

Assessment of the Physicochemical Properties and In Vitro Dissolution of Glibenclamide Tablets Marketed in Saudi Arabia

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ABSTRACT

Glibenclamide (GBD), also known as glyburide, is an oral hypoglycemic of the sulfonylurea group that is frequently prescribed for the treatment of noninsulin dependent diabetes mellitus. The aim of this study was to assess the pharmaceutical quality of new formulations and four generic marketed glibenclamide tablets in Saudi Arabia in comparison with the innovator product (Daonil tablets). Friability, uniformity of dosage unit, disintegration, and in vitro drug release for the investigated products were determined. The friability was less than 1% for all products. The innovator and the tested products all passed the content uniformity test according to *USP 34*. The acceptance values ranged from 3.8 to 6.4. The disintegration time of all products in distilled water, ranging from 3 to 14 min, met *USP* requirements. In vitro release testing of innovator, new formulations, and generics was carried out in phosphate buffer pH 7.4 and pH 7.8, and in borate buffer pH 9.5. The similarity in dissolution profiles (f_2) was assessed using the FDA recommended approach. The f_2 factor increases with increasing pH from 7.4 to 9.5; pH 9.5 is optimum for correlation for some generics (Brands II, III, and IV), while pH 7.8 is optimum for Brand I. Formula IV exhibited a dissolution profile similar to that of the innovator and had the highest f_2 similarity factor at pH 7.4.

KEYWORDS: Glibenclamide; dissolution; similarity factor; formulations.

INTRODUCTION

Drug absorption is affected by the release of the drug from the dosage form, dissolution of the drug from dissolution media resembling physiological media, and the permeability of the drug through the gastrointestinal tract. Therefore, the in vivo performance of a drug can be assessed by in vitro dissolution.

Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability.

In drugs with low aqueous solubility and high permeability, a relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated (1).

For FDA approval, generic drugs have to contain the same active ingredients, be identical in strength, and be bioequivalent to the innovator product (2). Compared with the innovator product, the structure of the active pharmaceutical ingredient in a generic formulation is exactly the same, but it can be formulated in different ways (3).

In a multinational, postmarket comparative study, the dissolution behavior of different glibenclamide formulations was correlated to oral performance and bioavailability of such products (4).

Glibenclamide (Glb), an oral hypoglycemic agent belonging to the sulfonylurea class, is used for the treatment of noninsulin dependent diabetes (Figure 1). It has a his-

tory of low bioavailability, which is attributed to its poor dissolution properties. As a weak acid with a pK_a of 5.3, its solubility strongly depends on the pH of the test medium and particle size (5). Its hypoglycemic effect is mainly due to stimulation of insulin release from pancreatic beta cells and sensitization of the peripheral tissues to insulin (6). Glb controls sugar levels by stimulating insulin secretion in the pancreas and increases tissue sensitivity to insulin (7).

Because of its low aqueous solubility and high permeability, Glb is therefore a Class II drug based on the Biopharmaceutics Classification System (BCS). Bioavailability is not used to classify the drug under BCS (8). Glibenclamide is currently marketed in Saudi Arabia by a number of pharmaceutical companies.

The aim of the present study was to evaluate four marketed Glb tablets (5 mg) in Saudi Arabia and compare new Glb tablet formulations with the innovator product according to the *United States Pharmacopeia* and Food and Drug Administration guidelines.

MATERIALS AND METHODS

Materials

Glibenclamide micronized powder was a gift from SPIMACO (Saudi Arabia). Sodium phosphate dibasic, dicalcium phosphate (DicaPh), monopotassium phosphate, and magnesium stearate were purchased from Riedel de Haën (Seelze, Germany). Sodium hydroxide, boric acid, and phosphoric acid were supplied by BDH Laboratory Supplies (England). Microcrystalline cellulose (MCC,

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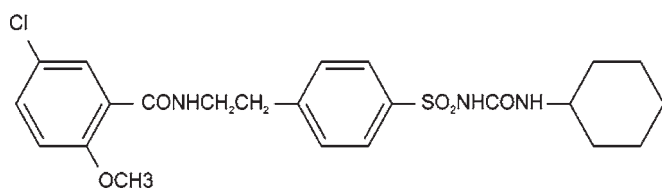


Figure 1. Chemical structure of glibenclamide.

Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Acetonitril was purchased from Merck (Germany). The innovator product (Daonil 5-mg tablets) and the four generic products—Euglucon, Glidibet, Glibil, and Diatab (each containing 5 mg Glb)—were purchased from the local market of Saudi Arabia.

Methods

Preparation of Glb New Formulation Tablets by Direct Compression Method

The corresponding amounts of Glb, dicalcium phosphate (DCP), and Avicel PH 101 (Table 1) were accurately weighed and mixed using a Turbula mixer (Erweka, S2Y, Heusenstamm, Germany) for ten minutes. The specified amount of sodium laurate was then mixed with the powder in the turbula mixer for an additional one minute. The powder was compressed into tablets weighing 200 mg using a Korsh single-punch machine with a 9-mm shallow concave punch (Erweka, EKO, Germany).

Differential Scanning Calorimetry (DSC)

The powdered samples (3–5 mg) were hermetically sealed in aluminum pans and heated from 25 to 200 °C at a constant rate of 10 °C/min (DSC-60, Shimadzu, Japan). Data were processed using a TA 50I PC system with Shimadzu software programs. An indium standard was used to calibrate the DSC temperature and enthalpy scale, and nitrogen was used as a purging gas at a rate of 40 mL/min.

Tablet Friability

Friability of tablets was carried out using Roche friabilator. Friability was evaluated from the percentage weight

loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by fracture was recorded as the percentage weight loss. Friability less than 1% was considered acceptable.

$$\% \text{Friability} = 100 \left(1 - \frac{W_1}{W_2} \right)$$

where W_1 is the total weight of six tablets before friability and W_2 is the total weight of six tablets after friability.

HPLC Analysis

The amount of Glb was analyzed using a previously validated method (9). The HPLC system was composed of a Waters HPLC system (Milford, MA, USA) equipped with a dual absorbance detector, a binary HPLC pump, and a reversed-phase C18 column (4.6 × 150 mm, Hypersil, Asheville, NC, USA). The HPLC system was monitored by Empower (Waters) software. The mobile phase was a mixture of acetonitrile/water (40:60) filtered through 0.45-μm membrane filter and eluted at a flow rate of 1 mL/min; the injection volume was 20 μL, and the retention time was 2.8 ± 0.2 min. The effluent was monitored at 225 nm.

Uniformity of Dosage Units

The uniformity of dosage units can be demonstrated by either content uniformity or weight variation according to USP 34 (10). Content uniformity is based on the assay of the drug substance in a number of individual dosage units to determine whether the individual contents are within set limits. Ten tablets were taken, and each tablet was assayed individually as stated in the monograph. Individual tablets were placed in 50-mL volumetric flasks, 1 mL of water was added to each, and the flasks were shaken till disintegration of the tablets occurred. Ethanol (10 mL) was added, and the flasks were shaken mechanically for 30 min. Each flask was then brought to volume with ethanol. An aliquot was centrifuged at about 3000 rpm, and 20 μL of the clear supernatant was injected to the chromatograph.

Dissolution Studies

In vitro drug release was performed for the tablets according to the USP 34 <711> Dissolution procedure for immediate-release dosage forms. Six tablets from each new formula and twelve tablets for the brands were tested. The dissolution of Glb from tablets was monitored using an automated dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ, USA). The USP Apparatus 2 paddle was used at 50 rpm. The media used were phosphate buffer pH 7.4, phosphate buffer pH 7.8, and borate buffer pH 9.5 (all prepared according USP) maintained at 37 ± 0.5 °C. The amount of Glb released from each tablet in the dissolution samples was determined by the HPLC method mentioned above. Dissolution

Table 1. Composition of Glb Tablet Formulations

Formula No.	Ingredients (% w/w)			
	Glb	MCC	Dicalcium Phosphate	Mg Stearate
I	5	193	-	2
II	5	168	25	2
III	5	143	50	2
IV	5	118	75	2
V	5	93	100	2

Tablet weight: 200 mg

profiles for the prepared formulas and for each product were compared with the innovator to determine the efficacy of the generic products and new formulations. The dissolution medium at pH 9.5 was selected in accordance with the USP monograph of Glb. The two other pH values (7.4 and 7.8) were selected to mimic the physiological pH of the GIT.

Data Analysis

Analytical data were analyzed using Excel software programs for statistical and graphical comparisons. To compare the dissolution profiles of all generic and innovator brands, the model-independent approach of similarity factor (f_2) was employed. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum-of-squared error and is a measurement of the similarity in percent dissolution between the two curves calculated as (11)

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where n is the sampling number, R_t and T_t are the percent dissolved of the reference and test products, respectively, at each time point t . The percent error is zero when the test and drug reference profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles.

WHO has set a public standard of the f_2 value between 50 and 100 to indicate similarity between two dissolution profiles (12).

RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC) offers information about melting, crystallization, decomposition, or a change in heat capacity and is useful to assess the physicochemical status of the entrapped drug as well as the interaction among different compounds. As shown in Figure 2, the thermogram of pure Glb is typical of a crystalline anhydrous substance showing a sharp endothermic peak at 174 °C corresponding to its melting point. The DSC thermogram of the physical mixture was approximately the superposition of the raw material DSCs where the individual components are clearly distinguishable. This indicates there is no interaction between Glb and the excipient used.

Tablet Friability

The results of friability tests of the new formulas and Glb tablets brands are depicted in Table 2. All brands of Glb tablets showed friability values less than 1%.

Uniformity of Dosage Units

The content uniformity of Glb tablets was performed, and the acceptance value was calculated according to USP 34 (10). The acceptance values for all new formulas

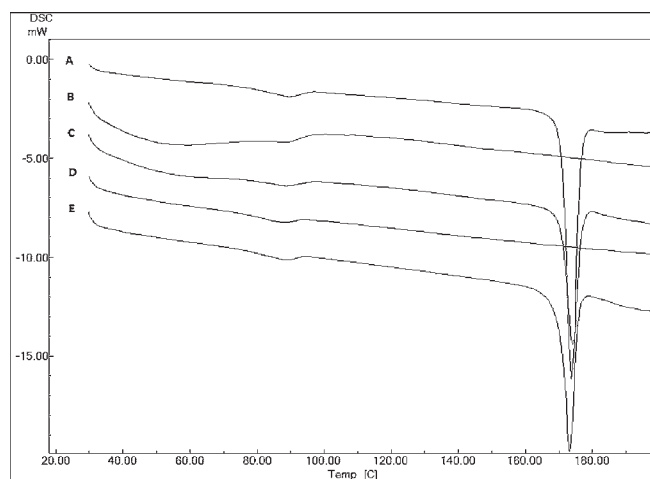


Figure 2. DSC thermogram of (A) Glb, (B) Avicel 101, (C) Glb/Avicel 101 (physical mix 1:1), (D) DCP, and (E) Glb/DCP (physical mixture 1:1).

Table 2. Percent Friability of New Formulas and Glb Tablet Brands

Product/New Formulation	% Friability
Innovator	0.11
Brand I	0.3
Brand II	0.14
Brand III	0.38
Brand IV	0.18
Formula I	0.73
Formula II	0.57
Formula III	0.73
Formula IV	0.57
Formula V	0.48

Table 3. Content Uniformity of Glb Tablets

Product/New Formulation	Acceptance Value
Innovator	5.7
Brand I	3.8
Brand II	5.52
Brand III	5.67
Brand IV	4.87
Formula I	6.4
Formula II	5.8
Formula III	6.2
Formula IV	6.1

and Glb tablets were less than 15 (the maximum allowed acceptance value, L_1) as shown in Table 3.

In Vitro Release Studies

The dissolution test is a measure of the amount of the drug released into the dissolution medium over time. Dissolution tests are a standard method used to ensure the batch-to-batch conformity of oral dosage forms. Today most pharmacopeias describe four different dissolution test apparatus: basket, paddle, reciprocating cylinder, and flow-through cell. The most often recommended methods are the basket and the paddle because of their precise and simple setup and handling (5).

Figures 3–5 show dissolution profiles of the generic and the innovator products at pH 7.4, 7.8, and 9.5. The results of Glb dissolved from the innovator and generics after one hour were 58%, 63%, 70%, 36%, and 67% at pH 7.4. At pH 7.8, the results of Glb dissolved from the innovator and generics after one hour were 73%, 68%, 100%, 60%, and 83%, while

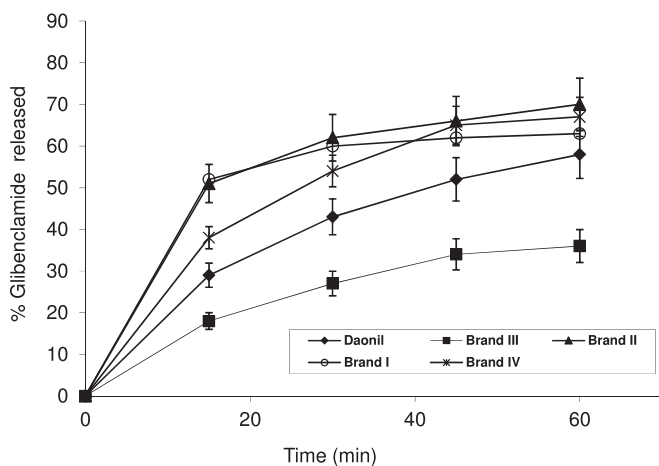


Figure 3. Dissolution profiles of Glb reference standard and four brands in phosphate buffer at pH 7.4.

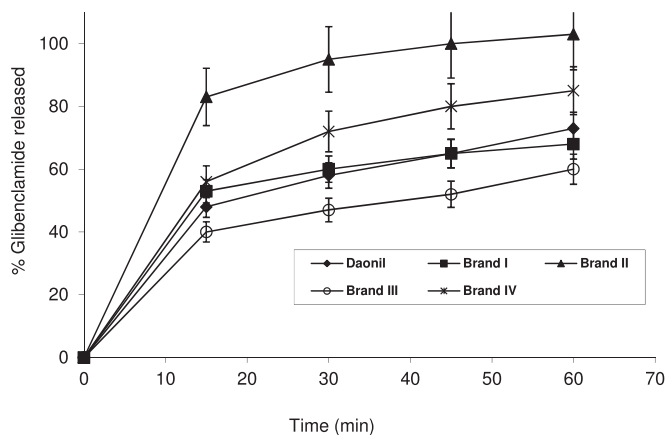


Figure 4. Dissolution profiles of Glb reference standard and four brands in phosphate buffer at pH 7.8.

at pH 9.5, the results of Glb dissolved from the innovator and generics after one hour were 99%, 68%, 100%, 93%, and 98%. These results show that there are differences among dissolution profiles of the generic and innovator products. These differences are reflected by f_2 ratios as shown in Table 4. These findings are in agreement with those in a previous study by Blume et al. (13) of 142 glibenclamide tablet formulations from 28 countries from Europe, Africa, North and South America, Asia, and Australia. They recorded marked differences among product in vitro dissolution behavior.

The f_2 factor increases with increasing pH from 7.4 to 9.5. This might be due to the fact that Glb is a weak acid with a pK_a of 5.3 and its solubility strongly depends on the pH of the test medium. It seems that a pH of 9.5 is optimum for a correlation in similarity with the tested generics (Brands II, III, and IV). The exception was with Brand I, which shows a higher f_2 ratio at pH 7.8 and could be due to formulation factor.

Figure 6 and Table 5 show dissolution profiles and f_2 values of the new formulas and the innovator at pH 7.4. These results show that a correlation can be developed at this pH, and that more than one dissolution time point is needed to characterize release from the dosage form completely. This is consistent with the FDA guideline for IR products, which states that for slowly dissolving or poorly water-soluble drugs (BCS Case 2), a two-point dissolution specification, one at 15 min to include a dissolution range (dissolution window) and the other at a later point (30,

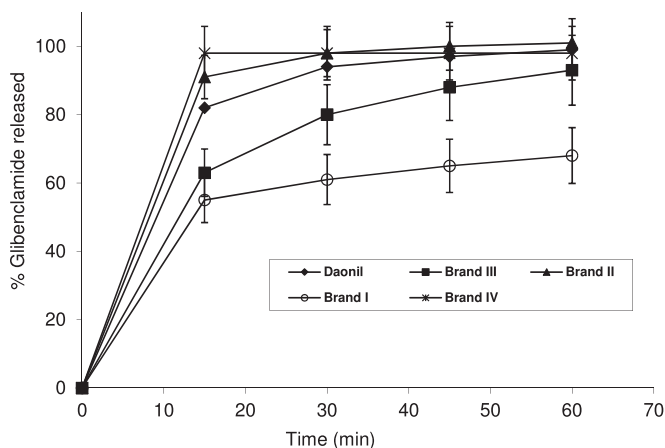


Figure 5. Dissolution profiles of Glb reference standard and four brands in phosphate buffer at pH 9.5.

Table 4. f_2 Values of the Four Brands at Different pH Values

Product	f_2 value		
	pH 7.4	pH 7.8	pH 9.5
Brand I	37.82	74.3	25.58
Brand II	36.46	22.37	60.99
Brand III	40.74	48.11	50
Brand IV	47.61	44.72	50.91

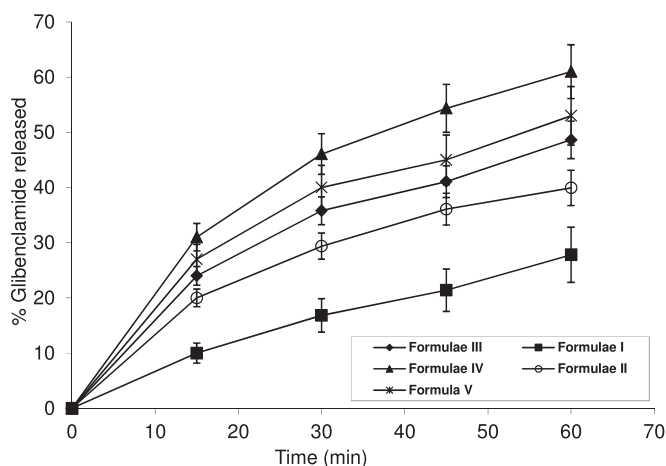


Figure 6. Dissolution profiles of Glib Formulas I–V in phosphate buffer at pH 7.4.

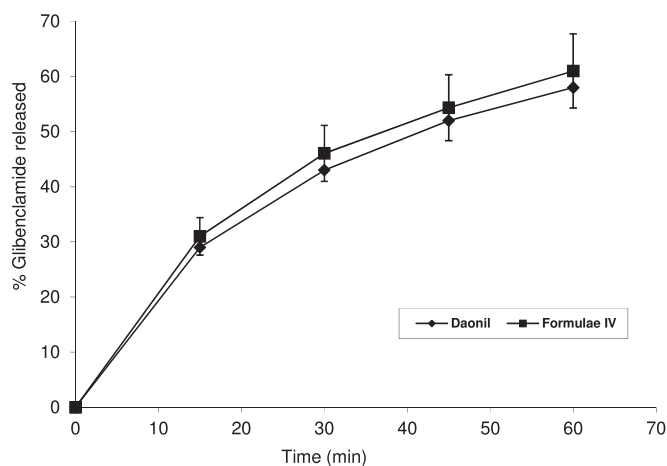


Figure 7. Dissolution profiles of Glib reference standard and Formula IV in phosphate buffer at pH 7.4.

Table 5. f_2 Values of New Formulations Compared with the Innovator at pH 7.4

Product	f_2 value at pH 7.4
Formula I	36
Formula II	57
Formula III	75.5
Formula IV	83
Formula V	59

45, 60 min) to ensure 80% dissolution, is recommended to characterize the quality of the product (5). In a previous report (14), the effect of magnesium hydroxide on the absorption and efficacy of two Glib preparations was investigated in healthy volunteers in two separate studies, using a randomized cross-over design with two phases. Concomitant ingestion of magnesium hydroxide and non-micronized Glib may greatly enhance the absorption and efficacy of Glib. The absorption of micronized Glib appears to be only slightly influenced by magnesium hydroxide. These findings could explain the enhancement effect of the presence of calcium phosphate dibasic on GLB release from formulas II, III, and IV, which contain 25, 50, and 75 mg calcium phosphate dibasic, respectively, compared with the formula that does not contain calcium phosphate dibasic. This could be attributed to the increase in the microenvironmental pH within the stagnant layer during dissolution process, which resulted in an increase in dissolution rate of the weak acid GLB. However, increasing the amount of calcium phosphate dibasic to 100 mg resulted in a decrease in dissolution rate compared with formula IV. This could be attributed to a delay in disintegration time as seen in Table 3. Figure 7 shows that the new formula IV seems to have a dissolution profile similar to that of the innovator (f_2 similarity factor of 83).

CONCLUSIONS

Different dissolution patterns were observed for the different brands of glibenclamide tablets that were evaluated. However, increasing the pH of the dissolution medium from 7.4 to 9.5 decreased the differences in the dissolution behavior. New formulations prepared by direct compression showed good physicochemical properties. Formula IV exhibited a dissolution profile similar to that of the innovator and had the highest f_2 similarity factor at pH 7.4, which mimics the physiological pH of the GIT.

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