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Quality assessment of metformin hydrochloride tablets commercially available in Brazil

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Abstract: Metformin hydrochloride (MET) is considered the main oral hypoglycemic for the treatment of diabetes mellitus II. MET coated tablets are available in various dosage forms on the national market and are manufactured by different laboratories. The present study is justified by the need to carry out quality control of these pharmaceuticals which are commonly used by the population, and are easily acquired in drugstores. Pharmaceutical specialties were evaluated in the form of coated tablets of 500 mg and 850 mg doses, being two reference formulations (R1, R2) and six generic medicines (G1 – G6), amounting to eight samples. The tablets were analyzed by the tests listed in the monograph, Metformin Hydrochloride Tablets, of the Brazilian Pharmacopoeia (FB 5), including the determination of tablet weight, hardness, disintegration, content uniformity, dissolution, and assay. All 850 mg MET (4/4 = 100 %) were approved for all tests. However, 25 % disapproval was found among laboratories (1/4) that produced 500 mg MET tablets. It should be pointed out that standard deviations must be identified and eliminated throughout the production process in order to guarantee the total quality related to the benefit of the pharmacotherapeutic treatment. Therefore, effective health surveillance policies should be adopted to verify the quality of MET-containing tablets available in Brazil.
Keywords: tablets, metformin, quality control, diabetes mellitus, quality deviation.

Introduction

According to the International Diabetes Federation, the etiologic factors that characterize the pathology of diabetes mellitus include a heterogeneous group, through metabolic disorders that involve alterations and complications in the organism, the most common being hyperglycemia and vascular diseases [1].

Type 1 diabetes mellitus is responsible for 10 to 15 % of diabetes cases, and it is characterized by hyperglycemia, which can occur at any age, but with a higher prevalence of diagnosis in children and teenagers. It is a disease in which there is no production of a sufficient amount of insulin by the pancreas [2].

In agreement with the Ministry of Health, type 2 diabetes mellitus (DM2) is one of the most prevalent diseases in the world, due to the increase in its incidence and prevalence in different populations, being that the pathogenesis of both mechanisms is related to genetic and environmental factors, mainly as a consequence of obesity in children and adolescents, and also in adults with a long history of overweight, which result from defects in insulin secretion and action [3].

The Brazilian Diabetes Society describes that there are factors that contribute

to the increase in the prevalence of DM2, which include sedentary lifestyle and obesity, as well as aging and increased life expectancy [4].

The treatment of DM2 requires a change in dietary habits with the adoption of a restricted diet in sugars, carbohydrates and hypercaloric foods, as well as the practice of physical activity [5], which may be associated with the administration of hypoglycemic drugs such as biguanides and sulfonylureas [4, 6].

Metformin hydrochloride (MET) is a drug that belongs to the class of biguanides that is widely prescribed for the control of DM2 [7, 8]. The hypoglycemic effect of MET occurs through the action exerted on the hepatic and muscle tissues, in which they sensitize the effect of insulin, leading to the inhibition of gluconeogenesis and glycogenolysis, and also the stimulation of glycogenesis in the hepatocyte, and especially in the skeletal muscles, and causes an increase in glucose production, leading to a decrease of glycemia [9].

The absorption of MET occurs in the upper part of the small intestine, being slow and incomplete, leading to delayed absorption since approximately 30 % of the oral dosage is eliminated in the feces, though it does not suffer interference with food intake [10]. It presents bioavailability of 50 to 60 %, not being metabolized, having its circulation in the free form [11].

This drug does not undergo metabolism, being eliminated in an unchanged form by the kidneys, and may accumulate in patients with renal impairment, leading to an increased risk of lactic acidosis; the same may occur in the elderly, of whom have limited renal function [12, 13].

MET is a drug that presents high solubility and low intestinal permeability, and as a consequence is class III according to the biopharmaceutical classification system (BCS) proposed by Amidon et al. in 1995 [14, 15].

The BCS is an important tool in the development of new oral formulations, guiding the selection of adjuvant substances in order to ensure adequate bioavailability of the drug [16, 14].

According to Amidon et al., as cited by Postali, class III drugs have as the main limitation their absorption, leading to variation in rates and amplitude of absorption, but if in 15 minutes the absorption is greater than 85 %, this variation is due to changes in gastrintestinal flow, intestinal contents, and membrane permeability, rather than characteristics of the dosage form [17, 18].

After registration of generic medicine, the producing company must guarantee the quality of all produced lots. At the same time, it is the duty of the regulatory agency to adopt surveillance measures through sanitary surveillance actions that allow verification of the quality of the generic medicines marketed in the country [19].

Subsequent to the development and stability studies related to a formulation, it is necessary to guarantee its quality. In this sense, the objectives of quality control include quality assurance of increasingly effective and safe medications, with less toxicity and greater stability [20]. A fact that leads to clinical efficacy, as described by Dickinson; Lee; Stott and Peña et al., is the way in which the drug will behave in the body, as well as its clinical efficacy; it depends not only on the activities of the active substance, but also on excipients and manufacturing processes [21, 22].

For this the drugs must be submitted to the analytical methods of the physical, chemical and physicochemical character described by official pharmaceutical codes, such as the Brazilian Pharmacopoeia.

The national market of medicines offers a great diversity of products, with which several studies report problems with the quality of medicines, since they may interfere with their therapeutic efficacy, especially when it comes to the disintegration, hardness, friability and average weight tests [23].

To this end, this study was justified by the fact that it is necessary to evaluate the quality of MET tablets, in different dosage forms, manufactured by different

pharmaceutical laboratories, since these products are available to the population in drugstores in Brazil.

Material and methods

Pharmaceutical Specialties

Pharmaceutical specialties acquired in the period from September to November 2017, under the form of immediate release coated MET tablets of 500 mg and 850 mg doses: two reference medicines (R1, R2) and six generic medicines (G1 – G6), totaling eight samples were analyzed. The characteristics of each are presented in Table 1.

Reference chemical solution

In the preparation of the standard solution, FRAGON Metformin Hydrochloride (lot 15010491E) solution was used, of Indian origin, with a content of 100.10 % and expiry date of 09/2019.

Reagents

In the preparation of the phosphate buffer solution 0.05 mol/L, pH 6.86, reagents of analytical grade were used: sodium dibasic phosphate anhydrous and potassium phosphate monobasic anhydrous were purchased from Synth (Diadema, Brazil); sodium hydroxide was obtained from Isofar (Duque de Caxias, Brazil); and freshly distilled water was produced by a Distillation Machine, model BD1 DL (Biopar, Brazil).

Equipment

Ultrasonic digital cleaner, Sanders Medical, SoniClean 2PS model; Analytical balance, EVEN, model FA2204C; Digital Hardness Tester, Ethik Technology; Disintegrator, Ethik Technology, model 301; Magnetic stirrer, IKA Werke, RT10 power model; Dissolution Testing Machine, Ethik Technology, model 299/3; Distillation Machine, Biopar, model BD1 DL; Spectrophotometer, Nova Instruments, model 1600 UV; Laboratory glassware, automatic pipette Digipet (5.0 mL), and volumetric calibrated pipettes.

Quality assessment of 500 mg and 850 mg Metformin Hydrochloride Tablets

The drugs were analyzed for the tests in the monograph, Metformin Hydrochloride Tablets, from the Brazilian Pharmacopoeia, fifth edition, volume 2: determination of weight, hardness, disintegration, content uniformity, dissolution, and assay [24].

The number of samples tested varied according to the pharmacopoeial specification of each test and respective stages of approval [25]. Thus, units (n = 20) were used for the determination of weight as described for *Uncoated or film-coated tablets*, ten units were used in the hardness test (n = 10), and in the disintegration test six units were used (n = 6) using water maintained at 37 ± 1 ºC as the immersion liquid [25].

In relation to the unit dose uniformity by the content uniformity method applying the L_1 stage, ten units were initially employed (n = 10) and later in the L_2 stage, when applicable, another twenty units (n = 30); finally, the acceptance value (AV) was calculated according to equation [25]:

$$AV = \left|M - \overline{X}\right| + ks$$

Table 1. Characteristics of metformin hydrochloride (MET) tablets used in the study.

Sample	Dosage (mg)	Lot number	Expiration date
R1	500	BR 84381	Mar/2019
R2	850	BR82575	Nov/2018
G1	500	16050278	Apr/2018
G2	500	2647537	Jan/2019
G3	500	16K62K	Nov/2018
G4	850	17020672	Jan/2019
G5	850	26485088	Nov/2018
G6	850	17D02I	Apr/2019

Table 2. Composition of excipients present in the pharmaceutical specialties evaluated in this work.

Sample	Composition
R1	Magnesium stearate, hypromellose, povidone.
R2	Magnesium stearate, hypromellose, povidone.
G1	Microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, povidone, hypromellose, titanium dioxide, macrogol.
G2	Microcrystalline cellulose, silicon dioxide, magnesium stearate, ethyl alcohol, povidone, hydrogenated vegetable oil, talc, reverse osmosis water.
G3	Starch, polyvinyl alcohol copolymer and macrogol, silicon dioxide, povidone, magnesium stearate, sodium starch glycolate, macrogol.
G4	Microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, povidone, hypromellose, titanium dioxide, macrogol.
G5	Microcrystalline cellulose, silicon dioxide, magnesium stearate, ethyl alcohol, povidone, hydrogenated vegetable oil, talc, reverse osmosis water.
G6	Starch, polyvinyl alcohol copolymer and macrogol, silicon dioxide, povidone, magnesium stearate, sodium starch glycolate e macrogol.

Where M is the reference value, $\bar{X}$ is the mean of the individual contents, n is the number of units tested, k is the acceptability constant of 2.4 for n = 10 and 2.0 for n = 30 and s is the standard deviation of the sample [25].

Among the acceptance criteria for the dissolution test of immediate release pharmaceutical forms, three stages are described. In order to achieve the first (E_1), six units (n = 6) were used, each of which must present a result greater than or equal to Q (75 %) + 5 % tolerance allowed in relation to the declared quantity of MET dissolved in 45 minutes. If the tablets submitted to dissolution are not in accordance with the E_1 criteria, proceed to the second stage (E_2) where a further six units should be tested (n = 12). In this context, the mean of the 12 units ($E_1 + E_2$) must be equal to or greater than Q (75 %) and no unit should have a result lower than Q (75 %) – 15 %. In the case of stage E_2 criteria not being met, a further 12 units should be tested in the final stage, E_3, in which 24 units ($E_1 + E_2 + E_3$) must be equal to or greater than Q, with no more than 2 units being less than Q (75 %) – 15 % and no unit being less than Q (75 %) – 25 % [24, 25].

For the assay, twenty units were weighed and pulverized, subsequently transferring the amount of powder equivalent to 100 mg of MET (n = 1) to a volumetric flask by performing successive dilutions up to 0.001 % (w/v) concentration using water as the solvent. In parallel, a standard solution was prepared under the same conditions. The amount of MET, in mg, was determined from reading the solutions at 232 nm using water for zero adjustment [24].

Statistical study

Statistical data were obtained using GraphPadPrism® version 5.0 (GraphPad Software Inc., CA, USA). Results were expressed as the arithmetic mean of the values and standard deviation ($\bar{X}$ ± SD). One-way analysis of variance (ANOVA) and Tukey HSD post-test for multiple comparisons as appropriate. p-value was set at <0.05 as significant.

Results and Discussion

The weight determination aims to verify if the units of the same batch have weight uniformity, the results of which are shown in Tables 3 and 4.

According to the results described in Table 3, it can be observed that all the samples were approved, because in no case more than two units tested showed deviation greater than ± 5.0 % in relation to the average value found, fulfilling the specifications of FB 5 [25].

It can be observed that samples G2 and R2 presented deviations higher than ± 5.0 %, but they were approved since only one unit obtained a deviation higher than the established limits.

This agrees with the report of Olusola *et al.* which evaluated eight different brands of 500 mg MET tablets marketed in Nigeria, and they also obtained satisfactory results in the weight-determination test [26]. Oliveira *et al.* found similar values when compared to the MET weight test at the 850 mg dose, where three brands of the same drug were tested, obtaining mean weight values of 899.65 mg, 934.06 mg and 1008.69 mg, which were approved in the weight determination test [27].

Table 4 shows results for hardness, AV for content uniformity, dissolution rate, and assay of MET tablets containing 500 and 850 mg, respectively.

According to Mansour and Isbera, the hardness test aims to evaluate the resistance and continuous change of the tablets, being held mainly to demonstrate the efficacy of the tablets in supporting the conditions of transport, handling and packaging [28]. The hardness of a tablet is proportional to the compression force and it is inversely proportional to its porosity [29], consequently this parameter may influence the disintegration time of solid dosage forms.

Table 3. Values found from the determination of weight for coated tablets containing 500 mg and 850 mg of MET.

Sample	Weight (mg)	% Deviation
R1	529.1 ± 6.04	-2.15 to 2.10
G1	618.3 ± 4.47	-1.59 to 1.26
G2	633.2 ± 9.54	-1.88 to 5.29
G3	597.4 ± 6.25	-1.91 to 1.71
R2	898.2 ± 13.81	-1.33 to 6.10
G4	1034.9 ± 13.59	- 2.15 to 2.48
G5	981.0 ± 13.94	-4.62 to 1.61
G6	998.8 ± 12.82	-2.09 to 3.07

Table 4. Hardness, acceptance value (AV) for content uniformity, dissolution, amount and assay of tablets containing 500 mg and 850 mg of MET.

Sample	Hardness (KgF)	Content uniformity (AV)	Dissolution (%)	Amount (g) and Asssay (%)
R1	11.8 ± 0.60	14	83.1 – 110.2	503.5 (100.7)
G1	9.9 ± 2.21	14	83.9 – 108.9	492.5 (98.5)
G2	9.5 ± 2.08	13	87.1 – 109.1	525.0 (105.0)
G3	10.2 ± 1.98	11	84.3 – 104.6	471.5 (94.3)
R2	11.9 ± 0.65	14	83.7 – 94.4	838.9 (98.7)
G4	12.1 ± 1.78	9	80.7 – 88.3	861.9 (101.4)
G5	11.7 ± 1.13	9	63.2 – 94.3[(b)]	892.5 (105.0)
G6	12.1 ± 0.49	14[(a)]	80.1 – 86.9	855.9 (100.7)

(a) approved in the L_2 stage (30 units tested); (b) approved in the E_2 stage (12 units tested).

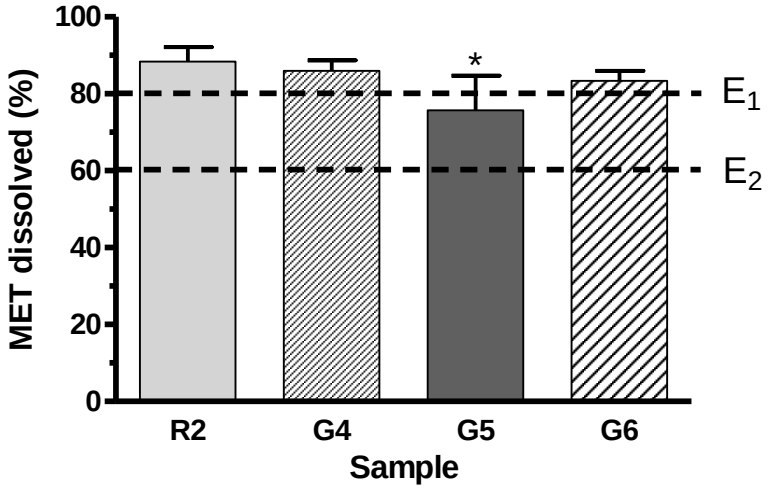

Figure 1 – Dissolution rate found for tablets containing 850 mg of MET, being the E_1 stage with n = 6, and E_2 with n = 12. *Significant difference in comparison with R2 ($p<0.01$) and G4 ($p<0.05$).

The eight samples tested showed good mechanical strength, in which the highest hardness was observed in G4, while the lowest was observed in G2, as shown in Table 4. The test result is informative since this parameter is defined by the planning and production control team [25].

The hardness of a tablet is directly related to its disintegration and dissolution, so if it presents high hardness, a high disintegration time and dissolution difficulty are expected.

The disintegration test was used for the eight samples of MET medicine, both at the 500 mg and at the 850 mg dose, where all samples showed the disintegration time in aqueous medium lower than 30 minutes, fulfilling the specifications of FB 5 [25].

As shown in Table 4, the highest hardness was observed in G4, so it was expected that its disintegration time was higher than the others, however the highest disintegration time was observed for the G5 sample (14 minutes).

According to Table 2, all the samples present in their composition adjuvants the wet granulation process, for example povidone which is a binding agent, so the performance of the samples in the disintegration test fulfilled the expected for film-coated tablets [25], where all samples disintegrated rapidly, a remarkable characteristic related to the immediate release of coated solid dosage form.

According to Afifi and Ahmadeen, the results achieved in their experiments, when undergoing the disintegration test using six different brands of the MET at a dosage of 500 mg, were satisfactory, leading to their approval, since all the tablets tested disintegrated in less than 30 minutes [30].

According to Mansour and Isbera, in determining the uniformity of dosage unit by the method of content uniformity in samples of MET 850 mg, they presented data within the specified standards, in accordance with the specifications for approval [28].

In agreement with values shown in Table 4, the AV calculation performed with ten tablets (L_1) in all brands showed an AV lower than 15, fulfilling the content uniformity test, and the same occurred with MET 850 mg (Table 4). However in relation to the G6 sample that was submitted to the test, using first the amount of ten tablets (L_1) to calculate the AV, a value higher than 15 was obtained, so another 20 tablets were tested and, for the calculation of the AV, the results of the 30 tablets (L_2) were considered, obtaining the result lower than 25, thus fulfilling the content uniformity test.

For the dissolution test, as in Table 4, all tested samples showed results that comply with the specifications, where the permitted tolerance level is not less than 75 % (Q + 5 %) of the declared quantity of MET dissolved in the time of 45 minutes. Thus, samples containing 500 mg of the drug were approved at stage E_1 according to acceptance criteria established for the dissolution test.

MET is a drug that presents high solubility and low permeability, being therefore class III, according to the Biopharmaceutical Classification System [14, 15]. Thus in agreement with Oyetunde *et al.* for drugs of this nature, if the time of dissolution is rapid, being the medicine of immediate release, it can behave as an oral solution, since the limitation refers to absorption and permeability [31].

The samples R2, G4 and G6 (Table 4) showed similar values of dissolving MET, achieving a tolerance level of 75 % (Q + 5 %), which were therefore approved in the E_1 stage for the dissolution test. However, considering the first six tablets tested of the G5 sample, the values found were lower than the acceptance criteria for stage E_1, consequently another six units were submitted to the test, according to stage E_2, and through the average of the 12 units 75.7 % of the MET dissolved was found.

It is known that the average of the 12 units should be equal to or greater than Q (75 %) and any unit should present a value lower than Q – 15 % (in this case, up to 60 %); the G5 sample therefore exhibited the results in

The slower release regarding the amount of active ingredients dissolved may be related to the crushing force due to excessive use of the granulating agent or other preparation factors, such as high- pressure compression [32].

According to the specifications of FB 5, the amount of the drug present in the tablets should not be less than 95 % and greater than 105 % of the labeled value [25]. For this, the samples were submitted to the assay, and the results are presented in Table 4.

With the exception of sample G3, the results for the other MET 500 mg tablets (Table 4) were satisfactory, with their values within the specification limits of between 95 % and 105 % of the labeled value. G3 achieved the result of 94.3 %, being lower than the established limits. Regarding the samples of MET 850 mg (Table 4), all were approved as they presented results within the specification limits.

It is important to point out that patients who use MET should regularly perform blood glucose tests to monitor glycemic levels, and also monitor the pharmacotherapeutic treatment in order to check the hypoglycemic effect, ensuring the success of the treatment.

Conclusion

In Brazil, fourteen (14) pharmaceutical laboratories concomitantly manufacture immediate release coated tablets containing MET in dosages of 500 and 850 mg [33]. In this work, it could be observed that all MET tablets of 850 mg (4/4 = 100 %) were approved

relation to stage E_2, as shown in Figure 1. It could be noted that in spite of this sample having been approved, it exhibited a dissolution rate significantly lower in comparison with R2 and G4.

in the physicochemical tests. However 25 % (1/4) disapproval was found for the dosage form of 500 mg MET. In order to guarantee the total quality related to the benefit of the pharmacotherapeutic treatment, it is indispensable to recognize all quality deviations, identifying and eliminating them throughout the production process. This result evidences the importance of effective public health policies, which should be intensified along with increased surveillance of health surveillance to verify the quality of MET tablets available in Brazil.

Conflict of Interest

The authors report that they do not have any conflicts of interest.

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Contribution of the Authors

A. E. Meri Jun and A. D. Meri purchased, performed most of the tests, produced the tables and figures, interpreted and discussed the results, and also wrote the text. M. G. Silva prepared disintegration and dissolution media and partially performed the dissolution tests. W. V. Castro was responsible for the co-orientation of this work and aided to write the manuscript. A. J. P. S. Gomes was responsible for the orientation of this work and improved the manuscript.

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