ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 03, pp. 34587-34591, March, 2020

RESEARCH ARTICLE OPEN ACCESS

IN VITRO DISSOLUTION STUDIES AND PHARMACEUTICAL EQUIVALENCE ASSESSMENT OF METFORMIN HYDROCHLORIDE TABLETSCOMMERCIALLY AVAILABLE IN SALVADOR, BAHIA, BRAZIL

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ARTICLE INFO

Article History:
Received 08th December, 2019
Received in revised form
24th January, 2020
Accepted 04th February, 2020
Published online 31st March, 2020

Key Words:
Metformin Hydrocloride Tablets,
Dissolution Studies and
Pharmaceutical Equivalence.

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ABSTRACT

Metformin is a drug widely used in worldwide for type 2 diabetes mellitus treatment. The aim of this study was to compare the dissolution profiles of Metforminhydrocloride tablets (850 mg) available as the reference drug (R), generic (G) and similar (S) commercialized in Bahia, Brazil using a simple, fast and low cost ultraviolet spectrophotometric method. The tests were performed in compliance with the Brazilian Pharmacopoeia and United States Pharmacopeias. The proposed methodology for quantifying the drug was validated presenting precision, linearity and accuracy. All the products released metformin satisfactorily (>75% of the drug dissolved within 45 min). The product R, G and S showed dissolution efficiency of 83.85, 76.67 and 75.04%, respectively. From the calculation of similarity factor (*f2*), the formulations were considered pharmaceutical equivalents.

Citation: ***Gilmar Antôniode Carvalho Teles Júnior, Fernanda de Souza Dias, Matheus da Silva Ferreira et al.*** **2020.** "In vitro dissolution studies and pharmaceutical equivalence assessment of Metformin Hydrochloride tabletscommercially available in Salvador, Bahia, Brazil*", International Journal of Development Research*, 10, (03), 34587-34591.

INTRODUCTION

Metformin is an oral anti-hyperglycemic of the biguanide class recommended as the first selection oral therapy for the treatment of type 2 diabetes mellitus (DM2), unless the patient has any renal impairment or other contraindications. This drug reduces insulin resistance and blood glucose levels by inhibiting hepatic gluconeogenesis, increasing the sensitivity of peripheral tissues to insulin. Clinical studies show its use in polycystic ovary syndrome, type 1 diabetes mellitus, as well as in obesity, including in adolescents with insulin resistance (ShurrabandArafa, 2020; Khomitskaya *et al*., 2018; Wang *et al*., 2017). Used as a hydrochloride, metformin is available in three manufacturing categories, in Brazil: reference, generic, and similar drugs. "Similar" drug products contains the same active ingredient and concentration, pharmaceutical form, route of administration, posology, and therapeutic indication. It is equivalent to the medicine registered in the federal agency responsible for sanitary surveillance, and may differ only in characteristics related to the size and shape of the product, shelf-life, packaging, labeling, excipients, and vehicle. Similar drugs must always be identified by trade name or brand (Brasil, 2011). The aqueous solubility of metformin in the pH range of 1.2 to 6.8 is 300 mg/mL at 25 °C. However, 850 mg of metformin hydrochloride is dissolved more slowly in pH 1.2 and 4.5, than in pH 6.8 dissolution medium. It has two acid dissociation constants (pKa_1 = 2.8 and pKa2 = 11.5) and, depending on pH, three different species are produced - $Metf_1^{1+}$ e $Metf_2^{1+}$ and bioprotonated form $Metf^{2+}$ (Patiño-herrera *et al*., 2019). It is hypothesized that the additional protonation of metformin at acidic pH results in greater solvation and a larger hydrodynamic radius, leading to slower diffusion and dissolution. Belongs to class 3 of the biopharmaceutical classification system (BCS), with high water solubility and low permeability to cell membranes (Wang *et al*., 2017; Desai *et al*., 2014; Patiño-herrera *et al*., 2019). The main site of absorption of metformin is the proximal part of small intestine. It has absolute oral bioavailability (50 to 60%),

peak plasma concentration (approximately 3 h) and plasma elimination half-life (2.0 to 6.0 h). The biological half-life of metformin hydrochloride is 1.5 to 1.6 hours and, the drug is commonly administered in high doses (500 or 1000 mg), in 2 to 3 times a day, to obtain an effective treatment eficaz (Kimand Park, 2015; Oh *et al*., 2013). Oral route is the most commonly used for administration of solid pharmaceutical forms. Factors, such as particle size, excipients, compaction strength, dosage form, drug release profile, gastric emptying, gastrointestinal transit time, and drug absorption location can affect the drug release rate. Drug dissolution and release are critical aspects of quality, which can affect bioavailability and pharmacokinetics, which implies the efficacy and safety of drugs. Therefore, the dissolution test is used to guarantee the *in vitro* similarity of dissolution between two drugs, which is related to pharmaceutical equivalence and, consequently, to bioavailability and bioequivalence between products (Oh *et al*., 2013; Dumarey *et al*., 2015; Ariyasu *et al*., 2016; Pawar *et al*., 2016; Dias *et al*., 2020). Regulatory agenciesand several pharmacopoeias, such as Brazilian (BP, 2019) and United States (USP, 2018), recommend the use of UV spectrophotometry for the quantitative analysis of the drugs in dissolution test samples, ensuring that a specified amount of the active pharmaceutical ingrediente is dissolved at a predefined time. In the present study, were obtained *in vitro* dissolution profiles using a UV spectrophotometric method to evaluate the release of tablets containing 850 mg of metformin (reference, generic and similar drugs), commercially available in Salvador, Bahia, Brazil. Dissolution profiles were compared by similarity factors (f_2) and the area under a dissolution curve (AUC) to assess pharmaceutical equivalence.

MATERIAL AND METHODS

Material (chemicals/reagents and samples): All reagents were of analytical grade. Monobasic potassium phosphate (KH_2PO_4) and, dibasic potassium phosphate (K_2HPO_4) were obtained from Neon Comercial (São Paulo, SP, Brazil)and used as the dissolution medium for the dissolution tests.Doubly distilled water was obtained from a Q341 Quimis distiller (São Paulo, SP, Brazil) and used throughout the experiments. All laboratory material was washed in a 10% (v/v) HNO_3 solution bath for 24 h, washed with high purity water and dried at room temperature. Metformin referencestandard was obtained from National Institute for Quality Control in Health (INCQS), at Oswaldo Cruz Foundation (Fiocruz), indicated by the Brazilian Pharmacopeia.

Metformin tablets (reference, generic, and similar products) containing 850 mg were purchased from three drug stores in Salvador, Bahia, Brazil. The metformin tablets were subjected to weight variation, friability, disintegration, and dissolution tests in accordanceat Brazilian and United States Pharmacopoeias general methods applied to drugs. All tests were performed on products within the expiration date. The products (labeled to contain 850 mg of the drug) were designated as: R (reference product)and the following excipients: hypromellose, magnesium stearate and, povidone.; G (generic product) and the following excipients: hypromellose, magnesium stearate, povidone, polyethylene glycol, ethyl alcohol, crospovidone, croscarmellose sodium, microcrystalline celulose and, silicon dioxide; and, S (similar product) and the following excipients: hypromellose, magnesium stearate, povidone, polyethylene glycol, polysorbate 80 and, purified water.

Calibration standards: A reference stock solution of 1000 µg/mL was prepared with the reference chemical. Calibration standards with concentrations ranging from 50 to 1000 µg/mL were prepared daily from the standard solution by appropriate dilution, stored in decontaminated polyethylene bottles and analyzed in triplicate by UV spectrophotometry at λ = 233 nm.

Physical Tests (Weight Uniformity, Friability and Disintegration): For determination of weight uniformity, an analytical balance M164-AI (Mark, Piracicaba, SP, Brazil) was used.For each product (reference, generic and similar) containing 850-mg of metformin, 20 tablets were selected at random and weighed individually on the analytical balance.Then, the average weight, standard deviation and individual deviation of each tablet from the mean for the three products (reference, generic and similar) were determined.The Brazilian Pharmacopoeia (2019)and United States Pharmacopoeia (USP) establishes a maximum variation of ± 5.0%. No more than two units outside the specified limits can be tolerated in relation to the average weight. However, none can be above or below twice the indicated percentages. Friability was determined was determined on friabilometer HX 300-2 (Ethik, Vargem Grande Paulista, SP, Brazil). For the friability test, 10 metformin tablets (850 mg) were weighed and submitted to the friabilometer at a speed of 25 rpm for 4 minutes (100 cycles). After this period, the powders were removed and the tablets were weighed again. With the difference in weights, the percentage of loss was calculated and, compared with the value established in the Brazilian and USP pharmacopeias (≤1.5% of weight loss)(BF, 2019). Disintegrator 301/AC 01system (Nova Ética, Vargem Grande Paulista, SP, Brazil) and a multiple bath dissolver (n = 6) (Ethik, 299, Vargem Grande Paulista, SP, Brazil) were used for tests.In the disintegration test apparatus, six units of each sample (tablets) of each brand were used under the following conditions: distilled water as disintegration medium at 37 °C ± 1 °C and time of 30 minutes, in accordance at Brazilian Pharmacopoeia (2019) and United States Pharmacopoeia (USP).

Invitro Physicochemical Equivalence (Dissolution Studies): A PG 2000pH meter (Gehaka, , São Paulo, SP, Brazil) was used to determine the pH of dissolution medium and all spectrophotometric measurements were performed using a UV-Visible spectrophotometer (Shimadzu, 1240 model, Kyoto, Japan) equipped with a diode matrix detector (DAD), which was set at λ = 233nm and, the absorbances of sample solutions were read in 1-cm quartz cells, in triplicate. Dissolution tests were performed in the dissolver Model 299 (Ethik, Vargem Grande Paulista, SP, Brazil) with six replicates, in 900 mL of the dissolution medium, phosphate buffer (pH 6.8) at a temperature of 37 ± 0.5 ° C and rotation of 100 rpm with apparatus 1 (basket), as described in Brazilian pharmacopoeia. To obtain dissolution profiles, 10 mL sample aliquots were taken at predetermined time intervals (1, 3, 5, 10, 15, 20, 30, 45 and 60 min) and replaced with an equal volume of the dissolution medium for maintain a constant total volume. The collected aliquots were filtered (0.44 µm membrane filters) and transferred to amber flasks for later reading by UV spectrophotometry at λ = 233 nm. The absorbances were converted into concentrations obtained from the equation on the standard curve. The calculations were performed considering the amount of drug removed in each aliquot. The results were expressed as a percentage as a function of time. Dissolution profiles were compared to two methods: similarity

factor (f_2) and dissolution efficiency (ED), in accordance to RDC 31/2010, which provides for Pharmaceutical Equivalence Studies and Comparative Dissolution Profile. The comparison of dissolution profiles is useful in cases where it is desired to know the behavior of two drugs before submitting them to a study of relative bioavailability / bioequivalence. Comparative dissolution profiles are evaluated only using the calculation of the similarity factor (f_2), which corresponds to a measure of similarity between the dissolved percentages of both profiles (Brasil, 2010). The calculation of the similarity factor (f_2) was performed using the equation:

$$f_2 = 50 \text{ X } \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0,5} \text{ X } 100\right\}$$

n= number of data points, R_t and T_t = % dissolved, from each of the two formulations at a specific time point. The dissolution profiles are considered similar if$f_2$is ⩾50 (Al durdunji *et al*., 2016). From dissolution profiles, the dissolution efficiency (DE) was calculated by the percentage ratio of the area under the dissolution curve up to time *t* in relation to the area of the rectangle described by 100% dissolution at the same time (Simionato *et al*., 2018). The calculation of DE was performed using the equation:

$$\%DE = \frac{AUC_0^t}{Q_{100.t}} \text{ x } 100$$

DE values were analyzed using the Student's t test with a significance level of $p \leq 0.05$ and, DE of tested products were subjected to analysis of variance (ANOVA), using the Statistical Package for the Social Sciences (SPSS) software (version 22.0, IBM).

Analytical validation: The method for dissolution test was validated following the Brazilian Resolution 166/2017 (Brazil, 2017) and International Harmonization Conference - ICH (ICH, 2005). Selectivity, linearity, precision (repeatability and intermediate precision), accuracy, limit of detection (LOD) and quantification (LOQ) were determined. Possible interferences were assessed by testing the components of products (excipients) of the formulations and comparing them with a placebo. Linearity was obtained through the correlation coefficient, by linear regression analysis using the least squares method, of three analytical curves with seven different concentrations, ranging from 100 to 1000 µg/mL of metformin. Repeatability and intermediate precision were performed to assess the precision of method. The relative standard deviation (RSD) was used to calculate the quantification precision of three known concentrations of metformin (50, 400 and 900 µg/mL) on the same and alternate days. Accuracy was expressed as the agreement between the defined reference value and the measured value of each concentration, in triplicate, by the UV-VIS spectrophotometer.

RESULTS AND DISCUSSION

Analytical method validation: The method was validated to demonstrate selectivity, linearity, LOD, LOQ, precision and accuracy (Table 1).There was no interference from the matrix components (excipients).The standard calibration curve resulting from the working concentration range (50.0 to 1000.0 µg/mL) was obtained with a correlation coefficient (r) above (0.99).UV spectrophotometry method proposed in this study confirmed the ability of rapid analysis with good repeatability of this analytical technique for the determination of metformin in pharmaceutical products. [Table 1. Evaluation of analytical parameters for metformin determinations, in tablets.]

Table 1. Evaluation of analytical parameters for metformin determinations, in tablets

Analytical parameter	Results
Regression equation	y = 0.0963x – 0.0047
Linear range (µg/mL)	50 – 1000
Correlation coefficient (r)	0.9981
Limit of detection (LOD), in µg/mL	0.8
Limit of quantification (LOQ), in µg/mL	1.9
Precision* (%)	3.57 – 5.78
Accuracy* (%)	97.82 – 100.17

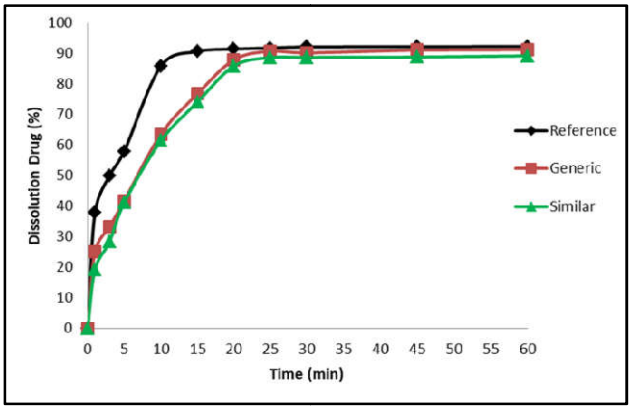

Figure1. Comparative dissolution profiles of metformin (850 mg) tablets of reference, generic, and similar products. (USP type 1 apparatus at 100 rpm with 900 mL phosphate buffer (pH 6.8) at 37.0 ± 0.5 °C for 1 h.)

Physical Tests (Weight Uniformity, Friability and Disintegration): The weight variation test is applicable to solid oral dosage forms (capsules, uncoated and film-coated tablets), and makes it possible to check whether the units in the same batch have uniform weight. The results showed that the R, G and S products had satisfactory average weight values (0.8925; 1.0053 and 0.9509 mg, respectively), according to the Brazilian and USP pharmacopoeias (variation of ± 5.0%). For generic drug, there was a greater variation in weight, which can be explained by the irregular diameter of the tablets. Friability is the tendency for a tablet to lose component particles due to abrasion, friction or mechanical shock. High friability leads to unacceptable loss of drug content during storage and handling. In addition to the potential loss of therapeutic effects due to underpower, the damaged appearance of the tablet also raises doubts about the quality of the tablet. The test applies only to uncoated tablets (Osei-yeboahand Sun, 2015;BF, 2019). R, G and S products showed friability within the limit established by the Brazilian pharmacopeia (BF, 2019), which indicates a loss of mass equal to or less than 1.5% of its weight. Disintegration is a physical phenomenon, where tablets break down into smaller particles after exposure to fluids, leading to an increase in the surface area of the dosage form.It is promoted by the presence of disintegrants in the formulation, allowing greater wettability and expansion of the tablet size.The pressure generated by the expansion of the size creates micro-cracks that propagate, favoring the entry of additional water and, finally, leading to complete rupture (Bisharat *et al*., 2019). All products tested met the Brazilianand USP pharmacopoeias requirements for tablets, i.e., disintegration time less than 30 minutes.

Reference, generic and similar products disintegrated in 8'13"; 9'35"and 9'26", respectively. The results of this study showed disintegration times longer than those found by Venkateswara Rao *et al*. (2017), in range of 4'58'' to 8'45'', in metformin hydrochloride tablets in Vijayawada, Índia.

Dissolution Test, Dissolution Profiles (DP) and Dissolution Efficiency (DE): Brazilian and USP pharmacopoeias recommends that at least 75% of the amount of metformin declared on the product label (850 mg) be dissolved in 45 minutes. In vitro dissolution studies are important for the development, characterization of pharmaceutical forms and prediction of the respective in vivo performance (Capková-helesicová *et al*., 2019). Multipoint analysis graphs (Figure 1) were plotted to assess the amount of the drug dissolved versus the time of the metformin tablets (reference, generic and similar). [Figure1. Comparative dissolution profiles of metformin (850 mg) tablets of reference, generic, and similar products. (USP type 1 apparatus at 100 rpm with 900 mL phosphate buffer (pH 6.8) at 37.0 ± 0.5 ^{o}C for 1 h.)]. Products R, G and S showed comparable levels of metformin (850mg), in 45 minutes, have dissolved and relesead the drug in accordance with the Brazilian and USPpharmacopoeias (>75% of drug within 45 min), with 92.3, 91.2 and 88.9%, respectively. Across dissolution profiles obtained was noted that the drugs (similar and generic) released metformin more slowly at the onset of process, when compared with the reference drug. It is suggested that this difference may be associated with the presence of polyethylene glycol in these products. In solid dosage formulations, polyethylene glycols, due to their higher molecular weight, can increase the effectiveness of tablet binders and give plasticity to the granules, which can prolong disintegration if present in concentrations above 5% w/w (Rowe *et al*., 2009). The results obtained for similar product, in this study, were contradictory with Sevenine and (2016), which compared dissolution profiles of drugs (reference and similar) containing metformin (850 mg), marketed in Brazil. The authors found amounts of 95.66% and 20.32% of metformin released, in 45 minutes, respectively, for the reference and similar products. These results indicate poor quality of similar tablets, in disagreement with the Brazilian and USPpharmacopoeias (Silva *et al*., 2016).On the other hand, the data were in agreement with Venkateswara Rao *et al*. (2017), in their studies conducted in India. These authors obtained release (> 70%) of metformin hydrochloride from all brands of tablets, within 45 minutes.

Dissolution profiles can be analyzed by mathematical methods, using the independent method using the parameters: AUC and f_2 (similarity factor).The application of these different methods to compare dissolution profiles can provide more accurate information on the dissolution behavior of products (Viana *et al*., 2015).The $f_2$calculation was performed for generic and similar products in relation to the reference drug, as they did not present a very fast dissolution (they did not reach more than 85% in the period of up to 15 minutes).Both products (similar and generic) showed similarity over 50 and, therefore, were considered pharmaceutical equivalents (Oliveira *et al*., 2014). Dissolution efficiency (DE%) is a parameter widely used to assess pharmaceutical equivalence between formulations. Through DE, it is allowed to evaluate not only the amount of drug released after a certain time, but the release kinetics throughout the period in question.This concept has the advantage of being theoretically related to in vivo data, since the extent of absorption of a drug in vivo is proportional to its dissolved concentration and the time it remains in contact with the absorption regions of the gastrointestinal tract (Oliveira *et al*., 2014).From dissolution profiles of each product, it was possible to calculate DE (83.85%, 76.67% and 75.04%, for R, G and S, respectively).

Conclusion

Metformin is a drug widely used in Brazil and worldwide for type 2 diabetes mellitus treatment.Products R, G and S showed comparable levels of metformin (850 mg), in 45 minutes, have dissolved and relesead the drug in accordance with the Brazilian and USP pharmacopoeias (>75% of drug within 45 min). From the calculation of the similarity factor (f2), the formulations were considered pharmaceutical equivalents.In the comparative studies of the dissolution profile, the reference drug released more than 87% drug reached in 15 min.Differences observed in the disintegration times and in the dissolution profiles for similar and generic products may have been influenced by the drug production process and the presence of excipients that delay dissolution in these specialties. For dissolution studies for metformin tabletsa rapid and sensitive UV spectrophotometric method was developed with good linearity, precision, and accuracy.

Acknowledgements

The authors are grateful for the financial support received from Bahia State Research Support Foundation (FAPESB) and Brazilian National Council for Scientific and Technological Development (CNPq). Research Group: "Biopharmaceutics and Drugs", State University of Bahia (UNEB).

Conflict Of Interest

The authors declare that there arenot conflicts of interest regarding this manuscript.

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