ORIGINAL ARTICLE

QUALITY ASSESSMENT OF CIPROFLOXACIN TABLETS COMMERCIALLY AVAILABLE IN GONDAR TOWN, NORTH-WEST ETHIOPIA

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ABSTRACT

***Background**: Pharmaceuticals play a vital role in protecting human health and encouraging wellness. The safety, efficacy, and consistency of the drugs should, however, be maintained to provide a desired pharmacological effect. The accessibility and utilization of substandard and counterfeit ciprofloxacin products in the market may lead to risk of treatment failure and microbial resistance. This study was conducted to assess the quality and physicochemical equivalence of nine brands of ciprofloxacin hydrochloride tablets sold in Gondar town, Ethiopia.*

***Methods:** Nine brands of ciprofloxacin tablets were subjected to in vitro tests related to the quality of the tablet dosage form, and the tests were carried out according to the procedures in standard books (USP and British Pharmacopeia).*

***Results:** This study showed that all ciprofloxacin brands met the requirements stated in standard books for weight uniformity, friability, crushing strength, and assay of active ingredient. The disintegration times varied between 3-7 min for all nine ciprofloxacin products. All nine of the products passed dissolution testing in compliance with USP requirements. Code 6 tablets displayed the highest percentage release (107.12 %), while Code 3 had the least percentage release (96.16 %) at 45 min. Accordingly, all products passed the drug content test as defined in USP, where the drug content should range from 90% to 110%. Code 5 showed the highest percentage content (102.76 %), while Code 2 possessed the least active drug (91.73 %). Mathematical model-dependent methods have shown that data relating to drug release match well with the Weibull release model.*

***Conclusion:** This study showed that all brands of ciprofloxacin met the quality requirement according to standard books in terms of weight uniformity, crushing strength, friability, disintegration, dissolution, and assay.*

***Keywords:** Ciprofloxacin, assay, weight uniformity, friability, hardness, dissolution profile, Gondar.*

BACKGROUND

Ciprofloxacin is one of the antibiotics grouped under flouroquinolones used to treat infectious diseases (1). It is one of the main medicines required in the basic health care system, grouped as essential medicines (2). To strengthen the overall health care delivery system, generic pharmaceutical products from different sources are introduced into many developing countries' health care delivery systems (3). This has however been followed by a number of issues, the most important of which is the widespread distribution of fake and below-standard drug products (4).

Counterfeit and substandard medicines can cause failure in therapeutic response and resistance to antibiotics, which can pose a major threat to public health and the world economy (4). Approximately 10 percent of pharmaceuticals on the market are counterfeit medicines (5). The estimate increases in developing countries up to 25 percent, and in some of

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them may surpass 50 percent (2). Among the counterfeit drugs, an estimated 50 percent are antimicrobial agents, 78 percent of which come from Asian and African countries (5). A counterfeit medication is described, according to the World Health Organization (WHO), as "one that is intentionally and fraudulently mislabeled in terms of identity and/or source" (6). Counterfeiting can involve items with the right ingredients or the wrong ingredients, with insufficient active ingredients, or with fake packaging (4). Substandard medicinal products, also referred to as "out of specification," are classified by WHO as "approved medicinal products which do not meet either their quality standards or specifications, or both" (7).

Pharmaceuticals must fulfill the key requirements for dosage quality of the drug namely safety, potency, efficacy, consistency, acceptability by patients and compliance with regulation (8). Pharmaceutical quality must be consistent and reproducible from lot to lot to ensure pharmaceutical products safety and effectiveness (9). To ensure that the necessary quality criteria are met, the drug product must be checked during the shelf life of the product at various intervals during and after manufacturing (10). Generic prescription medications play a crucial role in supplying cost-effective health care (11). They must be comparable in chemical and bio-pharmaceutical terms to replace brand products (13, 14).

Drug products with bio-pharmaceutical and chemical equivalence must have the same quality parameters like intensity, purity, uniformity of active pharmaceutical ingredient (API) content, time of disintegration (TD) and rate of dissolution (14, 15). In vitro quality control testing of pharmaceutical products helps to avoid uncertainty concerning pharmaceutical safety, efficacy, and stability (16). Routine quality testing of drugs on the market is crucial in protecting public health, especially in developing countries where counterfeit and poor quality drugs have become a major challenge for healthcare services. The goal of this study was to assess the quality of various brands of tablet formulations of ciprofloxacin hydrochloride commercially available on the market in Gondar town, North West Ethiopia.

METHOD

Drugs and chemicals : Nine groups of ciprofloxacin hydrochloride tablets each claiming to contain 500 mg API commercially available in the local market were purchased from the various retail and hospital pharmacies of Gondar town in Ethiopia. Detailed information about the brands is shown in Table 1. The samples were blindly named as Code 1, Code 2, Code 3, Code 4, Code 5, Code 6, Code 7, Code 8 and Code 9. The standard ciprofloxacin hydrochloride powder was obtained from Addis Pharmaceuticals Factory (APF), Adigrat, Ethiopia. All other chemicals were of analytical quality, unless otherwise specified.

Weight variation test: According to weight variation test procedures in the United States Pharmacopeia-National Formulary (USP-NF), from each brand 20 tablets were individually weighed using an electronic balance, then the average weight was calculated and the actual tablet weight was compared with the average. The difference in the two weights was used with the following formula to measure the weight variation (17):

Weight variation = $[I_w - A_w]/A_w \times 100\%$

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

The tablet met the standard if not more than 2 weights deviate by more than 5% from the average weight (17).

Table 1: Label details of nine commercially available ciprofloxacin tablet brands found in the local market of Gondar town, North-West Ethiopia

Brand name	Manufacturing country	Date of Manufacture	Expiry date
CIFLOX 500	Ethiopia	August 2017	August 2020
CIPROLEB 500	India	August 2017	July 2020
CIPROBID 500	India	April 2018	March 2021
BRUCIPRO	India	October 2018	September 2020
CIPROPHARM	Jordan	October 2018	October 2021
ZINDOLIN 500	India	September 2018	September 2023
FLOXINE	S/Korea	April 2018	April 2021
CIPROKIN 500	India	December 2017	November 2020
CIPROEPHARM	Ethiopia	January 2017	January 2021

Friability test: Twenty tablets were weighed and placed in the plastic chamber friabilator (Pharma test, Germany) from each of the nine brands, and then revolved for 4 min at 25 rpm. The tablets were then dedusted and weighed. The difference between the two weights was used to calculate friability using the equation (3, 18) below:

Friability = $(I_w - F_w)/I_w \times 100\%$

Where, I_w = Total Initial tablet weight and F_w = Total final tablet weight. The tablet met USP-NF friability requirement if tablets lose less than 1% of their weight (3, 18).

Hardness test: Ten tablets from each brand were randomly selected and hardness was measured using hardness tester (Pharma test, Germany). The tablets were placed between the two hardness tester jaws and the hardness was measured by applying diametrically breaking pressure to the tablet (18, 19).

Disintegration test: For each brand, one tablet was placed in each of the 6 tubes of the USP disintegration apparatus (Pharma test, Germany), and the basket rack was placed in a 1000 ml vessel containing 900 ml of water maintained at 37 ± 2 ° C. A standard motor controlled system was used to move the basket assembly which contained the tablets up and down at a frequency of 30 cycles per minute over a distance of 5–6 cm. Perforated plastic discs were used to prevent tablets from floating. The apparatus worked for 30 min (17, 18). The tablets must disintegrate and all particles must move through the 10-mesh panel within 30 min to comply with the USP-NF requirements. If any residue remains, it must have a soft mass with no palpably firm core (17, 18).

Preparation of Standard Calibration Curve: Twenty milligram of pure ciprofloxacin powder was weighed and dissolved in 100ml of distilled water. The solution was used as a stock solution having a concentration of 0.2 mg/ml. The stock solution was further diluted with distilled water to obtain concentrations of 0.5 µg/ml. Absorbance of the samples was taken at 276 nm in a UV spectrophotometer (Cary 60-UV-Vis, Agilent technologies). A plot of absorbance versus concentration was constructed using the absorbance data obtained from the determination.

Dissolution test: A comparative in-vitro dissolution study using type II USP dissolution apparatus (BIOBASE, China) was performed. One tablet, with 900 ml 0.1 M hydrochloric acid (HCl) as a dissolu-

tion medium maintained at 37 ± 0.5 ° C, was placed in each of the 6 vessels for each brand. The device's rotational speed was kept constant at 50 rpm. At a fixed time interval (5, 10, 20, 30, 45 and 60 min) a sample of 10 ml was withdrawn and this was immediately replaced by the same amount of fresh test media (17, 18, 20). Using 0.1 M HCl as blank, each sample solution was filtered, diluted, and the absorbance measured by UV-Vis spectrophotometer at 276 nm. The percentage releases of the drug were calculated at various time intervals. According to the USP -NF, tablets meet the requirements of this test if not less than 75% of the active drug dissolves in 45 min (17, 18).

Assay of the active ingredient: Twenty tablets from each brand were finely crushed and a powder quantity equal to 100 mg of ciprofloxacin hydrochloride powder was correctly weighed and dissolved in distilled water and diluted to a concentration of 1000 µg/ml stock solution of 100ml. To get concentrations ranging from 5 µg/ml to 30 µg/ml, the stock solution was further diluted. Absorbance of the samples in a UV-Vis spectrophotometer was taken at 276 nm. The USP-NF requirement is that ciprofloxacin hydrochloride content should not be less than 90% and not more than 110% (17).

Drug release kinetics: The findings of an in vitro drug release analysis of formulations were fitted with various kinetic equations such as zero order, first order, Higuchi, and Korsmeyer–Peppas model (21) to test the kinetics of drug release from the tablets. The equations of these kinetics for drug release are given below:

Zero-order kinetics: $Q_t = Q_0 + K_0t$

First-order kinetics: $\log Q_t = \log Q_0 + K_1t/2.303$

Higuchi kinetics: $Q_t = K_ht^{1/2}$

Korsmeyer−Peppas kinetics: $Q_t/Q_0 = Kt^n$

Weibull Kinetics: $\log [-\ln(1-m)] = \beta\log (t–T_i) – \log\alpha$

Where, K_0, K_1, and K_h represent zero-order, first-order, and Higuchi rate constants respectively; Q_t /Q_0 means fraction of drug released at time t; K means rate constant; n means release exponent; m is accumulated fraction of the drug; β is shape parameter; T_i is location parameter; and α is the scale parameter. The kinetics that gives high regression coefficient (R^2) value is considered as the best fit model (21–24).

Statistical analysis: All outcomes were represented as mean ± SD. The statistical analysis was performed using Microsoft Excel 2010(Roselle, IL, USA) and Origin 8 (Origin Lab TM Corporation, USA).

RESULT

At the time of the study, all brands of ciprofloxacin tablets used in the study were within their shelf life and different physical parameters were successfully analyzed. Tablet weight uniformity assurance for all brands gave values that conform to both USP and BP weight uniformity specifications since none of the brands had a dosage unit that deviated by as much as 5 percent from the brand mean value which is in line with pharmacopoeial specifications (17) (Table 2). Among all tested tablets, highest mean weight variation was recorded for code 2 (1.413 %) and the lowest for code 6 (0.685%). Similarly, the friability results for all brands also met official specifications; all brands gave weight loss of less than the official tolerable 1 percent w/w amount (Table 2). The mean crushing force indicating the hardness of the tablets also showed that codes 3, 5, and 6 showed the highest crushing strength of 223.64, 204.77 and 174.73 N, respectively (Table 2).

Table 2: Summary of physical properties of ciprofloxacin tablets of nine different brands collected from the local market of Gondar town, North-West Ethiopia

Code	Weight variation (%) ± SD n=20	Crushing Strength (N) ± SD n=10	Friability (%) n=20	Thickness (mm) ± SD n=10
1	1.34±0.892	167.54 ±24.577	0	6.626 ± 0.094
2	1.413± 0.815	149.03 ±11.637	0	5.621 ± 0.038
3	1.395 ±0.941	223.64 ±43.942	0.137	5.848 ±0.138
4	0.991 ±0.603	133.01 ±24.651	0.268	5.744 ±0.151
5	0.901 ±0.658	204.77 ±40.037	0.129	4.497 ±0.430
6	0.685±0.550	174.73 ± 10.500	0	6.437 ±0.239
7	0.874 ±0.544	172.79 ± 13.174	0.137	6.762 ±0.023
8	1.304±0.897	174.22 ± 14.569	0.131	6.139 ±0.085
9	1.194 ±0.863	119.67 ±27.009	0.153	5.296 ±0.165

All ciprofloxacin tablet brands met the pharmacopoeial standard for disintegration (20) that stipulates a disintegration time of no more than 15 minutes for uncoated tablets (Figure 1). Relatively slow disintegration time was obtained for samples coded 7 & 9 (7 minutes) whereas faster disintegration was witnessed in code 4 & 8 samples (3 minutes).

The standard ciprofloxacin calibration curve is given in Fig. 2 ($y = 0.1068x + 0.0061$, $R^2 = 0.9867$); the dissolution rate profile obtained revealed that the percentages of drug release in 45 min for the nine ciprofloxacin tablet brands were within the range of 96.16% (code 3) and 107.12% (code 6) (Figure 3). All of the nine products tested in this study meet the dissolution standard set by USP-NF; more than 80 percent of the active drug was released within 45 minutes in all of the products.

The active drug content per tablet was determined using the calibration curve described in Figure 2 ($y = 0.1068x + 0.0061$, $R^2 = 0.9867$); all nine products of ciprofloxacin tablets met the BP and USP-NF specifications (Fig. 4) for drug content. For code 5 the highest percentage of drug content was obtained (102.76%), whereas the lowest percentage of drug content was obtained from code 2 (91.73%).

The drug release kinetics of the various brands of ciprofloxacin tablets was treated in various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas, and Weibull, as shown in (Table 3).

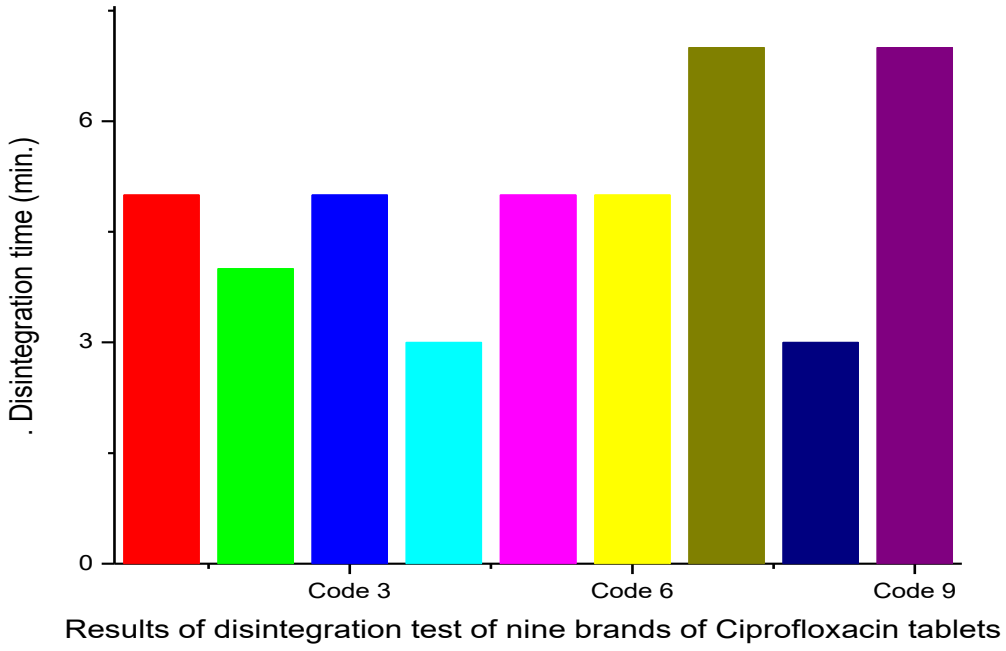

Figure 1: *Results of disintegration test of nine brands of ciprofloxacin tablets collected from the local market of Gondar town, North-West Ethiopia*

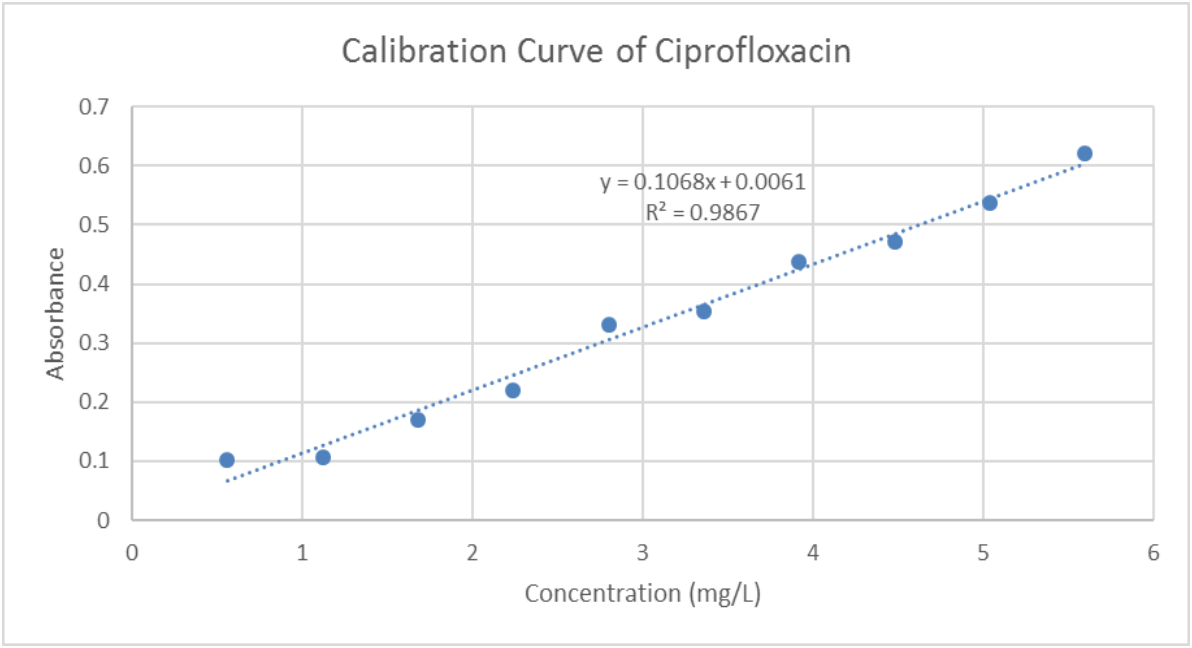

Figure 2: *Calibration curve constructed using known concentrations of ciprofloxacin solutions for the determination of ciprofloxacin HCl tablets included in the study*

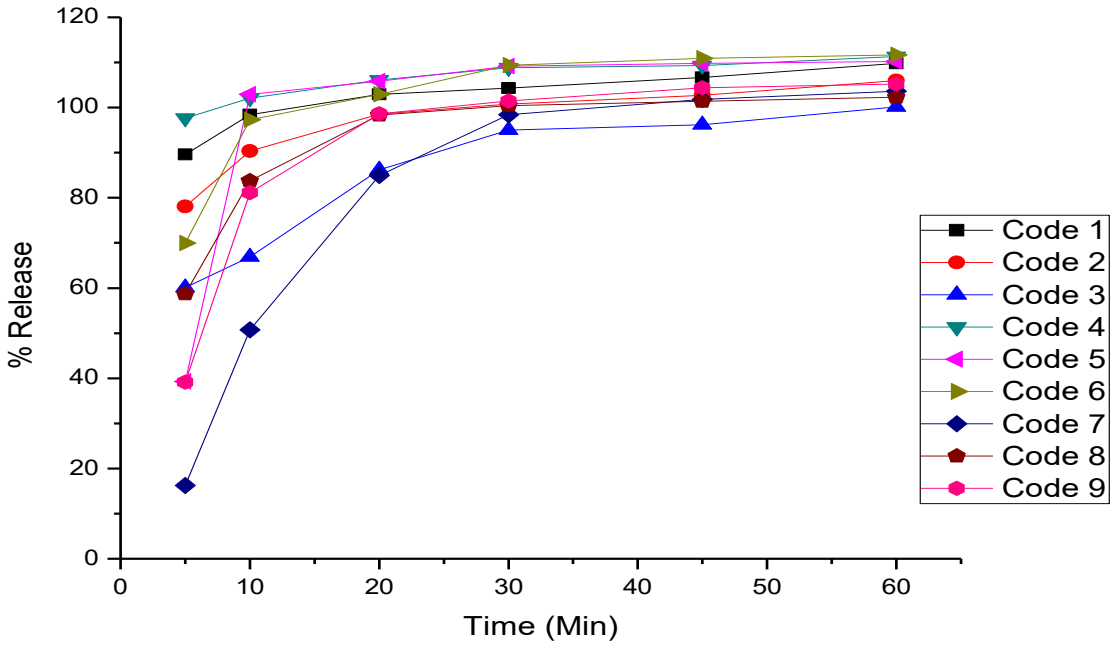

Figure 3: *Dissolution profile of various ciprofloxacin manufacturer products collected from the local market of Gondar town, North-West Ethiopia*

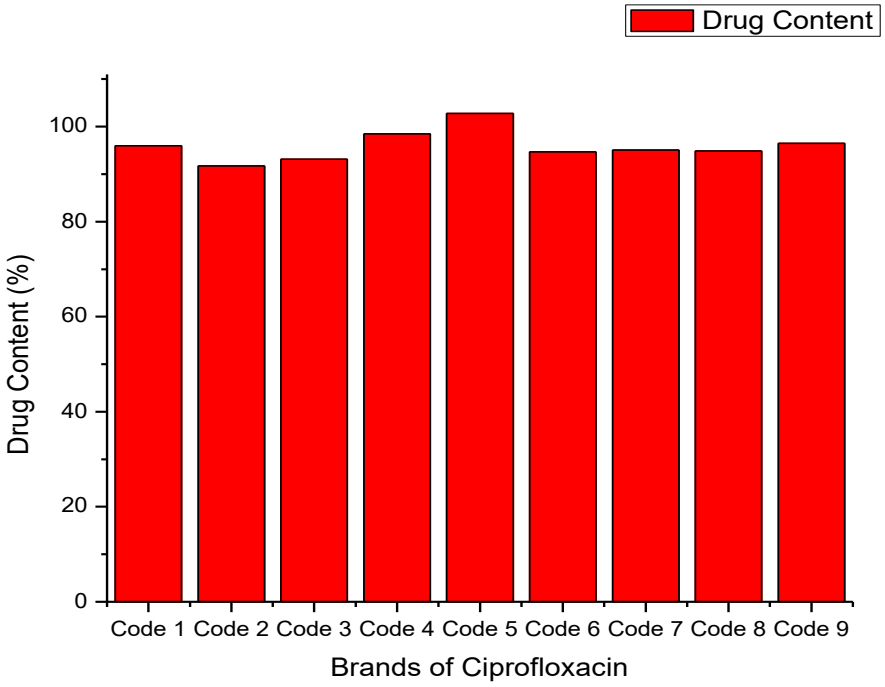

Figure 4: *Percentage content of ciprofloxacin HCl in different brands of tablets collected from the local market of Gondar town, North-West Ethiopia*

Table 3: A summary of nine brands of ciprofloxacin tablets drug release kinetics

Code	Regression coefficient (R2)				
	Zero order kinetics	First order kinetics	Higuchi kinetics	Korsmeyer–Peppas kinetics	Weibull Kinetics
1	0.7532	0.7277	0.8444	0.7532	0.9648
2	0.6920	0.6580	0.8002	0.6920	0.9628
3	0.7584	0.7218	0.8559	0.7584	0.9693
4	0.7869	0.7738	0.8834	0.7869	0.9763
5	0.3401	0.3103	0.4538	0.3401	0.8681
6	0.5560	0.5087	0.6812	0.5560	0.9213
7	0.6524	0.5113	0.7753	0.6524	0.9350
8	0.5155	0.4763	0.6438	0.5155	0.9033
9	0.5032	0.4317	0.6298	0.5032	0.8983

DISCUSSION

Quality is the performance of the product as per the commitment made by the producer to the consumer and it is the end result of wise efforts (25). At the time of the study all of the brands used were within their shelf life. In order to assess their biopharmaceutical and chemical equivalence, nine different brands of ciprofloxacin hydrochloride tablets from different retail pharmacy outlets within Gondar town were subjected to a number of tests. The tablet weight indicates the quantity of granules containing the labeled quantity of the active ingredient and used to confirm the tablet content uniformity (2, 25). As per the results of weight variation test described in Table 2, code 6 had a smaller weight variation (0.685±0.550) whereas Code 2 had the highest weight variation (1.413 ±0.815) among all brands included in the study. In addition, all brands of ciprofloxacin tablets possessed acceptable weight uniformity as none had weight deviation by greater than 5 percent as specified in the USP. According to the USP-NF weight variation test specification, for tablet strengths > 324 mg, the tablet passes the test if not more than two of the individual weights deviate by > 5 percent from the average weight and none by 10 percent (17, 26).

Tablets require some degree of hardness to withstand mechanical shocks during manufacturing, packaging, and shipping (27). Tablet hardness test measures tablets' ability to withstand stress or pressure during handling, packaging, and transport (28). All the brands examined gave a hardness value of > 50 N; hence all products complied with the hardness test requirement. Nevertheless, the average hardness of the products varied from product to product, i.e., tablet hardness ranged from 119.67± 27.009 N for Code 9 to 223.64 ±43.942 N for Code 3. The underlying cause for this inconsistency among brands could have been related to the formulation conditions of the pharmaceutical manufacturer, such as alteration in machine speed, granulation methods, type/ amount of binder, and the amount of lubricants added during production processes (29).

Tablet friability is the ability to resist shock and abrasion during packaging, handling, and transportation.

The drug's therapeutic effectiveness may be adversely affected if tablet friability is present beyond permissible levels due to weight loss on the tablet (30). Loss caused by abrasion or tablet friability measurement may be a more relevant parameter for measuring potential tablet behavior during handling and packaging (31). The present study uncovered that the entire tablet brands examined had friability values ranging from 0.00 to 0.268 percent (Table 2). All brands have satisfied the pharmacopoeial friability requirement, which states that a maximum weight loss of not more than 1 percent of the tablet weight to be generally considered acceptable (17) and the result of this finding is similar to that of a 2017 Bangladesh-based study on ciprofloxacin hydrochloride tablet brands (2).

The first important step towards dissolution for most tablets is the splitting of the tablet into smaller particles or granules, which is why a reasonable rate of disintegration is a prerequisite for optimum rate of dissolution (31, 32). For all nine brands the disintegration times were less than 30 minutes. Codes 4 & 8 had the lowest disintegration times, while codes 7 & 9 had the highest disintegration times, but all brands met the compendial requirement. Kahsay and G/ Egziabher (34) reported similar findings.

Dissolution test is one of the quality control tests usually carried out in vitro to predict the in vivo performance of solid oral pharmaceutical dosage forms such as tablets and capsules. Moreover, this may also serve as a surrogate to bioavailability and bioequivalence (33). The dissolution study results are shown graphically in Figure 3. For dissolution studies conducted using USP type II (17) devices, ciprofloxacin tablets should release not < 80 percent of the labelled amount within 30 minutes as per the USP-NF specification. The current study discovered that all of the nine brands analyzed for ciprofloxacin tablets passed USP-NF's single point dissolution test specification. The percentages of ciprofloxacin release in 45 min for nine different products were within the range of 96.16 percent (code 3) and 107.12 percent (code 6).

Assay of active drug is very important in pharmaceutical products to determine the presence, absence, and/or quantity of one or more active components in the dosage form (10). The results obtained from the nine brands of ciprofloxacin tablets assessed in this study are shown in figure 4. Code 5 had the highest percentage of active ingredient content (102.77%) and code 2 had the lowest percentage of active ingredient content at 91.73%. In addition, all products containing ciprofloxacin comprised within 100% ±10% of the labeled claim. As stated in the USP requirements, the content of ciprofloxacin should not be less than 90% and not more than 110% of the labeled amount for ciprofloxacin. Consequently, all ciprofloxacin brands showed results of assays complying with the criteria.

Similarly, various kinetic models were also incorporated into the dissolution data in the present work in order to clarify the overall release of drug from the dosage forms. The model which gives high correlation coefficient (r^2) value is considered the best fit of the release data after fitting models to the individual unit of the dissolution data (35). As shown in Table 3, the Weibull model was the best fit to the dissolution data of all products among the five models fitted to each dissolution profile as this model demonstrated the highest value of the correlation coefficient for all dissolution data. For this reason, it can be noted that all brands under investigation had the same process of release.

CONCLUSION

This study attempted to determine both the consistency and physicochemical equivalence of imported and locally manufactured ciprofloxacin tablets available on the Gondar town local market. The physicochemical examination showed that all the tablets met the requirements for weight variation, hardness, friability, disintegration, dissolution, and assay specified in the official monographs.

A model-dependent approach employed in the study of dissolution shows the data relating to drug release fits well with the Weibull release model. The results of this study only mean the overall quality status and in vitro bioequivalence of the products used in the study are sufficient. It does not mean that all potential ciprofloxacin products from the same manufacturers will be of good quality as such post-marketing quality tests should be carried out on a regular basis as long as a product remains on the market.

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