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Comparative Study of Brand and Generics Ciprofloxacin Tablets Available in the Saudi Market

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ABSTRACT

Introduction: Ciprofloxacin is a fluoroquinolone class of antibiotics with broad-spectrum antibacterial activity. Biowaiver studies of generic ciprofloxacin products can be used to establish bioequivalence with the reference product. *Methods*: The experiments are carried out using the reference product, Ciprobay (Bayer, Germany), and three generic products, Cipromax (Spimaco Addwaeih, Saudi Arabia), Ciproxen (Jamjoom Pharma, Saudi Arabia), and Quinox (Tabuk Pharmaceuticals, Saudi Arabia). In vitro tests were done according to the United States Pharmacopeia (USP) standards to evaluate the physicochemical characteristics including weight variation, hardness, thickness, disintegration, and dissolution. *Results*: All four products tested met the standard limits for physical and physicochemical parameters. In addition, the dissolution test indicated that the three generics are equivalent to the reference product in terms of quality, and all products released more than 80% of drug within 30 minutes. *Conclusion:* The four tested brands of ciprofloxacin can be used interchangeably.

KEYWORDS: Ciprofloxacin, bioequivalence, physicochemical parameters, dissolution

INTRODUCTION

Choosing medicine from different generic products from the market is a necessary procedure in therapy management that has a medical practitioner's attention (*1*). Bioequivalence between the reference brand and generic products is based on having similar bioavailability, which is defined as a measurement of the extent of an active ingredient that reaches systemic circulation. Bioavailability is a risk possibility index of chemicals affecting human health and surroundings (*2*). Therefore, bioequivalence studies are essential to investigate and evaluate if generic medicines have the same characteristics as the reference brand in terms of purity and quality of materials and dissolution and disintegration. Suppose that some generics are not bioequivalent to the reference brand. This may cause severe problems for patients, like sub-therapeutic effects or toxicity without benefit. For this reason, some physicians do not trust local generic products (*3*).

Generic medicines have been established in the international healthcare market to reduce medication expenditures (*4*). The World Health Organization (WHO) has encouraged the use of generic products to decrease the burden of drug spending on the government's healthcare

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system, but this should be backed with enough proof for the replacement of a brand with a quality generic, and this could not be accomplished without bioequivalence studies (*5*). In Saudi Arabia, several problems in medication production, marketing, or distribution leads to withdrawal from the market by the Saudi Food and Drug Administration (SFDA), such as absence of the batch number, production date, and expiration date on the external packaging (*6*). Other products have been withdrawn for not conforming to the manufacturer's specifications (*6*). Adding another source of the active ingredient without the approval of the SFDA also led to withdrawal of medicines from the market (*6*). There have been many generics withdrawn from the market because of fundamental bioequivalence problems (*6*).

Because of the time and the money consumed by in vivo studies, a biowaiver allows researchers to use an in vitro dissolution test to establish bioequivalence for certain drugs under certain circumstances and conditions (*7*, *8*).

This research will investigate quinolones discovered in 1962 (*9*). The first generation of quinolone was synthetic nalidixic acid in 1962, which has excellent antimicrobial activity against gram-negative bacteria (*9*). Fluoroquinolones are one of the antibiotics used against gram-positive and gram-negative bacterial infections. It is considered a fourth-generation antibiotic and is used worldwide because of its preferred pharmacokinetic features (*10*). It includes ciprofloxacin, which is a second-generation fluoroquinolone used to treat various types of infections like skin infections, urinary tract infections (UTIs), bone and joint infections, and respiratory tract infections (*11*).

Fake or low-quality medicines are among the most critical reasons for mortality, morbidity, and loss of confidence among the public regarding medicines and health structures (*12*). Ciprofloxacin was discovered by Bayer Pharmaceuticals (Germany) in the 1990s, and it is one of the most effective fluoroquinolones class of antibiotics with broad-spectrum antibacterial activity (*13*, *14*). Ciprofloxacin is one of the first choices physicians prescribe as empirical and sometimes after laboratory investigations for most infections. For patients to use generic ciprofloxacin interchangeably, bioequivalence must be established with the reference brand product. This means that we should monitor post-marketing drug quality (*13*).

Several studies have been conducted to assess the bioavailability of generic ciprofloxacin in different countries. A study conducted in Nigeria with six generic ciprofloxacin tablets (500 mg) (Ciproval, Ciprogem, Ciprobom, Cipro-J, Ivacip, and Vitapro) found that three were not equivalent with innovator brand (*13*). Another study performed in Singapore established bioequivalence between two oral formulations of ciprofloxacin (Bayer and RAZA pharmaniaga) (*15*). A study in Bangladesh reported that five generics (DFX, Neofloxin, Flontin, Beuflox, and Ciprocin) were interchangeable (*16*). A study in India found six different local products to be interchangeable (*17*). A 2014 study in UAE reported that six generics were interchangeable with the branded ciprofloxacin product (*18*). Another study conducted in the UAE compared five generics with Bayer and found them to be interchangeable (*19*). A study in Saudi Arabia of two generics (Ciflox and Bactall) established bioequivalence with Bayer (*20*). Lastly, a study Bangladesh established bioequivalence with five generics and Bayer (*21*).

This study aims to evaluate the potential interchangeability of four different products of ciprofloxacin (500 mg) tablets available in the Saudi market, including the reference product

(Ciprobay, Bayer) and three generic products, thereby ensuring physicians and patients that these generic medicines are equally effective as the reference brand.

METHODS

Materials

Ciprofloxacin tablets used in this study were purchased from local pharmacies and included one reference product, Ciprobay (exp. Date: 12/05/2020, batch no. BXHGOL4A, Bayer Pharma Ag, Germany), and three generic products: Cipromax (exp. date: 10/2019, batch no. 106694, Saudi Pharmaceutical Industries & Medical Appliances Corporation [Spimaco], Saudi Arabia), Ciproxen (exp. date: 10/2021, batch no. UL0189, Jamjoom Pharmaceuticals Company, Saudi Arabia), and Quinox (exp. date: 03/2021, batch no. 8KB321, Tabuk Pharmaceuticals, Saudi Arabia). Hydrochloric acid was of analytical grade.

Weight Variation

From each product, 20 tablets were weighted on the weighing balance (A&D Company Ltd., Tokyo, Japan) and the standard deviation calculation.

Tablets Dimension and Hardness Measurement

Ten tablets from each product were measured separately for length and thickness. A hardness tester (EBT-2PRL, Electrolab) was used. The results were reported as mean (mm) and percentage relative standard deviation (%RSD) for length and thickness, whereas hardness was reported in kg/cm^2.

Friability Test

Twenty tablets were taken from each product. The tablets were dedusted, weighed together (W1), and tested using a friabilator (D-63150 Heustenstamm, Germany) with 100 revolutions (i.e., 25 revolutions/minute for 4 minutes). The tablets were reweighed (W2), and percentage friability was calculated by comparing W1 and W2.

Disintegration Test

A disintegration apparatus (DIST-3, Germany) was used for the disintegration tests with. For uncoated tablets, the disintegration medium used was 0.1 N hydrochloric acid, maintained at 37 ± 0.5 °C. Six tablets from each batch were used for the test. The mean disintegration time was recorded as the time required for the tablets to disintegrate into particles capable of passing through the screen into the disintegration medium (*22*).

Standard Calibration Curve for Ciprofloxacin

Standard ciprofloxacin hydrochloride powder (100 mg) was weighed accurately and dissolved in 10 mL of distilled water in a volumetric flask then sonicated for 20 minutes to get a stock clear solution, then diluted up to 100 mL to get 1000 µg/mL concentration of the standard stock solution. From this stock solution, 10 mL was diluted to 100 mL in a volumetric flask to get 100 µg/mL of drug concentration. Then, using this stock solution for further serial dilutions, six different concentrations were prepared at 5, 10, 15, 20, 25, and 30 µg/mL. The average absorbance values of these concentrations were measured at 277 nm using a UV

spectrophotometer (Shimadzu, UV-1800) (n = 6). The standard graph was plotted by taking absorbance values on y-axis and concentration values on x-axis.

Dissolution Test

Dissolution tests were performed using the *USP* general method in distilled water (900 mL) at 37 ± 0.5 °C with a rotating paddle apparatus (Electrolab, Edt 08lx) at 50 rpm. At specified time points, samples (5 mL) were withdrawn from midway between the top of the rotating paddle and the surface of the dissolution medium and replaced with fresh dissolution medium to preserve sink conditions. The samples were diluted with distilled water and filtered with a 45-µm Millipore membrane filter and measured at 277 nm using the UV spectrophotometer, and the corresponding concentration was calculated using the equation from the standard calibration curve. The cumulative percent of ciprofloxacin HCL released over time was plotted for each formulation. The amount dissolved in 5, 10, 15, 20, 25, 30, 40, 50, and 60 min was obtained for each type of Ciprofloxacin HCL. All determinations were in quadruplicate.

RESULTS AND DISCUSSION

Fluoroquinolones are used against gram-positive and gram-negative bacterial infections (*22*). Several generics of ciprofloxacin tablets are available in Saudi Arabia, leading to confusion about their cost and quality.

As shown in Tables 1 and 2, weight variations and friability were within the acceptable limits of ± 5% and ±1%, respectively. The most weight variation was noted for Cipromax, but it was still within the standard limit of USP. No product had friability greater than 1.0% (range: 0.02–0.09%). Hardness and thickness were within the acceptable limits of ± 5%. Quinox and Ciprobay had the highest hardness values, and tablet thickness for all products ranged from 5.35–6.08 mm.

Table 1. Hardness, Thickness, and Length of Ciprofloxacin Tablets (N = 6)

Product	Hardness (kg/cm^2)	Thickness (mm), Mean ± 5%	Length (mm), Mean ± SD
Ciprobay	9	5.64 ± 2.4%	18.17 ± 0.06
Cipromax	7.7	6.08 ± 0.34%	18.31 ± 0.176
Ciproxen	8.8	5.35 ± 0.35%	19.42 ± 0.084
Quinox	9.9	5.78 ± 3.31	18.12 ± 0.09

Table 2. Mean Weight and Friability Tests of 4 Ciprofloxacin Tablet Products (N = 6)

Product	Weight (mg) ± 5%	Friability (%) ± 1%
Ciprobay	765 ± 1.4%	0.09
Cipromax	830 ± 3%	0.02
Ciproxen	678 ± 1.9%	0.06
Quinox	772 ± 0.9%	0.06

All four products passed the disintegration test (i.e., within 30 minutes), as shown in Figure 1. The percentage of drug release was measured using the calibration curve with R^2 = 0.9999 (Fig. 2). Ciproxen had a dissolution profile identical to Ciprobay, with almost 90% drug release in less than 10 minutes, and the other two brands, Quinox and Cipromax, took about 15 and 20 minutes to reach 90% release, respectively. All tested tablets met the USP specification. Almost 100% of the drug was released within 30 minutes (Fig. 3).

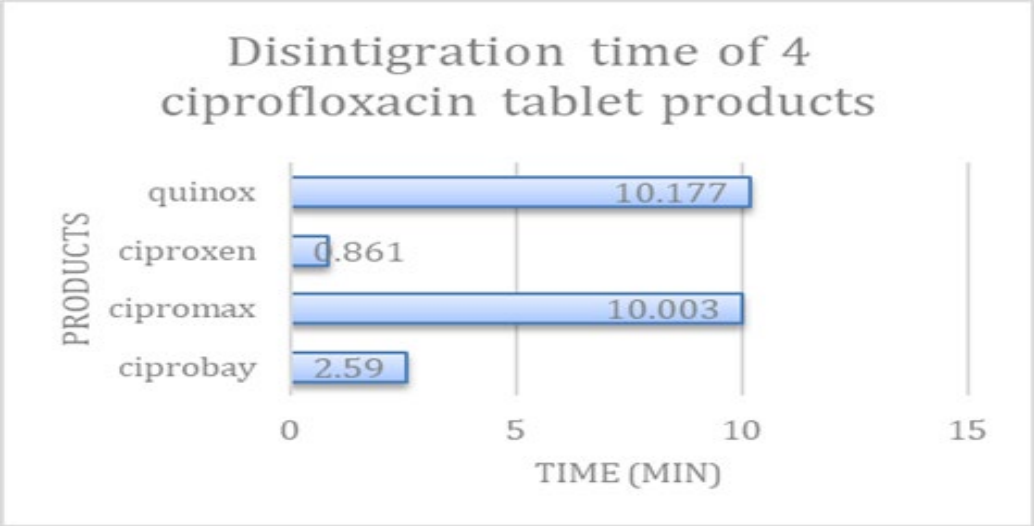

Figure 1. Disintegration time of ciprofloxacin tablet products.

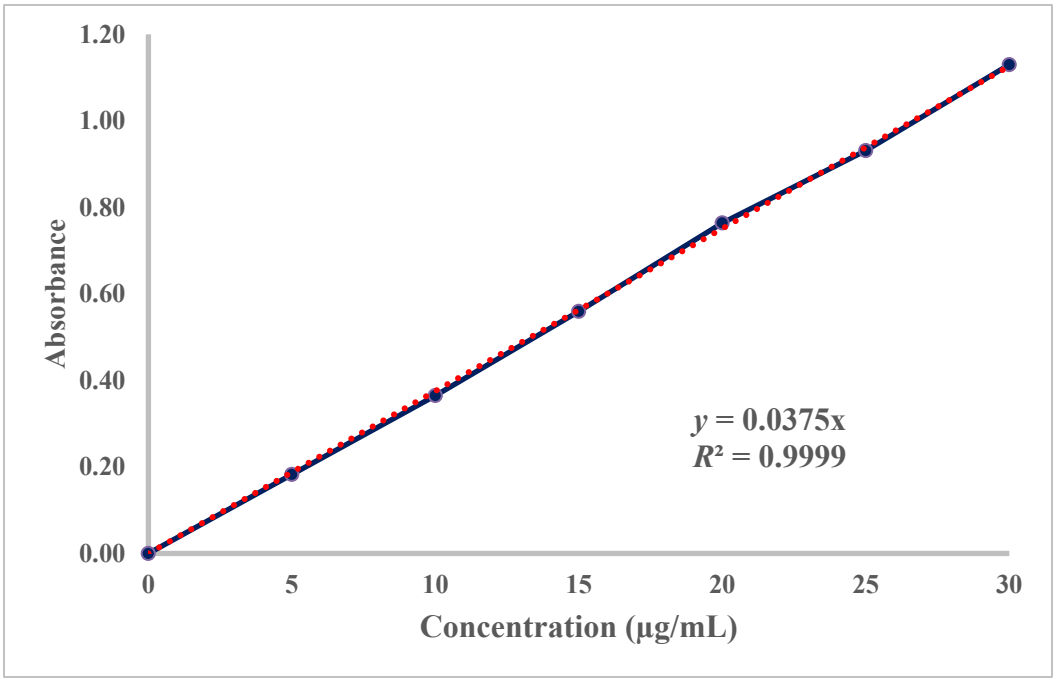

Figure 2. Standard calibration curve for ciprofloxacin.

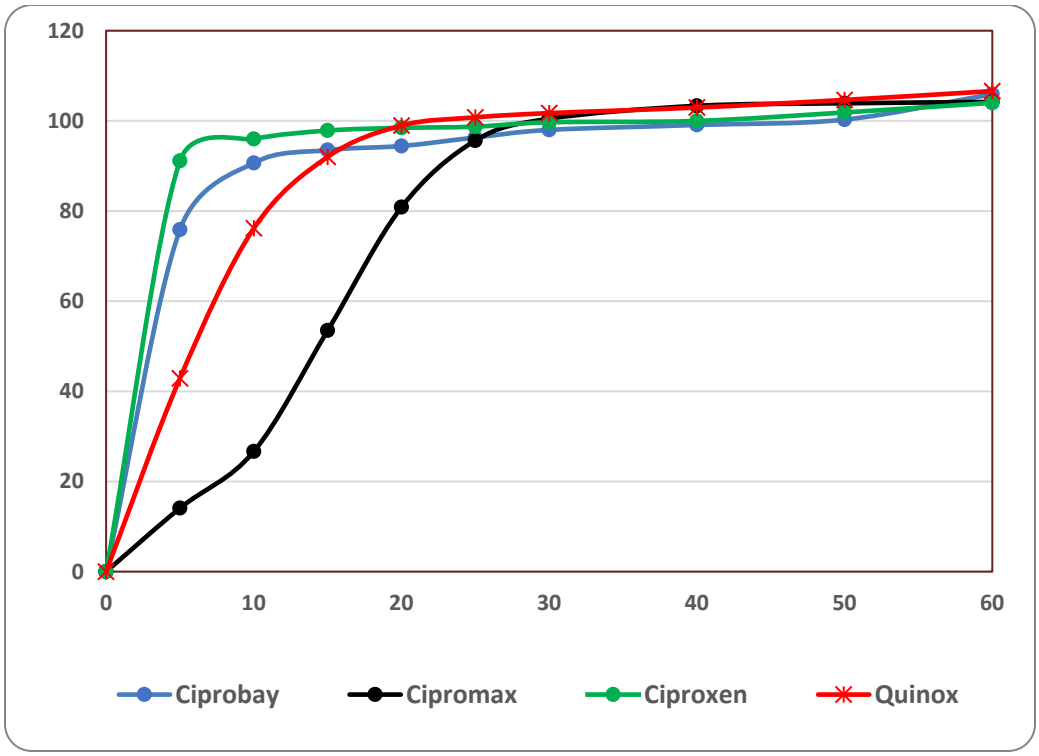

Figure 3. Dissolution profile of ciprofloxacin tablets.

CONCLUSION

The three tested generic ciprofloxacin tablets achieved results as good as the brand Ciprobay (Bayer, Germany) in terms of pharmaceutical characterization and, most importantly, drug release. Thus, these four products can be used interchangeably. Physicians should be provided with information on the bioequivalence and price differences between the available brands and generics of ciprofloxacin products in the Saudi market for potential cost savings.

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CONFLICT OF INTEREST

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

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