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Therapeutic Equivalence Evaluated Through In Vitro Studies of Multi-Source Drugs: A Moxifloxacin Case Study in Lima, Peru

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ABSTRACT

This study aimed to determine the therapeutic equivalence of four multi-source drugs containing moxifloxacin (400 mg tablets) in vitro studies to establish their interchangeability with the reference product. Four multi-source products were acquired in pharmaceutical establishments in metropolitan Lima, each from different manufacturing sites (two products from India, one from Brazil, and one from Peru). The reference product was Avelox (400 mg) coated tablets (Bayer AG, Germany). Quality control and dissolution profile tests were performed. For dissolution tests, a validated ultraviolet-visible spectrophotometry method was used to determine the percentage of drug released. The similarity factor (*f2*) analysis was used to establish therapeutic equivalence of the drug release curves. The dissolution rates were considered equivalent if the values of *f2* were between 50 and 100. Concerning the quality control tests, the moxifloxacin content was 98.5% in the reference product and 97.1–100.0% in the multi-source products. Three out of four multi-source products passed the *f2* test at pH 1.2. Therefore, there is at least one moxifloxacin multi-source product circulating in Peru, manufactured in India, that does not is not interchangeable with the reference product.

KEYWORDS: Therapeutic equivalency, generic drugs, biopharmaceutics, bioequivalent drugs, dissolution, moxifloxacin

INTRODUCTION

The Biopharmaceutical Classification System (BCS) is a predictor of drug absorption, considering its solubility and permeability. A drug is highly soluble when the maximum single dose is soluble in 250 mL of aqueous medium (pH range 1–6.8) and is highly permeable when the absorption percentage is greater than 85–90% of the total administered dose (*1*). In Peru, Supreme Decree No. 024-2018-SA indicates that class I (high solubility and high permeability) and class III (high solubility and low permeability) drugs can opt for in vitro studies or bio-exemption based on the BCS to demonstrate therapeutic equivalence between drugs (*2*). Therapeutic equivalence is an attribute that allows the interchangeability of safe and effective drugs on the market.

In vitro dissolution methods play an important role in evaluating the quality and impact of the formulation. Likewise, they are useful to simplify regulatory processes when there

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are minimal changes in formulations (*3*). In addition, they allow the evaluation of the consistencies between batches and could even be predictive for in vivo comparisons (*4*).

Currently, due to the low accessibility and high cost of innovative medicines, generic medicines are widely used, which should present the same qualitative/quantitative concentration of the active principle and the same pharmaceutical form comparable to the innovative reference medicine (*5*). However, the in vivo therapeutic equivalence of generic drugs is questioned because some may not reach the same plasma and tissue concentrations compared to the innovative reference drugs, which could lead to failure in the treatment of infections and increase the risk of antimicrobial resistance (*5*, *6*).

Moxifloxacin is a broad-spectrum antibiotic belonging to the quinolone group, used for the outpatient treatment of respiratory infections (acute exacerbation of chronic bronchitis, community-acquired pneumonia), abdominal infections, purulent cellulitis, and tuberculosis, essentially for the treatment of multidrug-resistant tuberculosis (MDR-TB) and extremely resistant tuberculosis (XDR-TB) (*7*, *8*). In recent years, the resistance of *Bacteroides spp*. towards moxifloxacin in the United States was 15%, 20% in France, and 29% in Sweden. Likewise, in Belgium the susceptibility of *Clostridium spp.* to moxifloxacin was 88–66%, and 71–90% for *Fusobacterium spp*. (*9*).

A study carried out in Pakistan in 2019 evaluated four different brands of multi-source moxifloxacin tablets (400 mg), finding f_2 values of 77.20, 69.56, 76.98, and 82.17 respectively, which indicated that there was similarity in the release profile of the four brands compared to the reference brand (*10*). An investigation carried out in Macedonia in 2018, evaluated a generic drug of moxifloxacin tablets (400 mg), determining the *f2* value of 50.85 at pH 1.2, concluding that the similarity of dissolution in vitro could be used as an important part of the approach to ensure bioequivalence in vivo and therapeutic equivalence (*11*).

In Peru, there have been no studies of this active pharmaceutical ingredient; however, there are data on microbial resistance to this antibiotic, which could be related to a lack of efficacy of some formulations. In 2013, Horna-Ruiz et al. evaluated uropathogenic *Escherichia coli* strains from female patients from health institutions in North Lima, finding resistance values to moxifloxacin of 43% (*12*). In 2017, Neyra et al. evaluated the bacteriology and frequency of bacterial resistance in patients with the infected diabetic foot from the Hospital Nacional Arzobispo Loayza, reporting that the bacterial resistance to moxifloxacin was 43% (*13*).

In Peru, moxifloxacin is marketed in oral (400 mg tablets and 400 mg coated tablets) and intravenous (400 mg/250 ml solution) dosage forms. According to the Observatory of Pharmaceutical Products of the General Directorate of Medicines, Supplies, and Drugs (DIGEMID), there are seven commercial oral products. The objective of this study is to determine the therapeutic equivalence through in vitro studies of four multi-source drugs containing moxifloxacin, acquired in pharmaceutical establishments in metropolitan Lima, to establish their interchangeability with the reference product.

METHODS

Materials

We used the primary standard for moxifloxacin hydrochloride USP (United States Pharmacopeia); acetonitrile (Merck), and HPLC-grade methanol (Merck), monobasic

potassium phosphate (Merck), N-propyl alcohol (Merck), triethylamine (Sigma Aldrich), dibasic sodium phosphate, citric acid, sodium perchlorate, phosphoric acid, hydrochloric acid, sodium chloride, anhydrous sodium acetate, acetic acid, sodium hydroxide (Merck KGaA, Darmstadt, Germany); all of which were analytical grade, and HPLC-grade water (18.2 MΩ) obtained via Milli-Q Advantage water purifier equipment A10 (Merck, France).

Four multi-source moxifloxacin products were evaluated, acquired in pharmaceutical establishments in metropolitan Lima, containing 400 mg moxifloxacin, with different manufacturers (two products from India, one from Brazil, and one from Peru; see Table 1). The reference product was 400 mg Avelox coated tablets (Bayer AG, Germany). All products were evaluated at least 12 months before their expiration date.

Table 1. Manufacturer Information for Tested Products (400 mg Moxifloxacin Tablets)

Country	Marketing Authorization Holder	Product Designation	Lot No.	Expiration date
Germany	Bayer AG	Reference	BXJB901	August 2022
India	MSM Laboratories Private Limited	Multisource A (MMA)	BT1905193I	April 2024
India	MACLEODS Pharmaceuticals	Multisource B (MMB)	EMB901C	October 2021
Peru	IQFARMA	Multisource C (MMC)	20205310	February 2023
Brazil	EUROFARMA	Multisource D (MMD)	673761	March 2022

Quality Control Tests

Before the dissolution test, the moxifloxacin tablets were subjected to quality control tests to assess the weight, content, and uniformity.

The average weight was measured according to *British Pharmacopoeia* (BP) (*14*).

The tests for drug content and uniformity (i.e., variation of weight of moxifloxacin) were carried out according to *United States Pharmacopoeia* (USP) general chapters <621> and <905> (*15*).

Dissolution Profile Assays

The dissolution test was conducted according to USP <711> (*15*).

The dissolution media were simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8). They were prepared according to the *International Pharmacopoeia* (*16*). All media were prepared without enzymes. The media were filtered with 0.45-µm nylon and degassed under vacuum with mechanical agitation.

In all tests, a Hanson Vision Elite G2 eight-beaker dissolution equipment with a UV-VIS spectrophotometer (Janson V-650) and USP apparatus 2 (paddle) was used at 75 rpm and 900 mL of dissolution medium at 37 ± 0.5 °C. The dissolved amounts were determined by UV-VIS spectrophotometry, according to World Health Organization (WHO) guidelines (*17*). The sampling was manual (10 mL each time) with replacement. The sampling points were: 5, 10, 15, 20, 30, and 45 minutes.

The dissolution apparatus verification test is routinely performed every 6 months following the procedure recommended by the USP. For the performance verification

test, USP prednisone RS tablets are used, and the dissolution test is performed under the following dissolution conditions: 500 mL purified water (after degassing) at 37 ± 0.5 °C and 50 rpm (for USP apparatus 2) for 30 min. After manual sampling, prednisone release is determined by measuring absorbance at 242 nm. Calibration of the dissolution apparatus is performed annually according to the USP and manufacturer procedures.

Calibration of the UV spectrophotometer is performed annually following Official Medicines Control Laboratories (OMCL) guidelines (*18*). The calibration process is performed to evaluate absorbance and wavelength controls, fixed light limit, photometric linearity, resolving power, and suitability of baseline and sample cells.

Analytical Quantification

The analytical quantification of the dissolution profile samples was performed by spectrophotometry (UV-VIS) at 296 nm, using a 0.1-cm long cell. The conditions were carried out according to the USP monograph for moxifloxacin tablets (*15*).

Method Validation

The validation of the method for the development of the dissolution profile was carried out with the following parameters: linearity, precision, accuracy, stability, and influence of the filter, according to guidelines of the Institute of Public Health of Chile (Table 2) (*19*).

Table 2. *Method Validation Data for the Dissolution Test for 400-mg Moxifloxacin Tablets*

Parameters	Specifications	Moxifloxacin		
		pH 1.2	pH 4.5	pH 6.8
Linearity	$r \geq 0.999$	1.0000	1.0000	1.0000
	CV ≤ 2%	0.7%	0.1%	0.9%
	Intercepted different to 0	– 0.00093	– 0.00011	0.00002
Precision	CV ≤ 2%	0.2%	0.1%	0.1%
Accuracy	% Recovery 95–105%	103.2%	100.5%	102.2%
	CV ≤ 2%	1.6%	0.2%	0.2%
Stability	98%–102%	99.5%	100.3%	99.4%
Filter Evaluation	98%–102%	99.7%	99.8%	99.8%

CV: coefficient of variation

Statistical Analysis

Comparison of dissolution profiles was made according to WHO guidelines, calculating the similarity factor (f_2) (*17*). To establish the similarity of the curves, the f_2 values must be between 50 and 100. Microsoft Excel (version 2014) was used.

RESULTS

The reference product passed the quality requirements of the USP for weight, content, and uniformity. The content of moxifloxacin was 98.5% for the reference and of the multi-source drugs was 100.0% (MMA), 99.7% (MMB), 97.1% (MMC), 97.0% (MMD) for the multi-source drugs. The acceptance range is 90.0%–110.0%.

Figure 1 shows the dissolution profiles of the multi-source products containing moxifloxacin sold in Peru versus the reference product data. Of the four multi-source products, the MMA product did not pass the f_2 test at pH 1.2 (Table 3). The f_2 analysis

was not applicable for the other multi-source products because 85% or more drug dissolved within 15 minutes at all three media (pH 1.2, 4.5, and 6.8).

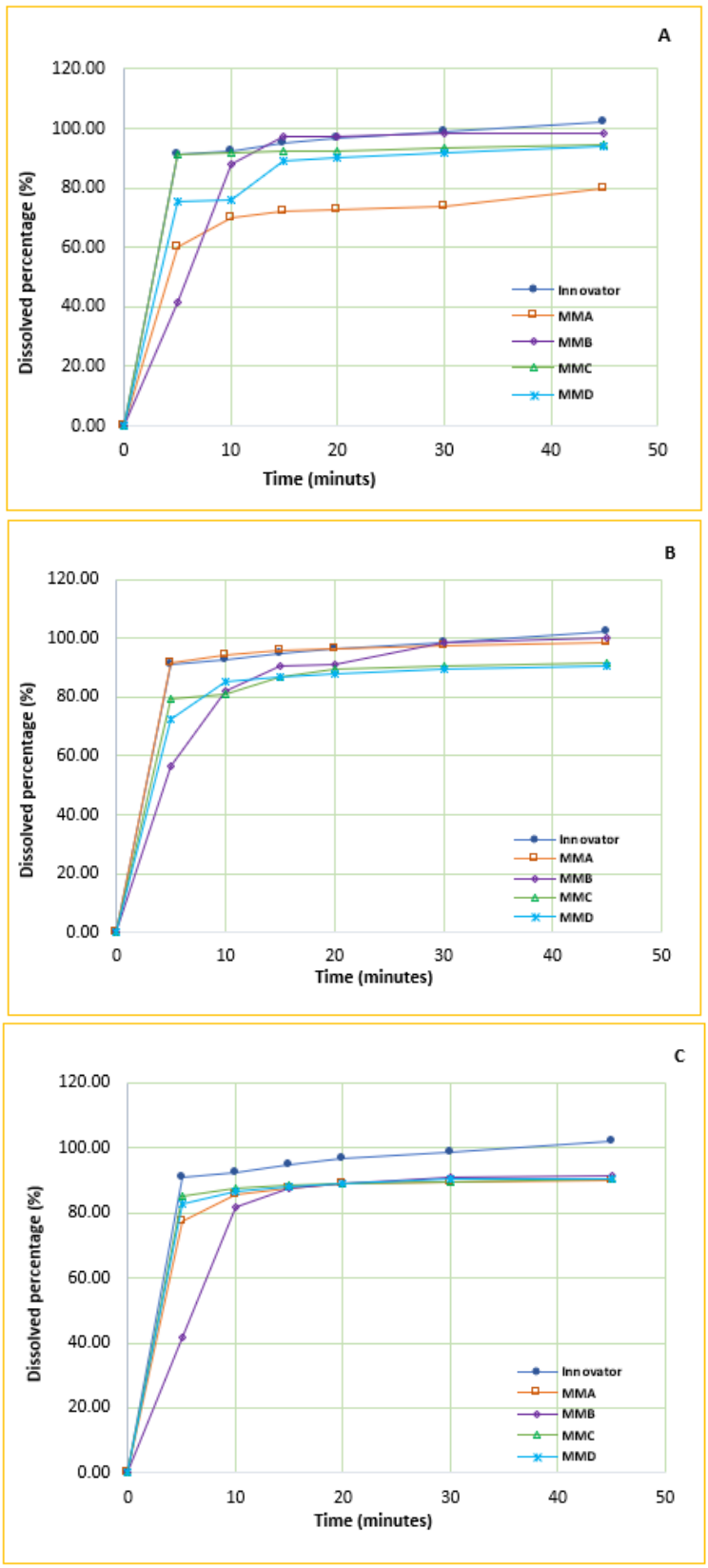

Figure 1. Dissolution profiles for moxifloxacin tablets (400 mg) in simulated gastric fluid, pH 1.2 (A), acetate buffer, pH 4.5 (B), and simulated intestinal fluid, pH 6.8 (C). Dissolution conditions: USP II, 75 rpm, 900 mL medium at 37 ± 2°C. Multi-source products are designated as MMA, MMB,

MMC, and MMD.

Table 3. *Similarity Factor (f_2) Analysis of Multi-Source Versus Reference Products (400 mg Moxifloxacin Tablets)*

Dissolution Media pH	Multisource A	Multisource B	Multisource C	Multisource D
1.2	30.2	-	-	-
4.5	-	-	-	-
6.8	-	-	-	-

Dash (-) indicates f2 analysis not applicable because dissolved average is > 85% of the declared amount at 15 mins.

DISCUSSION

Assessing the biopharmaceutical quality of multi-source antibiotics is a strategy to reduce antimicrobial resistance and achieve effective antibiotic therapy. In the present investigation, the therapeutic equivalence of four multi-source drugs containing moxifloxacin 400 mg was compared with the reference product. There are various methods to determine the interchangeability between drugs, thereby demonstrating therapeutic equivalence between multi-source and reference products. As mentioned in a 2019 study on determining relative potencies, some generic antimicrobial formulations may become interchangeable with the innovator (*20*).

A study conducted in Pakistan in 2016, by determining plasma concentrations in healthy volunteers, determined that a generic product of cefadroxil capsules 500 mg was bioequivalent with the innovator (*21*). Another study carried out in Pakistan in 2018, compared the antibacterial effect in vitro against strains of *Staphylococcus aureus* and *Escherichia coli*, showing that 11 multi-source products of levofloxacin 250 mg tablets were therapeutic equivalents with the innovator (*22*). Likewise, an in vitro, in vivo, and in silico study carried out in China in 2019 found that a generic product of metronidazole 200 mg tablets presented dissolution, bioequivalence, and bioavailability profiles similar to the innovative product (*23*). Similarly, a study conducted in Indonesia in 2020, through in vitro microbiological tests using strains of *E. coli* and *S. aureus*, showed that three generic amoxicillin 500 mg tablet products were therapeutic equivalents with two brand-name products, having similar antimicrobial effects against the strains studied, i.e., all products being interchangeable (*24*).

In the present investigation, using previously described and validated methods, we found that one of the evaluated moxifloxacin multi-source drugs (MMA), manufactured in India, did not meet the standards required to demonstrate therapeutic equivalence with the reference product. A study conducted in Japan in 2016 evaluated three generic formulations of levofloxacin tablets, finding that two formulations did not meet the dissolution profile test standards and their in vitro antimicrobial activity was significantly lower compared to brand name levofloxacin (*6*). Another study carried out in the United Arab Emirates in 2017 evaluated five multi-source products of amoxicillin/clavulanic acid tablets (875 mg/125 mg), finding that only three products were bioequivalent with the innovator based on dissolution profiles (i.e., releasing more than 85% of the amount declared in the first 15 minutes) (*25*). A study carried out in 2017 showed that of 10

multi-source products of ciprofloxacin (500 mg tablets; four from South Africa and six from India), only five (two from South Africa and three from India) were bioequivalent with the reference product because they met the bio-exemption criteria proposed by the WHO (*26*). Similar results were obtained by a study carried out in India in 2017, which evaluated dissolution and bioequivalence profiles in healthy volunteers, finding that a multi-source product of amoxicillin capsules (500 mg) was not bioequivalent with the reference product (*27*). Similarly, a dissolution study carried out in Peru in 2019 found that only two of four tested multi-source products of amoxicillin (500 mg capsules) were therapeutic equivalents with the reference product (*28*).

On the other hand, an important factor that was also evaluated in the present investigation is the content of active pharmaceutical ingredient (API) that is declared in the label, as determined by chromatography, as a factor for comparing therapeutic equivalence between innovative and multi-source products. The amount of API should be between 90% and 110% of the label amount to meet the required WHO standard. A 2020 study conducted in India found that a generic product of 300-mg isoniazid tablets did not contain the minimum amount of API (*29*). In the present study, all the multi-source products evaluated (400 mg moxifloxacin tablets) met the required amount of API.

In the present investigation, one of the multi-source products (MMA) of 400 mg moxifloxacin, manufactured in India, did not meet the requirements for therapeutic equivalence with the reference product. Furthermore, despite having the required amount of API, the MMA product failed the similarity factor (f_2) analysis.

Therefore, the present study highlights the importance of carrying out controlled studies of therapeutic equivalence for the evaluation of biopharmaceutical quality of multi-source antibiotics used in the population, and thus be able to reduce the global rates of antimicrobial resistance. This quality is directly related not only to the API but also to the excipients used in the dosage form.

CONCLUSION

In conclusion, the present investigation demonstrated that in Lima, Peru, three moxifloxacin (400 mg) multi-source products were therapeutically equivalent with the innovator brand, and one product was not.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to the article.

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