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In Vitro Characterization of Multi-Source Omeprazole Capsule Dissolution Performance Under Biorelevant Conditions

Yessica Imbriago, Alejandra Schiavo, Andrés Baptista, Patricia Rega, Marianela Lorier, Pietro Fagiolino, Cecilia Maldonado, Marta Vázquez, and Manuel Ibarra*

Department of Pharmaceutical Sciences, Universidad de la República, Montevideo, Uruguay

e-mail: mibarra@fq.edu.uy

ABSTRACT

Regulatory requirements for drugs approval in several countries allow pharmaceutical companies to market drug products after providing evidence of compliance with pharmacopeial quality requirements and good manufacturing practices, a policy that reduces drug treatment cost and increases accessibility. On the other hand, these policies lead to pharmaceutical markets characterized by a large share of similar drug products that favor price-oriented competition, thereby discouraging pharmaceutical innovation and increasing product-related variability in therapeutic response, potentially compromising patient outcomes and healthcare costs. Omeprazole, a widely prescribed drug for gastric secretion disorder treatment, has been historically marketed in Uruguay without the requirement of bioequivalence. The performance of omeprazole formulations, particularly the enteric-coated microgranules, have a significant impact on oral bioavailability because omeprazole is highly labile under acidic conditions. In this work, we aimed to assess the biopharmaceutical characteristics of 11 multi-source omeprazole (20-mg) capsules using in vitro biorelevant dissolution testing. The study included evaluations of enteric-coating performance, pH-dependent omeprazole degradation kinetics, and in vitro dissolution testing to simulate single and multiple doses. The findings revealed important variations in the enteric-coating performance among the tested formulations, with some products showing considerable drug release at pH levels under which the drug is rapidly degraded (pH ≤ 4.0). Dissolution testing revealed suboptimal results for several drug products and high formulation-related variability in omeprazole release profiles, which could potentially affect in vivo performance. This study highlights the need for biorelevant assessment of pharmaceutical quality for multi-source drug products.

Keywords: Pharmaceutical quality, regulatory compliance, biorelevant, enteric coating, therapeutic failure

INTRODUCTION

In several countries of Latin America, Africa, and Asia, the pharmaceutical companies are allowed to market drug products after providing evidence of compliance with pharmacopeial quality requirements and good manufacturing practices (*1, 2*). This policy reduces the costs of medicines and increases accessibility but leads to a large presence of similar products that satisfy these requirements but lack evidence of biopharmaceutical quality (i.e., bioequivalence). The production and registration of similar products is linked to lower costs for the pharmaceutical industry, leading to an often-disproportionate number of multi-source products authorized for a given drug, which favors price-oriented competition rather than product-oriented competition, thereby discouraging pharmaceutical innovation (*3*). In the clinical setting, a higher variabilty in drug exposure might be observed due to formulation-related variability among multi-source drug products. This variability may have implications on therapeutic efficacy and costs.

Omeprazole (OMP), a substituted benzimidazole that selectively inhibits the proton pump in the gastric

*Corresponding author

mucosa, is frequently prescribed to treat gastric secretion disorders (*4, 5*). In Uruguay, pharmaceutical products containing OMP are not required to prove bioequivalence. In turn, the local market has 11 similar drug products for capsules containing 20 mg of OMP. Notably, as a direct consequence of pharmaceutical regulation, the OMP brand name drug, Losec (AstraZeneca, UK), has never been marketed in the country. Due to OMP lability under acidic conditions, the formulation design plays a determinant role in OMP bioavailability (*6, 7*). The capsules contain enteric-coated microgranules to prevent OMP dissolution in the stomach, which would significantly reduce the amount of drug available for absorption. The gastro-resistant performance of these products is assessed through the dissolution assay of the pharmacopeial monography, which specifies that no more than 10% of the drug can be dissolved in 2 hours at a pH of 1.2 (*8*). However, as a proton pump inhibitor (PPI), OMP can lead to an increased basal gastric pH, reaching values between 3 and 6 after 2-3 days of treatment (*9*). The bioavailability of OMP after multiple doses is therefore strongly affected by the enteric coating performance at pH levels where the formulations are not evaluated prior to marketing (*8, 9*). Comparative analysis of the in vitro performance of different formulations containing OMP have been previously reported, including a study that found significant variability between similar products marketed in Uruguay (*10–12*).

The aim of this work was to perform an in vitro characterization under biorelevant conditions to study the performance of all multi-source products containing OMP (20 mg) marketed in Uruguay, including assessment of formulation-related differences affecting OMP oral bioavailability.

METHODS

In vitro biorelevant dissolution and degradation testing was performed for 11 brands of gelatin capsules containing 20 mg OMP in enteric-coated microgranules, which were purchased in the Uruguay pharmaceutical market. The manufacturers of these products are Abbott Laboratories Uruguay S.A, Laboratorios Celsius S.A., EFA Laboratorios Antía Moll S.A., Gramón Bagó de Uruguay S.A., Laboratorio ION S.A, Lazar S.A., Novophar S.A., PHS Pharmaservice (Norepley S.A.), Roemmers S.A., Laboratorio Servimedic S.A., and Teva Uruguay S.A. The identification number for each product was defined randomly. All products were within their shelf life at the time of the study. A high purity secondary standard of OMP was used as reference material. All other chemicals and reagents used in the analysis were of analytical grade.

Omeprazole (OMP) Quantification

A validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection was implemented for OMP quantification in the different in vitro assays. This method was developed introducing minor changes to the *United States Pharmacopeia* (USP) method described in the OMP delayed-release capsule monograph (*8*). The mobile phase consisted of 50 mM phosphate buffer (pH 7.2) and acetonitrile in a 65:35 v/v ratio, and the flow rate was 1 mL/min. A Phenomenex Luna 100 A C18 column (15 cm x 4.6 mm, 5 µm) was used. The diode array detector (Dionex Ultimate 3000 Series, DAD-3000) was set at 302 nm. The analysis was carried out at 40 °C, and the injection volume was 20 µL. Under these conditions, the retention time of OMP was 5.2 minutes. The lower limit of quantification (LLOQ) was 0.35 µg/mL, and linearity was proven up to 28 µg/mL. System suitability for the analysis of OMP was verified according to *USP* (*8*).

pH-Dependent Performance Assessment of Enteric-Coated OMP Microgranules

A Sotax CE7 flow-through dissolution system (USP apparatus 4) connected to a Sotax CP-7 35 piston pump operated in open mode was used to evaluate the performance of each formulation's enteric coating with varying pH (*13*). The dissolution cell was prepared by positioning a 5-mm glass bead in the tip and filling the cone 1-mm glass beads. The capsules (n = 3) were individually placed on a tablet holder inside the cell. The bath was set at 37 ± 0.5 °C, and the flow rate was set at 8 mL/min. The dissolution medium was changed every 30 minutes to test the enteric coating performance at pH 3, 3.5, 4, 4.5, and 5 sequentially. Acidic media were prepared by adding different volumes of 0.01-M hydrochloric acid (HCl) to a 50-mM potassium chloride (KCl) solution. The total time of the

assay was 2.5 hours. Glass fiber filters (GF/F, 0.7-µm pore size) were used, and samples for OMP quantification were collected every 15 minutes. To minimize OMP degradation after sample withdraw due to acidic exposure, 200 µL of 0.25 M NaOH was added to 1 mL of (accurately measured) sample.

Degradation Kinetics

OMP degradation kinetics were determined at pH 4.0, 4.5, 5.0, 5.5, 6.0, and 6.8. Acidic media were prepared as mentioned above, and 0.1 M phosphate buffer (pH 6.8) was prepared with dibasic sodium phosphate, based on test 1 in USP monograph (*8*). A sufficient volume (≈ 5 mL) of methanol was added to approximately 20 mg (accurately weighted) of OMP standard for complete dissolution. The degradation test was carried out in a Distek 2100C paddle dissolution system (USP apparatus 2) at 100 rpm (*13*). The standard solution was poured into a vessel containing 500 mL of the corresponding pH medium at 37 °C. Three replicates were performed for each pH. The media pH was verified at the beginning and end of each assay. Samples (1 mL) samples were collected at 1 (initial), 5,15, 20, 25, 30, 45, and 60 minutes; 200 µL of 0.25 M NaOH was added to each sample. The resulting solution was filtered using a 0.45-µm membrane filter. The filtrate was injected into the HPLC system for the quantification of OMP.

Dissolution Testing Under Biorelevant Conditions

In vitro dissolution testing was performed in a qualified Distek 2100C basket dissolution system (USP apparatus 1) at 100 rpm with an automatic sampling system coupled to a UV/Vis spectrophotometer (Agilent 8453) (*13*). The assays were adapted from test 1 in the USP monograph, which consists of an acidic stage followed by a neutral stage (pH 6.8) conducted at 37 °C (*8*).

Two dissolution assays with differences in the acidic stage were carried out: a single dose scenario (SDS), simulating fasted conditions at pH 1.2; and a multiple dose scenario (MDS), simulating fasted conditions at pH 4.0 to reflect the drug effect on gastric pH. Medium volume was 500 mL in both scenarios. The media pH was verified at the beginning and end of the acidic stage of the MDS assay to evaluate pH variation. In both assays, the acidic stage had a duration of 60 minutes followed by a neutral stage at pH 6.8, which was achieved by adding 400 mL of 0.235 M phosphate buffer at pH 9.2 in the SDS assay and 400 mL of 0.233 M phosphate buffer at pH 6.7 in the MDS assay. Samples (2 mL) were taken at 10, 20, 30, 45, 60, 65, 70, 75, 90, 105, 120, and 150 minutes.

To compare the performance of the tested formulations, dissolution efficiencies (DE) were calculated for each product in the SDS assay (*14, 15*). To correct for OMP degradation at pH 6.8, an adjusted DE (DE_{corr}) was calculated using the following equation:

$$\mathrm{DEcorr} = \frac{\int_0^t y.dt}{\int_0^t D * e^{-kdeg*t}.dt}$$

where *y* stands for drug dissolved at time *t*, *D* is the nominal OMP dose, and *kdeg* the first-order degradation rate constant for OMP at pH 6.8. A ratio of mean DE_{corr} between each product and the product with the best performance (i.e., highest dissolution percentage) was calculated. In addition, the similarity factor f_2 was calculated for each product in the SDS, using the product with the best performance as reference. Finally, for quantitative assessment of the product performance under the MDS, a ratio of mean drug release (%) at the end of the MDS and SDS assay (MDS/SDS) was calculated for each product.

The impact of gastric residence time on OMP release and degradation under MDS was evaluated by shortening the acidic stage of the dissolution test described above (from 60 to 30 min). The products that differed the most in their dissolution performance between SDS and MDS assays were selected for this test, and six capsules of each product were evaluated. Samples (2 mL) were withdrawn at 35, 40, 45, 60, 75, 90, 120, and 150 minutes.

RESULTS

pH-Dependent Performance Assessment of Enteric-Coated OMP Microgranules

Figure 1 shows the OMP release profile at varying pH from the 11 products tested. Significant differences were observed in the performance of the enteric coating between the multi-source products. Only one formulation (product 3) was successful in avoiding OMP release over the entire pH range (3.0–5.0).

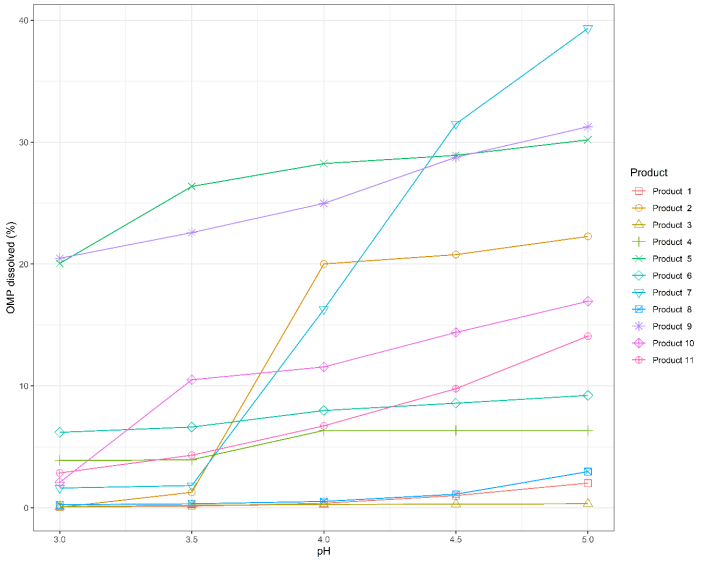

Figure 1. pH-dependent omeprazole release from enteric-coated (gastro-resistant) microgranules (pH 3.0–5.0).

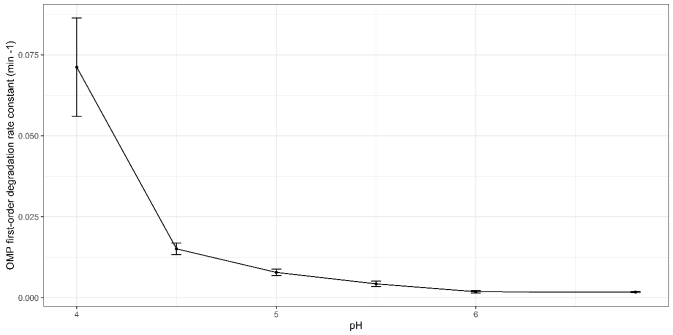

Figure 2. Mean degradation rate constants for omeprazole at different pH values (pH 4.0–6.8). Error bars are 95% CIs.

All other products exhibited some degree of drug release. Products 1 and 8 showed the lowest drug release while product 7 released 40% of the declared OMP dose at the upper limit of the pH range. Products 5 and 9 showed liberation of more than 20% of the declared OMP dose at pH 3.0. The enteric coating of products 4 and 6 was altered from the start of the assay, but no variation was observed with increasing pH, whereas other formulations showed a gradual increase in drug release with increasing pH.

Degradation Kinetics

First-order OMP degradation kinetics were verified at different pH values. Figure 2 depicts the pH-dependent degradation profile of OMP, with the degradation rate decreasing as pH increases. The magnitude decreased from 0.0712 min^{-1} at pH 4 (OMP in vitro half-life of 9.7 min) to 0.0018 min^{-1} at pH 6.8 (half-life of 385 min). Results shown in Figure 2

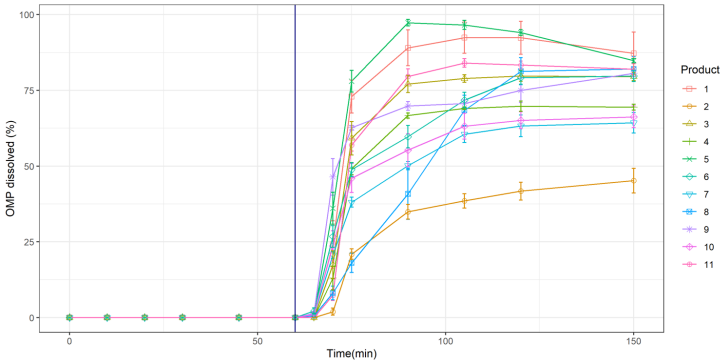

Figure 3. Dissolution profiles of 11 multi-source omeprazole products in the single dose scenario (SDS). Blue line indicates the end of the acidic stage by addition of neutralizing buffer at 60 min. Values are mean ± SE.

Table 1. Dissolution Efficiency (DE) and Similarity Factor (f_2) of Multi-Source Omeprazole Products

Product	f_2	Mean DE_{corr} (SE)	DE_{corr} Ratio*	95% CI
1	Ref	84.5 (3.1) (Ref)	-	-
2	13	35.7 (1.3)	0.42	0.40–0.44
3	45	72.9 (1.3)	0.86	0.83–0.90
4	29	54.2 (3.1)	0.64	0.60–0.68
5	64	88.2 (0.6)	1.04	1.01–1.08
6	34	67.8 (2.0)	0.80	0.77–0.84
7	25	57.3 (1.5)	0.68	0.65–0.71
8	26	59.8 (2.2)	0.71	0.67–0.74
9	37	70.9 (0.9)	0.84	0.81–0.87
10	26	58.5 (2.0)	0.69	0.66–0.73
11	52	74.9 (0.7)	0.89	0.85–0.92

**Relative to product 1 (highest dissolution performance).*
SE: standard error.

indicate that the OMP degradation rate might be significant up to a pH of 5.0, where the first-order degradation rate is 0.0079 min^{-1} (half-life of 87.7 min), a value that is well below the reported absorption rate constant for OMP (0.1 min^{-1}, half-life of 6.9 min) (*16*).

Dissolution Testing Under Biorelevant Conditions

Figure 3 shows the dissolution profiles of the 11 tested products under SDS. Table 1 shows the DE_{corr} and f_2 values calculated using product 1 as reference in SDS. Product 1 was chosen as the reference because it showed the best dissolution performance (highest OMP release achieved), while maintaining the enteric coating almost unaltered at pH 3–5. In the SDS, products 1 and 5 had the highest DE values, whereas product 2 showed poorest DE.

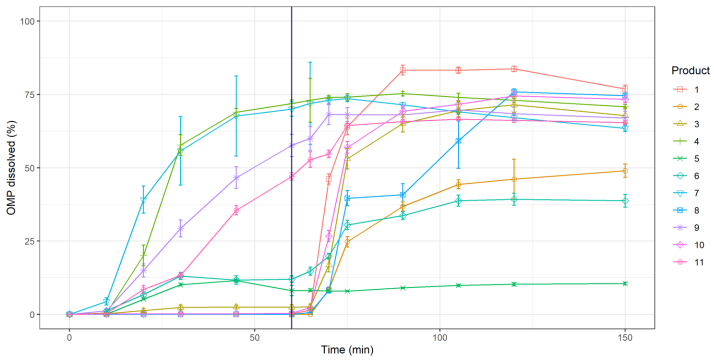

Figure 4. Dissolution profiles of 11 multi-source omeprazole products in the multiple dose scenario (MDS). Blue line indicates the addition of the neutralizing buffer at 60 min. Values are mean ± SE.

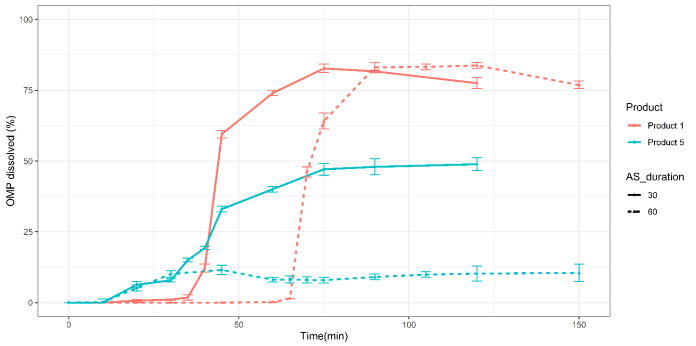

Figure 5. Dissolution profile of products 1 and 5 shows the impact of gastric residence time under the multiple dose scenario (MDS). AS: acidic stage duration (30 or 60 min).

Figure 4 shows the dissolution profiles of the 11 tested products under MDS. OMP release was observed for most multi-source drug products right from the beginning of the test, aligning with the expected outcomes from the enteric coating performance assay. Products 1, 4, 8, 9, and 10 showed the highest drug release. The dissolution profile of product 1 at the neutral stage in the MDS assay closely matched that seen in the SDS assay. On the other hand, the most significant contrast was observed with product 5, which exhibited poor enteric-coating performance during the MDS acidic stage, resulting in drug degradation. Consequently, OMP dissolution percentages were lower during the subsequent neutral stage compared to the SDS neutral stage.

Table 2 presents the MDS/SDS ratios of mean drug release at the end of the MDS relative to the SDS assay for each product. At the end of the acidic stage in the MDS, products 4, 7, 9, and 11 exhibited pH levels above 5.9, indicating a change that would prevent or decrease OMP degradation (data not shown).

Table 2. Comparison of Omeprazole (OMP) Dissolution After 150 min for Single and Multiple Doses

Product	OMP Release in SDS, %	OMP Release in MDS, %	MDS/SDS Ratio	95% CI
1	87.2 (7.1)	76.9 (1.3)	0.88	0.81–0.95
2	45.2 (4.1)	49.0 (2.3)	1.08	0.98–1.19
3	79.5 (1.3)	67.8 (2.6)	0.85	0.82–0.89
4	69.4 (1.0)	70.8 (0.8)	1.02	1.00–1.04
5	84.8 (0.7)	10.5 (0.5)	0.12	0.12–0.13
6	79.7 (1.8)	38.7 (2.2)	0.49	0.46–0.51
7	64.3 (3.4)	63.5 (1.0)	0.99	0.93–1.04
8	82.1 (4.1)	74.6 (0.9)	0.91	0.86–0.95
9	80.6 (1.1)	67.0 (2.3)	0.83	0.80–0.86
10	66.3 (3.6)	73.4 (1.1)	1.11	1.05–1.17
11	82.0 (1.8)	65.4 (0.5)	0.80	0.78–0.82

Values are mean (SE). SDS: single dose scenario; MDS: multiple dose scenario; SE: standard error.

Figure 5 shows the impact of gastric residence time (acidic stage duration) on the relative dissolution profile under MDS. Product 1 did not release OMP in the acidic stage and therefore reached a similar dissolved amount at pH 6.8 in the 30- and 60-minute tests. Product 5 released OMP at pH 4 and above, reaching a 3-fold higher percentage of drug dissolved in 30 minutes compared to the 60-min acidic stage.

DISCUSSION

In this in vitro study, we assessed characteristics of OMP formulations that potentially influence in vivo product performance (i.e., drug bioavailability) (*11*, *17*). The enteric-coating performance assay conducted in USP apparatus 4 at increasing pH levels allowed for determination of the pH at which the drug release process starts in each formulation. This is a critical attribute given that: i) OMP shows a significant degradation at pH < 4.0; ii) performance of the enteric coating is only evaluated for these formulations according to the USP monograph at pH 1.2; and iii) gastric fluids under OMP treatment can reach pH values up to 6.0 (*18*). Ten out of 11 products showed some extent of OMP release throughout the range of acidic pH tested, with considerable formulation-related variability in the pH at which OMP liberation begins. Degradation kinetics of OMP showed important lability of the compound at pH 4.0, with a degradation half-life of 9.7 min, indicating that under

this pH, degradation will compete with OMP absorption in the gastrointestinal lumen. OMP degradation is significantly reduced at pH 4.5 (half-life of 45.9 min), and 5.0 (half-life of 87.7 min). Taken together, these results show that oral formulations releasing OMP at pH < 4 in the gastrointestinal lumen could have reduced bioavailability. Four out of the 11 products tested showed significant drug release at pH ≤ 4.0.

Although a less acidic environment is reported for the intraluminal gastric fluid under fasting conditions (pH ≈ 2), it was decided to preserve pH 1.2 in the SDS, per the USP monograph, as a minimum pH in which the different products will display the best possible enteric-coating performance (*8*, *19*). In the MDS, a pH of 4.0 was chosen for the acidic stage to reflect the stomach conditions under chronic treatment of OMP at the time of drug intake, considering the drug effect and pH due to the increase in intraluminal volume from ingested water. In addition, because the gastric juice lacks buffer capacity, we measured the formulation-induced change in pH of the dissolution media at the end of the acidic stage in the MDS. Some formulations increased the initial pH in more than two units (products 4, 7, 9, and 11), indicating that these products contain excipients that might aid to reduce OMP acidic degradation.

As appreciated in Figure 3, although all products were equally successful in avoiding OMP release during the acidic stage in the SDS, significant variability in the OMP dissolution rate was observed during the neutral stage. This variability is evidenced by comparing the DE values (Table 1). Product 2 had the lowest DE, and product 5 had the highest DE. Conversely, product 5 had the worst performance in the MDS (Fig. 4). Interestingly, product 7, which showed the highest amount of OMP released in the enteric coating performance assay, presented a similar dissolution performance between the SDS and MDS. This is a formulation-related effect, as this product increased pH of the acidic stage from 4 to 6 in the MDS.

The dissolution performance of each product can be assessed by comparing the final amounts of OMP dissolved in the two tested scenarios using MDS/SDS ratio, as presented in Table 2. A ratio ≈ 1 was expected and confirmed for products 1, 3, and 8, which did not release OMP at pH < 4. For products that showed significant drug release at pH 4 or lower, an MDS/SDS ratio < 1 was expected; however, this was not consistently observed, as products 2, 4, 7, and 10 achieved MDS/SDS ratios of ≈ 1. As a common factor, these products exhibited dissolution percentages below 70% at the end of the SDS assay, which were attributable to a poor dissolution performance rather than to OMP degradation (i.e., no OMP release observed at pH 1.2). It is likely that drug dissolution for these formulations was enhanced in the MDS owing to longer exposure at pH levels above the release threshold. Products 5, 6, 9, and 11, which showed good dissolution performance in the SDS and significant drug release at pH ≤ 4.0, had an MDS/SDS ratio < 1.

The final dissolution assay was conducted to assess the impact of gastric emptying variability on the formulation performance and in turn on OMP bioavailability (Fig. 5). To this end, OMP products 1 and 5 were tested again in the MDS using two different lengths for the acidic stage (pH 4.0): 30 and 60 minutes. These products were chosen as representatives of high-quality and low-quality formulations, respectively. Product 1 shows an appropriate performance of the enteric coating, as the final dissolved amount of OMP at the end of the neutral stage was the same regardless of the duration of the acidic stage. On the other hand, product 5 released OMP from the start of the acidic stage, leading to a significant degradation, which is reflected in a lower dissolved amount of OMP at the end of the neutral stage for the test with the extended acidic stage (49% vs 17%, $p = 0.0003$). This indicates that the OMP bioavailability from formulations releasing the drug at pH 4.0 could be sensitive to varying gastric emptying times.

This in vitro characterization of product performance under biorelevant conditions shows that pharmacopeial conditions, as expected, are not enough to assess product quality aspects related to the biopharmaceutic phase. OMP products authorized for commercialization based solely on compliance with good manufacturing practices and pharmacopeial requirements could have a dissimilar, and in some cases defective, in vivo performance. The inclusion of

the enteric-coating performance tests up to pH 4.0 in the USP monograph could be an important step forward in the routine assessment of pharmaceutical quality.

CONCLUSIONS

In vitro performance testing of 11 multisource OMP 20-mg products in Uruguay showed product-related differences in drug bioavailability mainly after multiple doses. For some drug products, the bioavailability may decrease drastically after multiple doses in relation to the first day of treatment. This work highlights the real-world scope of pharmacopeial tests for evaluation of pharmaceutical quality. The observed results should alert regulatory authorities who currently authorize the commercialization of pharmaceutical products without requiring in vivo or biorelevant in vitro evaluations.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

DISCLOSURES

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The authors have no conflicts of interest.

REFERENCES

1. Storpirtis, S.; Gai, M. N.; Cristofoletti, R. Generic and similar products in Latin American countries: Current aspects and perspectives on bioequivalence and biowaivers. *Pharm Policy Law.* **2014**, *16* (3–4), 225–248. DOI: 10.3233/PPL-140386.
2. Adade, C. A.; Cheikh, A.; Cherrah, Y.; Bouatia, M.; Cardot, J. M. Bioequivalence regulation in emerging countries: Example of Moroccan regulations on immediate release formulations and comparison with international guidelines. *J. Appl. Pharm. Sci.* **2019**, *9* (11), 28–35. DOI: 10.7324/JAPS.2019.91104.
3. Garattini, L.; Padula, A. Competition in pharmaceuticals: more product- than price-oriented? *Eur. J. Health Econ.* **2018**, *19* (1), 1–4. DOI: 10.1007/s10198-017-0932-4.
4. Valle, B.; Díaz, J. A.; López, J. J.; Calderón, C. M. [Evaluation of prophylactic prescription of omeprazole and ranitidine by identifying risk factors for gastrointestinal bleeding] [in Spanish]. *Rev Colomb Ciencias Químico-Farmacéuticas.* **2017**, *46* (1), 49–60. DOI: 10.15446/rcciquifa.v46n1.67289.
5. Stedman, C. A. M.; Barclay, M. L. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment. Pharmacol. Ther.* **2000**, *14* (8), 963–978. DOI: 10.1046/j.1365-2036.2000.00788.x.
6. Davidson, A. G.; Mccallum, A. A Survey of the stability of omeprazole products from 13 Countries. *Drug Dev. Ind. Pharm.* **1996**, *22* (12), 1173–1185. DOI: 10.3109/03639049609063235.
7. Riedel, A.; Leopold, C. S. Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. *Drug Dev. Ind. Pharm.* **2005**, *31* (2), 151–160. DOI: 10.1081/DDC-200047787.
8. Omeprazole Delayed-Release Capsules Monograph. In: *USP 43–NF 38*. The United States Pharmacopeial Convention, Inc., **2020**.
9. Elkoshi, Z.; Behr, D.; Mirimsky, A.; Tsvetkov, I.; Danon, A. Multiple-dose studies can be a more sensitive assessment for bioequivalence than single-dose studies: The case with omeprazole. *Clin. Drug Investig.* **2002**, *22* (9), 585–592. DOI: 10.2165/00044011-200222090-00003.
10. Farinha, A.; Bica, A.; Martins, J. M.; Pais, J. P. Dissolution of omeprazole from delayed-release solid oral dosage forms. *Drug Dev. Ind. Pharm.* **2000**, *26* (7), 785–790. DOI: 10.1081/DDC-100101300.
11. Moore, T.; Smith, A.; Ye, W.; Toler, D. Y.; Westenberger, B. J.; Lionberger, R.; Raw, A.; Yu, L.; Buhse, L. F. Generic omeprazole delayed-release capsules: in vitro performance evaluations. *Drug Dev. Ind. Pharm.* **2009**, *35* (8), 917–921. DOI: 10.1080/03639040802698802.
12. Back, M.; Fagiolino, P.; Vázquez, M.; Martín, O.; Sela, F.; Fagiolino, A.; Hiriart, M. [Prognosis of bioequivalence of omeprazole delayed-release drugs using in vitro dissolution studies] [in Spanish]. *Rev OFIL*. **2007**;*18* (1), 43–50.
13. <711> Dissolution. In: *USP 43–NF 38*. The United States Pharmacopeial Convention, Inc., 2020.
14. 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.
15. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. World Health Organization Technical Report Series; No. 1019. World Health Organization, 2019.
16. Wu, F.; Gaohua, L.; Zhao, P.; Jamei, M.; Huang, S. M.; Bashaw, E. D.; Lee, S. C. Predicting nonlinear pharmacokinetics of omeprazole enantiomers and racemic drug using physiologically based pharmacokinetic modeling and simulation: application to predict drug/genetic interactions. *Pharm. Res.* **2014**, *31* (8), 1919–1929. DOI: 10.1007/s11095-013-1293-z.
17. Kaur, P.; Jiang, X.; Duan, J.; Stier, E. Applications of in vitro-in vivo correlations in generic drug development: case studies. *AAPS J.* **2015**, *17* (4), 1035–1039. DOI: 10.1208/s12248-015-9765-1.
18. Kirchheiner, J.; Glatt, S.; Fuhr, U.; Klotz, U.; Meineke, I.; Seufferlein, T.; Brockmöller, J. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *Eur. J. Clin. Pharmacol.* **2009**, *65* (1), 19–31. DOI: 10.1007/s00228-008-0576-5.
19. Freire, A. C.; Basit, A. W.; Choudhary, R.; Piong, C. W.; Merchant, H. A. Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery. *Int. J. Pharm.* **2011**, *415* (1-2), 15–28. DOI: 10.1016/j.ijpharm.2011.04.069.