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Original Article

BIOWAIVER STUDY OF IMMEDIATE RELEASE GLIMEPIRIDE TABLETS

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ABSTRACT

Objective: Demonstrating therapeutic equivalency regarding the efficacy and safety among originator products and generics is a key step in permitting the marketing of generic products. The study aimed to evaluate the bioequivalence of five different generic brands of Glimepiride tablets under biowaiver conditions.

Methods: The quality of the tablet products, including uniformity of weight, friability, and disintegration test, was assessed using the United State Pharmacopeia (USP) general monograph for the tablet dosage form. The content of glimepiride in the tablets was measured using UV spectrophotometer at the wavelength 229 nm. The release of Glimepiride from the tested and originator tablet products was evaluated using the dissolution profiles conducted in HCI buffer pH 1.2, and phosphate buffer pH 6.4 and 7.8 by USP dissolution apparatus II. The bioequivalence of test products was assessed using the similarity and difference factors.

Results: The tested products complied to USP requirements for quality standards; all the products show rapid disintegration, D1 show higher time (Three minutes) while D3 show lower time (28 seconds). The content of test products was (104.68, 93.75, 97.21, 97.03, and 102.10) for D1, D2, D3, D4, and D5 , respectively, compare to 103.70 for OB. Dissolution profiles revealed that the highest similarity to the originator was showed in pH 6.4; f2 ranged (74.5-68.4) for all the tested products and low similarity in pH 7.8; f2 ranged (45.2-64.7).

Conclusion: The study showed that the generic products has noticeable similarity with the originator brand and it can be interchangeable.

Keywords: Dissolution, Glimepiride, Bioavailability, Biowaiver, Generic drugs, Originator

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INTRODUCTION

Demonstrating therapeutic equivalency regarding the efficacy and safety among innovator and generic products is a key step in permitting the marketing of generic products [1, 2]. Bioavailability studies directed in animals and/or humans are considered as time and money consuming steps in the developing of a new pharmaceutical product [1, 3]. Using of dissolution tests can be considered as a substitute for *in vivo* bioavailability studies. It is a cheaper, easier, and less time-consuming test, consequently, it is used as substitute to *in vivo* studies [4, 5]. Generic products are varying in their bioavailability due to variation in manufacturing processing condition, type of formulation and techniques used; moreover, they must be equivalence to the innovator, so the regulatory authority required *in vivo* bioavailability study to ensure the equivalence of generic products [1-3] but these studies are expensive and take a long time, in order tominimize the number and type of bioequivalence studies that have to be carried out. The World Health Organization (WHO), International Council for Harmonization (ICH), and Food and Drug Administration (FDA) suggest wavier of *in vivo* bioequivalence studies using *in vitro* release dissolution data for immediate release oral solid dosage form based on Biopharmaceutical Classification System (BCS) [1, 6-11]. BCS is based on waiving bioequivalence studies depending on the solubility and gastrointestinal permeability of drug substance and it use for generic products development by manufacturer as it save time and resources [1] For registration of generic products it is required that a bioequivalence study must be provided to indicate generic products are equivalence to originator one that must be with same active ingredient, same dosage forms, and strength, in order to submit for marketing authorization[12]. Biowaiver studies are conducted to evaluate the therapeutic equivalence of two or more products alternative to the *in vivo* testing [13-16]. In addition, to determine the conditions required for the dissolution test [17, 18]. Glimepiride is an oral sulfonylurea agent for the treatment of type 2 diabetes mellitus it causes a decrease in blood glucose by inducing insulin secretion from β cells in the pancreas and by increasing peripheral tissue sensitivity to insulin [19]. Glimepiride available as an oral dosage form and completely absorbed from GIT After administration [20]. The peak plasma concentrations (C_{max}) will reach in 2 to 3 h; it possess highly plasma protein-bound (PPB) approximately 99.5% [21], It has a half-life around 5 to 8 h, which may increase with multiple doses up to 9 h; hence these factors contribute to an inconsistent profile of dissolution and absorption, and hence variations in bio-availability and drug action [22, 23]. The biopharmaceutical characteristic of Glimepiride is described as low solubility in aqueous media and high permeability in gastrointestinal tracts. The drug shows low, pH-dependent solubility. So, based on studied biopharmaceutical data, Glimepiride could be classified into BCS Class II [24]. According to WHO, biowaiver procedure eligible in Class II [highly permeable and poorly soluble] when rapidly dissolving (release of>85% of the labeled amount of drug in 30 min), [25]. Glimepiride displays pH-dependent solubility. The drug is extremely poorly soluble in acid and neutral media. On the other hand, the solubility of drugs is slightly raised to (0.02) mg/ml in alkali media with pH>7 [26].

The study aimed to evaluate the bioequivalence of five different generic brands of Glimepiride 3 mg tablets under biowaiver conditions, *in vitro* dissolution test were conducted for five generic products of Glimepiride immediate-release tablet in the market mentioned as D1, D2, D3, D4 and D5 in comparison to Originator brand [Amaryl® 3 mg] in three different pH media HCl buffer pH 1.2 and phosphate buffer pH 6.4 and 7.8.

MATERIALS AND METHODS

Materials

Reference Glimepiride was a kind gift sample from (Tabouk Co., KSA). Four generic brands of Glimepiride 3 mg tablets market in KSA named D1, D2, D3, and D4 and the Originator brand (OB) Amaryl®3 mg [Sanofi S. p. An Italy] was purchased from a registered pharmacy.

Hydrochloric acid (LobaChemiePvt. Ltd, India), potassium chloride (Avonchem limited, UK), potassium dihydrogen orthophosphate (LobaChemiePvt. Ltd, India), sodium hydroxide (May and Baker LTD, Bahenham, England) Potassium Chloride (AVONCHEM limited), methanol (Sigma-Aldrich, USA).

Characterization of physiochemical parameters

Physiochemical properties of the tablet products, including uniformity of weight, friability, disintegration test, and drug content, were assessed according to United State Pharmacopeia (USP) standard for the official test and to the manufacture specification to non-official tests [27].

Preparation of different buffer media

The buffer media used in the study are HCl buffer pH 1.2 and phosphate buffer pH 6.4 and 7.8 were prepared according to USP [27].

Ultraviolet scanning of glimepiride in different pH buffer media

Stock solutions of glimepiride in methanol were prepared and serial dilution was made using the three previously mentioned buffer media.

The spectrum of these solutions was run using a spectrophotometer at 200-400 nm to determine the maximum absorption wavelength (λ max).

The precision of the method was verified by inter-day and intra-day variation studies.

Preparation of standard calibration curves

A concentration ranged between 2-20 µg/ml of Glimepiride standard was prepared from stock solutions using methanol and the buffer system, using Ultra-violet spectrophotometric method at the predetermined maximum wavelength, the absorption of these solutions were measured and lines of regression were plotted. The calibration made in methanol was used for content determination while that in HCl buffer pH1.2 and phosphate buffer pH 6.4 and 7.8 were used for the dissolution studies of the sample tablets.

Drug content assay

Ten tablets from each brand were randomly selected and weighted to obtain the average. The tablets were crushed to powder using mortar and pestle, an exact quantity of the powder equivalent to 10 mg glimepiride was weighed and transferred to a 100 ml volumetric dissolve using methanol, the solution was sonicated for 10 min and the volume was completed to 100 ml with methanol, the resulting solution was filtered using Whatman filter paper, 5 ml of the filtrate was transferred to 50 ml volumetric flask and diluted with methanol to 50 ml, a concentration of 0.001% w/v of glimepiride was obtained. The resulting solution was measured at 229 nm using UV/visible spectrophotometer and the percentage content of each product was calculated using the calibration standard curve. The experiment was performed in triplicate for each brand; mean values and standard deviation were calculated [28].

Dissolution study

The dissolution was carried out using 900 ml of three different buffer media; HCl buffer pH 1.2, phosphate buffer pH 6.4 and phosphate buffer pH 7.8, using an eight-station USP dissolution apparatus II (VK 7020 Vankel®, Canada) and the temperature was maintained at 37 °C±0.5 and 75 rpm.

Five-milliliter samples were collected at predetermined time intervals 5, 10, 15, 30, 45 and 60 min. Five ml of fresh medium pre-warmed to 37 °C was replaced into dissolution medium after each sampling to maintain sink condition requirements. All samples were filtered using Whatman filter paper and were measured using a UV/Vis spectrophotometer at 229 nm. The percentage release was calculated at each time interval. The experiment was carried out in triplicate, and the mean values were obtained. The results were declared as the percentage of the cumulative amount of drug released versus time [29].

Analysis of data

Simple statistics measurement (mean±standard deviation) was used to analyze data of weight variation, diameter, thickness, friability, drug content, and disintegration. The dissolution profile differences were assessed based on the similarity factor (f2) and the difference factor (f1) as:

$$f2 = 50 * \log\{[1 + \left(\frac{1}{n}\right)\sum(Rt - Tt)2] - 0.5 * 100\}$$

f2; similarity factor and Rt and Tt are percents dissolved at each time point for reference and test products, respectively. f2 Values of 50 or higher (50-100) confirm the similarity of the products.

$$f1 = [\sum |Rt - Tt| / \sum Rt] * 100$$

f1 value of 0 to 15 confirms a slight difference between the two products[7, 30].

RESULTS AND DISCUSSION

Physical characteristics evaluation

Five generic brands D1, D2, D3, D4 and D5 of Glimepiride 3 mg immediate-release tablets were studied in comparison to the Originator Brand (OB). The quality test conducted was; tablet weight variation, friability, and disintegration, all products comply with the pharmacopeial standards of tablet dosage forms. The uniformity of weight test was conducted to ensure the uniformity of weight, which reveal the content uniformity also the test indicates the appropriate size of tablets [31]. All tested tablets showed a percentage weight variation within the range of±7.5% and thus it meets the USP Pharmacopeia standards specification of weight variation and the quality control test [32]. Friability test is conducted to assess the capability of the tablet to withstand mechanical stress during manufacturing, packaging and transportation, which lead to physical defect in tablets like capping, chipping, abrasion and breaking. Therefore, it is essential for tablets to withstand such stress. The USP stated that the loss of weight due to friability should be less than 1%, all the test products were within this standard. D3 and D5 showed the lowest loss in weight (0.09% and 0.11) respectively followed by D1 and D4 (0.12 and 0.14) respectively; which revealed their capability to withstand mechanical stress. Tablets disintegration is the break down of tablet to small particles and it is one of the most important indications of dissolution and hence bioavailability of products [33, 34]. The disintegration time of all tested products are within a specified time of less than 15 min for uncoated tablets, which will be influenced on the dissolution. All the generic and originator products disintegrate in time less than 1 minute to 3 min, with highest disintegration time obtained by generic D1 (3:00 min); which will revealed in better release (table 1).

Table 1: Physical characteristics evaluation of selected generic brands of tablets in comparison to originator brand [OB]

Brand	Colour andshape	*Thickness (mm),**n=10	*Diameter (mm),**n=10	*Uniformityof weight[mg] **n=20	Friability (%)**n= 10	*Disintegration min,** n=6
D1	Pink, Oblong with break	2.627±0.32	5.53±0.06	157.35±1.22	0.12	3:00±0.36
D2	Of white, Oblong with Break	3.133±0.02	5.19±0.03	166.15±1.32	0.36	0:28±0.83
D3	Of white, Oblong with Break	4.208±0.01	5.48±0.04	148.5±0.73	0.09	2:11±0.31
D4	Of white, Oblong with Break	4.478±0.01	5.62±.06	223.9±1.72	0.14	2:18±0.11
D5	Of white, Oblong with Break	3.128±0.011	6.53±0.048	172.9±1.89	0.11	0:37±0.10
OB	Of white, Oblong with Break	2.32±0.025	5.7±0.32	166.35±1.15	0.24	1:.24±0.07

***** Results expressed as mean±SD, ** n= number of sample

Spectrum of glimepiride in different pH media

Spectrums scan for Glimepiride standard solution in three different pH mediums 1.2, 6.4, and 7.8 were performed in a range between 200-400 nm. It showed a maximum wavelength absorption (λ_{max}) at 229 nm for all media as shown in fig. 1.

Calibration curve for glimepiride in the three buffer media

Glimepiride standard solution in the HCl buffer system pH 1.2 and phosphate buffer pH 6.4 and 7.8 show linearity in the concentration range 2-20 µg/ml as detected by linearity equation and regression as shown in fig. 2.

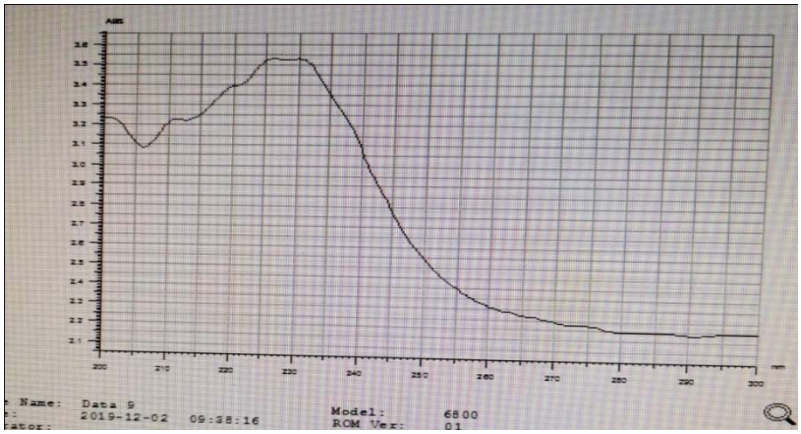

Fig.1: UV spectrum scan for glimepiride standard in pH 6.8 medium

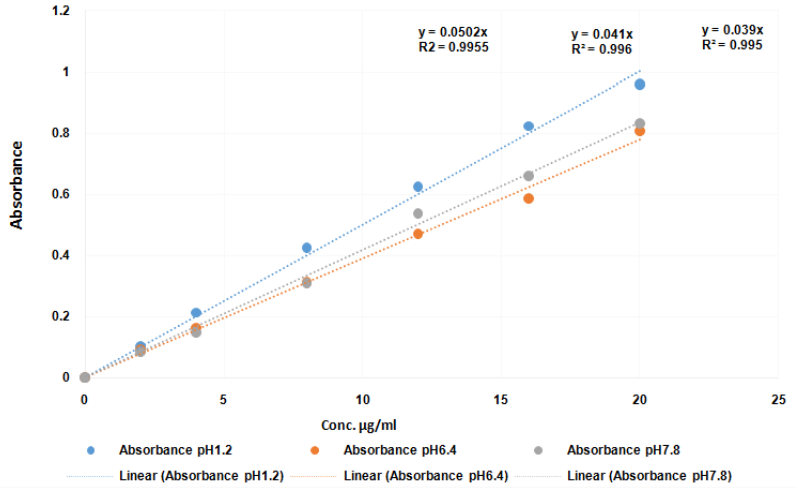

Fig.2: Calibration curve of glimepiride standard in three buffer system, *where y and x are the absorbance and the concentration, respectively

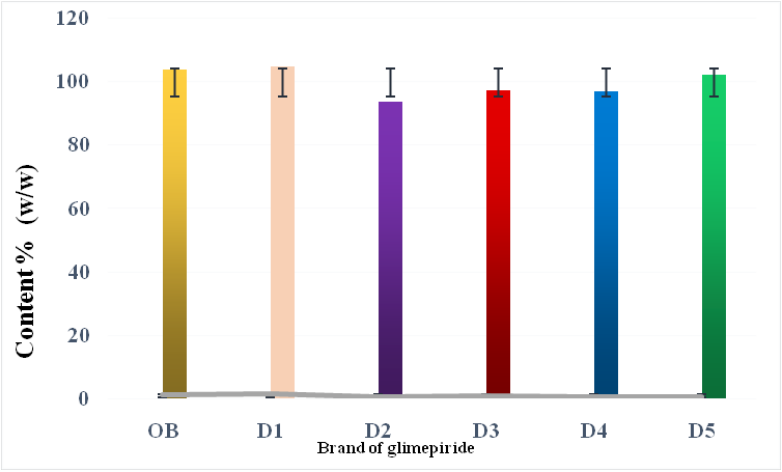

Fig. 3: Drug content of glimepiride tablets, *results expressed as mean±SD, sample size= 3

Drug content assay

The content uniformity results are shown in fig. 2. All tablet samples were complying with pharmacopeial limits, i.e. the percentage average drug content of all samples were (104.68, 93.75, 97.21, 97.03, and 102.10) for D1, D2, D3, D4, and D5, respectively compare to 103.70 for OB. All results within the USP standard range of 90% to 110% of the label statement amount.

Dissolution studies

In vitro dissolution profiles comparison was conducted to ensure quality equivalence and approval of generic formulations in HCl buffer pH 1.2 and phosphate buffer pH 6.4 and 7.8. Compared to the reference product, the dissolution profile and percent release in 60 min for each tablet in the three buffer system is shown in fig. 3-5. The similarity factor f2 and difference factor f1 are calculated in the three buffer system in comparison with the originator brand.

In the hydrochloric acid buffer media pH 1.2 all generic brands D1, D2, D3, D4, and D5 met originator requirement with similarity factor 60.0, 55, 57.67, 60.64 and 59.93, respectively. The difference factors were 4.69, 6.81, 4.14, 3.97 and 3.09 respectively in addition all the products release more than 85% of the active ingredient in 15 min, so they passed the WHO requirement of rapidly dissolving and met the biowaiver criteria.

In contrast, the release of the drug in phosphate buffer pH 6.4 revealed that all products meet the WHO requirements. As the similarity factor of all products more than 50 (74.5, 74.0, 68.5, 66.4 and 68.5 respectively) and the f1 values are less than 15 for all products. The release of the active pharmaceutical ingredient from OB, D1,D2,D3, D4, and D5 in phosphate buffer pH 6.4 and 7.8 is more than 85% in 15 min which indicates the fulfillment of WHO biowaiver criteria however the similarity factor of D1; in phosphate buffer pH7.8 is less than 50 and for the other products about 50 which revealed poor bioequivalence of D1 generic drugs compare to the originator in contrast to D5 show high similarity factor which may be due to the type of excipient and manufacturing process. From the results of dissolution profile in this study it observable that the generic drugs is mostly similar to the originator one in all buffer media specially phosphate buffer pH 6.4, and it released more than 85% of API in 15 min and crossed similarity factor in all pH medium so it can be considered as bioequivalent with the OB under experiment conditions. The dissolution profiles of different products under investigation did not show correlation between the strength and dissolution of tablets. ANOVA test results showed that different tablets had different strengths ($p<0.01$). OB and D2, which had different strength values (fig. 3), had more than 85% of the drug released within 15 min, which revealed the finding that not only content of drugs and the manufacturing conditions, affect drug release but also formula factors, such as disintegrates and diluents types play an important part in the disintegration of tablet and dissolution profiles.Based on biowaiver study results, D1 sample in pH 7.8 is not bioequivalent with the OB unless further an *in vivo* bioequivalent studies prove that as it comparable to Reddy, N. H., *et al.*, finding that some but not all Acyclovir, Atenolol, and Ciprofloxacin Hydrochloride products met the biowaiver criteria [35]. Excipients and additives used in manufacturing tablets have great effects on their dissolution, therefore to achieve biowaiver according to regulatory rules, good manufacturing practice should be followed and careful selection of the excipients used is mandatory.

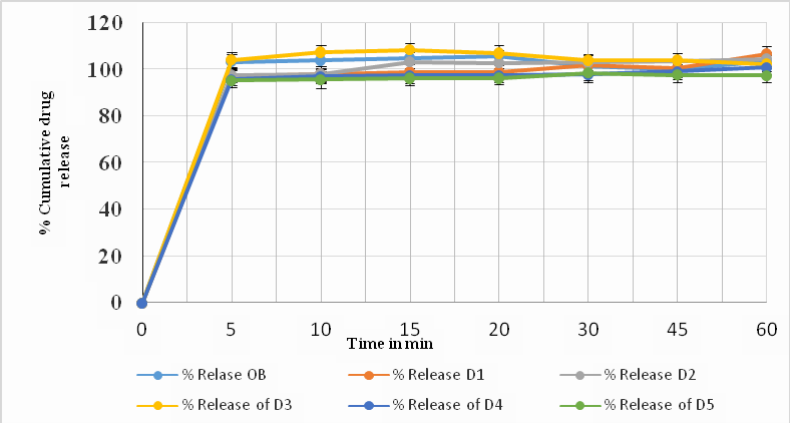

Fig. 4: Dissolution profiles of OB, D1, D2, D3, D4 and D5 tablets at pH 1.2 dissolution medium (n=3, mean±SD)

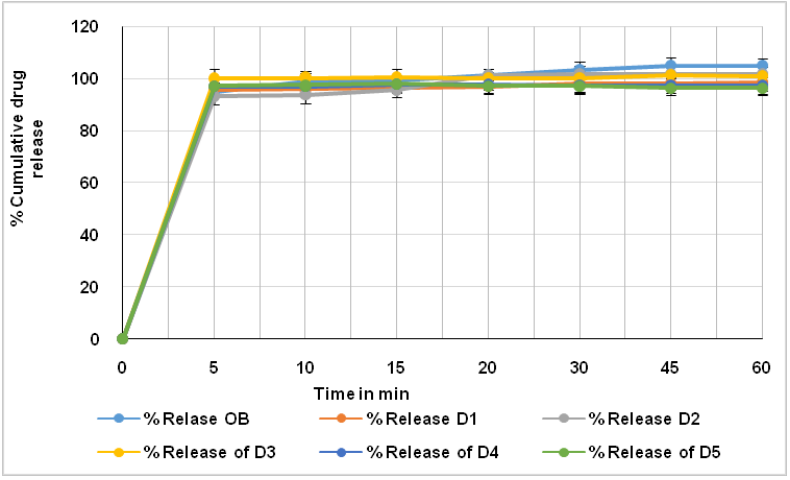

Fig. 5: Dissolution profiles of OB, D1, D2, D3, D4 and D5 tablets at pH 6.4 dissolution medium (n=3, mean±SD)

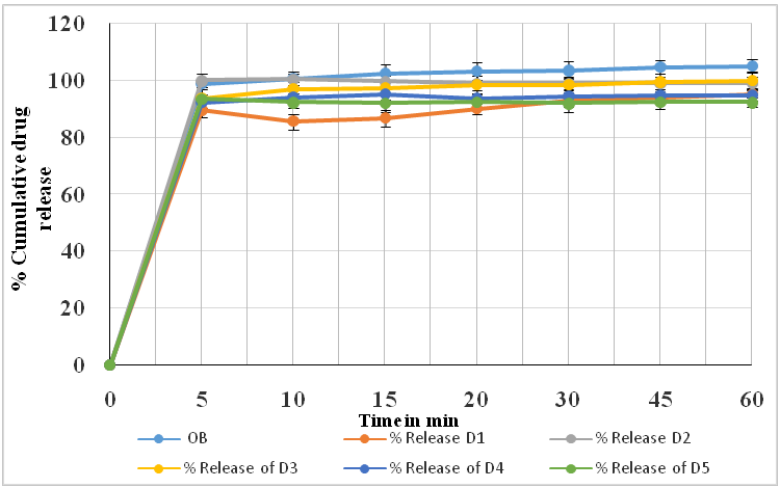

Fig. 6: Dissolution profiles of OB, D1, D2, D3, D4 and D5 tablets at pH 7.8 dissolution medium (n=3, mean±SD)

CONCLUSION

The regulatory authority is controlling the marketed drug products to prevent the substandard drug from market to safe patients from harmful substandard one and from therapeutics failure. The selected Glimepiride tablet generic products available in Saudi market show high quality and in comparable to the originator Amaryl, that revealed the strength of regulatory authority and quality control in KSA In order to decrease the cost of the health care system generic drugs are widely market, however they must be equivalence to originator to assure bioavailability. Biowaiver is an alternative to the costly bioequivalence study of generic drugs to the originator drug. The *in vitro* dissolution profile in our study showed that all generic brand has noticeable similarity with the originator brand and it can be interchangeable with it. Excipients and manufacturing process play an important role in equivalence of generic drug products to originator and to fulfil the biowaiver criteria.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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