Available online on 15.10.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

In Vitro Quality Evaluation of Ciprofloxacin Tablets Marketed in Dessie, Ethiopia

Haile Kassahun Desta*, Tekleab Teka Teklehaimanot

Department of Pharmacy, College of Medicine and Health sciences, Wollo University, Dessie, Ethiopia, P.O. Box, 1145

ABSTRACT

Good quality medicines are a prerequisite for a successful treatment. Post marketing surveillance is very crucial to ensure product quality and eliminating substandard products to be distributed and, consequently, ensure better patient clinical outcome. Hence, this study assesses quality of six brands of ciprofloxacin tablets marketed in Dessie, Ethiopia using *in vitro* quality control tests. Weight variation test, disintegration test, dissolution test and assay for the content of active ingredients was done according to United sates Pharmacopoeia, 2007. The percentage content of ciprofloxacin tablets were within the range of 90-110% and the disintegration time was found between 2.375- 6.31 minutes. In addition, ciprofloxacin tablets released more than 80% of the drug after 30 minutes. Hence, all brands of ciprofloxacin tablets met the quality control parameters as per United States Pharmacopoeial specifications.

Key words: Ciprofloxacin; Quality; Substandard; Pharmacopoeial specifications

Article Info: Received 02 July 2019; Review Completed 19 Sep 2019; Accepted 24 Sep 2019; Available online 15 Oct 2019

Desta HK, Teklehaimanot TT, *In Vitro* Quality Evaluation of Ciprofloxacin Tablets Marketed in Dessie, Ethiopia, Journal of Drug Delivery and Therapeutics. 2019; 9(5-s):7-10 http://dx.doi.org/10.22270/jddt.v9i5-s.3610

***Address for Correspondence:**

Haile Kassahun Desta, Department of Pharmacy, College of Medicine and Health sciences, Wollo University, Dessie, Ethiopia, P.O. Box, 1145

1. INTRODUCTION

Antibiotics are among the most frequently prescribed medications in modern medicine, and are used in the management of microbial infections. Ciprofloxacin (1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinolone-3-carboxylic acid) is the most potent fluoroquinolone derivative having a broader spectrum of antibacterial activity against Gram-negative and Gram-positive aerobic and anaerobic organisms [1, 2]. It acts by interfering with microbial DNA synthesis [3, 4]. The quantitative analysis of ciprofloxacin tablets is important to obtain the same pharmaceutical equivalence of generics as compared to innovator products. The potency of antibiotics can be determined by chemical and biological methods. These methods include microbiological assays, automated chemical assays (e.g. High performance liquid chromatography (HPLC)), immunological assays (e.g. fluorescence polarization immune assay, fluorescence immunoassay) and radioimmunoassay [5].

Good quality medicines are a prerequisite for a successful treatment. Quality control is a process that is carried out to ensure a desired level of quality in a product or service [6].The most important purpose of quality control is to make sure that the public can avail of safe and therapeutically effective medicine. In Ethiopia, the existing weak regulatory system, lack of informal market control, weak port control, and long border that Ethiopia shares with neighboring countries, may contribute to proliferation of poor quality medicines into Ethiopian market [7].

The prevalence of poor-quality antimicrobial medicines, are widespread in developing countries [8]. Counterfeit medicines may be brand and/or generic products with falsified packaging and may have too little, wrong, or no active ingredient. The use of counterfeit and/or substandard drugs can cause increased morbidity and mortality, increased health costs, loss of confidence in the health care system and in the drug regulatory authorities. Hence, evaluating the quality of essential medicines is crucial for delivering quality health services [9].

Generic medicines are those where patent protection has expired and which may be produced by manufacturers other than the innovator company. Expiration of drug patents leads to several companies producing generic forms of drugs [10]. The introduction of generic drug products from multiple sources into the health care delivery system of many developing countries may lead to proliferation of substandard drug products [11]. Hence, Post marketing surveillance is very crucial to ensure product quality and eliminating substandard products to be distributed and, consequently, ensure better patient clinical outcome.

Globally, there are several generics of ciprofloxacin tablets and several studies have been done on *in vitro* quality evaluation of generics of ciprofloxacin tablets. Igboasoiyi et al., (2018) showed seven out of the ten brands of

ciprofloxacin tablets analyzed (70%) met the British Pharmacopoeia specification for tablet purity [12]. Joda et al. also (2018) studied sixteen ciprofloxacin brands in LAGOS, NIGERIA and indicated that four brands (25%) did not pass the chemical assay test [13]. In addition, Adegbolagun *et al.,* (2007) reported that 40% of the brands tested in Ibadan failed the chemical test [14]. Moreover, Osonwa et al., (2018) studied 15 brands of ciprofloxacin tablets marketed in Anambra State, South eastern Nigeria and showed that all the brands complied with Pharmacopoeial standards except one brand failed dissolution test [15].

The increasing use of ciprofloxacin hydrochloride tablets recently is a result of its versatility in the management of microbiological infections [16] and necessitated the need to evaluate the quality of the various available products. Increasing the number of pharmaceuticals industries in the world leads to an increase the number of brands of ciprofloxacin in Ethiopian market. As ciprofloxacin is widely used antibiotic in Ethiopia, this study was conducted to assess the quality of different brands of ciprofloxacin 500 mg tablets marketed in Dessie, Ethiopia.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. Chemicals and reagents

The following chemicals and reagents were used in the study: HPLC grade Acetonitrile, BDH (UK), HPLC grade Methanol, phosphoric acid, and Triethylamine were obtained from Sigma-Aldrich (Germany), Hydrochloric acid (D.B.H Laboratory supplies, England) and distilled water. Standard ciprofloxacin Hydrochloride was obtained from Addis pharmaceutical factory (APF).Different products of 500 mg ciprofloxacin tablets were bought from various pharmacy retail outlets in Dessie town. The detailed descriptions of these products are presented in Table 1.

Table 1: products of ciprofloxacin tablets included in the study

Brand code	Country of origin	Batch Number	Mfg. date	Exp. date
Cipro-1	Ethiopia	22216	03/2017	03/2020
Cipro-2	India	G603564	08/2016	07/2019
Cipro-3	Germany	19823	10/2016	09/2019
Cipro-4	India	17919	05/2016	04/2019
Cipro-5	South Korea	THB606	06/2016	05/2019
Cipro-6	Cyprus	71271	01/2017	01/2022

2.1.2. Instruments and equipment: A high performance liquid chromatography (HPLC) (Agilent technologies corporation, stainless steel column (25 cm × 4.6 mm), Diode array detector,), a Pharma test dissolution tester and disintegration tester (Germany), double beam UV/VIS spectrophotometer (Shimadzu, Japan), Electronic balance (mettler toledo, Switzerland) were used for the study.

2.2. Methods

Six brands of ciprofloxacin 500 mg tablets were included in the study. Weight variation test, disintegration test, dissolution test and assay for the content of active ingredients was done as per United sates Pharmacopoeia [17].

2.2.1. Weight variation test

According to USP [17] weight variation can be used instead of content uniformity when the tablet contains 25 mg or more of an active drug or comprises 25% w/w. The test involved weighing 20 tablets individually using analytical balance from each product. The mean tablet weight and percentage deviation from the mean was calculated.

Weight variation = $(I_w - A_w)/A_w \times 100\%$

Where, I_w = Individual weight of the tablet and A_w=Average weight of the tablet

2.2.2. Disintegration time

A 900 ml beaker was filled with 0.01 N HCl and the temperature was maintained at 37 ± 0.5 °C. Six tablets were placed into the basket-rack assembly and the disintegration time was taken to be the time no particle remained on the basket of the system.

2.2.3. Dissolution test

Dissolution test was done according to USP [17] specifications using dissolution apparatus type II (Paddle apparatus). 0.01 N HCl (900 ml) at 37 ± 0.5 °C was used as a dissolution medium. The rotation of the paddle was set at 50 rpm. 10 ml sample was withdrawn at 30 min and was filtered and suitably diluted with the dissolution medium. The absorbance of the resulting solution was determined using UV-Visible spectrophotometry at 276 nm. The percentage release of ciprofloxacin was calculated from the absorbance of the test and standard solutions.

2.2.4. Assay of ciprofloxacin tablets

High pressure liquid chromatography equipped with a 278-nm detector was employed for assay of ciprofloxacin tablets. A stainless steel column (25 cm × 4.6 mm) packed with C_{18} was used. The flow rate is about 1.5 ml per minute.

Mobile phase: a filtered and degassed mixture of 0.025 M phosphoric acid, adjusted (with triethylamine) to a pH of 3.0 ± 0.1 and acetonitrile (87:13).

Standard preparation: 0.5 g of ciprofloxacin Hydrochloride standard was dissolved in a filtered and degassed mixture of 0.025 M phosphoric acid adjusted (with triethylamine) to a pH of 2.0 ± 01 and acetonitrile (87:13) and made up to100 ml. Then, 4 ml of the filtrate was taken and diluted to 100 ml to obtain a solution containing 0.2 mg of ciprofloxacin per ml.

Assay preparation: five tablets were powdered and transferred to a 500-mL volumetric flask. 400 ml of a filtered and degassed mixture of 0.025 M phosphoric acid adjusted (with triethylamine) to a pH of 2.0 ± 0.1 and acetonitrile (87:13) was added to the sample and sonicated for about 20 minutes. The sample solution was made up to volume with phosphoric acid and acetonitrile (87:13) and was mixed. Then, 4 ml of the filtrate was taken and diluted to 100 ml with phosphoric acid and acetonitrile (87:13) to obtain a solution containing the equivalent of about 0.2 mg of ciprofloxacin per ml. 10 µL of the Standard preparation and the Assay preparation was separately injected into the chromatograph and the chromatograms was recorded. The

content of ciprofloxacin was calculated from the peak areas of the chromatograms of the test and standard solutions.

2.3. Data Analysis

Data obtained was treated using Microsoft Excel 2007 and Windows SPSS Version 20. All the results were expressed as mean ± SD.

3. RESULTS AND DISCUSSION

Evaluating the quality of medicines circulating in the market is important to reduce risk of having poor quality medicines in the supply chain. Brands of ciprofloxacin tablets obtained from local market in Dessie, Ethiopia were subjected to a number of tests in order to assess quality parameters. Uniformity of dosage forms, assay, disintegration and dissolution tests are compendial standards used to assess quality of commonly available brands of ciprofloxacin tablets in Dessie, Ethiopia.

3.1. Weight variation test

Weight variation test was applied to demonstrate the uniformity of the dosage units for ciprofloxacin tablets. USP for weight variation test [17] states that more than 2 tablets should not differ from the average weight by more than 5% and none deviates by more than 10%. As shown in table 2, none of the tablets used in the study deviate from the average weight by more than 5% and hence all ciprofloxacin tablets fulfilled pharmacopeial specifications for weight variation test. Therefore, all ciprofloxacin tablets are thought to contain a uniform active pharmaceutical ingredient to give desired therapeutic response. For ciprofloxacin tablets, any weight variation obviously reflects variation in the content of active pharmaceutical ingredient [API] [14]. A large weight variation precludes good content uniformity. Patients receiving the overdose or under dose tablet, experiences unpredictable therapeutic response [18-19].

Table 2: Results of *in vitro* quality control tests of brands of ciprofloxacin 500 mg tablets

Brand	Weight variation (mg) (mean ± SD)	Disintegration time(min) ±SD	Percentage drug release (mean ±SD) at 30 min	Percentage Content (mean ±SD)
cipro-1	656.4±0.009	2.5±0.02	89.625±2.43	101.92±0.02
cipro-2	738.5±0.015	2.375±0.2	98.0275±2.13	100.85±0.002
cipro-3	735.7±0.009	4.25±0.12	95.07±2.1	99.64±0.03
cipro-4	769.96±0.023	2.47±0.007	92.8275±5.17	101.51±0.02
cipro-5	734.2±0.005	6.31±1.1	85.89±1.98	99.05±0.07
cipro-6	801±0.003	4.52±0.09	96.895±1.42	100.79±0.29

3.2. Disintegration test

According to USP specification, uncoated and film coated tablets should disintegrate within 30 min [17]. Hence, all brands of ciprofloxacin met the requirement as the disintegration time was found between 2.375- 6.31 minutes [Table 2]. Cipro-1, cipro-2 and cipro-3 had mean disintegration time of less than 3 min. cipro-5 showed the longest disintegration time.

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is a process known as disintegration [20]. Disintegration test is performed to find out that within how much time the tablet disintegrates. Disintegration test is very important for all coated & uncoated tablet because the dissolution rate of drug depends on the disintegration time, which ultimately affect the rate of absorption and subsequent bioavailability of drug [21].

3.3. Dissolution test

Dissolution test was performed to check the percentage of drug released from the tablet dosage forms and the test was done at pharamacopoeially specified time, 30 min. The amount of drug released was analyzed by UV- Visible spectroscopy. Dissolution is an important quality control parameters directly related to the absorption and bioavailability of drug.

For ciprofloxacin tablets, drug release should not be less than 80% of labeled amount in 30 minutes [17]. As shown in Table 2, all the brands of ciprofloxacin tablets studied released more than 80% within 30 min. Hence, all of the products complied with USP dissolution tolerance limits. The percentages of drug release for six brands of ciprofloxacin tablet in 30 min were in the resulting order: cipro-5(85.89%) < cipro-1 (89.625%) < cipro-4 (92.8275%) < cipro-3(95.07%) < cipro-6 (96.895%) < cipro-2 (98.0275%). Among six brands, cipro-2 was the fastest (98.0275%) and cipro-5 was the slowest (85.89%) in terms of drug release. Slow drug release from cipro-5 is in line with the longest disintegration time profile observed.

When a drug is administered orally in the form of the tablet, the absorption of the tablet depends on how fast it goes into solution, i.e., absorption of a drug is totally dependents on the dissolution of the tablet. Dissolution is a rate limiting step prior to absorption. The rate of dissolution is directly related to the efficacy of the tablet products, as well as to bioavailability difference between formulations [19].Disintegration and dissolution test suggest that the product might sufficiently release in the GIT followed by proper absorption from the GIT and thus provide desired therapeutic activity to the patient [22]. Dissolution study measures the rate and extent of drug release from any dosage form. The test usually reports the % of drug released at a specific period of time [21].

3.4. Assay of drug content

The averages of peak areas were used to calculate percentage content of the ciprofloxacin tablets. The USP states that ciprofloxacin tablets should contain not less than 90.0% and not more than 110.0% of the stated amount [17]. The percentages of the drug content of the six brands of ciprofloxacin tablet were obtained in the stated sequence: Cipro-5 (99.05%) < Cipro-3 (99.64%) < Cipro-6 (100.79%) < Cipro-2 (100.85%) < Cipro-4 (101.51%) < Cipro-1 (101.92%). The highest percentage content was obtained for cipro-1, while the least was obtained for cipro-5 [Table 2].All of the brands met USP-NF specifications for assay.

Tablets contain specific amount of active ingredient (drug) with allowable variable limit and assay of tablet ensures the amount of active ingredient which is indicative of its efficacy and stability of the product. Quantitative Analysis of drug is important to determine the strength or content of drug in a dosage form. Thus, interchangeable use of drugs containing

the same API will most probably result in a similar clinical efficacy [6]. Assay for the APIs is a critical test of quality and failure to meet the standard for content of active ingredients will result in poor quality.

4. CONCLUSIONS

This study was aimed to assess quality of six brands of ciprofloxacin tablets marketed in Dessie, Ethiopia. The present study revealed that all brands met the quality control parameters as per pharmacopoeial specifications. Hence, products of ciprofloxacin tablets available in Ethiopian market meet the quality parameter to satisfy therapeutic efficacy.

Data availability

All data are presented within the article

Conflict of interest

Authors declare no conflict of interest

Funding

This work was supported by Wollo University, Dessie, Ethiopia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgement

The authors would like to thank APF for donating standard and for providing laboratory facility. Additionally, we would like to thank the staffs of APF, Quality Control unit for their kind support and collaboration.

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