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IN VITRO COMPARATIVE ANALYSIS OF CIPROFLOXACIN- HCL TABLET AVAILABLE IN BANGLADESH

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Abstract: *Five generic ciprofloxacin HCl 500 mg tablets from different manufacturer have been evaluated to assess their bioequivalence using in vitro tests. Other general quality assessments of these tablets like assay, weigh variation, hardness, friability, disintegration and dissolution time were also determined and all these generic tablets passed compendial specifications. All the tablets contained ciprofloxacin from 90.51 ± 0.29 to 104.74 ± 1.53 of the labeled claim. The hardness of all generic tablets were within the range between 5.42 ± 0.25 to 6.76 ± 0.44 kg/cm^2. Friability test is used to evaluate the tablet resistance to abrasion. The friability (%) of all generic tablets was within the range of 0.11 to 0.22. We observed that Ciprofloxacin-HCl tablets have a disintegration time from 3.11 ± 0.54 to 11.77 ± 0.75 minutes and more than 96% of drug undergo dissolution within 30 minutes which meet compendial specifications. These results indicated that all generic ciprofloxacin HCl tablets included in this investigation were good in quality and meet compendial specifications.*

Keywords: *Ciprofloxacin-HCl, potency, weight variation, hardness, friability, disintegration time, dissolution time.*

Introduction

Bangladesh is a developing country and a percentage of populations are below the poverty line. Hence, they prefer to go for low priced medicines. To reduce the cost of medicines especially for the below poverty line group of developing countries, the World Health Organization (WHO) has continuously supported the use of generic drug products, aiming to improve the overall health care system[1]. The generic substitution could be considered when a generic copy of a reference drug contains identical amounts of the same active ingredient in the same dose formulation and route of administration as well as meet standards for strength, purity, quality, and identity[2]. Although the WHO issued guidelines for global standardization and requirements for the registration, assessment, marketing, authorization and quality control of generic drug products[3]. The generic products are usually far cheaper than its branded versions as generic manufacturers do not have the investment costs for the development of a new drug. To assist in substitution of branded with generics for affordability and at the same time achieve therapeutic efficacy, comparative studies become paramount. Bioequivalence has been described as the absence of a significant difference in the rate and extent to which the active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of

drug action (i.e., a significant difference in the bioavailability of two drug products) when they are administered at the equal molar dose under similar conditions in an appropriately designed study[4]. Two pharmaceutical products are considered to be bioequivalent when their bioavailability factors (from the same molar dose) are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse Effects[5]. Bioequivalence studies involve both *in vivo* and *in vitro* studies. With the introduction of biopharmaceutics classification system (BCS), *in vivo* bioequivalence studies could be waived for immediate release solid oral dosage forms for class I (high solubility and high permeability) and class III (high solubility and low permeability) [6-7]. Therefore, only *in vitro* testing may be utilized to determine bioequivalence for highly soluble and highly permeable drugs. Dissolution testing can serve as a tool to distinguish between acceptable and unacceptable drug products[8]. It is a surrogate marker for bioequivalence test is a practical and economic approach in developing countries, where both technology and resources are limited for *in vivo* studies. The drug release from a drug product (i.e., drug dissolution) under physiological conditions and the permeability across the gastrointestinal tract determines the drug absorption. Thus, *in vitro* dissolution may be vital in assessing *in vivo* performances.

Ciprofloxacin is a synthetic fluoroquinolone derivative with broad spectrum antibacterial activity[9].It is widely used in the treatment of urinary tract infections, lower respiratory tract infections, bacterial diarrhea, skin and soft tissue infections, bone and joint infections, gonorrhea, and in surgical prophylaxis[9-10]. In most of the cases, it would appear that for treatment of above said infections, physicians prescribe ciprofloxacin as a first choice of drug. This has resulted in higher demand and the need for increasing supply of ciprofloxacin products in generic versions for the use of bellow poverty line group in developing countries. It is a general psychology that the quality of generic products may poor as compared to leading brands available in the market. In the present study, we set out to assess the *in vitro* comparative study of some generic ciprofloxacin HCl tablets (500 mg) to justify the quality of generic substitution of ciprofloxacin brands in the Bangladeshi market. Other general quality assessments of the tablets were also determined.

Materials and Methods

Five generic ciprofloxacin HCl tablets, manufactured by different manufacturer with labeled contents of 500 mg each, were obtained from local market. All tablets were of same manufacturing year. All other reagents were of analytical grade.

Assay: Weighed and powdered 20 tablets of each generic. The powder equivalent to 100 mg of ciprofloxacin was taken and transferred to 100 ml of volumetric flask. Then, the volume made up to 100 ml with 0.1 N HCl. Vigorous shaking was done to dissolve the powdered material. After proper dilution, absorbance values were measured at the maximum wavelength (λ max) of these concentrations was measured using a UV-VIS spectrophotometer (U. V. 2440 Double beam spectrophotometer, SHIMADZU Corporation, JAPAN) against a blank. Maximum wavelength (λmax) was obtained by scanning all samples from 200 to 400 nm and this was 276 nm.

Weight Variation Determination: 20 tablets from each generic and innovator brand products were weighted individually using a weighing balance (Mettler 1180). The average weights of the tablet as well as their percentage deviation were calculated.

Hardness Testing: Hardness was determined using a tablet hardness tester (Monsanto).

Friability Testing: Friability test was conducted by employing a Friability tester USP 23 (Electro lab, India) at 25 rev/ min for 4 minutes. Percent friability was determined by using the following formula:

% Friability = 1 – F X 100 / I.....(1)

Where, I = Initial weight and, F = Weight after friability

Disintegration Testing: 6 tablets from each generic and innovator brand products were employed for the disintegration test in water at 37 ± 0.5 °C using a disintegration apparatus (E.D-1L, USP). The disintegration time was taken to be the time, when no particle remained on the basket.

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies were carried out using a dissolution apparatus IP/USP/BP (basket type). The dissolution medium was 900 ml of 0.1 N HCl, pH 1.2, which was maintained at 37 ± 0.5 °C. In all dissolution experiments, 5 ml of dissolution samples were withdrawn and replaced with equal volume fresh dissolution medium at regular intervals. Collected dissolution samples were used for determination of released ciprofloxacin concentrations by using a UV-VIS spectrophotometer (U. V. 2440 Double beam spectrophotometer, SHIMADZU Corporation, JAPAN) against a blank. Maximum wavelength (λmax) obtained by scanning all samples from 200 to 400 nm and this was 276 nm.

Result

All the generic of ciprofloxacin HCl 500 mg tablets used in this investigation were within their shelf life. All tablets obtained from local market were subjected to a number of tests in order to assess their *in vitro* potency, weight variation, friability, hardness, disintegration time and dissolution time.

Table-1: Determination of potency of Ciprofloxacin in different dosage forms of different BD manufactures collected from local market.

Tablets	Potency	Weight Variation
A-tab	90.51 ± 0.29	750.54 ± 0.84
B-tab	95.88 ± 1.68	747.58 ± 0.79
C-tab	96.34 ± 1.89	757.25 ± 0.46
D-tab	97.71 ± 0.59	752.17 ± 0.88
E-tab	104.74 ± 1.53	744.82 ± 1.02

The hardness tests of all tablets were done to assess the ability of tablets to withstand handling without fracturing or chipping. A force of about 4 kg/cm^2 is the minimum requirement for a satisfactory hardness of tablets[14].

Table- 2: Hardness and friability determination of five generic Ciprofloxacin-HCl

Tablet	Hardness (kg/cm^2)	Friability (%)
A-tab	5.42 ± 0.25	0.11
B-tab	6.76 ± 0.44	0.17
C-tab	5.82 ± 0.11	0.16
D-tab	6.52 ± 0.19	0.22
E-tab	6.04 ± 0.51	0.22

Table- 3: Disintegration profile of five generic of ciprofloxacin-HCl tablets

Tablets	Disintegration Time (Min)
A-tab	7.21 ± 0.55
B-tab	5.10 ± 0.52
C-tab	3.11 ± 0.54
D-tab	11.77 ± 0.75
E-tab	7.33 ± 0.84

According to the FDA guidance for industry, for the dissolution testing of immediate release solid oral dosage form, the biopharmaceutics classification system (BCS) suggests that 85 % w/w dissolution of the labeled content in 0.1 N HCl within 15 minutes ensure that the bioavailability of the drug is not limited by dissolution [15].

Table- 4: Dissolution profile of five ciprofloxacin–HCl tablet available in Bangladesh.

Tablets	% Dissolution time within 30 minute
A-tab	96.89 ±0.51
B-tab	97.80 ±1.02
C-tab	97.35 ±0.64
D-tab	97.12 ±0.44
E-tab	98.03 ±0.53

Discussion

Antibiotics are the most widely used drugs worldwide and among antibiotics Ciprofloxacin hydrochloride is a synthetic carboxyquinoline derivative with broad spectrum antimicrobial activity. It is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. In this study, different qualitative parameters like assay, weight variation, hardness, friability, disintegration and dissolution time were determined.

All the tablets contained ciprofloxacin within 100 ± 10 % of the labeled claim. The USP[11] and IP[12] specifications for assay are that the ciprofloxacin content should be less than

90% and not more than 110 % (Table 1). Therefore, the assay results meet compendia quality of ciprofloxacin in all the products.

Weight variation does serve as a pointer to good manufacturing practices (GMP) maintained by the manufacturers as well as amount of active pharmaceutical ingredient (API) contained in the formulation. The weight variation for all the tablets used in this study showed compliance within the official specifications (USP, 2000; BP, 1998)[11, 13], as none of the products deviated by up to 5 % from their average weight (Table 1).

A force of about 4 kg/cm^2 is the minimum requirement for a satisfactory hardness of tablets[14]. The results of the hardness testing showed that hardness of all generic tablets were within the range between 5.42 ± 0.25 to 6.76 ± 0.44 kg/cm^2. Hence, the results of the hardness testing were satisfactory. Friability test is used to evaluate the tablet resistance to abrasion. The compendial specifications of friability for tablets are less than 1 % w/w (USP, 2000; BP, 1998)[11, 13]. The friability (%) of all generic tablets was within the range of 0.11 to 0.22 (Table 2).

All the Ciprofloxacin-HCl tablets compiled with the compendia specifications for disintegration (Table 3). The BP specification is that the uncoated tablets should disintegrate within 15 minutes[13], while USP specifies that uncoated tablets should disintegrate within 30 minutes [11]. The drug incorporated in a tablet is released rapidly as the tablet disintegrates. Therefore, disintegration is a vital quality parameter of tablet as this is directly related with drug dissolution and subsequent bioavailability of drug. In our study we observe that Ciprofloxacin-HCl tablets have a disintegration time from 3.11 ± 0.54 to 11.77 ± 0.75 (Table 3) minutes and more than 96% of drug undergo dissolution within 30 minutes (Table 4), which meet compendial specifications.

Conclusion

In conclusion, our results indicated that all generic ciprofloxacin HCl tablets included in this study seem to have good overall quality with high dissolution rate and hence very good bioavailability. It is a general psychology that the quality local medicines may poor as compared to leading brands available in the market. But, this investigation will help to change the view of people towards local medicines available in Bangladesh.

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