Therapeutic Equivalence of Multisource Drugs Assessed by In Vitro Dissolution Studies: Amoxicillin/Clavulanic Acid Tablets

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ABSTRACT

The objective of this study was to determine the in vitro therapeutic equivalence of multisource amoxicillin/clavulanic acid (875 mg/125 mg) tablets to establish their interchangeability with the reference product. Six multisource products manufactured in Peru, Colombia, Argentina, Mexico, and India were analyzed. The reference product was Augmentin (875/125 mg) coated tablets (Smithkline Beecham LTD, UK) purchased from pharmaceutical establishments in Peru. Quality control and dissolution tests were performed. For dissolution tests, we used a validated ultraviolet-visible spectrophotometry method to determine the percentage of drugs released. Similarity factor (f2) analysis was used to establish therapeutic equivalence of the dissolution profiles, which were considered equivalent if f2 values were between 50 and 100. Amoxicillin content was 101.3% for the reference product and 97.0–105.0% for the multisource products. Clavulanic acid content was 104.0% for the reference and 99.0–109.0% for the multisource products. For amoxicillin, five of the six multisource products passed the f2 test at pH 4.5 and four passed the f2 test at pH 6.8. For clavulanic acid, five of the six multisource products passed the f2 test at pH 6.8. In conclusion, two out of six multisource amoxicillin/clavulanic acid tablets (manufactured in Peru and Colombia) are not interchangeable with the reference product based on comparison of in vitro drug release profiles.

Keywords: Therapeutic equivalency, amoxicillin, clavulanic acid, bioequivalent drugs, dissolution

INTRODUCTION

Worldwide, the lack of regulation on bioequivalence allows the commercialization of low-quality medicines (1). There are concerns about the empirical choice and overuse of antibiotics, especially because there are multisource products without therapeutic equivalence (2). Therefore, it is recommended to evaluate the quality of multisource drugs using guidelines proposed by regulatory agencies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (3).

In 2017, the World Health Organization (WHO) evaluated pharmaceutical products from various laboratories in low- and middle-income countries, and they reported that 33.6% of products were substandard or falsified medicines (4). Of these, 7.2% were antibiotics (4). In emerging and developing countries, substandard medicines are widespread and pose a threat to public health because they can inadvertently lead to healthcare failure, antibiotic resistance, and community spread of disease or death (5). Ozawa et al. assessed the prevalence of substandard and counterfeit medicines in low- and middle-income countries across various regions including Africa, Asia, South America (Peru, Ecuador, Colombia, Brazil, Bolivia, and Venezuela), Mexico, and Europe (6). They reported that 13.6% of medications were low quality, with 12.4% of those being antibiotics (6).

According to the U.S. FDA, low-quality drugs account for up to 25% of medicines in developing countries and approximately 10% worldwide (7). Antibiotics such as ampicillin, amoxicillin/clavulanic acid, doxycycline, cloxacillin, and chloramphenicol have
the highest risk of being counterfeit or substandard due to poor quality control at different levels (8). In addition, substitution of innovative drugs with generic antibiotics continues to generate controversy regarding their efficacy, as contradictory results have been reported (9, 10). One option for establishing therapeutic equivalence between generic medicines and reference products is through in vitro dissolution testing, which may predict the in vivo drug release profile. This applies to highly soluble drugs according to the Biopharmaceutical Classification System (BCS) (11). Therapeutic equivalence is an attribute that allows for the interchangeability of safe and effective drugs (12).

Amoxicillin/clavulanic acid is an essential antibiotic used to treat respiratory tract, genitourinary tract, skin and soft tissue, and bone and joint infections (13). It is also part of the treatment regimen for multidrug-resistant tuberculosis (MDR TB) proposed by the Ministry of Health of Peru and the WHO (14). According to the BCS, amoxicillin/clavulanic acid is classified as class I and III (13). In Peru, amoxicillin/clavulanic acid is available in tablet form (875 mg/125 mg and 500 mg/125mg) as well as oral suspension (600 mg/42.9 mg in 5 mL, 400 mg/57 mg in 5 mL, and 250 mg/62.5 mg in 5 mL) (15). In México, amoxicillin/clavulanic acid is available in the same dosage forms as in Peru (16).

In recent years, there has been a global increase in the resistance of various microorganisms to amoxicillin/clavulanic acid. Chelkeba et al. reported a 35% resistance rate of Staphylococcus aureus to amoxicillin/clavulanic acid in Ethiopia (17). Similarly, Qin et al. reported that in China, the resistance of Salmonella spp. to amoxicillin/clavulanic acid has been increasing, ranging from 25% to 50% (18). Khademi et al. identified that in Iran, the resistance of Streptococcus pyogenes to amoxicillin/clavulanic acid was as high as 89.5% (19). Monteiro et al. reported that in some locations in Africa, the resistance of Escherichia coli to amoxicillin/clavulanic acid ranges from 20.1% to 48.6% (20).

In Peru, no biopharmaceutical quality studies of amoxicillin/clavulanic acid have been conducted; however, there are data on microbial resistance to this antibiotic that suggest a lack of therapeutic efficacy for some formulations. Raraz-Vida et al. examined the prevalence of resistant strains of urinary tract infection caused by E. coli and S. saprophyticus in a public hospital in Peru (21). The study found that 23.1% of E. coli strains and 100% of S. saprophyticus strains were resistant to amoxicillin/clavulanic acid (21). Similarly, Tamayo-Contreras et al. reported that the resistance of E. coli strains to amoxicillin/clavulanic acid was 26% in Peruvian patients (22).

The objective of this research was to compare the therapeutic equivalence multisource products containing amoxicillin/clavulanic acid (875 mg/125 mg) manufactured in Latin American and Indian countries with the reference product using in vitro dissolution studies.

METHODS

Chemicals

We used lithium clavulanate primary standard (United States Pharmacopeia, USP) and amoxicillin trihydrate secondary standard with traceability to a primary standard. Sodium phosphate monobasic monohydrate (Fisher Scientific, USA), high performance liquid chromatography (HPLC)-grade methanol (Merck, Germany), potassium phosphate monobasic (Merck), phosphoric acid (J.T. Baker, USA), hydrochloric acid (Merck, France), sodium chloride (J.T. Baker, Mexico), sodium acetate anhydrous (J.T. Baker, USA), glacial acetic acid (J.T. Baker, Mexico), and sodium hydroxide (Merck), all of which were of analytical grade. HPLC-grade water (18.2 MΩ) was obtained through a Milli-Q Advantage A10 water purifier (Merck, France).

Amoxicillin/Clavulanic Acid Tablets

The reference product was Augmentin (875/125 mg) coated tablets (Smithkline Beecham LTD, UK), purchased from pharmaceutical establishments in Peru. Six multisource products containing 875 mg amoxicillin and 125 mg clavulanic acid that were manufactured by different companies in Peru, Colombia, Argentina, Mexico, and India were analyzed (Table 1). Four multisource products were purchased in Lima, Peru (products A–D), and two were purchased in Mexico City, Mexico (products E and F). All products were used at least 12 mos. prior to expiration.
Table 1. Amoxicillin/Clavulanic Acid Tablets Used for Dissolution Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>Manufacturer Location</th>
<th>Manufacturer Name</th>
<th>Lot No.</th>
<th>Exp. Date</th>
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<tbody>
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<td>Smithkline Beecham LTD</td>
<td>NY8N</td>
<td>08/2022</td>
</tr>
<tr>
<td>A</td>
<td>Amoden</td>
<td>Lima, Peru</td>
<td>Laboratorio Portugal SRL</td>
<td>2054921</td>
<td>05/2023</td>
</tr>
<tr>
<td>B</td>
<td>Clavumox</td>
<td>Bogota, Colombia</td>
<td>Syntofarma SA</td>
<td>01900521</td>
<td>05/2023</td>
</tr>
<tr>
<td>C</td>
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<td>Roemmers S.A.I.C.F.</td>
<td>00121</td>
<td>03/2023</td>
</tr>
<tr>
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<td>Clacidomox</td>
<td>Tamil Nadu, India</td>
<td>Medopharm Private Limited</td>
<td>21495001</td>
<td>12/2022</td>
</tr>
<tr>
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</table>

Quality Control Tests
Before conducting the dissolution tests, the medications underwent quality control tests to assess content and uniformity of dosage units. All experiments were conducted according to USP 43, in general chapters <621>, <711>, and <905> (23).

Preparation of Dissolution Media
Simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8) were prepared according to the International Pharmacopoeia (4th edition) (24). All media were prepared without enzymes. We filtered the media through 0.45-µm nylon and degassed it under a vacuum with mechanical agitation.

Dissolution Studies
For all dissolution tests, an eight-vessel Hanson Vision Elite G2 dissolution system (USP apparatus 2; paddle) was used with a UV-VIS spectrophotometer (Hanson V-650) with 900 mL of medium at 75 rpm for 60 minutes. Samples (10 mL) were taken manually with fresh media replacement at 5, 10, 15, 30, 45, and 60 minutes. The dissolved amounts were determined by ultra-HPLC according to WHO Technical Report 937 (25).

Analytical Quantification
Analytical quantification was performed by ultra-HPLC at 220 nm according to the USP monograph for amoxicillin/clavulanic acid tablets (23).

Method Validation
The dissolution method was validated according to the following parameters: linearity, precision, accuracy, stability, and the influence of the filter. This was done in accordance with the Technical Guide of the Public Health Institute of Chile, International Conference on Harmonization (ICH) guidelines, and internal technical procedures (26, 27). All validation parameters with within acceptable limits.

Statistical Analysis
Statistical comparison of dissolution profiles was carried out by calculating the similarity factor ($f_2$) (25). To establish the similarity of the curves, the $f_2$ values must be between 50 and 100. Microsoft Excel (2014) was used for the calculations.

RESULTS
All multisource products and the reference met the quality criteria according to USP 43. The acceptance range for drug content is 90.0–120.0% of the declared amount. The content of amoxicillin was 101.3% in the reference product, and the multisource drugs contained 103.7% (A), 97.2% (B), 104.5% (C), 97.0% (D), 105.0% (E), and 102.8% (F). Similarly, the content of clavulanic acid was 104.0% in the reference product, and the multisource drugs contained 109.0% (A), 105.0% (B), 99.1% (C), 106.6% (D), 99.0% (E), and 103.9% (F).

In all cases, the WHO requirement for comparison of dissolution profiles was met, i.e., < 5% difference in drug content between the reference and multisource products, as shown in Figures 1 and 2. Out of the six multisource products, only four can be considered interchangeable with the reference product (i.e., $f_2$ 50–100), as shown in Table 2. If at 15 minutes the mean dissolved amount was greater than 85% of the declared amount, then $f_2$ was not calculated (28).

Table 2. Similarity Factors ($f_2$) of Multisource Products

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<tr>
<th>Product</th>
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<th>pH 6.8</th>
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<td>46</td>
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<td>*</td>
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<td>35</td>
<td>*</td>
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<td>C</td>
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*Not calculated.
DISCUSSION

Antimicrobial resistance is a global public health problem, and one solution is to assess the biopharmaceutical quality of antibiotics administered to the population. In this study, in vitro therapeutic equivalence was established based on drug release profiles for four out of six multisource tablets containing amoxicillin/clavulanic acid when compared with the reference product.

Similar results were obtained by Grande-Ortiz et al., who evaluated the in vitro therapeutic equivalence of four multisource amoxicillin (500 mg) capsules in Peru through dissolution profile and chromatography tests, and two out of four products were therapeutically equivalent to the reference product (29). Hofsaess et al. evaluated the in vitro bioequivalence of five generic amoxicillin (500 mg)
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Table 3: Percentage of Drug Released from Reference (Innovator) and Multi-Source Products (MMA–MMF) at Three Different pH Levels.
tablets in Germany using dissolution profile assays, and three out of five products were bioequivalent with the reference (30). de Mattos et al. evaluated the bioequivalence of three generic amoxicillin suspensions (500 mg/5 mL) in Brazil using pharmacokinetic (PK) profile assays in rats and in vitro microbiological potency assays; two products were bioequivalent based on microbiological potency, and one was bioequivalent based on its PK profile (31). In Italy, Del Taca et al. evaluated the bioequivalence of two generic amoxicillin (1 g) tablets in healthy adults using PK parameters (AUC and $C_{\text{max}}$), and only one formulation was bioequivalent to the branded product (32). In India, Pathak et al. evaluated the bioequivalence of one multisource capsule formulation of amoxicillin in healthy adults using PK parameters (AUC, $C_{\text{max}}$, $T_{\text{max}}$, and Minimum Inhibitory Concentration [MIC]), and the formulation was not bioequivalent to the innovator product (33).

On the other hand, some investigations have found that all multisource drugs did meet the standards of therapeutic equivalence. For example, Avianto et al. evaluated the bioequivalence of five generic amoxicillin (500 mg) tablets in Indonesia using an in vitro microbiological assay that compared antimicrobial potencies by inhibition halos against S. aureus and E. coli, and all five formulations were bioequivalent to the innovator product (34). AlGaai et al. evaluated bioequivalence of two multisource formulations of amoxicillin (1 g) in Germany using PK parameters and chromatography assays in the plasma of healthy volunteers, and both formulations were therapeutically equivalent to the reference (35).

In addition, similar results as those obtained in the present study have been reported in other investigations of multisource amoxicillin/clavulanic acid tablets. For example, AlTabakha et al. assessed bioequivalence of five generic amoxicillin/clavulanic acid (875 mg/125 mg) tablets in the United Arab Emirates using chromatography, weight variation, crushing strength, and dissolution profile; only three out of five products were bioequivalent to the innovator product, Augmentin (36). In Nigeria, Olanrewaju et al. evaluated bioequivalence of six generic amoxicillin/clavulanic acid (500 mg/125 mg) tablets by analyzing the physicochemical characteristics of the preparations (e.g., weight uniformity, friability, hardness, disintegration, dissolution rate); only five out of six products were bioequivalent with Augmentin (37).

By contrast, in Venezuela, Cohen-Sabban et al. reported bioequivalence of a multisource amoxicillin/clavulanic acid (875 mg/125 mg) tablet with Augmentin based on serum levels by HPLC in healthy volunteers coupled with UV spectrophotometry (38). In Germany, Sourgens et al. reported therapeutic bioequivalence of a generic product (amoxicillin/clavulanic acid tablets 875 mg/125 mg) with Augmentin based on PK parameters ($C_{\text{max}}$ and AUC) in healthy volunteers (39).

Comparison of dissolution profiles is the most appropriate method to establish therapeutic equivalence with in vitro studies of solid drug formulations. Various investigations have reported that amoxicillin/clavulanic acid formulations have demonstrated bioequivalence for both compounds (amoxicillin and clavulanic acid) compared to the reference drug. However, there are investigations with controversial results. For example, in Pakistan, Waqas et al. reported that two generic products did not meet criteria for bioequivalence with the innovator product based on amoxicillin release but did for clavulanic acid (40). Although some PK studies have determined that the therapeutic effect of the amoxicillin/clavulanic acid formulation can be maintained if bioequivalence of amoxicillin alone is established, in vitro bioequivalence of both compounds should be established to ensure therapeutic success (13).

For determination of therapeutic equivalence of multisource antibiotics, the results from in vitro and in vivo studies may complement or differ from each other. To determine the therapeutic equivalence of certain antibiotics, such as norfloxacin and metronidazole, joint in vitro and in vivo evaluations of the various formulations should be performed (41, 42). Using a single model may not accurately determine the therapeutic equivalence between generic and innovator brands. Rodriguez et al. performed in vitro and in vivo bioequivalence evaluations of 11 generic formulations of oxacillin...
versus the innovator (Prostafilina) in Colombia (43). They found that seven out of 11 generic formulations met in vitro bioequivalence, but none were therapeutically equivalent in vivo (43).

Therapeutic equivalence can vary depending on the dosage form and country of origin. Therefore, future research should evaluate multiple dosage forms of amoxicillin/clavulanic acid manufactured in countries other than those evaluated herein. In addition, research with human biological samples is needed to correlate the in vivo and in vitro results.

CONCLUSIONS

The present investigation demonstrated that at least two multisource products containing amoxicillin/clavulanic acid (875 mg/125 mg tablets), manufactured in Peru and Colombia, are not interchangeable with the reference product based on dissolution profiles.

DISCLOSURES

This study was supported by the Universidad Nacional Mayor de San Marcos (UNMSM) (code: A21050011). The authors were responsible for the study design, data collection and analysis, decision to publish, and preparation of the manuscript.

The authors have no conflicts of interest.

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