dx.doi.org/10.14227/DT320125PGC1

Biopharmaceutical and Quality Evaluation of Immediate-Release Metformin Hydrochloride Tablets in Brazil

Angelo Elias, Meri Junior[1*], Adrila David Meri[2], Mariana Alves Souza[1], André Oliveira Baldoni[1], Cristina Sanches[1], Ana Julia Pereira Santinho Gomes[1], and Whocely Victor de Castro[1]

[1]Federal University of São João del-Rei, Divinópolis – MG, Brazil.
[2]Santa Mônica Divinópolis Hospital Hapvida NotreDame Intermédica, Divinópolis – MG, Brazil.
*Corresponding author

e-mail: angeloemj@gmail.com

ABSTRACT

Introduction: Metformin hydrochloride (MET) is considered the first drug of choice for the treatment of type 2 diabetes mellitus. Adverse events (AEs) related to the use of MET are mainly gastrointestinal-related. The speed of drug release and its accumulation in the intestine may explain gastrointestinal AEs. This work aimed to compare the quality and differences in the speed of drug release from tablets containing immediate-release MET (850 mg) available in Brazil. **Methods**: Four products were analyzed (a reference and three generic medicines [G1, G2, and G3]) for drug content, unit dose uniformity, and dissolution. Dissolution behaviors were performed and compared using mathematical models. **Results**: All samples satisfied quality parameters for pharmacopoeial tests. Regarding the dissolution behavior, the reference and G3 exhibited fast dissolution, whereas G1 and G2 were classified as very fast. The Peppas-Sahlin model was considered the best fit for R, and the Quadratic model was the best fit for G1 and G3 (it was not possible to determine the dissolution kinetics for G2 due to its very fast dissolution rate)**. Conclusion**: Although all medicines demonstrated adequate quality, there was no similarity among the dissolution behaviors. This reinforces the need to implement more efficient pharmacovigilance policies by the National Health Surveillance Agency (Anvisa) in Brazil.

Keywords: Type 2 diabetes mellitus, diarrhea, nausea, biguanides, quality control

INTRODUCTION

The treatment of individuals in the initial stage of type 2 diabetes mellitus (DM2) involves a change in lifestyle, mainly related to eating habits and physical activity. When these changes are not sufficient for glycemic control, continuous medication should be started (*1*). Currently, treatment with oral medicines is the main therapeutic option available for patients with DM2. Although other treatment options are available, metformin hydrochloride (MET) is considered the first drug of choice (*2*).

With a molecular formula of $C_4H_{11}N_5 \cdot HCl$, MET is a dimethylbiguanide, derived from the reaction between dimethylamine hydrochloride and cyanoguanidine under heat (*3*). Its physical characteristics are a white or almost white crystalline powder. It appears as a substance easily soluble in water, slightly soluble in ethyl alcohol, and practically insoluble in ether, acetone, and chloroform (*4*). It also has pKa equal to 12.4, thus cationic hydrophilic species are prevalent at physiological pH (*5*).

In 1897, Dokoumetzidis and Macheras published the first study demonstrating the importance of dissolution in the biopharmaceutical classification of drugs, thus dissolution was incorporated into the Biopharmaceutical Classification System (BCS) in 1995, which allowed the classification of drugs according to intestinal solubility and permeability into four classes (*6–8*). According to the BCS, MET is classified as class III, as it has high solubility and low intestinal permeability, which confers variations

in the speed of absorption, which is the main limiting factor of its bioavailability (*7*, *9*, *10*).

Adverse events (AEs) related to the use of MET, although frequent, are not considered serious and are mainly gastrointestinal-related, such as nausea, diarrhea, vomiting, abdominal discomfort, and loss of appetite. Several hypotheses are addressed in relation to the gastrointestinal adverse effects, such as the speed of drug release and its accumulation in the intestine (*11*–*17*). One of the alternatives for reducing these effects is to decrease the dose or replace the immediate-release (IR) formulation with the extended-release (XR) formulation (*12*, *18*, *19*).

The polymer matrices used in XR formulations provide prolonged and continuous release of the drug, which leads to gradual absorption and prevents its accumulation in high concentrations throughout the gastrointestinal environment, since it is a drug with low intestinal permeability (*11*, *20*).

After oral administration, the absorption of a drug from the solid pharmaceutical form depends on the release, solubilization, and dissolution, in addition to permeability through the gastrointestinal tract. Thus, in vitro dissolution studies using biorelevant media can be effective in predicting the in vivo performance of the drug (*8*, *21*). Assessing dissolution behavior allows for checking the amount of dissolved drug as a function of time. It is as a fairly fast and low-cost test that also allows analysts to study the kinetic parameters of drug release. These parameters are essential to determine the speed and efficiency of the process, in addition to the time required for the release of specific percentages of the drug, making it possible to characterize and compare the in vitro dissolution behavior of different formulations (*8*, *22*).

This study aimed to investigate whether there are differences in the quality and speed of drug release for different formulations of 850-mg MET IR tablets, as this drug is available free of charge from the Public Health System (SUS) and Popular Pharmacy Program in Brazil.

METHODS

Materials

Four Brazilian immediate-release MET tablets (850 mg) were acquired in October 2021 from different laboratories and tested within the expiration dates. This study was conducted blind to the brand, with one being coded as reference and three as generic (G1, G2, and G3). Except for sample G2, all tablets were film-coated. Table 1 provides the available information from packages and leaflets of the tablets used in the study.

To carry out the quality tests and dissolution behaviors, anhydrous dibasic sodium phosphate and anhydrous monobasic potassium phosphate were purchased from Synth (Diadema, Brazil), and sodium hydroxide was obtained from Isofar (Duque de Caxias, Brazil). A standard solution was prepared from the United States Pharmacopeia (USP) MET reference standard (RS). The water used in the preparation of the solutions was obtained using a Spencer deionizer (165p – 43V, Santo André, Brazil). The preparation of phosphate buffer 0.05 mol/L (pH 6.86) was performed according to USP (*4*).

Equipment

The equipment used included an analytical balance (M214 A, Bel, Monza, Italy), magnetic stirrer (RT10, IKA, USA), digital pH meter (MPA 210, Tecnopon, Piracicaba, Brazil), dissolution tester (UDT-812GS, Logan, USA), and ultraviolet spectrophotometer (UV-Mini 1240, Shimadzu, Kioto, Japan).

Table 1. Information From Packages and Leaflets of Immediate-Release Metformin Tablets (850 mg)

Sample	Composition (% related to tablet weight)	Batch no.	Expiration date
Reference	Magnesium stearate, hypromellose, and povidone (4.7%)	BR132475	Jan 2023
G1	Magnesium stearate, povidone, starch, polyvinyl alcohol copolymer, macrogol, silicon dioxide, sodium starch glycolate, and macrogol (14.4%)	L21G42J	Jul 2023
G2*	Magnesium stearate, povidone, microcrystalline cellulose, silicon dioxide, ethyl alcohol, hydrogenated vegetable oil, talc, croscarmellose sodium, and reverse osmosis water (13.2%)	26487135	Mar 2023
G3	Magnesium stearate, hypromellose, povidone, microcrystalline cellulose, crospovidone, silicon dioxide, titanium dioxide, and macrogol (18.8%)	LBKP00765	Dec 2022

**No coating. G1: generic brand 1; G2: generic brand 2; G3: generic brand 3.*

Quality Evaluation

The tablets were analyzed for drug content, unit dose uniformity, and dissolution as described in the USP monograph (*4*).

For the determination of drug content, 20 tablets were weighed and pulverized. The amount of powder equivalent to 100 mg of MET was transferred to a 100-mL volumetric flask, then about 50 mL of deionized water was added and stirred for 15 minutes. The volume was completed with the same solvent and the solution was homogenized to obtain a concentration of 1.0 mg/mL. The sample was subsequently filtered and diluted with the same solvent to a concentration of 10 µg/mL. Readings were performed in the UV-Visible spectrophotometer at 233 nm using water for zero adjustment. The test was performed in triplicate. The amount of MET was determined using MET RS solution prepared under the same conditions (*4*).

To assess uniformity of the drug in the pharmaceutical units, the weight variation method was applied. The number of samples tested varied according to the pharmacopeial specification and the respective approval stages. Calculation of the acceptance value (AV) was performed according to equation: $AV = \left|M - \overline{X}\right| + ks$, where *M* is the reference value, $\bar{X}$ represents the mean value of the individual contents, *n* is the number of units tested, *k* is the acceptability constant (*k* = 2.4 for *n* = 10; *k* = 2.0 for *n* = 30), and *s* represents the standard deviation of the sample (*4*).

Dissolution Test and Dissolution Behaviors

In accordance with USP, Dissolution tests were conducted using a paddle apparatus with 1000 mL of phosphate buffer pH 6.86 as the dissolution medium, rotating at 75 rpm for 30 minutes (*n* = 6). A 5-mL aliquot was manually withdrawn from the dissolution medium and filtered (qualitative filter, diameter: 12.5 cm; basis weight: 80 g/m²; thickness: 205 µm; porosity: 14 µm). Subsequently, 1 mL of the filtrate was transferred to a 100-mL volumetric flask. The volume was completed with buffer pH 6.8 to reach a concentration of 10 µg/mL. Measurements were taken at 232 nm using phosphate buffer for zero adjustment. The amount of MET present in the medium was calculated, for which the tolerance is 80% of MET dissolved at the end of the test. The amount of MET was determined using MET RS solution prepared under the same conditions (*4*). The operational conditions (temperature and rotation speed) of the dissolution test were previously confirmed by researchers.

Dissolution behaviors were also conducted under the same conditions as described above in accordance with Brazilian National Health Surveillance Agency (Anvisa) (n = 12) (*23*). Aliquots were withdrawn at 5, 10, 15, 20, 25, and 30 minutes, with replacement using fresh dissolution medium. Each sample was diluted as described above, then measured at 233 nm, using phosphate buffer for zero adjustment. The concentrations at each time were determined based on the analytical curve for MET RS.

The analytical curve of MET RS was prepared in triplicate using the same solvent in concentrations of 1.0, 4.0, 7.0, 10.0, and 13.0 µg/mL to quantify MET by spectrophotometry.

Comparison of Dissolution Behaviors

The drug dissolution behaviors were plotted using a graph of the average percentage dissolved (n = 12) as a function of time. The values obtained were compared using the independent model method, applying a similarity factor (f_2), and dissolution efficiency (DE). The f_2 value was calculated as established by Anvisa (*23*). Dissolution behaviors with f_2 values > 50 were considered similar (*23*, *24*). DE was determined as proposed by Khan (*25*).

Additionally, the following dependent models were used to evaluate and compare dissolution kinetics: zero-order, first-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell, Hopfenberg, Baker–Lonsdale, Peppas–Sahlin, Quadratic, Weibull, Logistic, and Gompertz. The best model was chosen based on the adjusted coefficient of determination ($R^2_{adjusted}$), as well as the model selection criteria (MSC). The mean dissolution time (MDT) was also determined for each sample. All calculations were performed using the Microsoft Office Excel add-in, DDSolver (*26*).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism (version 8.0, GraphPad Software Inc., USA). The results were expressed as mean values and standard deviations. Analysis of one-way variance (ANOVA) was applied, followed by Tukey's post hoc test for multiple comparisons. To compare the mean results of two groups, the student's t-test was used. In all tests, the significance level adopted was 95% ($p < 0.05$).

RESULTS AND DISCUSSION

Dissolution tests for solid oral pharmaceutical dosage forms are applied to evaluate the quality of a batch, provide guidance in the development of new formulations, certify the maintenance of quality after modifications to the formulation or technological process, and in the assessment of pharmaceutical equivalence between products from different manufacturers (*27*). The biggest challenge in the development of generic medicines involving solid oral pharmaceutical dosage forms is adjusting the formulation to obtain pharmacokinetic parameters similar to those of the reference medicine (*28*, *29*). Differences in dissolution can significantly impact the results in the performance of the medicine in the patient (*30*).

The analytical curve shown in Figure 1 was used for the quantification of MET in dissolution studies. The observed linear correlation coefficient complies with the minimum acceptance criterion ($r \geq 0.990$) (*31*).

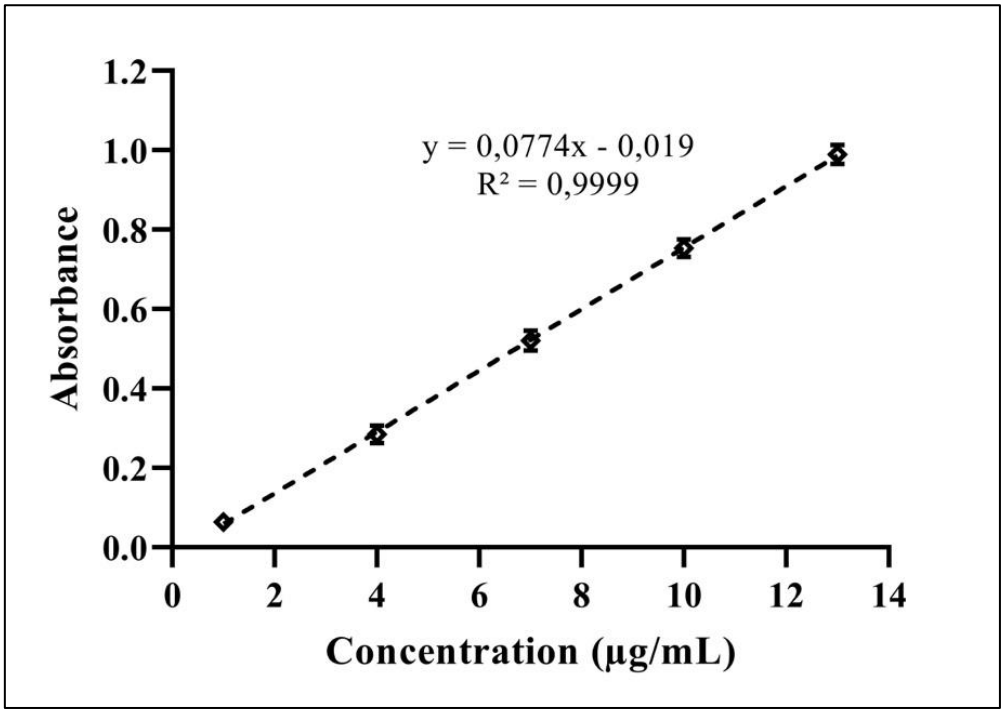

Figure 1. Analytical curve employed for Metformin quantification, using phosphate buffer as the solvent for dissolution. Data are expressed as mean ± SD, n = 9.

Results of the dose uniformity, dissolution, and assay evaluations are presented in Table 2. All samples showed satisfactory results according to criteria established by the USP (*4*).

Anvisa considers “very fast” dissolution to be when at least 85% of the active substance is released within 15 minutes, and “fast” dissolution is when 85% is released within 30 minutes (*23*). As shown in Figure 2, the reference and G3 showed fast dissolution, whereas G1 and G2 can be classified as very fast.

Table 2. Results of Unit Dose Uniformity Tests by Weight Variation Method, Dissolution, and Drug Assay in Immediate-Release Metformin Tablets (850 mg)

	Weight Variation	**Dissolution (%), *n* = 6**	**Assay (%), *n* = 3**
Specifications	≤ 15 for *n* = 10 ≤ 25 for *n* = 30	> 80%	95.0–105.0%
Reference	2.9	82–88	96.9 (1.6)
G1	4.6	103–110	95.5 (0.6)
G2	4.1	87–103	10.3 (2.9)
G3	1.7	86–96	100.1 (7.0)

**Data are expressed as mean (SD).*
G1: generic brand 1; G2: generic brand 2; G3: generic brand 3.

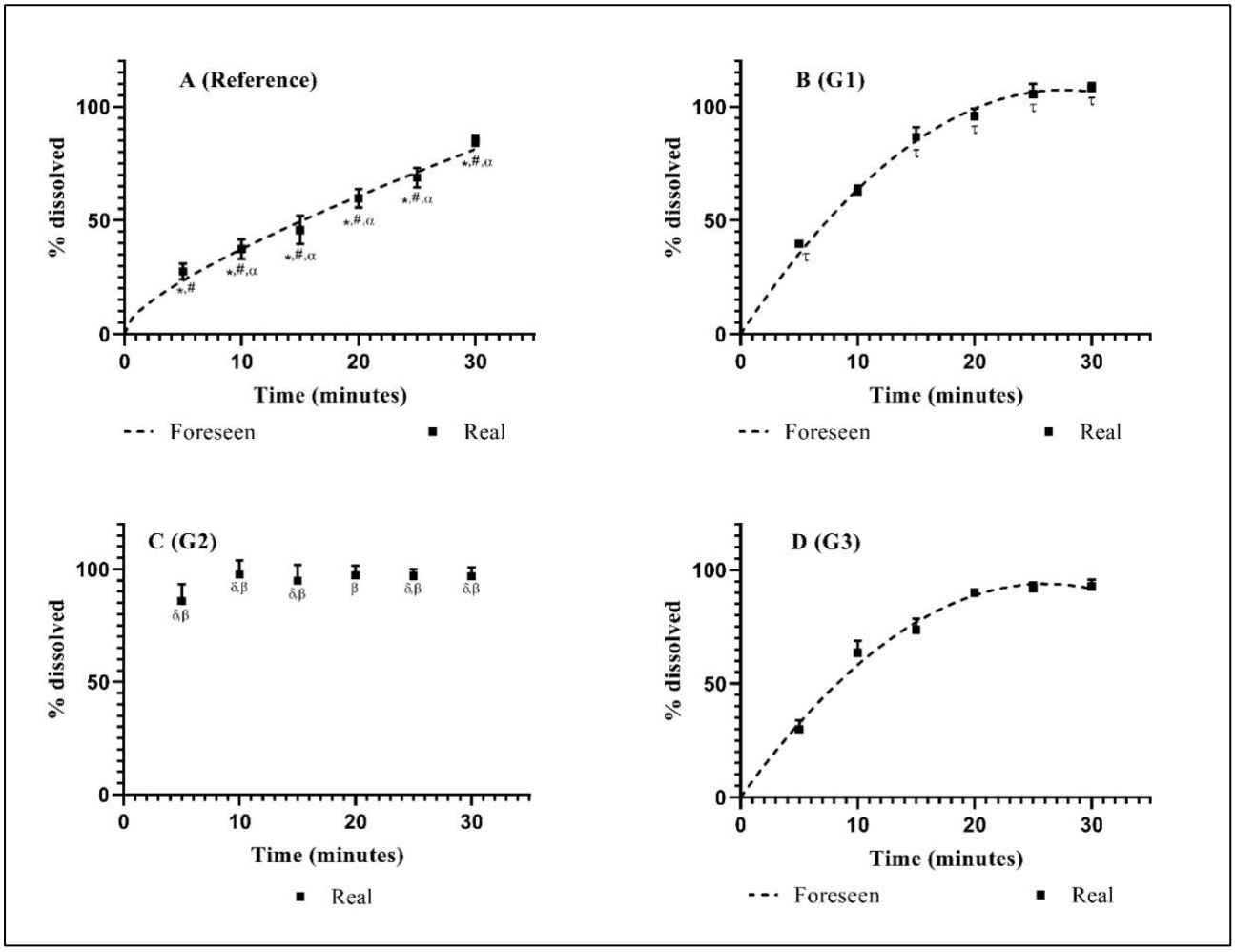

Figure 2. Dissolution behaviors of immediate-release metformin hydrochloride tablets (850 mg). Data are expressed as mean (± SD), n = 12. Dashed line represents values predicted (foreseen) by the Peppas-Sahlin (A: Reference) and Quadratic (B: G1; D: G3) models.
**Significant difference between Reference and G1 ($p < 0.05$).*
#Significant difference between Reference and G2 ($p < 0.05$).
αSignificant difference between Reference and G3 ($p < 0.05$).
τSignificant difference between G1 and G3 ($p < 0.05$).
δSignificant difference between G2 and G1 ($p < 0.05$).
βSignificant difference between G2 and G3 ($p < 0.05$).
G1: generic brand 1; G2: generic brand 2; G3: generic brand 3.

According to the data in Table 3, the dependent mathematical models that best describe the dissolution kinetics for 850-mg IR MET tablets were Peppas-Sahlin for the reference and Quadratic for G1 and G3.

It was not possible to determine the dissolution kinetics for G2 due to its very fast dissolution rate (Fig. 2C). This may be related to the presence of several disintegrating agents in the composition of G2, such as microcrystalline cellulose, silicon dioxide, and sodium croscarmellose; moreover, povidone is considered a dissolution enhancer (Table 1) (*32*). In addition, this tablet is not coated, a condition that increases its porosity. Other factors that may affect the dissolution rate of tablets include friability, compression force, hardness, polymorphisms, crystalline structure of drug, and isomers (*33*).

Table 3. Results of Kinetic Modeling of Dissolution Mechanisms for Immediate-Release Metformin Hydrochloride Tablets (850 mg)

	Reference		G1		G2		G3	
Model	**$R^2_{adjusted}$**	**MSC**	**$R^2_{adjusted}$**	**MSC**	**$R^2_{adjusted}$**	**MSC**	**$R^2_{adjusted}$**	**MSC**
Zero-order	0.8366	1.6422	0.5072	0.3823	–136.6402	–4.7645	0.3907	0.2300
First-order	0.8847	1.8947	0.8530	1.6352	–3.0821	–0.9363	0.9367	2.5031
Higuchi	0.8859	1.9217	0.9525	2.7491	–45.4219	–3.6235	0.8832	1.8679
Korsmeyer–Peppas	0.9193	2.2042	0.8348	1.5589	-	-	0.8128	1.2735
Hixson–Crowell	0.9025	2.0637	0.9448	2.6725	–126.5510	–3.1273	0.9294	2.4631
Hopfenberg	0.8870	1.8353	0.9422	2.4846	-	-	0.9232	2.2050
Baker–Lonsdale	0.3398	0.1824	–67.1117	-3.9720	-	-	0.8049	1.3407
Peppas–Sahlin	**0.9226**	**2.1949**	0.9175	2.0400	–1.9391	–0.7260	0.8144	1.2251
Quadratic	0.8860	1.8442	**0.9738**	**3.3017**	–40.9798	–3.6034	**0.9626**	**3.0657**
Weibull	0.7945	1.1466	0.8508	1.5533	-	-	0.9527	2.6972
Logistic	0.8318	1.3827	0.8432	1.4960	-	-	0.9597	2.9886
Gompertz	0.7620	1.0250	0.7932	1.1978	-	-	0.9407	2.6641

Data are expressed as mean values, n = 12.

Bold values correspond to the most significant mathematical models.

G1: generic brand 1; G2: generic brand 2; G3: generic brand 3; $R^2_{ajusted}$: adjusted determination coefficient; MSC: model selection criteria.

The coating on oral tablets is applied for functional or aesthetic reasons. Film-coating application can control drug release from its dosage form according to location, extent and speed (*34*). The selection process of the ideal polymer to be applied to the coating must consider solubility in different solvents to guarantee technological flexibility and mechanical resistance as well as solubility in gastrointestinal fluids to assure suitable bioavailability (*35*). Three of the four IR tablets evaluated in this study were film-coated: hypromellose for the reference and G3 and polyvinyl alcohol copolymer for G1. Although these coating agents do not have the function of modifying the release of the drug, their thickness may interfere in this process.

The Peppas-Sahlin model is related to a dissolution behavior involving a polymeric matrix. According to Table 1, excipients in the reference formulation represent almost 5% of the total composition of the tablet, with hypromellose and povidone being water-soluble polymers capable of forming a hydrophilic matrix barrier after contact with an aqueous medium, allowing for a rapid and constant drug release rate, as can be seen in Figure 2A (*36*, *37*). In the Quadratic model, represented by samples G1 and G3 (Fig. 2B and 2D), drug dissolution depends on time and particle contact surface (*26*). However, the dissolution of G1 was very fast, while G3 was fast. The percentage of excipients in these samples (G1 14.4%, G3 18.8%, Table 1) may be related to thickness of the coating, explaining the difference in dissolution rates. Additionally, it is noted that G1 and G3 contain three to four times more excipients compared to the reference medicine, explaining the distinction in the assigned mathematical models.

Low permeability of MET is a limiting factor, because permeability is directly related to drug absorption and bioavailability (*10*). The accumulation of MET in the intestine due to the saturation of its transporters (organic cation transporter [OCT1], plasma membrane monoamine transporter [PMAT], serotonin transporter [SERT], and choline transporter [CHT]), can be directly associated to the emergence of gastrointestinal-related AEs. The saturation of these transporters may also occur owing to interaction with other drugs or genetic polymorphism. Furthermore, MET can be transported via SERT, which could promote accumulation of serotonin in the intestine (*11*).

High oral doses of MET could also contribute to a reduction in the rate of absorption and consequently to the impairment of bioavailability (*38*). The average bioavailability of MET is known to be about 55% after 1.5 hours according to Jeong et al., who also reported incomplete absorption of IR MET formulations in men (*39*).

The antihyperglycemic activity of MET correlates with decreased glucose uptake in the intestine, increased glucose uptake by muscles, and reduction in hepatic glucose production (*5*). Due to accumulation of glucose in enterocytes, lactate is released, which causes changes in the intestinal microbiota (*11–13*). There are also reports about the toxic action of MET on certain species of bacteria, especially those that produce folic acid, such as those of the genera *Lactobacillus,* and *Bifidobacterium* (*40*). Considering the fast dissolution speed and high concentration of MET in the intestinal lumen, an additional imbalance in the intestinal microbiota may occur due to the accumulation of MET, which in turn presents low permeability. Consequently, potentially virulent strains can develop, causing colic, abdominal pain, and diarrhea, effects similar to those observed with the use of antimicrobials (*40*).

The dissolution behavior of the tablets analyzed in this study differed, with G1 and G2 showing

very fast drug release. The rapid release rate may contribute to the saturation of SERT and OCT1 and the consequent accumulation of both serotonin and lactate in the intestine, thus leading to the emergence of gastrointestinal AEs (*11–13*).

According to Moore and Flanner, the dissolution profiles of two formulations can be compared by an independent mathematical model called a similarity factor (f_2), which is used by several regulatory agencies as a tool to compare dissolution profiles of a generic drug candidate and a reference drug. As a form of evaluation, the tested medicine can be considered equivalent to the reference medicine if it presents an F_2 value greater than or equal to 50 (*23*, *24*). The results of f_2 are shown in Table 4. Data referring to DE and mean dissolution time (MDT) are shown in Table 5.

As shown in Table 4, no sample showed f_2 values greater than 50, meaning that the dissolution profiles are not considered similar. In parallel, MDT was significantly different between all samples (Table 5). There was also a significant difference of more than 10% between DE values, suggesting that the medicines are not interchangeable (*41*).

Table 4. Similarity Factor Analysis of Dissolution Profiles for Immediate-Release Metformin Hydrochloride Tablets (850 mg)

Samples	Similarity Factor (f_2)
Reference vs G1	25.65
Reference vs G2	17.65
Reference vs G3	32.58
G1 vs G2	30.45
G1 vs G3	47.88
G2 vs G3	27.29

G1: generic brand 1; G2: generic brand 2; G3: generic brand 3.

Table 5. Dissolution Efficiency (DE) and Mean Dissolution Time (MDT) for Immediate-Release Metformin Hydrochloride Tablets (850 mg)

Sample	DE (%)	MDT (min.)
Reference	47 (2.0)[a]	13.4 (0.02)[a]
G1	74.0 (2.0)[b]	9.4 (0.41)[b]
G2	87.0 (4.0)[c]	3.1 (0.73)[c]
G3	66.0 (2.0)	8.7 (0.89)

Data are expressed as mean (SD), n = 12.
[a]Significant differences were noted when the Reference was compared with G1, G2, and G3 ($p < 0.05$).
[b]Significant differences were noted when G1 was compared with G2 and G3 ($p < 0.05$).
[c]Significant differences were noted when G2 was compared with G3 ($p < 0.05$).
G1: generic brand 1; G2: generic brand 2; G3: generic brand 3.

In a study carried out in Jordan using MET, three out of five brands were not considered bioequivalent to the reference medicine (*42*). Moreover, Olusola et al. reported that four out of eight MET brands were considered interchangeable in vitro (*43*). These data corroborate our findings and reinforce the need for effective pharmacovigilance policies in Brazil; only four of the 14 brands available in the market were evaluated in the present study (*44*).

Non-adherence to treatment with MET can cause complications related to uncontrolled DM2, leading to harm to both patients and the public health system. To guarantee the quality of pharmacotherapy, it is necessary that quality deviations in medicines are avoided by being identified and eliminated during the production process.

CONCLUSION

All four samples demonstrated suitable quality; however, two samples showed fast dissolution (R and G3) and two were very fast (G1 and G2). There was no similarity between the dissolution profiles. Further studies are needed to assess the impact of dissolution speed on the perception of gastrointestinal-related side effects associated with the use of different formulations of IR MET (850 mg) as well as to investigate whether supplementation with folic acid can contribute to the reduction of gastrointestinal AEs. The results of this study show the importance of public health policies, which must be intensified together with increased health surveillance, to ensure the quality of medicines available to the Brazilian population.

DISCLOSURES

This study was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) (Finance Code 001). The authors have no conflicting interests.

REFERENCES

1. Bertoluci, M. C.; Forti, A. C.; Almeida-Pititto, B.; Vancea, D.; Valente, F.; Silva, J. C., Jr; Salles, J. E.; Sá, J. R.; Damaceno, L.; Zajdenverg, L.; Calliari, L. E. P.; Lauria, M.; Rodacki, M.; Montenegro Junior, R. M.; Lamounier, R. N.; Vencio, S. A. C.; Paz, S.; Ramos, S. *Brazilian Diabetes Society Guideline; Connecting People,* **2024.** DOI: 10.29327/5412848.
2. Elgawish, M. S.; Nasser, S.; Salama, I.; Abbas, A. M.; Mostafa, S. M. Liquid chromatography tandem mass spectrometry for the simultaneous determination of metformin and pioglitazone in rat plasma: Application to pharmacokinetic and drug-drug interaction studies. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2019**, *1124*, 47–57. DOI: 10.1016/j.jchromb.2019.05.036.
3. Bailey, C. J. Metformin: historical overview. *Diabetologia* **2017**, *60* (9), 1566–1576. DOI: 10.1007/s00125-017-4318-z.
4. *USP–NF.* United States Pharmacopeia, 2023**.**
5. da Trindade, M. T.; Kogawa, A. C.; Salgado, H. R. N. Metformin: a review of characteristics, properties, analytical methods and impact in the green chemistry. *Crit. Rev. Anal. Chem.* **2018**, *48* (1), 66–72. DOI: 10.1080/10408347.2017.1374165.
6. Noyes, A. A.; Whitney, W. R. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.* **1897**, *19* (12), 930–934. DOI: 10.1021/ja02086a003.
7. Amidon, G. L.; Lennernäs, H.; Shah, V. P.; Crison, J. R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* **1995**, *12* (3), 413–420. DOI: 10.1023/A:1016212804288.
8. Arrunátegui, L. B.; Silva-Barcellos, N. M.; Bellavinha, K. R.; Ev, L. S.; Souza, J. Biopharmaceutics classification system: importance and inclusion in biowaiver guidance. *Braz. J. Pharm. Sci.* **2015**, *51* (1), 143–154. DOI: 10.1590/S1984-82502015000100015.
9. Dahan, A.; Miller, J. M.; Amidon, G. L. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. *AAPS J.* **2009**, *11* (4), 740–746. DOI: 10.1208/s12248-009-9144-x.
10. Meri, A. E., Junior.; Meri, A. D.; Silva, M. G.; Castro, W. V.; Gomes, A. J. P. S. Quality assessment of metformin hydrochloride tablets commercially available in Brazil. *Japhac* **2020**, *7* (1), 117–127.
11. McCreight, L. J.; Bailey, C. J.; Pearson, E. R. Metformin and the gastrointestinal tract. *Diabetologia.* **2016**, *59* (3), 426–435. DOI: 10.1007/s00125-015-3844-9.
12. Bonnet, F.; Scheen, A. Understanding and overcoming metformin gastrointestinal intolerance. *Diabetes Obes. Metab.* **2017**, *19* (4), 473–481. DOI: 10.1111/dom.12854.
13. F Fatima, M.; Sadeeqa, S.; Rashid Nazir, S. U. Metformin and its gastrointestinal problems: a review. *Biomed. Res.* **2018**, *29* (11). DOI: 10.4066/biomedicalresearch.40-18-526.
14. Morita, Y.; Nogami, M.; Sakaguchi, K.; Okada, Y.; Hirota, Y.; Sugawara, K.; Tamori, Y.; Zeng, F.; Murakami, T.; Ogawa, W. Enhanced release of glucose into the intraluminal space of the intestine associated with metformin treatment as revealed by [^{18}F]Fluorodeoxyglucose PET-MRI. *Diabetes Care* **2020**, *43* (8), 1796–1802. DOI: 10.2337/dc20-0093.

15. Rittig, N.; Aagaard, N. K.; Sundelin, E.; Villadsen, G. E.; Sandahl, T. D.; Holst, J. J.; Hartmann, B.; Brøsen, K.; Grønbaek, H.; Jessen, N. Metformin Stimulates Intestinal Glycolysis and Lactate Release: A single-dose study of metformin in patients with intrahepatic portosystemic stent. *Clin. Pharmacol. Ther.* **2021**, *110* (5), 1329–1336. DOI: 10.1002/cpt.2382.
16. Zhou, S.; Zeng, S.; Shu, Y. Drug-drug interactions at organic cation transporter 1. *Front. Pharmacol.* **2021**, *12*, 628705. DOI: 10.3389/fphar.2021.628705.
17. I Ito, J.; Nogami, M.; Morita, Y.; Sakaguchi, K.; Komada, H.; Hirota, Y.; Sugawara, K.; Tamori, Y.; Zeng, F.; Murakami, T.; Ogawa, W. Dose-dependent accumulation of glucose in the intestinal wall and lumen induced by metformin as revealed by ^{18} F-labelled fluorodeoxyglucose positron emission tomography-MRI. *Diabetes Obes. Metab.* **2021**, *23* (3), 692–699. DOI: 10.1111/dom.14262.
18. Derosa, G.; D'Angelo, A.; Romano, D.; Maffioli, P. Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. *Drug Des. Devel. Ther.* **2017**, *11*, 1481–1488. DOI: 10.2147/DDDT.S131670.
19. Shurrab, N. T.; Arafa, E.-S. A. Metformin: a review of its therapeutic efficacy and adverse effects. *Obes. Med.* **2020**, *17*, 100186. DOI: 10.1016/j.obmed.2020.100186.
20. Davidson, J.; Howlett, H. New prolonged-release metformin improves gastrointestinal tolerability. *Br. J. Diabetes Vasc. Dis.* **2004**, *4* (4), 273–277. DOI: 10.1177/14746514040040041101.
21. Herds, R.; Pina, M. E.; Veiga, F. In vitro dissolution in predicting oral absorption of drugs in modified release pharmaceutical forms. *Rev. Bras. Cienc. Farm.* **2002**, *38* (4). DOI: 10.1590/S1516-9332202000400002.
22. Storpirtis, S.; Oliveira, P. G.; Rodrigues, D.; Maranho, D. Relevant biopharmacotechnical considerations in the manufacturing of generic drugs: factors affecting drug dissolution and absorption. *Braz. J. Pharm. Sci.* **1999**, *35* (1), 1–16.
23. Anvisa Resolução da Diretoria Colegiada - RDC no. 31: Provides for the Conduct of Pharmaceutical Equivalence and Comparative Dissolution Profile Studies. Brazilian Health Regulatory Agency (Anvisa), Aug 11, 2010.
24. Moore, J. W.; Flanner, H. H. Mathematical comparison of dissolution profiles. *Pharm. Technol.* **1996**, *20* (6), 64–74.
25. Khan, K. A. The concept of dissolution efficiency. *J. Pharm. Pharmacol.* **1975**, *27* (1), 48–49. DOI: 10.1111/j.2042-7158.1975.tb09378.x.
26. Zhang, Y.; Huo, M.; Zhou, J.; Zou, A.; Li, W.; Yao, C.; Xie, S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *AAPS J.* **2010**, *12* (3), 263–271. DOI: 10.1208/s12248-010-9185-1.
27. Rodrigues Neto, E. M.; Marques, L. A. R. V.; Ferreira, M. A. D.; Lobo, P. L. D.; Girão, F. J., Jr..; Camarão, G. C.; Moraes, M. E. A. Metformin: a literature review. *Health & Res.* **2015**, *8* (2), 355. DOI: 10.17765/1983-1870.2015v8n2p355-362.
28. de Oliveira, G. H. O.; do Nascimento, S. B.; de Oliveira, F. M.; Belo, V. S.; de Alencar Danda, L. J.; Soares-Sobrinho, J. L.; Fialho, S. L.; Bedor, D. C. G.; de Castro, W. V. Systematic evaluation of the impact of solid-state polymorphism on the bioavailability of thalidomide. *Eur. J. Pharm. Sci.* **2019**, *136*, 104937. DOI: 10.1016/j.ejps.2019.05.015.
29. Brossard, C.; Wouessidjewe, D. Contrôle de dissolution des formes pharmaceutiques orales solides à libération ralentie [Article in French]. *Stp Pharma* **1990**, *6* (10), 728–741.
30. Torres-Moreno, A. Y.; Luque-Ortega, F.; Torres-Moreno, A. J.; García-Medina, A. L.; García-Medina, S. Dissolution test of patent and generic drugs of metformin hydrochloride. *Dissolut. Technol.* **2024**, *31* (2), GC23–GC29. DOI: 10.14227/DT310224PGC23.
31. Anvisa Resolução da Diretoria Colegiada - RDC No. 166: Provides for the validation of analytical methods and provides other measures. Brazilian Health Regulatory Agency (Anvisa), July 24, 2017.
32. Rowe, R. C.; Sheskey, P. J.; Owen, S. C. *Handbook of Pharmaceutical Excipients*, 5th.; Pharmaceutical Press. 2017.
33. Conceição, A. P.; Sá, R. R.; da Silva, V. C.; Ferreira, M. S.; Cazedey, E. C. L.; Magalhães, H. I. F.; Santos Júnior, A. F. A Comparative Study of Propranolol Release by In Vitro Dissolution Profiles in Pharmaceutical Formulations. *Dissolut. Technol.* **2018**, *25* (4), 54–61. DOI: 10.14227/DT250418P54.
34. Seo, K.-S.; Bajracharya, R.; Lee, S. H.; Han, H.-K. Pharmaceutical Application of Tablet Film Coating. *Pharmaceutics* **2020**, *12* (9), 853. DOI: 10.3390/pharmaceutics12090853.
35. Porter, S. C. Chapter 27 - Coating of pharmaceutical dosage forms. In: *Remington, 23rd ed*; Elsevier. 2021;

pp. 551–564. DOI: 10.1016/B978-0-12-820007-0.00027-1.
36. Brady, J.; Dürig, T.; Lee, P. I.; Li, J.-X. Chapter 7 - Polymer properties and characterization. In: *Developing Solid Oral Dosage Forms, 2nd ed.*; Elsevier. 2017**;** pp. 181–223. DOI: 10.1016/B978-0-12-802447-8.00007-8.
37. Awasthi, R.; Manchanda, S.; Das, P.; Velu, V.; Malipeddi, H.; Pabreja, K.; Pinto, T. D. J. A.; Gupta, G.; Dua, K. Chapter 9 - Poly(vinylpyrrolidone). In: *Engineering of Biomaterials for Drug Delivery Systems*; Elsevier. 2018; pp. 255–272. DOI: 10.1016/B978-0-08-101750-0.00009-X.
38. Kinaan, M.; Ding, H.; Triggle, C. R. Metformin: An Old Drug for the Treatment of Diabetes but a New Drug for the Protection of the Endothelium. *Med. Princ. Pract.* **2015**, *24* (5), 401–415.DOI: 10.1159/000381643.
39. Jeong, Y.-S.; Jusko, W. J. Meta-assessment of metformin absorption and disposition pharmacokinetics in nine species. *Pharmaceuticals.* **2021**, *14* (6), 545. DOI: 10.3390/ph14060545.
40. Olgun, A. "Metformin-resistant" folic acid producing probiotics or folic acid against metformin's adverse effects like diarrhea. *Med. Hypotheses* **2017**, *106*, 33–34. DOI: 10.1016/j.mehy.2017.07.009.
41. Anderson, N. H.; Bauer, M.; Boussac, N.; Khan-Malek, R.; Munden, P.; Sardaro, M. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. *J. Pharm. Biomed. Anal.* **1998**, *17* (4-5), 811–822. DOI: 10.1016/S0731-7085(98)00011-9.
42. Hamdan, I. I.; Jaber, A. K. B. Pharmaceutical evaluation of metformin Hcl products available in the Jordanian Market. *Jordan J. Pharm. Sci.* **2010**, *3* (1), 1–7.
43. Olusola, A. M.; Adekoya, A. I.; Olanrewaju, O. J. Comparative evaluation of physicochemical properties of some commercially available brands of metformin Hcl tablets in Lagos, Nigeria. *J. Appl. Pharm. Sci.* **2012**, *2* (2), 41–44.
44. Electronic Data Sheet; Brazilian Health Regulatory Agency (Anvisa). consultas.anvisa.gov.br/#/bulario/ (accessed June 29, 2024).