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Pharmaceutical Equivalence and Similarity Studies of Metoclopramide Tablets

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ABSTRACT

Dissolution studies have evolved from a simple quality control test to a surrogate of in vivo interchangeability. Pharmaceutical equivalents are drug formulations with the same molar amount of the same active pharmaceutical ingredient (API), in the same dosage form, meet comparable quality standards, and are intended to be administered by the same route. Pharmaceutical equivalents imply therapeutical equivalence when, after administration, their effects are essentially the same; these effects can be demonstrated by bioequivalence studies or, in some cases, by in vitro studies based on the Biopharmaceutics Classification System. In this scheme, biowaivers are recommended for immediate-release solid oral dosage forms containing Class 3 drugs (like Metoclopramide) using dissolution testing as a surrogate for in vivo bioequivalence studies, with special consideration regarding excipient composition. The present work aimed to compare in vitro dissolution characteristics and other critical quality attributes of Metoclopramide tablets purchased in Argentina to establish their pharmaceutical equivalence and similarity. All evaluated products fulfill the pharmaceutical equivalence criteria. Three of the tested products and the reference formulation complied with the criteria for 'very rapidly dissolving,' so they could be described as essentially similar. Nevertheless, it is important to have access to additional information about the excipient composition of these formulations to assure a safe interchangeability process for this Class 3 drug.

KEYWORDS: Dissolution, metoclopramide, interchangeability, biowaiver, similarity

INTRODUCTION

Over two decades ago, Amidon et al. proposed a Biopharmaceutics Drug Classification scheme for correlating in vitro drug product dissolution and in vivo bioavailability based on recognizing drug dissolution and intestinal permeability are the fundamental parameters controlling rate and extent of absorption (*1*). Considering this Biopharmaceutics Classification System (BCS), drugs are classified into four classes, where Class 3 drugs correspond to active pharmaceutical ingredients (APIs) with high aqueous solubility and low permeability (*1*). Of 123 oral drugs in immediate-release (IR) dosage forms on the World Health Organization (WHO) Essential Model List provisionally classified into BCS classes, the majority (around 34% to 38%) belong to Class 3 (*2, 3*).

For products to be interchangeable, the WHO states the products must be therapeutically equivalent, which includes pharmaceutical equivalence or alternative formulations with equivalent dosage forms, similar dose, route of administration, indications, and directions for usage, labeling, efficacy, safety, and bioequivalence to the comparator (*4*). In this framework, the BCS serves as a tool to identify compounds eligible for biowaiver, which implies that in vivo proof of bioequivalence may be replaced by in vitro dissolution studies comparing test and reference product (*5, 6*). The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties), the similarity in in vitro dissolution profiles and excipient comparisons and risk–benefit analysis can be used to document equivalence of a multisource product with a comparator product and waive in vivo bioequivalence testing (*4*). This BCS-based biowaiver scheme has important advantages such as economic impact, time-saving, and avoidance of unnecessary testing in humans (*3, 6*).

The regulations on BCS-based biowaivers were different between the WHO and the regulatory agencies US Food and Drug Administration (FDA) and European Medicines Agency (EMA) until 2015 (*5*). Currently, the FDA, EMA, and

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WHO agree to allow BCS biowaivers both for Class 1 and Class 3 drugs (*4, 7–9*). Argentina adopted these guidelines and published their own guidance documents (*10, 11*). Furthermore, scientists had already recommended the biowaiver extension, and some even considered that BCS Class 3 drugs are more suitable for biowaiver than Class 1 APIs (*3, 12–18*).

The absorption of a Class 3 drug is limited by its permeability and is less dependent upon the formulation. Therefore, if the in vitro dissolution of a Class 3 drug product is rapid enough, under all physiological conditions, the variation is attributable to alterations of physiology and/or membrane permeability rather than dosage form factors (*19*). Besides, if the amount and nature of the excipients are not expected to affect bioavailability, in vivo behavior will be similar to an oral solution, and Class 1 criteria can be applied (*19, 20*). For Class 3 drugs, the excipients of the formulation may be more critical than those for Class 1 drugs. For this reason, it is recommended that only excipients which have already appeared in products with a marketing authorization in an ICH or associated country are used, and types and amounts of excipients should be similar in the test and comparator product (*5*). Thus, the WHO, FDA, and EMA would grant BCS-based biowaivers for drug products containing BCS Class 3 drugs, if 'very rapid dissolution' is established (i.e., at least 85% dissolved in up to 15 minutes), and excipients are qualitatively the same and quantitatively very similar (*4, 7–9, 20, 21*).

Metoclopramide (MET) is a centrally acting anti-emetic and prokinetic agent widely used for the treatment of ileus, gastro-oesophageal reflux disease, dyspepsia, nausea, and vomiting during migraine or cancer therapy (*2, 22, 23*). The recommended dose for MET is 10 mg (hydrochloride, HCl), according to the WHO Model List of Essential Medicines (*24*). In the BCS framework, MET is conservatively assigned to Class 3, or a boundary Class 1/3, depending on the reviewed literature (*2, 22, 23*). MET has a biowaiver recommendation if, according to the biowaiver monograph, (a) the test product contains only excipients also present in MET HCl containing IR solid oral drug products approved in ICH or associated countries, (b) in amounts in normal use in IR solid oral dosage forms, and (c) the test product and the comparator both comply with the criteria for 'very rapidly dissolving' (*5, 23*). In those cases, the risk to accept a bioinequivalent drug product is extremely low, and if a bioinequivalent product passes the evaluation, the consequences for the patient will not be serious (*5, 23*). Moreover, in these cases where 85% of the labeled amount is dissolved within 15 minutes (for the test and reference products in all media), the similarity of dissolution profiles may be accepted as demonstrated without any mathematical evaluation (i.e., f_2 calculation) (*4, 8, 9, 25, 26*).

This research aimed to evaluate critical quality parameters, compare the dissolution profiles, and assess pharmaceutical equivalence and similarity of five solid oral IR MET formulations commercially available in Argentina.

MATERIALS AND METHODS

Chemicals

MET exists as a base, as a monohydrochloride, and as a dihydrochloride (*23*). Both the European Pharmacopoeia and the United States Pharmacopeia (*USP*) use the name 'metoclopramide hydrochloride' for the monohydrochloride monohydrate (*23*). The MET HCl monohydrate bulk drug for our study (100.49% purity, on dried base) was purchased from Saporiti (Buenos Aires, Argentina). Five solid oral IR dosage forms (Samples A to E), were acquired from the pharmacies of Bahía Blanca city (Argentina). Sample D was the reference product; the other samples were multisource products. All tests were performed within product expiration dates (which were similar among samples). The information of the evaluated products is shown in Table 1. As MET is classified as a BCS Class 3 drug, the composition of excipients must be qualitatively the same and quantitatively very similar (*9*). A list of excipients is shown in Table 2.

Table 1. Evaluated Products

Sample	API Content (mg)[a]	Calculated MET Content as Base (mg)	Price per 10 Tablets[b]	Storage Conditions[a]
A	MET dihydrochloride 10 mg	8.04	7.76	Between 15 and 30 °C
B	MET (as HCl) 10 mg	10	5.60	Room conditions (preferably between 15 and 30 °C), protect from light
C	MET (as HCl) 10 mg	10	5.64	Between 8 and 30 °C, in a fresh place in original container
D	MET HCl (as monohydrate 10, 54 mg) 10 mg	8.92	5.85	Below 30 °C, protected from light
E	MET dihydrochloride 10 mg	8.04	3.95	Room conditions, under 25 °C

[a]*As indicated on product label;* [b]*Price in Argentinian Pesos, at the time of analysis.*
API, active pharmaceutical ingredient; MET, metoclopramide; HCl, hydrochloride

Table 2. Qualitative and Quantitative Composition of Excipients

Excipient type[a]	Sample / Excipient	A	B	C	D (reference)	E
Filler	Lactose	80.486	n/s	n/s	38.70 (Anhydrous)	13.000 (Monohydrate)
	Powdered cellulose[b]	-------	-------	n/s	-------	30.290
	Microcrystalline cellulose[b]	-------	n/s	-------	50.00	76.417
Disintegrant	Corn starch[b]	30.000	-------	-------	30.00	-------
	Povidone	6.000	n/s	-------	-------	-------
	Sodium starch glycolate	-------	n/s	n/s	10.00	-------
Glidant	Talc[b]	1.750	n/s	-------	0.70	-------
	Colloidal silicon dioxide[b]	-------	n/s	-------	-------	-------
Lubricant	Magnesium stearate	1.750	n/s	n/s	0.70	0.320
Others	Colorants	0.014 (Sunset yellow)	-------	n/s (Ponceau 4R)	-------	0.873 (Sunset yellow - Indigo carmine - Tartrazine)
TOTAL[c]		130.0	-------	-------	140.64	130.9

All values are expressed in mg.
[a]List of 'excipient type' as specified in WHO Guidelines, for 'quantitatively very similar' evaluation (4); [b]This excipient has multiple functions; [c]This value includes the quantity of metoclopramide present in the formulation.
n/s, not specified (package, labels, patient information leaflets and/or literature).

Hydrochloric acid, glacial acetic acid, potassium chloride, sodium acetate trihydrate, sodium hydroxide, and monobasic potassium phosphate analytical grade (Anedra, Argentina), and distilled water were used for assay and preparation of dissolution media. Buffer solutions including pH 1.2 hydrochloric acid buffer solution, pH 4.5 acetate buffer solution, and pH 6.8 phosphate buffer solution were prepared according to *USP* (*27*).

Equipment

An Acculab ALC-210.4M electronic analytical balance (Acculab North America, USA) was used for weight measurements. The pH levels of the prepared buffer solutions were checked using an Altronix TPX-1 pH meter (Saen, Argentina). Tablet characteristics were evaluated using a Scout FGM02 friability tester, a Scout EGM02 disintegration apparatus, and a Scout DGM02 hardness tester (Scout Electronic, Argentina). An Erweka DT60 dissolution apparatus (Erweka GmbH, Germany) was used for dissolution testing of dosage forms. A Varian Cary 50Conc spectrophotometer (Varian Instruments, Australia) was used for assay and quantification of dissolved MET. An ultrasonic bath (Testlab, Argentina) was used for degassing of dissolution media.

Methods

Labels and patient information leaflets of all evaluated products were carefully examined to detect similarities and differences among the provided information (e.g., storage conditions) according to Argentine regulations (*28, 29*). Tablet friability (n = 10), hardness (n = 5), and disintegration tests (n = 6) were performed according to Farmacopea Argentina (FA) (*29*). MET assay and uniformity of dosage units (n = 10) were performed by ultraviolet spectrophotometry (*29, 30*). Dissolution tests were performed using a calibrated *USP* Apparatus 1 (basket) at 50 rpm, and 900 mL of water as dissolution media (*27, 29*). Prior to testing, the dissolution media was preheated and degassed. Quality control dissolution tests (n = 6) were performed using distilled water at 37.0 ± 0.5 °C as dissolution medium. Samples were withdrawn at 30 minutes, filtered through a 0.45-µm pore-size nylon membrane (Microclar, Argentina), and suitably diluted. Drug concentration was determined by spectrophotometric analysis at 308 nm, in triplicate, and compared with a MET calibration curve (R^2 = 0.9995).

To assess similarity, dissolution profiles (n = 12) were performed at pH 1.2, 4.5, and 6.8 under the same experimental conditions of dissolution quality control test. Samples (10 mL each) were withdrawn at 5, 10, 15, 20, 30, and 45 minutes, fresh medium was replaced, and samples were subsequently filtered, suitably diluted, and spectrophotometrically measured. The concentration in each sample was calculated from MET calibration curves constructed in each dissolution medium (R^2 was between 0.9992 and 0.9999). Average cumulative drug-release percentages were calculated for dissolution profile estimation. Each point of the dissolution profile corresponds to a mean value and its respective standard deviation.

Data Analysis

The generated analytical data was processed using a Microsoft Excel spreadsheet. The statistical evaluation of dissolution profiles was performed using analysis of variance (ANOVA) over dissolution efficiency (DE) values (*31*). DE is defined as the area under the dissolution curve up to a certain time, *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (*32*). In vitro equivalence between the reference and multisource products was established based on the acceptance criteria for similarity factor f_2 (*4, 7–9*).

RESULTS AND DISCUSSION

The *USP* requires MET tablets to contain an amount of MET HCl monohydrate equivalent to 90.0% to 110.0% of the labeled amount of MET base (*27*). FA also indicates that MET tablets should contain an amount of MET HCl equivalent to 90.0% to 110.0% of the labeled amount of MET base, and the WHO recommendation for oral administration 'tablet, 10 mg (HCl)' most probably means as anhydrous HCl (*23, 29*). As it was stated by Stosik et al. and noted in Table 1, the expression of the drug in marketed drug products was confusing (*23*). All evaluated products suggested the same strength, as a '10' accompanied their brand name, but, in fact, they contained different amounts of MET base (Table 1). This situation represents a typical problem in different countries and should be addressed by regulatory agencies. USP and FA specifications for packaging and storage indicate MET must be preserved in tight, light-resistant containers. Different criteria for the storage conditions are described in all evaluated products (Table 1). Some products (Samples A and B) specified more restricted temperature ranges than others (Samples C, D, and E), and only Samples B and D indicated protection from light. Standardization of the given information should also be addressed by regulatory agencies.

For BCS Class 3 products biowaivers, the excipient composition of the test product must be qualitatively the same and quantitatively very similar to the reference product (*4, 7*). As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS (*4*). Nevertheless, the definition of 'quantitatively very similar' is stated in the WHO Guideline, which presents a table with the limits on the relative difference in the amount of excipient in two solid oral pharmaceutical products for the products to be considered 'quantitatively similar' in that excipient (*4*). This criterion seems to be difficult to apply in the case of excipients that serves multiple functions (e.g., cellulose, powdered; cellulose, microcrystalline; talc).

The excipient compositions of evaluated samples are shown in Table 2. It is important to highlight the absence of excipients known to affect the absorption and bioavailability of APIs (e.g., mannitol, sorbitol, surfactants like sodium lauryl sulfate or polysorbates, polyethyleneglycol, and poloxamers, among others), which must be compulsorily declared for BCS Class 3 drugs (*4, 33*). All evaluated formulations contained the same qualitative composition, in terms of excipient type, but did not have the same excipients. Besides, most excipients listed in Table 2 were present in MET solid oral IR dosage forms, with marketing authorizations in ICH or associated countries (*23*). With respect to the 'quantitatively very similar' requirement, Samples B and C did not fulfill it, as they do not declare the amount of each excipient (Table 2). In the case of Sample A, the lubricant content difference (in terms of magnesium stearate) was higher than the limits specified by WHO Guidelines (*4*). Finally, in the case of Sample E, more information is needed on excipients that serves multiple functions to achieve relative differences determination and state an adequate conclusion.

Results of friability, hardness, disintegration time, assay, uniformity of dosage units, and dissolution tests are shown in Table 3. For friability tests, the specification states that 'a maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products' (*27, 29*). As it can be seen in Table 3, all evaluated samples fulfilled the requirements for the friability test. On the other hand, because tablet hardness is not part of pharmacopoeia specifications,

Table 3. Critical Quality Attributes Evaluation Results

Sample	Fraibility (%)[a]	Hardness (kp)[b]	Disintegration time (s)[c]	Tablet weight (mg)[b]	Assay (%)[b,d]	Uniformity of dosage units (%)[e]	Dissolution test (S1 Stage)[f]
A	0.00	8.0 ± 0.8	235	131.0 ± 0.7	98.6 ± 0.9	[99.2–100.5] / 1.1	[91–92] / 0.7
B	0.04	3.3 ± 0.6	143	101.4 ± 0.1	96.8 ± 1.6	[96.3–99.6] / 1.2	[84–93] / 3.2
C	0.15	4.5 ± 0.4	161	200.4 ± 4.7	100.5 ± 2.5	[97.3–106.2] / 3.4	[85–91] / 2.4
D	0.16	3.4 ± 0.2	118	140.5 ± 2.5	95.3 ± 1.7	[94.3–102.7] / 3.7	[79–84] / 1.9
E	0.02	5.0 ± 0.4	15	132.3 ± 0.6	98.5 ± 0.8	[97.3–99.7] / 1.0	[85–94] / 3.6

[a]*Percentage of weight loss;* [b]*Mean ± SD;* [c]*Maximum time needed for complete disintegration of all evaluated tablets;* [d]*Percentage of labeled amount;* [e]*[range] of labeled amount / RSD;* [f]*[range] of labeled amount dissolved / RSD.*
kp, kilopond, SD, standard deviation; RSD, relative SD.

and release limits are product-specific, the obtained results were considered acceptable (Table 3). For disintegration tests, the specification states 'at the end of the time limit specified in the monograph, lift the basket from the fluid and observe the tablets: all of the tablets have disintegrated completely' (*27, 29*). Although the MET tablets monograph did not state disintegration specifications, all samples completed their disintegration process within four minutes, which could be considered a suitable value (Table 3). Formulation A had the highest disintegration time, which corresponds with its higher lubricant content, as it is shown in Table 2 and discussed above.

MET tablets should contain an amount equivalent to 90.0% to 110.0% of the labeled amount of MET base (*27, 29*). Assay results for all evaluated products were between those limits (i.e., the formulations fulfilled the assay requirements, see Table 3). Finally, the uniformity of dosage unit specifications indicates that API content should be between 85.0% to 115.0% of the labeled amount in each evaluated dosage unit, and the relative standard deviation should not exceed 6.0% (*27, 29*). As noted in Table 3, all evaluated products fulfilled the requirements for uniformity of dosage units test, and content uniformity results were in agreement with weight variation results (where Samples C and D, with higher variability in uniformity of dosage units test, correspond with the same behavior in tablet weight comparison).

The MET tablets monograph includes specifications for dissolution testing, stating 'not less than 75% (Q) of the labeled amount of MET is dissolved in 30 minutes' (*27, 29*). According to the results presented in Table 3, reference formulation D did not fulfill the dissolution test in Stage 1 (*27, 29*). Nevertheless, it fulfilled the acceptance criteria for Stage 2 (data not shown).

Figure 1 shows the dissolution profiles at pH 1.2, 4.5, and 6.8. All formulations reached a plateau of approximately 100% of MET dissolved at 45 minutes, with the exception of Sample E at pH 1.2, which exhibited a maximum of 85% dissolution. The highest dissolution rate corresponded to Samples B and E in all media. Formulation A showed the lowest dissolution rate at all evaluated media and reached the dissolution plateau at about 20 or 30 minutes of dissolution study. However, all other samples reached the plateau at earlier sampling points in all media. Sample A did not fulfill the 'quantitatively similar' requirement for lubricant content (Table 2), and magnesium stearate is hydrophobic and may retard the dissolution of a drug in a solid IR dosage form (*34*). Formulations B, C, D, and E were 'very rapidly dissolving,' in the three media (Fig. 1). On the other hand, Sample A was 'rapidly dissolving' (i.e., more than 85% of the labeled amount dissolved within 30 minutes) in all dissolution media, so it could not be considered for biowaiver estimation because it did not fulfill the 'very rapid dissolution' criteria required for Class 3 drugs (Fig. 1).

MET dissolution was also assessed through statistical comparison of profiles in terms of DE. As noted in Figure 2, Samples B and E exhibited a higher DE performance than the reference in almost all conditions. Formulation C was the only sample that did not show statistical differences with the reference formulation in all evaluated media. In contrast, the only sample that was significantly different to the reference formulation in all dissolution media was

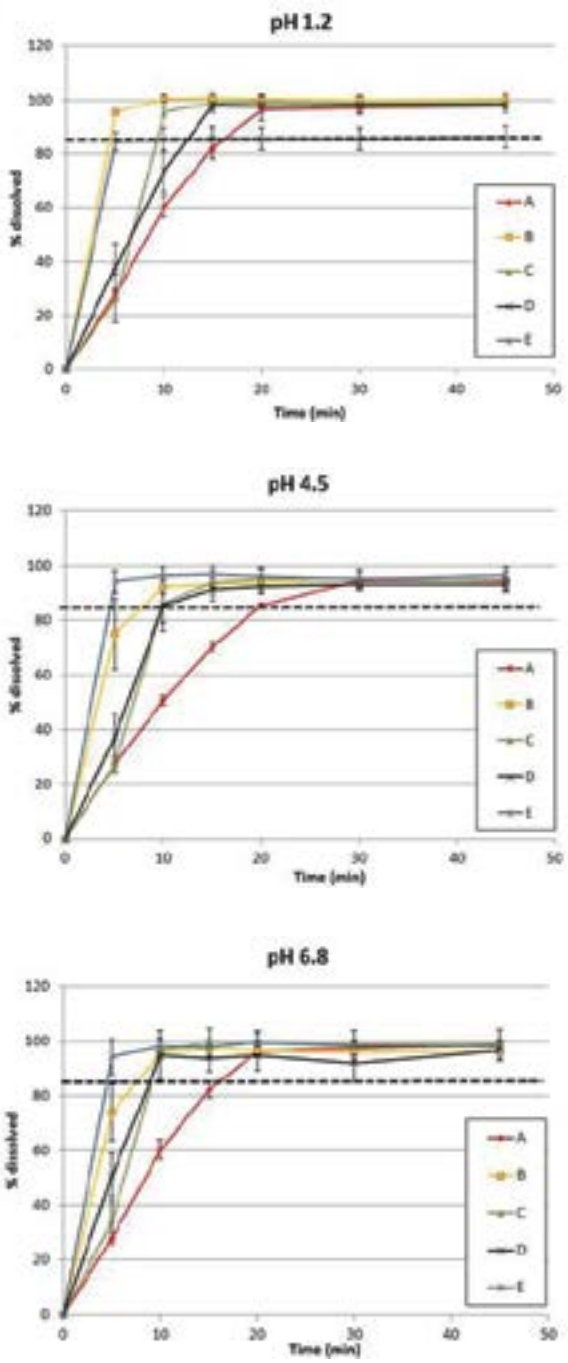

Figure 1. Dissolution profiles for similarity evaluation at pH 1.2, 4.5, and 6.8. Each point on the curve represents a mean value (n = 12) and its respective standard deviation (SD). Dotted line marks 85% dissolved (of labeled amount) level.

formulation A, with lower DE values in all cases.

Finally, in a biowaiver scenario, dissolution profiles need to be compared in terms of similarity factor f_2. However, as the reference and many of the test formulations (B, C, and E) showed a 'very rapidly dissolution' behavior, the profile similarity could be concluded as such without further mathematical comparison (*4, 7*). Nevertheless,

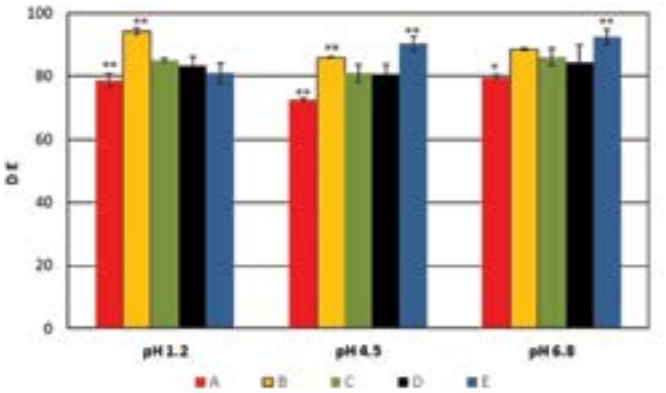

Figure 2. DE values at pH 1.2, 4.5, and 6.8 dissolution media. Each bar represents a mean value (n=12) and its respective standard deviation (SD). DE is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (32).
**: Significant statistical differences were found between the multisource formulation and the reference sample, D ($p<0.05$)*
***: Highly significant statistical differences were found betweenthe multisource formulation and the reference sample, D ($p<0.01$)*

to declare the interchangeability of these formulations, special consideration must be made regarding excipients composition issue (Table 2). Only formulation A could not be included in the similarity estimation because it did not fulfill the 'very rapidly dissolution' condition requested for Class 3 biowaivers or the 'quantitatively similar amount of excipient' criteria for lubricant content (Table 2). This formulation also had the highest hardness and disintegration time values (Table 3) and was the most expensive sample (Table 1).

CONCLUSION

All evaluated formulations could be considered pharmaceutical equivalents because they fulfilled critical quality properties (i.e., tablet mechanical properties, assay, disintegration, and dissolution tests). In a biowaiver scenario, formulations B, C, and E could be considered essentially similar to the reference, as they fulfilled the 'very rapidly dissolving' requirement for BCS Class 3 drugs. However, it is important to have access to the quantitative excipient composition (Samples B and C) and greater precision to establish reliable results on 'quantitatively very similar' determination (Sample E) to assure a safe interchangeability process for the present study. Only formulation A could not be declared interchangeable with the reference because it did not fulfill the 'very rapidly dissolution' or the 'quantitatively similar amount of excipient' criteria as required for Class 3 biowaivers.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Amidon, G. L.; Lennernäs, H.; Shah, V. P.; Crison, J.R. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res*. **1995**, *12*, 413–420. DOI: 10.1023/A:1016212804288.
2. Kasim, N. A.; Whitehouse, M.; Ramachandran, C.; Bermejo, M.; Lennernas, H.; Hussain, A. S.; Junginger, H. E.; Stavchansky, S. A.; Midha, K. K.; Shah, V. P.; Amidon, G. L. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Mol. Pharm*. **2004**, *1*, 85–96. DOI: 10.1021/mp034006h.
3. Cook, J. A.; Davit, B. M.; Polli, J. E. Impact of Biopharmaceutics Classification System-based Biowaivers. *Mol. Pharm*. **2010**, *7,* 1539–1544. DOI: 10.1021/mp1001747.
4. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*; WHO Technical Report Series, No. 992, 49th report, Annex 7, pp 131-184. World Health Organization: Geneva, Switzerland, 2015. http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf (accessed Jan 11, 2018).
5. Barends, D. M.; Shah, V. P.; Dressman, J. The biowaiver monographs – what have we learned? In: *Biowaiver Monographs 2004-2012*, Fédération Internationale Pharmaceutique (FIP): The Netherlands, 2012; pp. 8–33.
6. Bergström, C. A. S.; Andersson, S. B. E.; Fagerberg, J. H.; Ragnarsson, G.; Lindahl, A. Is the full potential of the biopharmaceutics classification system reached? *Eur. J. Pharm. Sci*. **2014**, *57*, 224–231. DOI: 10.1016/j.ejps.2013.09.010.
7. *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070246.pdf (accessed Jan 11, 2018).
8. *Guideline on the Investigation of Bioequivalance*; CPMP/EWP/QWP/1401/98; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency: London, 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (accessed Jan 12, 2018).
9. Davit, B. M.; Kanfer, I.; Tsang, Y. C.; Cardot, J. M. BCS Biowaivers: Similarities and differences among EMA, FDA, and WHO requirements. *AAPS J*. **2016**, *18*, 612–618. DOI: 10.1208/s12248-016-9877-2.
10. *Disposición 758/2009: Criterios de bioexención de estudios de bioequivalencia para medicamentos sólidos orales de liberación inmediata*. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT): Buenos Aires, 2009. http://www.anmat.gov.ar/webanmat/legislacion/medicamentos/disposicion_anmat_758-2009.pdf (accessed Jan 12, 2018).
11. *Disposicion 6766/2016: Guía para la solicitud de bioexenciones de ingredients farmacéuticos activos con requerimiento de bioequivalencia*. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT): Buenos Aires, 2016.http://www.anmat.gov.ar/boletin_anmat/BO/Disposicion_6766-2016.pdf (accessed Jan 12, 2018).
12. Blume, H. H.; Schug, B. S. The biopharmaceutics classification system (BCS): Class III drugs—Better candidates for BA/BE waiver? *Eur. J. Pharm. Sci*. **1999**, *9*, 117–121. DOI: 10.1016/S0928-0987(99)00076-7.
13. Kortejarvi, H.; Urtti, A.; Yliperttula, M. Pharmacokinetic simulation of biowaiver criteria: The effects of gastric emptying, dissolution, absorption and elimination rates. *Eur. J. Pharm. Sci*. **2007**, *30,* 155–166. DOI: 10.1016/j.ejps.2006.10.011.
14. Cheng, C. L.; Yu, L. X.; Lee, H. L.; Yang, C. Y.; Lue, C. S.; Chou, C. H. Biowaiver extension potential to BCS Class III high solubility–low permeability drugs: Bridging evidence for metformin immediate-release tablet. *Eur. J. Pharm. Sci.* **2004**, *22*, 297–304. DOI: 10.1016/j.ejps.2004.03.016.
15. Tsume, Y.; Amidon, G. L. The Biowaiver extension for BCS class III drugs: The effect of dissolution rate on the bioequivalence of BCS class III immediate-release drugs predicted by computer simulation. *Mol. Pharm.* **2010**, *7*, 1235–1243. DOI: 10.1021/mp100053q.
16. Crison, J. R.; Timmins, P.; Keung, A.; Upreti, V. V.; Boulton, D. W.; Scheer, B. J. Biowaiver Approach for Biopharmaceutics Classification System Class 3 Compound Metformin Hydrochloride Using In Silico Modeling. *J. Pharm. Sci*. **2012**, *101*, 1773–1782. DOI: 10.1002/jps.23063.
17. Yu, L. X.; Amidon, G. L.; Polli, J. E.; Zhao, H.; Mehta, M. U.; Conner, D. P.; Shah, V. P.; Lesko, L. J.; Chen, M. L.; Lee, V. H.; Hussain, A. S. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm. Res.* **2002**, *19*, 921–925. DOI: 10.1023/A:1016473601633.
18. Jantratid, E.; Prakongpan, S.; Amidon, G. L.; Dressman, J. B. Feasibility of biowaiver extension to Biopharmaceutics classification system class III drug products: cimetidine. *Clin. Pharmacokinet*. **2006**, *45*, 385–399. DOI:10.2165/00003088-200645040-00004.
19. Basanta Kumar Reddy, B.; Karunakar, A. Biopharmaceutics Classification System: A Regulatory Approach. *Dissolution Technol*. **2011**, *18*, 31–37. DOI: 10.14227/DT180111P31.
20. Zheng, N.; Lionberger, R. A.; Mehta, M. U.; Yu, L. X. The Biowaiver monographs: BCS based Biowaivers. A regulatory overview. In: *Biowaiver Monographs 2004-2012*, Fédération Internationale

Pharmaceutique (FIP): The Netherlands, 2012; pp. 52–71.
21. Garcia Arieta, A.; Gordon, J.; Potthast, H. On the effect of common excipients on the oral absorption of Class 3 Drugs. *J. Pharm. Sci.* **2016**, *105*, 1353–1354. DOI: 10.1016/j.xphs.2016.01.005.
22. Lindenberg, M.; Kopp, S.; Dressman, J. B. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur. J. Pharm. Biopharm*. **2004**, *58*, 265–278. DOI: 10.1016/j.ejpb.2004.03.001.
23. Stosik, A.G.; Junginger, H. E.; Kopp, S.; Midha, K. K.; Shah, V. P.; Stavchansky, S.; Dresman, J. B.; Barends, D. M. Biowaiver monographs for immediate release solid oral dosage forms: metoclopramide hydrochloride. *J. Pharm. Sci.* **2008**, *97*, 3700–3708. DOI: 10.1002/jps.21276.
24. WHO Model List of Essential Medicines 19th ed. (April 2015) World Health Organization Website. http://www.who.int/entity/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1 (accessed Jan 12, 2018).
25. Potthast, H. Update on regulations on in vitro equivalence testing. In: *Biowaiver Monographs 2004-2012*; Fédération Internationale Pharmaceutique (FIP): The Netherlands, 2012; pp 34–51.
26. Welink, J.; Gordon, J. D.; Stahl, M. Biowaiver implementation for immediate release oral formulation in the World Health Organisation. In: *Biowaiver Monographs 2004-2012*; Fédération Internationale Pharmaceutique (FIP): The Netherlands, 2012; pp 86–107.
27. *The United States Pharmacopeia and National Formulary USP 40-NF35*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2017.
28. Disposicion ANMAT 5904: Definiciones y lineamientos generals acerca del modo como debiera incluirse la información que deben contener los prospectos de las especialidades medicinales cuya condición de expendio sea la de venta bajo receta en sus tres categorías. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT). Buenos Aires, Argentina, 1996. http://www.anmat.gov.ar/webanmat/NORMATIVA/NORMATIVA/MEDICAMENTOS/DISPOSICION_ANMAT_5904-1996.PDF (accessed Jan 12, 2018).
29. *Farmacopea Argentina, Séptima Edicion;* Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT): Buenos Aires, Argentina, 2013.
30. *Japanese Pharmacopoeia,* 15th ed; Ministry of Health, Labour, and Welfare: Tokyo, Japan, 2006.
31. Di Rienzo, J. A.; Casanoves, F.; Balzarini, M. G.; Gonzalez, L.; Tablada, M.; Robledo, C.W. InfoStat 2014 version. Grupo InfoStat, FCA, Universidad Nacional de Córdoba, Argentina. http://www.infostat.com.ar (accessed Jan 12, 2018).
32. Khan, K. A. The concept of dissolution efficiency. *J. Pharm. Pharmacol.* **1975**, *27*, 48–49. DOI:10.1111/j.2042-7158.1975.tb09378.x.
33. Garcia Arieta, A. Interactions between active pharmaceutical ingredients and excipients affecting bioavailabity: Impact on bioequivalence. *Eur. J. Pharm. Sci*. **2014**, *65*, 89–97. DOI: 10.1016/j.ejps.2014.09.004.
34. Rowe, R.C.; Sheskey, P.J.; Owen, S.C., Ed. *Handbook of Pharmaceutical Excipients*, 5th Ed.; Pharmaceutical Press: London, 2006; pp 430–433.