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Comparative Study of Metformin Hydrochloride Tablets in Argentina

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ABSTRACT

Metformin, a class III drug in the Biopharmaceutics Classification System, is an orally administered drug used to lower blood glucose concentrations in patients with non-insulin-dependent diabetes mellitus. Critical quality attributes were evaluated and compared for metformin immediate-release tablets (500 mg) obtained from pharmacies in Argentina to ascertain pharmaceutical equivalence and interchangeability. Label evaluation, hardness, friability, disintegration time, uniformity of dosage units, assay, and in vitro dissolution behavior were assessed in accordance with the Argentine Pharmacopeia requirements. Mathematical and statistical comparative models were used to characterize the dissolution profiles obtained under physiological conditions. All evaluated products fulfilled the pharmaceutical equivalence criteria. However, the requirements for a biowaiver application were not met because not all formulations, including the reference product, fulfilled the very rapidly dissolving criterion applicable to class III drug products.

Keywords: Biowaiver, dissolution profiles, immediate-release tablets, metformin hydrochloride, pharmaceutical equivalence

INTRODUCTION

Metformin (MET) is the first-line pharmacologic treatment for type 2 diabetes and the most prescribed drug for this condition worldwide, either alone or in combination with insulin or other blood glucose-lowering therapies. MET is a biguanide, a drug of herbal origin that has been widely used to treat diabetes since the 1950s (*1*, *2*). Seventy years of clinical experience and trial data have revealed almost no safety concerns for MET. The main exception is that it leads to a subclinical increase in lactic acid and appears to cause lactic acidosis in case of extreme overdose (*3*). MET is nowadays the most prescribed therapy worldwide for lowering blood glucose levels and is included in the World Health Organization's (WHO) list of essential medicines (*4*). Guidelines still recommend MET as the first-line treatment for most patients due to its safety, efficacy, and significant cost advantage over newer drugs (*5*).

MET, a hydrophilic cation at physiological pH, is a prototypical class III drug according to the Biopharmaceutics Classification System (BCS), having high aqueous solubility and low permeability to cell membranes (*6*–*9*). Both local and international guidelines allow biowaivers for rapidly dissolving immediate-release tablets of class III drugs. In this case, a waiver could be granted if both products (reference and test) exhibit very rapid dissolution behavior (i.e., ≥ 85% of the labeled amount dissolves in ≤ 15 min at three physiological pH levels) and all excipients of the multisource formulation are qualitatively the same and quantitatively similar to those of the innovator drug product (*10*–*14*).

In Argentina, MET tablets are available as both reference and multisource products (i.e., copies of innovator formulation). In this country, it is a widespread practice for patients to substitute the reference with various multisource products. Given the economic situation in Argentina, there is a

clear shift towards cheaper brands. It is important to note that multisource products must have proven pharmaceutical and therapeutic equivalence regardless of price. To establish that products containing the same active pharmaceutical ingredient (API) are pharmaceutically equivalent (i.e., the same dose, dosage form, and route of administration), it is necessary to verify that they all meet comparable critical quality standards (*10*, *11*, *15*, *16*).

The assessment of dissolution behavior in physiologically relevant media completes the critical evaluation of pharmaceutical equivalence. To ensure interchangeability, both in vivo and in vitro approaches could be used. Although non-insulin-dependent diabetes mellitus is prevalent in Argentina and MET is widely used, there are no reports on the bioavailability and bioequivalence of different brands of MET tablets in this country. Studies of quality control, similarity, and interchangeability of immediate-release MET tablets in other countries can be found in the literature (*17*–*27*). However, some of the prior studies do not consider the concept of very rapid dissolution or the influence of excipients to evaluate interchangeability, as required for class III drugs (*17*, *20*, *23*–*25*). In addition, some studies assessed similarity without performing in vitro dissolution at the three physiologically relevant pH levels (pH 1.2, 4.5, and 6.8) (*17*, *20*–*22*, *24*–*26*).

The objective of this study was to evaluate the critical quality attributes and pharmaceutical equivalence of commercial tablets of MET marketed in Argentina according to local and international pharmacopoeia guidelines and to assess the similarity in terms of in vitro dissolution under physiological conditions.

METHODS

Chemicals and Reagents

MET was acquired from Prest SA. (Abh Ilash Chemicals, India). Distilled water was used for assay and preparation of dissolution media. Analytical grade chemicals (Anedra, Argentina) were used for the same purpose, namely sodium hydroxide (NaOH), hydrochloric acid (HCl), glacial acetic acid, potassium chloride, sodium acetate trihydrate, and monobasic potassium phosphate.

Aqueous buffer solutions (pH 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate) were used as dissolution media of physiological significance and were prepared in compliance with the *United States Pharmacopeia* (USP) (*15*).

Commercial MET Tablet Brands

Fourteen different brands of immediate-release tablets containing MET hydrochloride (labeled amount 500 mg) were purchased in local pharmacies of the Argentine market. The tablet brands were randomly identified from A to N, with brand I being the reference product (of French origin). The other formulations were multisource products manufactured in Argentina, with exception of brand M (of German origin). The composition of the evaluated formulations is shown in Table 1. All tests were conducted within the expiry date of the products.

Equipment

An Acculab ALC-210.4M electronic analytical balance (Acculab, USA) was used to weigh the materials and tablets. Hardness, friability, and disintegration of the tablets were measured using a Scout DGM02, a Scout FGMO2, and a Scout EGMO2 (Scout Electronics, Argentina), respectively. In vitro dissolution studies were performed with an Erweka DT60 (Erweka GmbH, Germany), previously calibrated in terms of eccentricity, shaft straightness, alignment and centering of the paddle, paddle position, stirring rate, and vibration. A spectrophotometer (Cary 50 Conc, Varian Instruments, Australia) was used to quantify API in assay and dissolution studies.

Table 1. Qualitative Composition of Excipients of MET 500-mg Tablets

Excipient type	Excipient	A	B	C[b]	D[b]	E[b]	F[b]	G	H	I[c]	J	K[b]	L	M[b]	N
Diluents	Lactose	-	+	+	-	+	-	+	-	-	-	-	-	+	-
	Microcrystalline cellulose[a]	+	+	-	-	+	-	-	+	-	-	+	-	+	+
	Talc[a]	-	-	+	-	-	+	-	-	-	-	+	-	-	-
	Starch[a]	+	-	-	+	-	-	+	-	-	-	+	-	+	+
Disintegrants	Croscarmellose sodium		+	-	-	+	-	+	+	-	-	+	-	-	+
	Povidone	+	+	-	+	+	+	+	+	+	+	+	-	-	+
	Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Binder	Hydroxipropylmethyl-cellulose[a]	-	+	+	-	+	-	-	+	+	-	-	-	-	-
Glidant	Colloidal silicon dioxide	-	+	-	-	+	-	-	-	-	+	-	-	+	+
Lubricant	Magnesium stearate	+	+	+	+	+	+	+	+	+	+	+	-	+	+
Plasticizer	Polyethylene glycol	-	-	+	-	-	+	-	+	-	+	-	-	+	-
Sweetener	Sodium saccharin	-	-	-	-	-	-	+	+	-	-	-	-	-	+
	Titanium dioxide[a]	-	+	+	-	-	+	-	-	-	-	-	-	-	-
	Coloring agents	-	+	-	-	+	+	+	-	+	-	-	-	+	+
	Triacetin	-	+	-	-	-	-	-	-	-	-	-	-	-	-

[a]*This excipient has multiple functions.*
[b]*Label and/or leaflet inform qualitative and quantitative composition of excipients.*
[c]*Reference formalation.*
+ indicates presence; - indicates absence.

Equipment

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Manufacturer Label Information

The information on the labels (primary and secondary packaging) and leaflets was evaluated and compared to verify compliance with local legislation (*16*, *28*). The *Argentine Pharmacopeia* states that the correct storage conditions for MET immediate-release tablets are 'to be kept in well-sealed containers' and that this should be indicated on both the secondary packaging and leaflet (*16*). Well-sealed containers are defined as those that prevent the entry of foreign bodies and the loss of the contents under normal conditions of storage, distribution, and transportation (*16*).

Critical Quality Attributes

To analyze the weight variation, ten randomly selected tablets from each brand were weighed individually. Mean weight and standard deviation (SD) were calculated.

Friability, hardness, and disintegration tests were performed according to the Argentine Pharmacopeia (*16*). Ten tablets of each brand were weighed individually and placed in the friability tester. After 100 revolutions (rotation at 25 rpm for 4 min), the tablets were removed from the tester and weighed, and the result was compared with the initial weight. The hardness of 10 individual tablets of each brand was measured by the force in kilopounds (kp) required to break each tablet

across the diameter. The disintegration time of the tablets was measured at 37.0 ± 2.0 °C, in distilled water (n = 6 for each brand).

For the assay test, 20 tablets of each brand were randomly selected, weighed, and finely pulverized. A precisely weighed quantity of the powder, containing approximately 100 mg MET, was transferred to a 100-mL volumetric flask, dissolved with distilled water, and filtered using Whatman quantitative filter paper (ash-free, grade 40). Subsequently, 10 mL of the solution was diluted to 100 mL with distilled water and filtered. The MET concentration was determined by UV spectrophotometry at a wavelength of 232 nm using the standard calibration curve developed for this purpose ($y = 0.0767x + 0.0002$; r^2 = 0.9995; concentration range 1.0–12.0 µg/mL). The same methodology was applied individually to 10 tablets of each commercial brand to ensure uniformity of dosage units (*15*, *16*).

Dissolution tests were performed using a calibrated USP apparatus 1 at 100 rpm with 900 mL of deaerated pH 6.8 phosphate buffer at 37.0 ± 0.5 °C as the dissolution medium (*15*, *16*). Six replicates of each product were scored at Stage 1 (S1) of the dissolution acceptance criteria. Samples were collected at the time indicated in the corresponding monograph (i.e., 45 min), filtered through a nylon membrane with a pore size of 0.45 µm (Gamafil, Argentina) and appropriately diluted with the same medium. Drug concentration was determined by spectrophotometric analysis (233 nm) using a standard calibration curve ($y = 0.0799x - 0.0003$; r^2 = 0.9994, concentration range 2.0–10.0 µg/mL). The *Argentine Pharmacopeia* specifies that not less than 70% (Q) of the labeled amount of MET should be dissolved within 45 minutes (*16*).

Biopharmaceutical Performance

To evaluate the biopharmaceutical performance, dissolution profiles were performed under physiological conditions (i.e. buffer solutions with a pH of 1.2, 4.5 and 6.8), using the same experimental conditions as in the dissolution test for quality control (n = 12 for each brand) (*15*, *16*). Samples (10 mL) were withdrawn after 5, 10, 15, 20, 30, 45, and 60 minutes (with replacement of fresh medium) and then filtered, diluted, and measured by UV analysis. The concentration in each sample was calculated using standard calibration curves generated in each dissolution medium (r^2 = 0.9973–0.9994). The cumulative percentages of dissolved MET were calculated for the dissolution profile assessment, with each point of the profile corresponding to the mean dissolved percentage of the label claim associated with its respective SD.

Statistical Analysis

The dissolution profiles were characterized using the model-independent parameter dissolution efficiency (DE) (*29*). DE values were statistically analyzed using analysis of variance (ANOVA) followed by least significant difference (LSD) using InfoStat software.

RESULTS AND DISCUSSION

Manufacturer Label Information

Not all the evaluated products could be considered equivalent regarding the information provided on storage conditions (Table 2). Although none of the brands contained the requirement of ‘well-sealed’ packaging, several brands (B, C, D, E, I, K, and N) indicated storage in their original container. On the other hand, brand L had no information about storage conditions on either the secondary packaging or the patient leaflet, and brands F and K only had information on the patient leaflet. Most brands refer to storage temperature, generally with an upper limit of 30 °C (except for brand L), and only brands G and N refer to protection from light. It should be noted that the USP specifies storage at controlled room temperature.

Regarding the excipient information provided by the manufacturer, brand L did not include any information on the qualitative or quantitative composition of the tablet excipients (Table 1), which is a local regulatory requirement (*28*).

Table 2. Description of 500-mg MET Tablets and Information on Product Storage Conditions

Brand	Appearance	Storage Conditions
A	White, round, scored	B and L: Store at temperatures below 30 °C.
B	Yellow, round, scored	B and L: Store in a dry place at a temperature below 30 °C. Keep in original container until use.
C	White, round, scored	B and L: Storage: Ambient temperature between 15 and 30 °C. Should be kept in its original packaging.
D	White, round, scored	B and L: Store between 15 C and 30 ºC, in a dry place and in its original packaging.
E	Yellow, round	B and L: Store at room temperature no higher than 30 °C. Store in its original container.
F	Orange, oblong, scored	B: No indications. L: Keep in a dry place, at a temperature not exceeding 30 °C.
G	White, round, scored	B and L: Store in a cool place away from light.
H	White, round, double scored	B and L: Store at room temperature not exceeding 30 °C, in a dry place.
I (Ref)	White, round	B and L: Store at room temperature between 15 and 30 °C, in a dry place and in its original container.
J	White, round	B and L: Store in a dry place, between 15 and 30 °C.
K	White, round	B: No indications. L: Store in a cool, dry place in its original container.
L	White, round	B and L: No indications.
M	White, oblong, scored	B and L: Store at a temperature below 25 °C.
N	White, round	B and L: Store in its original container at a temperature below 30 °C, away from light.

B: secondary packaging; L: leaflet; Ref: reference formulation.

Critical Quality Attributes

The results of the evaluation of the quality characteristics are shown in Table 3. The average weight values of the different brands ranged from 521.5–731.0 mg. This wide range of results can be explained by the differences in the composition of excipients (Table 1), which are typical for each manufacturer, without altering the API content or dissolution performance. All brands showed acceptable results for hardness, with mean values between 11.0 and 34.2 kp, and friability, with mean weight loss less than 1% (*16*). All evaluated products passed the disintegration test, with results between 293 and 1185 seconds (4.8–19.8 mins, i.e., < 30 mins) for immediate-release tablets (*16*).

The assay results complied with the MET criterion described in the immediate-release tablet monograph, which states that the tablets should contain an amount equivalent to 95–105% of the stated amount (*16*). As shown in Table 3, the results ranged from 95.5% (brand E) to 104.0% (brand H). Statistically significant differences were found between all the evaluated products at the 95% confidence level ($p < 0.0001$). All brands met the specifications for uniformity of dosage units, i.e., API content should be 85.0–115.0% of the declared amount (evaluated individually) and relative standard deviation (RSD) should not exceed 6.0% (Table 3) (*16*). Additionally, all formulations easily met the specification for the S1 dissolution test (i.e., ≥ 70% of stated amount dissolved in 45 min) (Table 4).

Table 3. Evaluation of Critical Quality Attributes

Brand	Tablet weight (mg), mean ± SD	Hardness (Kp) , mean ± SD	Friability (%)	Maximum Disintegration Time (s)	Assay (%), mean ± SD[a]	Uniformity of dosage units (%), [range]/RSD
A	689.8 ± 6.5	14.7 ± 0.3	0.21	660	98.3 ± 1.6	[95.5–99.0] / 0.9
B	602.6 ± 8.4	16.7 ± 0.2	0.02	600	101.8 ± 0.0	[98.6–104.4] / 1.2
C	685.5 ± 6.5	32.8 ± 0.4	0.03	570	102.2 ± 0.3	[100.5–103.6] / 1.0
D	521.5 ± 2.5	17.5 ± 0.8	0.36	460	98.1 ± 0.0	[97.3–98.9] / 0.5
E	694.2 ± 7.9	20.1 ± 2.2	0.00	1185	95.5 ± 0.0	[93.7–97.4] / 1.2
F	533.2 ± 8.1	14.8 ± 0.2	0.03	660	102.4 ± 0.1	[99.8–104.3] / 1.4
G	719.0 ± 6.4	23.6 ± 2.3	0.02	478	101.2 ± 0.1	[100.2–102.8] / 0.9
H	541.1 ± 4.7	16.0 ± 2.0	0.57	450	104.0 ± 0.1	[102.8–105.4] / 0.9
I (Ref)	530.1 ± 6.6	15.8 ± 1.9	0.01	422	101.5 ± 0.0	[99.2–103.7] / 1.2
J	552.2 ± 5.4	17.5 ± 2.1	0.40	408	99.7 ± 0.0	[97.3–100.8] / 1.0
K	612.9 ± 6.7	11.0 ± 1.2	0.23	326	101.5 ± 0.1	[99.3–103.5] / 1.1
L	546.1 ± 10.7	13.2 ± 2.4	0.05	293	101.7 ± 0.0	[98.7–104.3] / 2.0
M	680.1 ± 5.8	34.2 ± 0.0	0.04	506	102.3 ± 0.1	[101.0–104.1] / 0.9
N	731.0 ± 5.6	14.1 ± 0.8	0.11	300	102.2 ± 0.0	[101.1–103.5] / 0.7

[a]*Percentage of labeled amount, as mean value ± standard deviation.*
Ref: reference formulation; RSD: relative standard deviation.

Table 4. In Vitro Dissolution Results

Brand	Dissolution Test, [range] / RSD	Dissolution efficiency (%), mean ± SD		
		pH 1.2	pH 4.5	pH 6.8
A	[91.5–97.9] / 3.6	61.3 ± 2.0	64.3 ± 0.5	66.6 ± 0.9
B	[98.9–100.3] / 0.7	59.7 ± 0.8	60.6 ± 2.4	72.0 ± 1.8
C	[97.6–102.3] / 2.4	67.8 ± 1.7	81.9 ± 1.1	84.5 ± 3.7
D	[97.1–100.7] / 1.8	81.3 ± 0.9	89.0 ± 0.9	89.6 ± 0.8
E	[96.3–99.3] / 1.5	62.5 ± 1.8	68.0 ± 0.6	69.2 ± 0.2
F	[101.4–104.5] / 1.7	79.3 ± 1.4	86.6 ± 1.1	90.2 ± 1.6
G	[102.7–103.0] / 0.1	77.6 ± 0.5	86.6 ± 0.8	90.9 ± 0.9
H	[104.8–105.8] / 0.6	78.7 ± 0.9	84.1 ± 0.7	94.7 ± 0.6
I (Ref)	[103.3–104.8] / 0.7	68.8 ± 0.7	75.9 ± 0.4	89.4 ± 0.6
J	[101.3–101.5] / 0.1	79.0 ± 1.4	80.2 ± 0.5	89.8 ± 0.9
K	[101.3–103.0] / 0.8	79.3 ± 1.6	90.0 ± 0.5	88.9 ± 0.7
L	[102.9–105.2] / 1.2	82.4 ± 1.0	94.3 ± 0.8	93.4 ± 1.3
M	[97.8–104.1] / 3.1	72.4 ± 0.5	85.6 ± 0.2	86.1 ± 1.6
N	[103.7–106.4] / 1.3	83.3 ± 1.4	96.1 ± 0.3	95.2 ± 1.2

Ref: reference formulation; RSD: relative standard deviation.

Biopharmaceutical Performance

Dissolution profiles obtained in physiologically relevant media are presented in Figures 1–3. Brands D, F, G, K, L, and N fulfilled the criterion for very rapid dissolution (≥ 85% dissolved in the first 15 min) at pH 1.2, 4.5, and 6.8. Reference formulation I, as well as brands H, J, and M, met this criterion only at pH 6.8. Brands H, J, and M fulfilled the criterion for rapid dissolution (i.e., ≥ 85% dissolved within 30 min) at pH 4.5 and 1.2; and the reference formulation only presented such behavior at pH 4.5. On the other hand, brands A, B, and E had slow dissolution compared to the rest of the brands. Brands A, B, C, and E could not be considered as very rapidly dissolving in any of the dissolution media. Brand C could be considered as rapidly dissolving at all three buffer solutions, and brand B was rapidly dissolving only at pH 6.8.

The DE results are presented in Table 4. Brands A and B had the lowest DE values, and brand N had the highest. DE values ranged from 66.6% (A) to 95.2% (N) at pH 6.8, 60.6% (B) to 96.1% (N) at pH 4.5, and 59.7% (B) to 83.3% (N) at pH 1.2 (Table 4). The statistical comparison of these results revealed significant differences ($p < 0.0001$).

Dissolution profiles with very rapid dissolution (brands D, F, G, K, L, and N) could be compared using the similarity factor, f_2; however, the reference formulation (brand I) did not meet the criteria for very rapid dissolution. Thus, the similarity factor could not be calculated using the reference product, and the requirements for biowaiver application were not fulfilled.

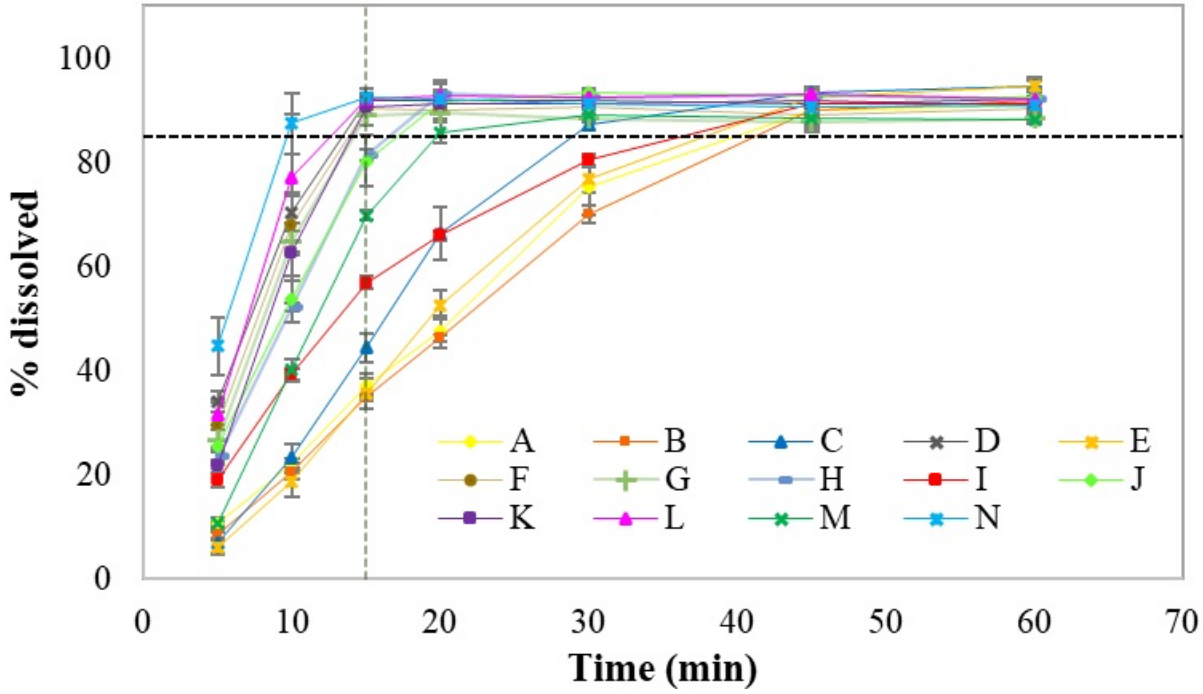

Figure 1. Dissolution profiles obtained in hydrochloric buffer solution pH 1.2. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving' limit (85% dissolved at 15 min).

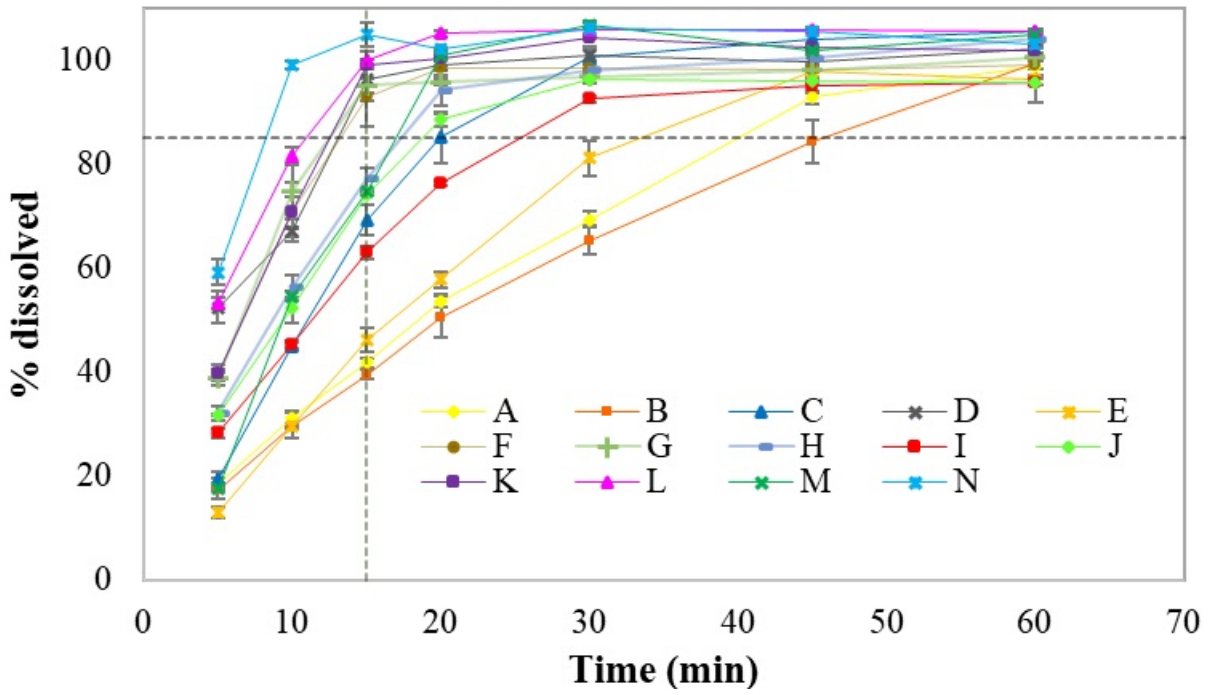

Figure 2. Dissolution profiles obtained in acetic buffer solution pH 4.5. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving' limit (85% dissolved at 15 min).

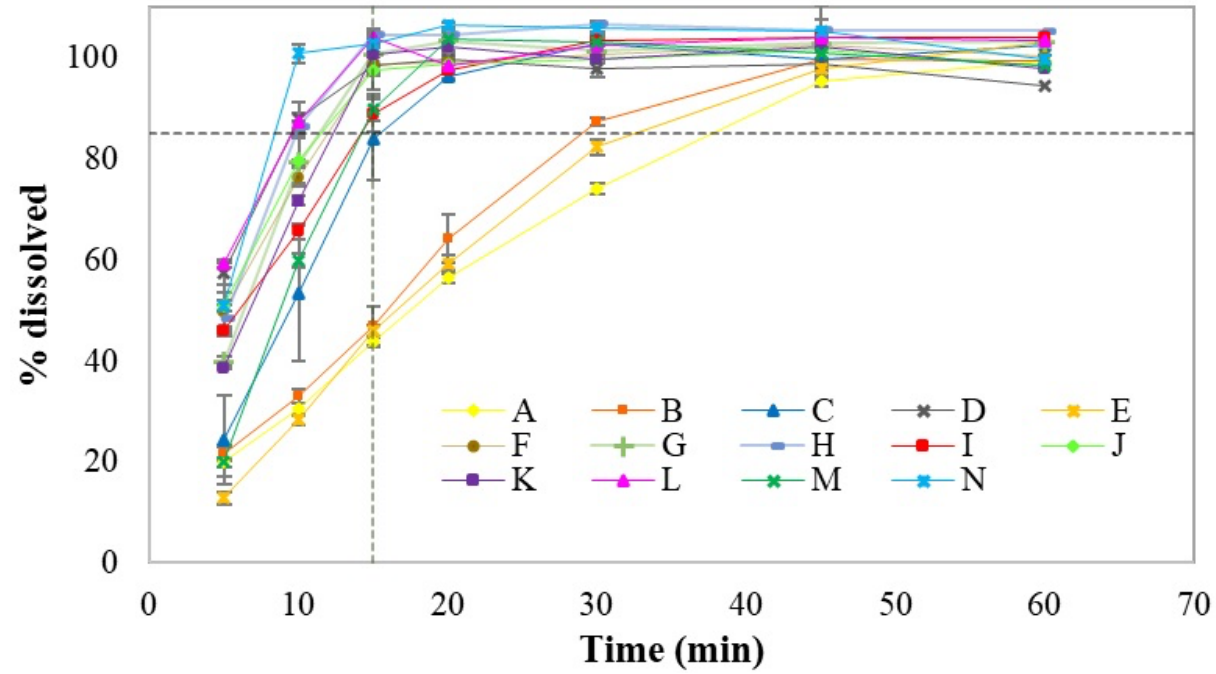

Figure 3. Dissolution profiles obtained in phosphate buffer solution pH 6.8. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving' limit (85% dissolved at 15 min).

CONCLUSION

All evaluated products met the *Argentine Pharmacopeia* specifications for critical quality attributes under the experimental conditions employed. The tested 500-mg MET tablets could be considered pharmaceutical equivalents; however, not all brands (including reference) fulfilled the criteria for very

rapid dissolution. Considering that patients may interchange multisource products for economic reasons, regardless of biopharmaceutical performance, caution is needed especially with brands A, B, and E (having slow dissolution compared to the other brands).

DISCLOSURES

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