was crushed and suspended in 100 mL of distilled water to a concentration of 20 µg/mL. The conversion dose of the drug was 0.018 mg/200 g body weight (BW), based on the human dose of 1 mg/70 kg(*16*). Initially, several test subjects given the product were weighed to determine the volume of administration. Subsequently, the volume of drug suspension given was 0.9 mL when the weight of subjects was 200 g.

The rats underwent an overnight fast lasting approximately 10 hours prior to the experiment with unrestricted access to water. The glucose oxidase/peroxidase method was employed to measure BGLs. Blood samples were taken before (t_0) administration of the test product by making a slight incision on the tail. The dripping blood was applied to the stick of glucometer, which served to measure BGLs and was used as a control (BG_0). Subsequently, the subjects were given drug suspension of glimepiride test product at a dose of 0.018 mg/200 g BW. Food was not available to the subjects until 5 hours after drug administration, but they were allowed to drink water. Blood samples were collected at 1, 3, 5, 7, 9, and 11 hours after drug administration, followed by immediate measurement of BGLs (BG_t) (*11*, *17*).

Data Analysis

The similarity of dissolution profiles was expressed as a similarity factor (f_2) by comparing the

cumulative drug release curve of the innovator product vs each test product. The f_2 value represents a logarithmic transformation of the sum-squared error of differences between two products across specific time points. An f_2 value ranging from 50 to 100 shows similarity between the two dissolution profiles.

Reduction in BGLs serves as an indicator of hypoglycemic response. BGL data from the in vivo pharmacodynamic study were used to calculate the percentage of decrease in BGLs, according to the following equation:

$$\%\ Reduction\ in\ BGL = \frac{BG(0)-BG(t)}{BG(0)} \times 100\%.\ ,$$

where *BG* (0) is BGL *before* drug administration and *BG* (*t*) is BGL *after* drug administration.

Subsequently, a relationship curve was created between the mean percentage of reduced BGL versus time, and the area under the curve (AUC_{0-11h}) was computed. AUC, C_{max}, and t_{max} values for each generic product were statistically compared with the innovator using Student's *t*-test. The two products are similar if the *p* value is above 0.05 (*11*).

RESULTS AND DISCUSSION

The assay results of 2-mg glimepiride tablets ranged from 99.51% (product A) to 102.25% (product D), as shown in Table 2, which satisfied the USP requirements for content (90.0–110.0%). The content assay of pharmaceutical products is a crucial quality parameter that is necessary to verify the presence of the labeled amount of drug in a specific dosage form. An insufficient amount of drug can lead to suboptimal treatment outcomes, whereas excessive drug content can lead to overdosing, increasing the likelihood of adverse drug reactions and treatment failure.

Table 2. Chemical Assay Results

Product	Glimepiride Content (%)
A	99.51 ± 1.21
B	100.18 ± 0.42
C	100.78 ± 2.32
D	102.25 ± 0.53
E	101.40 ± 0.99
F	101.47 ± 2.50
G	100.68 ± 3.06
H	99.83 ± 1.50
Innovator	100.58 ± 3.36

Values are expressed as mean ± SD.

The dissolution profiles of generic glimepiride tablets in three different media are shown in Figure 1. In the acidic medium of pH 1.2, only one product (D) releases 80% in 60 minutes, while others including the innovator did not. The reduced dissolution of glimepiride in pH 1.2 is due to its low solubility in acidic to neutral pH. At pH 4.5 and 6.8, the tablets released approximately 80% in 45 minutes (and more than 80% at pH 6.8). These results indicate that glimepiride solubility relies on pH, as higher values contributed to an increase in the dissolution rate.

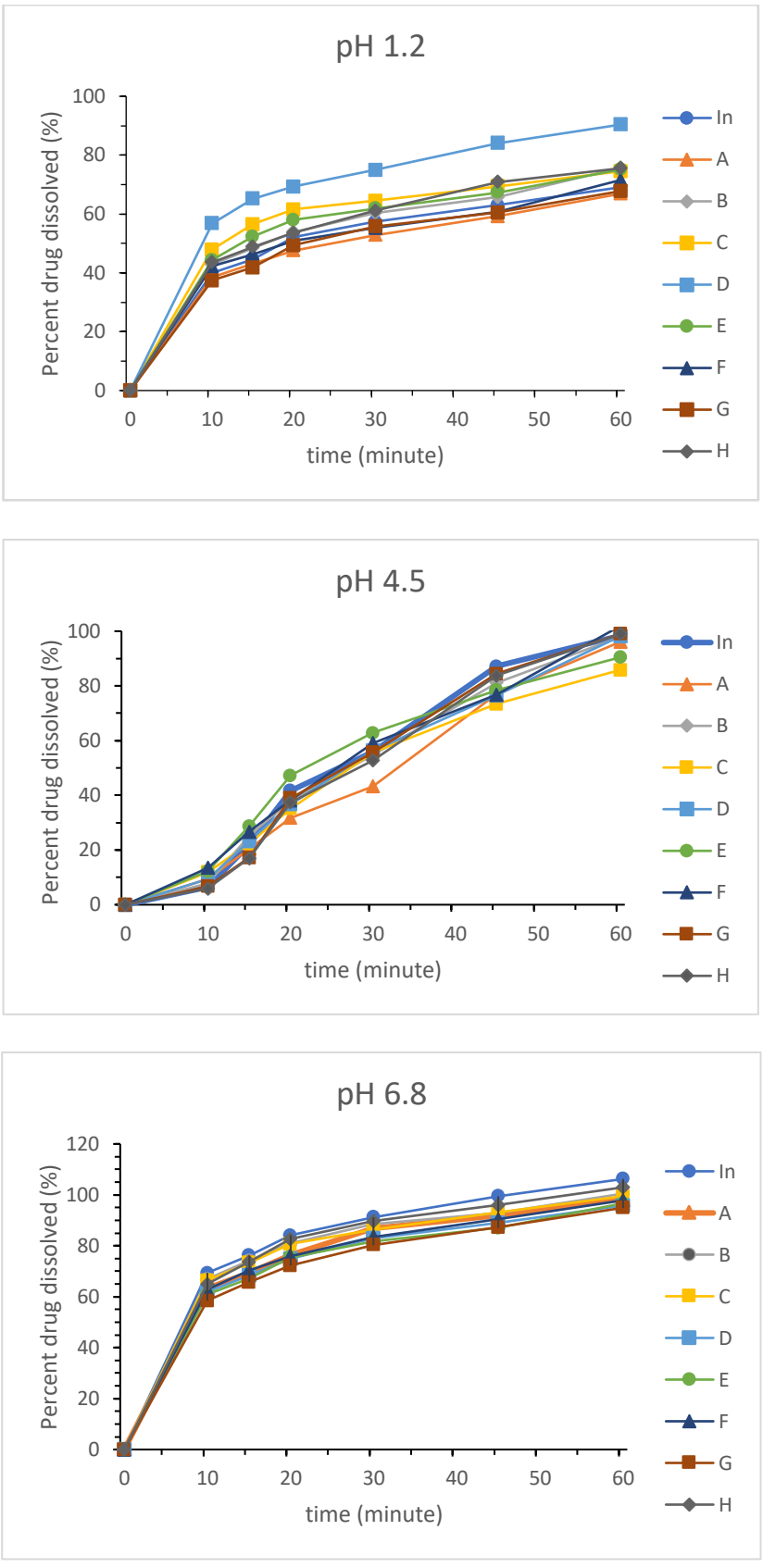

Figure 1. Dissolution profiles of generic (A-H) and innovator (In) glimepiride (2 mg) tablets in pH 1.2, pH 4.5, and pH 6.8 medium.

The tolerance standard for dissolution acceptance in USP (Q) states that glimepiride tablets should release no less than 80% of the active substance in 15 minutes in phosphate-buffered saline medium pH 7.8 (Test 1). When this condition is not met, Test 2 is carried out in 45 minutes with a higher buffer capacity, or Test 3 uses the same medium as Test 1 in 20 minutes(*18*). The dissolution test results at pH 6.8 showed that all products dissolved approximately 80% in 30 minutes, in line with the solubility of glimepiride, which depends on pH of the medium. When the medium had a lower pH, the time required for the dissolution process was longer. Despite variation in pH between the comparative dissolution test and the USP monograph for glimepiride tablets, the results adequately describe the performance in gastrointestinal fluids.

Similarity of the dissolution profiles for each generic product and the innovator at each pH level was assessed using f_2 values (Table 3). At pH 1.2, all generic products were similar to the innovator with the exception of product D ($f_2 < 50$). At pH 4.5 and 6.8, all generic products had a similar dissolution profile as the innovator ($f_2 \geq 50$).

Table 3. Similarity Factor (f_2) Results

Product	pH 1.2	pH 4.5	pH 6.8
A	73.19	54.89	58.28
B	70.28	73.36	68.55
C	53.92	53.69	65.34
D	35.85*	64.75	52.09
E	62.31	57.44	50.64
F	81.87	60.81	55.53
G	79.70	78.64	57.23
H	64.62	73.19	75.12

**Not similar; f_2 value < 50.*

Despite dissimilarity of the dissolution profile for product D at pH 1.2, the percentage of glimepiride dissolved was greater than innovator due to the presence of an alkalizing component present in the formulation. When the tablet was in a pH 1.2 medium, this alkalizing component increased pH.

Quantifying the pharmacologic effect provides a potential method for assessing the bioavailability of drugs in vivo. This method operates under the assumption that a specific intensity of response corresponds to a particular drug concentration at the action site. In this study, the reduction of BGLs after dose administration in healthy/normal state Wistar male rats was assessed spanning 11 hours, which is approximately twice the elimination half-life of glimepiride (5 h). For similarity determination, a curve was drawn between the percentage reduction in BGL versus time (Fig. 2), and parameters such as area under curve (AUC), peak reduction in BGL, and time to reach the effect (t_{max}) were calculated (data not shown).

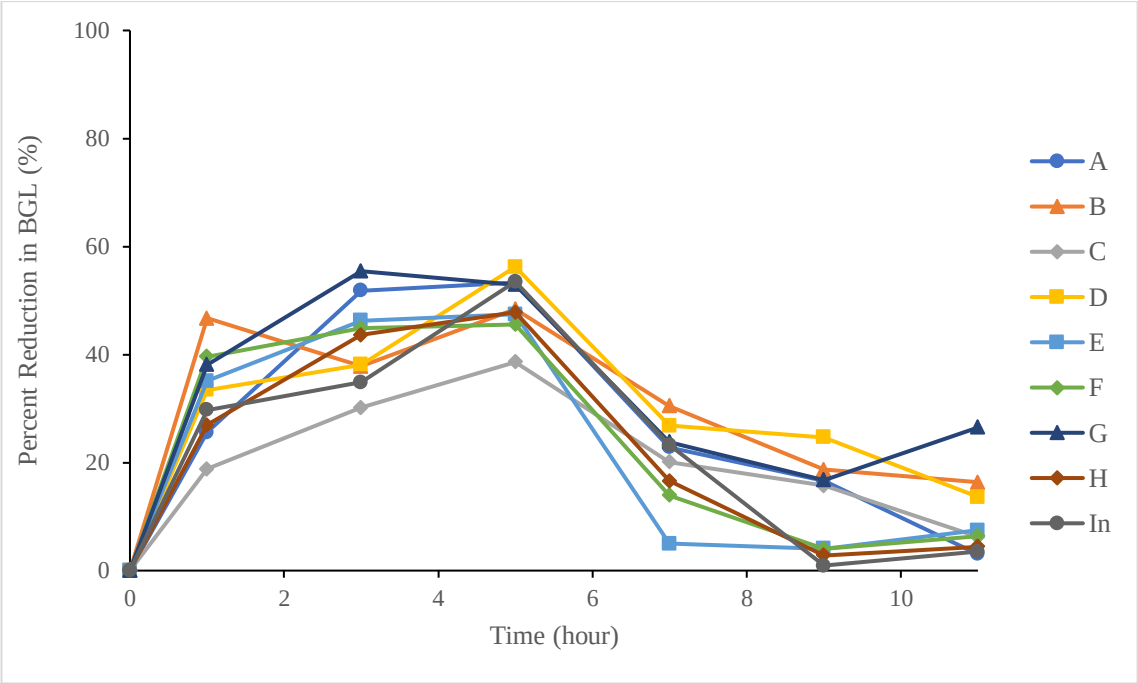

Figure 2. Pharmacodynamic profile in the form of percent reduction in blood glucose level of normoglycemic rat for generic glimepiride products (*A-H*) *and innovator* (*In*).

The results of pharmacodynamic study in rats showed that reduction in BGL for all generic glimepiride products was similar to the innovator. After 1 hour of administration, BGLs were substantially reduced and continued until the fifth hour. The peak reduction in BGL was observed in the range of 30–55% for each test product, occurring in the third–fifth hour. At the seventh hour, there was a reduced effect due to subjects being fed, leading to a significant increase in BGL and limited reduction. This phenomenon continued until the 11th hour when BGL stagnation occurred (glimepiride elimination half-life is 5 h).

The calculated $AUC_{0\text{-}11}$ of all tested products ranged from 415–533. There were no significant differences in the percentage reduction of BGLs between all generic products and the innovator at a 95% confidence level. This finding indicates that the drug effect on serum blood glucose profiles was similar across all products.

At pH 1.2, the in vitro dissolution test did not match the results of in vivo pharmacodynamic study owing to the presence of one product (D) with a dissimilar dissolution profile; however, at pH 4.5 and 6.8, a significant correlation was observed between the in vitro and in vivo results. The lack of correlation at pH 1.2 was influenced by several factors. The absence of enzyme components led to inadequacy of the selected medium to accurately represent similarity with gastric conditions. Glimepiride is difficult to dissolve in a medium with low pH; However, various components in the rat gastrointestinal tract may contribute to enhanced drug solubility, facilitating easier dissolution of glimepiride. Although glimepiride might not have dissolved optimally in vitro, satisfactory results were reported in the pharmacodynamic study in rats. Product D showed faster dissolution at pH 1.2 compared to other samples, which correlated with pharmacodynamic testing in rats. This correlation is attributed to the nature of the rat gastrointestinal tract, so drug absorption did not occur solely in the stomach. In rats, drug residence time in the stomach is brief and considerably longer in the intestine. Therefore, similarity of dissolution profiles in pH 6.8 medium determines the in vivo performance in rats due to the length of drug presence in the intestine.

In vitro dissolution studies demonstrated slight variations among the generic products of glimepiride tablets. Seven out of eight multisource glimepiride products circulating in Indonesia were found to be BE to the innovator product. These results are similar to a study in Ethiopia on generic glibenclamide products(*11*). Despite the slight variability, the tested glimepiride products have good quality. This can be attributed to rigorous adherence to good manufacturing practices, effective control measures implemented by the Indonesian Food and Drug Authority, and proper storage practices maintained by pharmacies and wholesalers.

CONCLUSION

In conclusion, this study showed that eight multisource glimepiride products in the Indonesian market had similar dissolution profiles in pH 4.5 and 6.8 media. However, one product had a dissimilar dissolution profile to the innovator at pH 1.2. Seven products are bioequivalent and considered interchangeable with the innovator product.

DISCLOSURES

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