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*Review*

# Gliclazide: Biopharmaceutics Characteristics to Discuss the Biowaiver of Immediate and Extended Release Tablets

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**Featured Application:** In line with the principles of the Pan American Health Organization and the World Health Organization (WHO), which permeates the development of technical cooperation, with a focus on producing timely evidence for health decision-making, our research group has contributed, for over a decade, with the production and analyses of information related to the biowaiver of medicines and with the related public policies. In this article, biopharmaceutics information about gliclazide was compiled and evaluated carefully, as it is the only oral antidiabetic agent indicated concomitantly as essential therapy by the WHO and Brazil, as well as a potential candidate for biowaiver according to the International Pharmaceutical Federation (FIP). Our results help close the gap in the literature on the biopharmaceutics classification by the Biopharmaceutics Classification System (BCS) and brings light to the possibility of biowaiver for new medicines containing gliclazide. Therefore, it also contributes to the aspirations of the WHO and the FIP.

**Abstract:** The lists of essential medicines of the World Health Organization (WHO) and Brazil include gliclazide as an alternative to the oral antidiabetic drug of first choice, metformin, in the treatment of type 2 diabetes mellitus because of its pharmacokinetic profile and few side effects. Thus, it is also considered by WHO and the International Pharmaceutical Federation (FIP) as a drug candidate to biowaiver, which is the evaluation of how favorable the biopharmaceutics characteristics are in order to obtain waiver from the relative bioavailability/bioequivalence (RB/BE) studies to register new medicines. This paper presents a review about the solubility, permeability and dissolution of gliclazide. A critical analysis of the information allowed to identify gliclazide as a Biopharmaceutics Classification System (BCS) Class II drug. Therefore, new drugs in immediate release dosage forms will not be eligible for biowaiver. Regarding the extended release dosage forms, besides the limited solubility, no information on the comparative dissolution profile was found, which would be necessary to analyze a possible biowaiver for a smaller dosage. It can be concluded that the registration of new medicines containing gliclazide must undergo RB/BE studies, since there is not enough evidence to recommend the replacement and waiver of such studies for immediate and extended release formulations.

**Keywords:** gliclazide; biopharmaceutics characteristics; biowaiver; essential medicines; dissolution; permeability; solubility

## 1. Introduction

Gliclazide is an oral antidiabetic drug (OAD) used to treat the most common type of diabetes mellitus, the type 2 (DM2), one of the most prevalent chronic non-transmissible diseases in the world, with estimated 463 million cases (20–79 years old) in 2019, accountable for high death rates and health costs worldwide [1]. Gliclazide is considered an effective OAD, because it promotes good glycemic control and reduces the markers of endothelial inflammation and the risks of serious macrovascular and microvascular events combined [2].

Therapy with gliclazide, OAD of the class of sulfonylureas, confers beneficial effects in diabetic vascular disease, in improving endothelial function and alleviating oxidative stress [3]. Additionally, it is observed that, possibly due to its antioxidant properties, it promotes intensive glycemic control [4], reduces markers of endothelial inflammation [5], and reduces the risks of major macrovascular and microvascular events combined [2]. In addition, the use of this drug is associated with a reduction in platelet hyperreactivity [6], low risk of hypoglycemia and excellent results in relation to long-term cardiovascular safety [7]. It is an appropriate therapy for diabetic patients who do not obtain glycemic control only with an adequate diet [5] and it can be a therapy considered for patients with signs of partial failure of insulin production, with mild to moderate hyperglycemia, thin and oligosymptomatic [8,9].

Some studies show that in monotherapy gliclazide was equally effective in improving glycemic control when compared to monotherapy with metformin [10,11]. Although metformin is recommended as OAD of first choice for the treatment of DM2 [12–14], with the evolution of the disease, only a small number of patients remain responsive to monotherapy, which makes it necessary to associate with another ADO to obtain glycemic control [13]. In this sense, gliclazide has also been used successfully in combination with metformin. This association provides, in addition to better benefits in the control of DM2 [3,10], low risk of hypoglycemia [15], reduction of cardiovascular risk factors in patients with DM2 [3], as well as better results in the lipid profile [10]. The therapy with this drug is widely recommended: when metformin is not recommended or not tolerated; when the patient presents low body mass index. It is also prescribed in association with other OAD and lifestyle change when the glycemia is not controlled by monotherapy [16,17].

Worldwide, gliclazide is commercially available in approximately 100 countries in immediate-release solid oral dosage form (SUPAC-IR) and in 122 countries in its extended-release solid oral dosage form (SUPAC-MR) [18]. As an active pharmaceutical ingredient (API), after its release from different pharmaceutical forms and dissolution in the fluids of the gastrointestinal tract, gliclazide presents complete absorption and linear pharmacokinetics up to 120 mg, maximum recommended dosage per day [19].

Due to this favorable pharmacokinetic profile and lower tendency to generate side effects [2], the lists of essential medicines of the World Health Organization (WHO) and Brazil include gliclazide as an alternative to the oral antidiabetic drug of first choice, metformin [20,21]. Moreover, it is considered by WHO and the International Pharmaceutical Federation (FIP) as a drug of interest for studies concerning the biowaiver [22]. Biowaiver consists in the waiver of in vivo studies of relative bioavailability/bioequivalence (RB/BE) for registration and approval of a medicine, when a proper in vitro essay associated to the information of the drug bioavailability enables the substitution of the referred in vivo studies. New medicines registered by the criterion of biowaiver contribute to promote a decrease in prices and to increase the access of poor populations to the medicine [23,24], which reinforces its importance in the context of world public health.

Within this scope, the Biopharmaceutics Classification System (BCS) has been used as a tool to exempt SUPAC-IR from RB/BE studies [25]. As for SUPAC-MR, it is possible to exempt them from RB/BE essays for other dosages of medicines that present the same pharmaceutical form, release mechanism and proportional formulations [26].

In this sense, and by complying with the principles of the Pan American Health Organization (PAHO) and WHO, which involve the development of technical cooperation focusing on the production of timely evidence for the decision making in health [27], it is fundamental to gather and carefully evaluate the biopharmaceutics information of gliclazide.

Our research group has been contributing for over a decade with the production and analyses of information related to the aforementioned context, aiming to collaborate with the study and development of data on this important world public policy of medicine in the realm of biowaiver [28–31]. Thus, in this work, the evaluation of biopharmaceutics data on solubility, permeability and dissolution of gliclazide was carried out from SUPAC-IR and SUPAC-MR, which brings, as a starting point, scientific evidence concerning the possibility to replace RB/BE clinical studies by in vitro studies, for approval and registration of new medicines containing gliclazide.

## 2. Methods

A narrative review of the literature was performed, focusing on biopharmaceutics studies and physical-chemical properties of gliclazide. The bibliographic survey was carried out using the following databases: Portal de Periódicos Capes, PubMed, Scientific Electronic Library Online (SciELO), Cochrane, Scopus, and SciFinder. Searches were made in English and Portuguese, without time restriction concerning the year of publication, until the completion of this paper on August 12th, 2020, and using a combination of the terms: (gliclazide) AND (absorption), (bioavailability), (dissolution), (solubility), (partition coefficient), (permeability), (pKa), (plasma protein binding), (polymorphism). Moreover, the bibliographic references of the papers extracted in the survey were examined in order to identify other potentially eligible papers.

## 3. Results and Discussion

### *3.1. Physical-Chemical Features*

Gliclazide (Figure 1) is characterized as crystalline white or almost white powder, with molecular formula C15H21N3O3S, and whose chemical name is N-[[(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)amino]carbonyl]-4-methylbenzenesulfonamide. It has molecular weight of 323.41 g/mol and melting point of 163 °C–172 °C [32,33]. Gliclazide is an amphoteric drug, with pKa values of 5.8 and 2.9 due to the presence of the sulfonamide group and the aliphatic amine group, respectively, in its chemical structure [34,35].

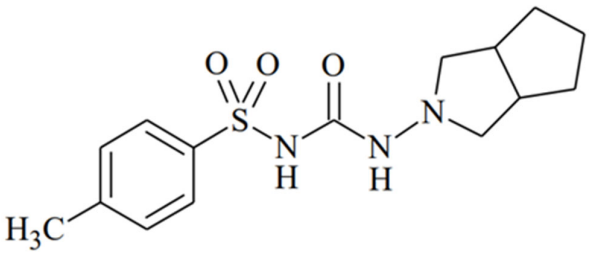


**Figure 1.** Gliclazide Chemical Structure.

### *3.2. Biopharmaceutics Features and Waiver from Relative Bioavailability/Bioequivalence Studies for Tablets of Immediate Release Containing Gliclazide*

For drugs presented in SUPAC-IR, BCS has been used as a tool to support the possibility to replace RB/BE studies for in vitro studies of solubility and permeability, factors which are essential for absorption and consequently, for the bioavailability of the drug. From the results, BCS categorizes the drugs into four classes: I (high solubility and high permeability), II (low solubility and high permeability), III (high solubility and low permeability) and IV (low solubility and low permeability) [25].

WHO and the regulatory agencies, Food and Drug Administration (FDA) and European Medicines Agency (EMA), indicate the possibility of biowaiver for medicines in SUPAC-IR containing drugs of Classes I and III [24,36,37], whereas the National Agency of Sanitary Surveillance (ANVISA) in Brazil considers only drugs of Class I, in SUPAC-IR, eligible for biowaiver [26].

Therefore, the discussion of the biopharmaceutics characteristics and possibility of biowaiver for gliclazide in the context of BCS is valid only for medicines presented in SUPAC-IR.

3.2.1. Solubility

Gliclazide has been reported as a drug practically insoluble in water [38], freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol [39]. It presents low solubility in water at 25 °C (34–37 μg/mL) as well as at 37 °C (52–55 μg/mL) [32,38,40–43].

To evaluate the waiver of RB/BE studies, the solubility of the drug must be analyzed in the range of the physiological pH, in order to check how much the pH variation influences the kinetics of API release [44]. In these cases, the solubility, which is usually measured by the shake-flask method, refers to the ratio of the highest dose administered orally, and its solubility experimentally determined [24,26,36,37]. Thus, this parameter is essential to calculate the conditions of non-saturation and, consequently, to propose analytical conditions for dissolution studies from the pharmaceutical form.

The solubility data available in the literature for this drug were compiled and presented in Table 1. Besides that, the values of the ratio dose/solubility (D/S) were calculated from the experiments performed at 37 °C, using as basis the highest single oral dose administered of gliclazide (160 mg) [45], as well as the basis in the highest commercial dose (80 mg) [46].

**Table 1.** Gliclazide solubility in buffered media and dose/solubility ratio (D/S) calculated from the values collected for experiments carried out at physiological temperature (37 °C).

| Media | Temperature (°C) | Solubility (mg/mL) | RPM | Reference | Calculated D/S **(mL) | Calculated D/S ***(mL) |
|---|---|---|---|---|---|---|
| pH 4.5 | 25 | 0.0337 | ------ | [47] | NA | NA |
| pH 5.5 | | 0.0433 | Shaker | | | |
| pH 6.0 | | 0.0619 | | | | |
| pH 6.4 | | 0.1133 | | | | |
| pH 6.8 | | 0.2164 | | | | |
| pH 7.0 | | 0.2646 | | | | |
| pH 6.8 | | 0.2774 | | | | |
| Distilled water | | 0.0373 | ------ | | | |
| pH 2.67 | 25 | 0.0715 | Magnetic shaker | [42] | NA | NA |
| pH 3.69 | | 0.0326 | | | | |
| pH 4.47 | | 0.0338 | | | | |
| pH 5.73 | | 0.0689 | | | | |
| pH 7.4 | | 0.1751 | | | | |
| pH 8.24 | | 0.7856 | | | | |
| pH 9.74 | | 1.4754 | | | | |
| pH 4.5 | room temperature | 0.0578 | 250 | [48] | NA | NA |
| pH 5.4 | | 0.0742 | | | | |
| pH 6.8 | | 0.2954 | | | | |
| pH 7.4 | | 0.6375 | | | | |
| pH 1.2 | | 1.6940 | | | | |
| pH 4.5 | room temperature | 0.0335 | Mechanical agitation | [41] | NA | NA |
| Distilled water pH 7.0 | | 0.3485 | | | | |
| pH 7.4 | | 1.8415 | | | | |
| pH 1.2 | 37 | 0.4 * | 50 | [49] | 400 | 200 |
| pH 4.5 | | 0.1 * | Magnetic shaker | | 1600 | 800 |

| | | | | | | |
|---|---|---|---|---|---|---|
| pH 5.8 | | 0.1 * | | | 1600 | 800 |
| pH 6.8 | | 0.6 * | | | 267 | 133.3 |
| pH 7.2 | | 1.2 * | | | 134 | 66.7 |
| pH 7.4 | | 1.5 * | | | 107 | 53.33 |
| pH 1.2 | 37 | 0.81 | ---- | [50] | 197.5 | 98.7 |
| pH 1.1 | | 0.8 * | 250 | | 200 | 100 |
| pH 6.8 | 37 | 0.3 * | (shake flask) | [51] | 533.3 | 266,7 |
| pH 7.4 | | 1.1 * | | | 145.5 | 72,7 |
| Distilled water | | 0.0526 | ---- | | 3041.8 | 1520.9 |
| pH 1.2 | 37 | 0.1242 | Shaker | [40] | 1288.2 | 644.1 |
| pH 4.5 | | 0.0404 | | | 3960.4 | 1980.2 |
| pH 6.8 | | 0.1824 | | | 877.2 | 438.6 |

* Estimated values based on the graphic representation present in the referenced article. ** D/S: solubility dose ratio calculated based on the highest administered unit dose (160 mg) of gliclazide in solid oral dosage form (SUPAC-IR), for studies performed at 37 °C [45]. *** D/S: solubility dose ratio calculated based on the highest commercialized dose (80mg) of gliclazide in SUPAC-IR, for studies carried out at 37 °C [46]. NA: not applicable.

For a drug in its oral solid pharmaceutical form to promote its therapeutic action, it needs to solubilize in the biological fluids, having its solubility influenced by some factors, among which, the pKa of gastrointestinal tract (GI tract). By knowing the solubility and pH of a drug it is possible to predict the dissolution along the GI tract and to avoid potential bioavailability problems [28,52].

According to Table 1, the values of solubility for gliclazide found by distinct authors, for the same pH value, are widely variable. This probably happens because of the different conditions in which these studies were performed. However, it can be observed that gliclazide presents solubility values dependent on pH.

Starting from pH 4.5, there is a direct relation of the increase of pH and of the solubility. This was expected, since the drug behaves like a weak acid due to its sulfonamide group (pKa 5.8) [34,35] ionizing in media with higher pH values, resulting in higher solubilities in these conditions [40,47]. Furthermore, this drug behaves like a base due to the alicyclic aliphatic amine group (pKa 2.9) which, in acid pH (1.2) protonates and acquires positive charge [40]. Therefore, in acidic media (pH 1.1 and pH 1.2), solubility values are higher than in the range 4.5–5.8, which is the neutral form of the drug [40,41,49,51].

For purposes of BCS classification, a drug is considered highly soluble if the highest orally administered dose is completely solubilized in a volume ≤ 250 mL of buffered solution presenting the physiological pH of the GI tract. Such proof must be carried out, in triplicate, employing at least three aqueous media with pH in the range of 1.2 to 6.8, maintained at 37 °C ± 1 °C [24,26,50,51].

In the study performed by El-Sabawi and Hamdan (2014) [40], gliclazide presented low solubility in all buffered media tested, being 438.6 mL the smallest result to calculate the D/S ratio. In accordance, this low solubility was also reported in pH 6.8 according to the studies performed by Grbic et al. (2011) [51]. Gliclazide presented low solubility in pH 1.2 to 6.8 when the highest daily unitary dose (160 mg) was used in order to calculate the D/S ratio, and in pH 4.5 to 5.8 when the highest commercial dose (80 mg) was used to calculate the D/S ratio [49], therefore, showing the solubility limitations of this drug in the buffers that simulate the pH of the GI tract.

On the other hand, as expected, the D/S ratio of gliclazide was higher in the pH extreme ends, presenting values lower than 250 mL in pH 1.1 [50] and 1.2 [51], pH 7.2 [49] and pH 7.4 [49,51]. However, it is important to point out that only the study performed by Grbic et al. (2011) [51] used the gold standard shake flask method to evaluate the solubility in balance for the BCS classification.

So, from the data just described, gliclazide can be considered a low solubility drug according to the BCS (Class II or IV), as, in none of the presented studies, the D/S ratio was lower than 250 mL in the pH range that simulates the fluids of the GI tract (pH 1.2, pH 4.5 and pH 6.8).

3.2.2. Permeability

According to the regulatory agencies and WHO, for purposes of biopharmaceutics classification, a drug is considered highly permeable when it presents extent of absorption higher than 85% [24,26,36,37].

Permeability should be evaluated based on the extent of absorption of the drug in humans and/or on the measure of the mass transfer ratio through the intestinal membrane [24,26,36,37]. However, there are other systems to predict the extent of absorption of a drug in humans that can be used, such as: in vitro models using membranes formed by monolayers of human colon adenocarcinoma cells (Caco-2) and in situ models, which resemble human physiological data as they keep innervations and blood supply. Moreover, predictive models such as the use of parallel artificial membranes prepared by using synthetic lipids (PAMPA—parallel artificial membrane permeation assay) and in silico models help to elucidate the permeation mechanisms [52,53].

The permeability data obtained for gliclazide from the studies described in the literature, using in vivo, in situ, and in vitro models were compiled in Table 2.

**Table 2.** Permeability data obtained for gliclazide.

| Method | Reference Value | Results | Reference |
|---|---|---|---|
| Partition coefficient octanol-water (Log P) | High: ≥1.72 * | 1.97 | [54] |
| Partition coefficient octanol-water (Log P) | High: ≥1.72 * | 1.73 | [49] |
| Cell Caco-2 ($P_{app}$) | > $1 \times 10^{-6}$ cm/s ** | $25 \times 10^{-6}$ cm/s | [55] |
| Absolute bioavailability | High: ≥85% *** | 113.4% | [56] |
| | High: ≥85% *** | 86–89% | [57] |

* High permeability standard drug Log P, metoprolol [58]; ** [59]; *** [37].

The values found in the literature for the partition coefficient octanol-water (Log P) of gliclazide, obtained by in silico models, suggest high permeability of the drug, once the Log P values were higher than the reference value of metropolol (Log P = 1.72), a standard drug of high permeability. However, it is important to observe that these values provide us with only an estimate of the permeability of the drugs [58].

In conformity with in silico studies [49,54], from the results of the study that used Caco-2 cells, it is possible to suggest that gliclazide is a highly permeable drug. Moreover, it indicates that the transcellular passive pathway is the main permeation route of the drug [55]. However, it is worthy to highlight that some studies suggest the influence of efflux transporters, such as MRP2 and MRP3, in the oral absorption of gliclazide [51,60]. However, in diabetic rats, the efflux mediated by MRP2 and MRP3 is inhibited, not presenting any damage to the drug absorption [61].

Regarding the absolute bioavailability of gliclazide in SUPAC-IR, the compiled studies reported absolute bioavailability of 86% to 113.4% [56,57]. This way, according to the results of permeability in vivo, the drug has absolute bioavailability higher than 85%, therefore being considered highly permeable.

Therefore, based on the results presented, gliclazide can be classified as a highly permeable compound [24–26,36,37], BCS Class I or II.

3.2.3. Dissolution

The dissolution essay is an important physical-chemical test to demonstrate, in vitro, the performance of medicines that need the yield of the drug and later dissolution for absorption and, consequently, therapeutic effect. The dissolution profile is a fundamental tool that enables us to evaluate the process of API release, which allows us to establish the experimental conditions and proper specifications to monitor the performance of the product [62]. The experimental conditions and the results obtained by using the dissolution profiles for the SUPAC-IR containing gliclazide (80 mg tablets) found in the literature were compiled in Table 3.

**Table 3.** Experimental conditions for dissolution studies and percentage amount of gliclazide dissolved from immediate-release solid oral dosage form.

| Drug | Medium/Volume (mL) | USP Apparatus/ Stirring Speed (rpm) | Temperature (°C) | Dissolved Quantity (%)/min | Reference |
|---|---|---|---|---|---|
| Diamicron 80mg | pH 1.2/900 | II/100 | 37 | <50/30 | [51] |
| Glioral 80 mg | | | | <85/30 | |
| Glikosan 80 mg | | | | <60/20 | |
| Diamicron 80 mg | pH 4.0/900 | | | <30/30 | |
| Glioral 80 mg | | | | <60/30 | |
| Glikosan 80 mg | | | | <30/30 | |
| Diamicron80 mg | pH 7.2/ 900 | | | ≥85/30 | |
| Glioral 80 mg | | | | ≥85/30 | |
| Glikosan 80 mg | | | | ≥85/30 | |
| Diabezidum 80 mg | pH 7.4/900 | II/100 | 37 | 81.62/60 | [43] |
| Diabrezide 80 mg | | | | 88.83/20 | |
| Diabezid 80 mg | pH 1.2/--- | II/100 | 37 | 50.95/15 | [56] |
| Diabrezide 80 mg | | | | 11.9/15 | |
| Diamicron 80 mg | pH 1.2/900 | II/100 | 37 | <70/60 | [63] |
| Diberin 80 mg | | | | <80/60 | |
| Diamicron 80 mg | pH 4.0/900 | | | <40/60 | |
| Diberin 80 mg | | | | <50/60 | |
| Diamicron 80 mg | pH 7.2/900 | | | ≥ 85/30 | |
| Diberin 80 mg | | | | ≥85/30 | |
| Diamicron 80 mg | pH 7.4/900 | II/100 | 37 | 90.43/20 | [64] |
| Diamicron 80 mg | pH 7.4/900 | II/100 | 37 | 84.3/20<br>95.6/30 | [65] |
| Diamicron 80 mg | pH 7.4/500 | II/50 | 37 | 33/480 | [66] |

The studies using media with pH 4.0, performed for gliclazide from the immediate-release tablets, presented slow dissolution (less than 85% in 30 min) for all formulations tested by Hong et al. (1998) [63] and Grbic et al. (2011) [51], which was expected due to the low solubility of this drug in the pH range 3.0–4.2 [42,49]. Moreover, during the evaluation of the drug release in the dissolution studies, one must ensure the fulfilment of the sink conditions, defined as three times the volume of the media necessary to obtain a saturated solution of the pharmaceutical ingredient, considering its highest commercial dosage [44]. Such condition was not met in the studies using media with pH 4.0 [51,63], which may have contributed to reduce the speed of release related to the time.

Despite the good solubility of gliclazide in pH 1.2 [40,41,49,51] the release of the drug from the tablets in this medium was considered slow (less than 85% dissolved in 30 min) [51,63], which

indicates that solubility is not an important factor that controls the dissolution speed of gliclazide in this medium [51].

The dissolution profiles of gliclazide in the studies presented in Table 3 showed that the drug's speed of release was higher using buffers with pH 7.2 and 7.4, whose products presented fast dissolution (≥85% in 30 min) in the works of Grbic et al. (2011) [51], Hong et al. (1998) [63], Demirtürk e Öner (2005) [64], Mahjabeen et al. (2011) [65], and for one of the tablets tested by Hermann et al. (2005) [43], which corroborates with the results of solubility previously discussed (Table 1) that were also higher when these buffers were used [40–42,47–49,51]. On the other hand, Nazief et al. (2020) [66] reported the slow dissolution of gliclazide tablets in pH 7.4, probably due to the reduced volume of buffer used and the stirring speed during the experiments.

None of the studies showed a very fast release profile (85% in 15 min) [24,26,36,37]. No studies reporting the experimental conditions necessary to fill out the variables in Table 3 and which had used buffer dissolution media with pH 6.8 were found.

The regulatory agencies include the possibility to replace the RB/BE studies for SUPAC-IR, whose drugs are placed in BCS Class I [24,26,36,37] or BCS Class III [24,36,37], as long as they present fast release profile (85% in 30 min) or very fast (85% in 15 min) [24,26,36,37].

According to the studies compiled, besides inferring gliclazide as BCS Class II drug (low solubility and high permeability), none of the dissolution studies (Table 3) presented fast or very fast release profiles in all pH range demanded. Therefore, there is no indication of biowaiver for this drug using BCS as a tool.

Although some guidelines also preconize biowaiver based on the proportionality of dosage in the formulations [24,25], gliclazide in SUPAC-IR is only commercially available in one dosage (80 mg), which makes this alternative unviable. Thus, there is no indication to recommend the waiver of RB/BE studies for gliclazide in SUPAC-IR.

### *3.3. Extended-Release Solid Oral Dosage Forms Containing Gliclazide*

In Brazil, currently, there are commercial medicines containing gliclazide only in SUPAC-MR, in tablets of 30 mg or 60 mg, for the reference medicine [67] as well as generic [68] and similar [69], as described in Table 4.

**Table 4.** Extended release drugs containing gliclazide available in the Brazilian market.

| Drug | Concentration (mg) | Industry | Date of Registration | Commercial Name® |
|---|---|---|---|---|
| **Reference** (07/08/2020) * | 30 | Servier | 12/11/2012 | Diamicron MR |
| | 60 | | 21/1/2013 | |
| **Generic** (05/08/2019) * | 30 | Ranbaxy | 24/09/2012 | --- |
| | 30 | Torrent | 26/10/2015 | --- |
| | 30; 60 | Pharlab | 31/10/2016 | --- |
| | 30; 60 | EMS S/A | 23/04/2018 | --- |
| | 30; 60 | Germed | 02/07/2018 | --- |
| | 30; 60 | Legrand Pharma | 02/07/2018 | --- |
| | 30; 60 | Nova Química | 02/07/2018 | --- |
| **Similar** (06/02/2020) * | 30 | Torrent | 27/07/2015 | Azukon MR |
| | 30; 60 | Pharlab | 31/03/2016 | Dicazid MR |
| | 30 | Ranbaxy | 15/12/2014 | Tezara MR |
| | 30; 60 | Nova Química | 30/11/2018 | Beteglid |
| | 30; 60 | Germed | 30/11/2018 | Clazi XR |
| | 30; 60 | Legrand Pharma | 30/11/2018 | Dagli |

* Updates of the respective National Agency of Sanitary (ANVISA) lists of reference, generic and similar drugs.

### *3.4. Waiver of RB/BE Studies for Extended-Release Solid Oral Dosage Forms Containing Gliclazide*

For SUPAC-MR, it is possible to subsidize the discussion concerning the waiver of RB/BE studies on criteria different from those based on BCS. Biowaiver is possible for other dosages of medicines presented in SUPAC-MR which meet specific parameters, among them, the same pharmaceutical form, release mechanism, proportional formulations, and manufactured by the same manufacturer in the same manufacturing site. However, when there is limitation of the drug's solubility, RB/BE studies should be performed for the highest as well as for the lowest dosage [26].

Gliclazide behaves as a drug of pH-dependent solubility in the pH range of the buffers that simulate the pH of the GI tract [40,49,51], presenting minimal solubility in the pH range 3.0–4.2 [51]. Thus, RB/BE studies should be performed for the highest as well as for the lowest dosage. In Brazil, as there are only two dosages of gliclazide in SUPAC-MR (30 mg and 60 mg) available in the market, its waiver from RB/BE studies the lowest dosage becomes unviable according to Brazilian criteria [26].

It is worth to highlight that, although gliclazide presented limitation in its solubility, this does not impact in the absolute bioavailability of the drug from its SUPAC-MR, whose values vary from 97% to 101.2% [70,71].

According to the WHO [24] and FDA [72] recommendations, when two different dosages of the SUPAC-MR available in the market are proportionally similar and have the same mechanism of drug release, in vivo RB/BE studies may be conducted with the highest dosage. The lower dosages are eligible for biowaiver if they present dissolution profiles similar to those of the higher dosage, ($f_2 \geq 50$), in three different buffers between pH 1.2 and 7.5. Therefore, the dissolution profiles of gliclazide in SUPAC-MR found in the literature were compiled in Table 5.

**Table 5.** Experimental conditions for dissolution studies and percentage of dissolved glicazide from extended-release solid oral dosage form.

| Drug. | Medium/volume (mL) | Apparatus USP/stirring speed (rpm) | Temperature (°C) | Dissolved quantity (%)/time h | Reference |
|---|---|---|---|---|---|
| Azukon® MR30 mg | pH 4.5/1000 | I/50 | 37 | 54.2/24 | [47] |
| | pH 6.4/1000 | | | 63.9/24 | |
| | pH 6.8/1000 | | | 67.1/24 | |
| | pH 4.5/1000 | I/ 100 | 37 | 75.7/24 | |
| | pH 6.4/1000 | | | 104.8/24 | |
| | pH 6.8/1000 | | | 99.6/24 | |
| | pH 4.5/1000 | II/50 | 37 | 63.69/24 | |
| | pH 6.4/1000 | | | 71.60/24 | |
| | pH 6.8/1000 | | | 74.97/24 | |
| | pH 4.5/1000 | II/100 | 37 | 100.62/24 | |
| | pH 6.4/1000 | | | 101.34/24 | |
| | pH 6.8/1000 | | | 98.56/24 | |
| Azukon® MR30 mg | pH 6.8/1000 | II/100 | 37 | 73.8/24 | |
| Diamicron® MR 30 mg | | | 37 | 98.6/24 | |
| Azukon® MR30 mg | pH 4.5 por 1 h; pH 5.5 por 1 h; pH 6.0 por 1 h; pH 7.0 por 1 h; pH 6.4 por 1 h; pH 6.8 por 1 h; /250 ml pH 6.8/250 ml | III (Bio-Dis) 10 dpm, 420 mesh | 37 | 73.03/24 | |
| Diamicron® MR 30 mg | pH 7.4/900 | I/100 | 37 | 72.13/24 77/10 | [49] |

| | | | | | |
|---|---|---|---|---|---|
| Diamicron® MR 30 mg | pH 1.2/900<br>pH 6.8/900<br>pH 7.4/900 | II/100 | 37 | 80/4<br>80/8<br>80/8 | |
| Diamicron® MR 30 mg | pH 1.2 for 1 h; pH 4.5 for 2 h;<br>pH 5.8 for 1 h;<br>pH 6.8 for 5 h<br>pH 7.2 for 1 h; /250ml | III(Bio-Dis)/<br>30 dpm, 400 $\mu$m mesh | 37 | 95.45/10 | |
| Azukon® 30mg | pH 1.2 for 1 h; pH 4.5 for 2 h;<br>pH 5.8 for 1 h;<br>pH 6.8 for 5 h<br>pH 7.2 for 1 h; /250ml | | | | |
| Diaprel 30mg<br>Diaprel 80mg | pH 7.4/900 | II/100 | 37 | 59.64/6<br>67.35/8 | [43] |
| Diamicron®30mg<br>Nuzide 30mg<br>Azukon 30mg | pH 1.2/900 | I/100 | | 90/5.8<br>90/5.3<br>90/3.3 | |
| Diamicron®30mg<br>Nuzide 30mg<br>Azukon 30mg | pH 4.5/900<br>pH 7.4/900<br>distilled water/900 | | 37 | 90/26.8<br>90/12.4<br>90/15.6<br>90/12.8<br>90/13.0<br>90/11.0 | [41] |
| Diamicron®30mg<br>Nuzide 30mg<br>Azukon 30mg | | | | 90/10.2<br>90/10.7<br>90/11.7 | |
| Glizid® MR 60 | pH 1.2/---<br>pH 7.4/---<br>distilled water/--- | I/-- | | 90/9.1<br>90/7.7<br>90/16.9 | [73] |
| Gliclazide MR 30 mg | pH 4.5/900<br>pH 6.8/900<br>pH 7.4/900 | II/75 | 37 | 73/24<br>89/24<br>99/24 | [48] |

The evaluation of dissolution studies of gliclazide is really important, since they are capable of providing information about the bioavailability of the product, indicating similarity between the generic and the reference medicines; evaluating possible in vivo impacts when alterations are carried out in the formulations, production processes, sizes of lots, manufacturing sites and other alterations after registration; evaluating the consistency and reproducibility within a lot and between lots and, finally, exempt the other dosages from bioequivalence studies [52].

The highest percentage of dissolved drug along the time happened using the buffer pH 1.2 and apparatus I [41]. The SUPAC-MR were developed to modulate the drug liberation, thus prolonging the dissolution stage of the medicine. Therefore, they present as a benefit, a less frequent intake when compared to the conventional pharmaceutical forms, which in turn, increase the adherence of the patient to the treatment. Moreover, they reduce the chances of toxic or subtherapeutic levels, once they decrease the alterations in the drug concentration in the blood after its intake [74,75].

The apparatus USP III (alternating cylinders or BioDis) was designed specifically to evaluate the dissolution of the SUPAC-MR, since it is able to demonstrate higher hydrodynamic controls in comparison with the apparatuses USP I and II. This apparatus enables uncountable options in terms

of experimental conditions, facilitating the procedures aiming to change the composition of the media and pH and also the stirring speed, thus, being able to simulate the GI tract more effectively [76].

In both dissolution studies that used the apparatus USP III, pH was altered in function of time [47,49] and the dissolution profile presented divergent results, releasing 73.03% in 24 h [49] and 95.45% in 10 h [49]. One justification for this difference may be linked to the use of the medium with pH 7.4, only in the study of Bezerra et al. (2018) [49], which promotes higher solubility, and consequently, a better process of dissolution is expected. Another possibility is due to the difference in the speed of basket immersions, which was higher in the study of Bezerra et al. (2018) [49]. This may have generated higher dissolution of the medicine. Moreover, the pharmaceutical equivalence of Azukon™ MR and Diamicron™ MR was obtained in the studies of Bezerra et al. (2018) [49], (f1 = 6.26 and f2 = 65.74), showing its adequation for the in vitro dissolution essays of gliclazide in SUPAC-MR.

However, no studies that evaluated the comparative dissolution profile of gliclazide in its SUPAC-MR of 30 mg and 60 mg, in three different buffers between pH 1.2 and 7.5 were found. This makes impossible to evaluate the criteria for biowaiver for the lower dosage of gliclazide in its SUPAC-MR, preconized by WHO [24] and FDA [72]. Therefore, further works that approach the dissolution comparative study of SUPAC-MR containing gliclazide in both dosages are required, highlighting one opportunity to develop future research.

## 4. Conclusions

The development of biopharmaceutical studies to replace RB/BE studies should be encouraged, aiming at reducing the time and costs involved in the drug registration and development process. However, it should be put into practice with caution, in order to carefully evaluate the possibility of dispensing these studies [77]. This would be especially important for gliclazide, considering its therapeutic importance to DM2, due to the clinical benefits both in use in isolated therapy and in combination.

According to the scientific information collected in the literature, analyzed and compiled in this work, there is an indication of gliclazide as a Class II drug (high permeability and low solubility) according to the BCS. Since the regulatory agencies include the application of the classification according to the BCS as a possibility of replacement of RB/BE studies, for the SUPAC-IR containing drugs of Class I [24,26,36,37] or Class III [24,36,37], it would not be recommended the waiver of these studies for gliclazide in its SUPAC-IR.

For tablets in SUPAC-MR, the waiver of RB/BE studies is possible, for medicines of lower dosages, of the same pharmaceutical form, same release mechanism, proportional formulations and manufactured by the same manufacturer at the same manufacturing site. However, when there is limitation of the drug solubility, as in the case of gliclazide, RB/BE studies should be performed with the highest as well as with the lowest dosage [26]. Therefore, since there are only the dosages of 30 mg and 60 mg available in the Brazilian market, the development of RB/BE studies is inevitable. Additionally, comparative studies of dissolution profiles were not found in the literature for tablets of 30 mg and 60 mg, studies which would be necessary to subsidize the analysis of biowaiver for the lower dosage based on the FDA's and the WHO's criteria.

Based on what has been exposed, from the analysis of the studies described in the literature and compiled in this work, it can be concluded that the registration of new medicines containing gliclazide must undergo RB/BE studies, as there is not sufficient evidence for the recommendation of replacement and waiver from these studies for both SUPAC-IR and SUPAC-MR containing gliclazide. Furthermore, due to these gaps found after carrying out this narrative review, one can notice the necessity to develop future research on this matter. Thus, this work has contributed in the strengthening of the decision-making, based on timely scientific evidence, as well as the production and spread of the scientific knowledge regarding such important theme. However, on the other hand, if a new medicine is prepared with the good manufacturing practices and in compliance with all the criteria of the BE/BR studies, its effectiveness and safety will be ensured and, consequently, its important clinical applicability in DM2.

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