Pharmaceutical Equivalence and Similarity Studies of Metoclopramide Tablets

María A. Varillas¹, Marta I.V. Brevedan¹, Noelia L. Gonzalez Vidal¹,²,*
¹Control de Calidad de Medicamentos, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Bahía Blanca, Argentina
²CONICET-UNS, Bahía Blanca, Argentina.

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 (BCS). 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
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

<table>
<thead>
<tr>
<th>Sample</th>
<th>API Content (mg)*</th>
<th>Calculated MET Content as Base (mg)</th>
<th>Price per 10 Tablets$^b$</th>
<th>Storage Conditions$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MET dihydrochloride 10 mg</td>
<td>8.04</td>
<td>7.76</td>
<td>Between 15 and 30 °C</td>
</tr>
<tr>
<td>B</td>
<td>MET (as HCl) 10 mg</td>
<td>10</td>
<td>5.60</td>
<td>Room conditions (preferably between 15 and 30 °C), protect from light</td>
</tr>
<tr>
<td>C</td>
<td>MET (as HCl) 10 mg</td>
<td>10</td>
<td>5.64</td>
<td>Between 8 and 30 °C, in a fresh place in original container</td>
</tr>
<tr>
<td>D</td>
<td>MET HCl (as monohydrate 10, 54 mg) 10 mg</td>
<td>8.92</td>
<td>5.85</td>
<td>Below 30 °C, protected from light</td>
</tr>
<tr>
<td>E</td>
<td>MET dihydrochloride 10 mg</td>
<td>8.04</td>
<td>3.95</td>
<td>Room conditions, under 25 °C</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Excipient type</th>
<th>Excipient</th>
<th>Sample</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D (reference)</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
<td>Lactose</td>
<td>80.486</td>
<td>n/s</td>
<td>n/s</td>
<td>38.70 (Anhydrous)</td>
<td></td>
<td>13.000 (Monohydrate)</td>
</tr>
<tr>
<td></td>
<td>Powdered cellulose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-------</td>
<td>-------</td>
<td>n/s</td>
<td>-------</td>
<td></td>
<td>30.290</td>
</tr>
<tr>
<td></td>
<td>Microcrystalline cellulose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-------</td>
<td>n/s</td>
<td>-------</td>
<td>50.00</td>
<td>76.417</td>
<td></td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Corn starch&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30.000</td>
<td>-------</td>
<td>-------</td>
<td>30.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Povidone</td>
<td>6.000</td>
<td>n/s</td>
<td>-------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium starch glycolate</td>
<td>-------</td>
<td>n/s</td>
<td>n/s</td>
<td>10.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gildant</td>
<td>Talc&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.750</td>
<td>n/s</td>
<td>-------</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colloidal silicon dioxide&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-------</td>
<td>n/s</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td>Magnesium stearate</td>
<td>1.750</td>
<td>n/s</td>
<td>n/s</td>
<td>0.70</td>
<td>0.320</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Colorants</td>
<td>0.014</td>
<td>(Sunset yellow)</td>
<td>-------</td>
<td>n/s (Ponceau 4R)</td>
<td>------</td>
<td>0.873 (Sunset yellow - Indigo carmine - Tartrazine)</td>
</tr>
<tr>
<td>TOTAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>130.0</td>
<td>-------</td>
<td>-------</td>
<td>140.64</td>
<td>130.9</td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed in mg.
<sup>a</sup> List of ‘excipient type’ as specified in WHO Guidelines, for ‘quantitatively very similar’ evaluation (4); <sup>b</sup>This excipient has multiple functions; <sup>c</sup>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).

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 medium (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<sup>2</sup> = 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 \((R^2 \text{ was between } 0.9992 \text{ and } 0.9999)\). 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). \text{ DE is defined as the area under the dissolution curve up to a certain time, } t, \text{ expressed as a percentage of the area of the rectangle described by } 100\% \text{ 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 \text{ (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). \text{ 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). \text{ 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 serve 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, polyethylene glycol, and poloxamers, among others), which must be compulsorily declared for BCS Class 3 drugs \((4, 33). \text{ 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). \text{ Finally, in the case of Sample E, more information is needed on excipients that serve 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). \text{ 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,
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

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

aPercentage of weight loss; bMean ± SD; cMaximum time needed for complete disintegration of all evaluated tablets; dPercentage of labeled amount; e[range] of labeled amount / RSD; f[range] of labeled amount dissolved / RSD. kp, kilopond; SD, standard deviation; RSD, relative SD.

Table 3. Critical Quality Attributes Evaluation Results
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, 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.

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