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 Samples (10 mL) were withdrawn after 5, 10, 15, 20, 30, 45, and 60 minutes (with replacement of fresh medium) and then filtered, diluted, and measured by UV analysis.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.

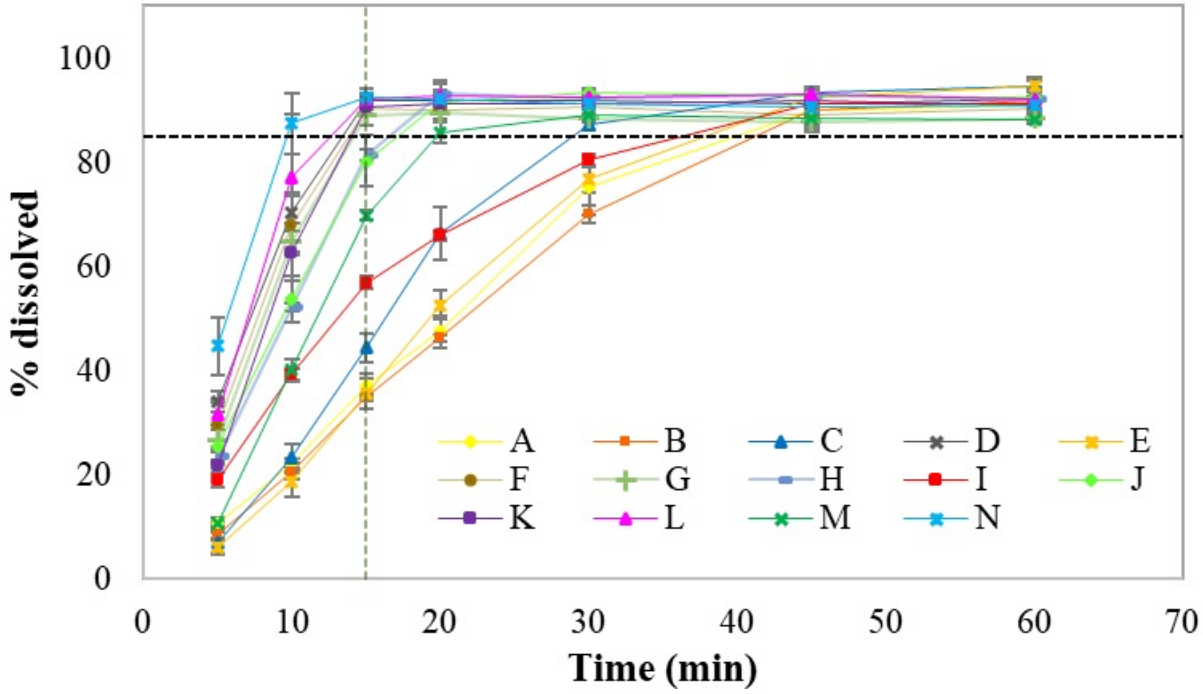

Figure 1. Dissolution profiles obtained in hydrochloric buffer solution pH 1.2. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving'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

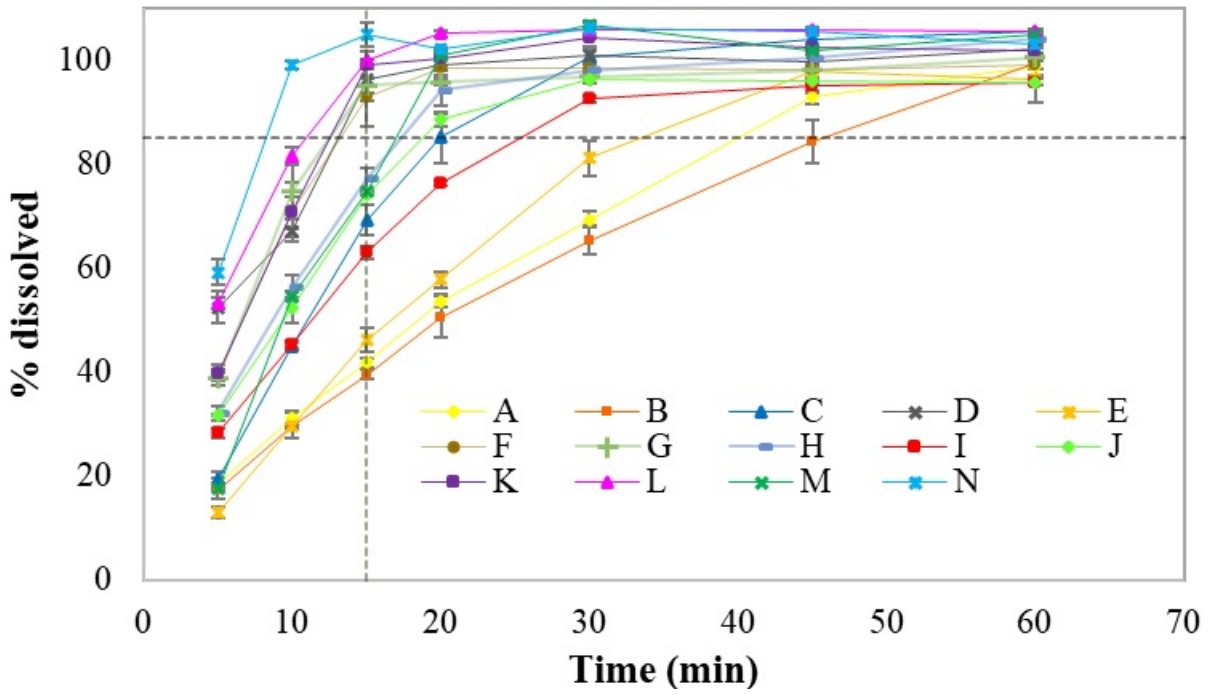

Figure 2. Dissolution profiles obtained in acetic buffer solution pH 4.5. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving' limit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

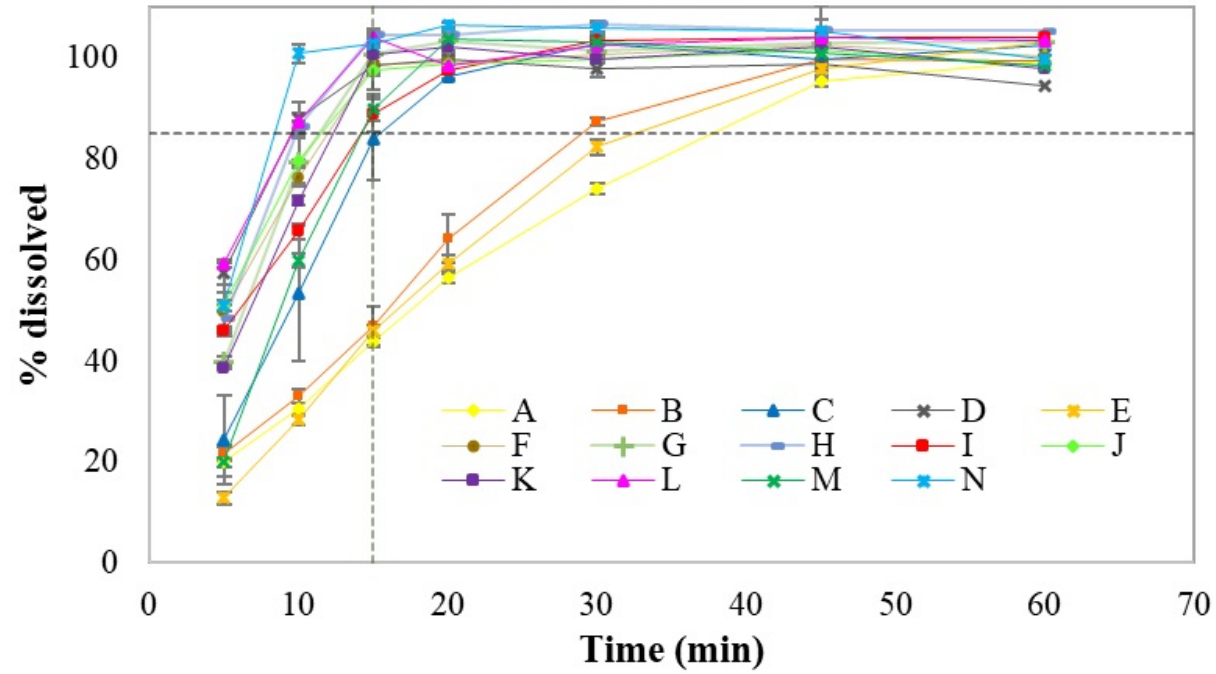

Figure 3. Dissolution profiles obtained in phosphate buffer solution pH 6.8. Each point of the profile represents the mean result for the percentage of Metformin labeled amount dissolved at each sampling time with corresponding error bars (SD). Dotted lines represent the 'very rapidly dissolving' limit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