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In vitro comparative quality assessment of different brands of ciprofloxacin tablets available in Iraq

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ABSTRACT

Background: The in vitro quality assessment of different brands of the same drugs is essential in preventing substandard or counterfeit products, especially in developing countries, including Iraq. Ciprofloxacin, which is a fluoroquinolone antibiotic, is used in the management of different types of infections. **Objectives:** In vitro comparative quality assessment of ciprofloxacin tablets for five different pharmaceutical companies. **Methods:** The present study compared five quality control parameters, including weight variation, hardness, thickness, diameter, and disintegration time of the five different brands of ciprofloxacin HCl 500 mg available in Iraq. **Results:** All five brands tested complied with the specifications for the quality tests except Brand B, which failed to comply with the requirements of the weight variation test. The average weight variation results ranged from 0.7319 g to 0.77265 g. The average hardness results ranged from 15.59 kp to 28.2 kp. The average thickness and diameter results ranged from 5.289 mm to 6.297 mm and 17.177 mm to 19.279 mm, respectively. All the brands showed disintegration times between 2.38 minutes to 4.46 minutes. **Conclusion:** The present study revealed that all five brands of ciprofloxacin HCl had complied with the quality control parameters according to pharmacopeial specifications except the weight variation test for Brand B. Also, the present study showed that the price of the brand does not necessarily reflect the quality of the drug. Also, the local Brand C met all the specifications regarding the five quality tests.

INTRODUCTION

Medicine quality is an important aspect of the process of ensuring that pharmaceutical goods are fit for their intended purpose, meet marketing authorization requirements, and do not put consumers in danger. To achieve this goal, there must be a quality assurance system, which includes, besides other things, product development, manufacture, distribution, and storage (Kahsay, Debella, & Asres, 2007). Many developing countries lack the resources to effectively monitor the quality of generic medication items on the market. As a result, substandard and/or counterfeit drug goods are widely spread. Between January 1999 and October 2000, the WHO surveyed counterfeit medicine in 20 countries, finding that 60% of counterfeit incidents occurred in developing countries and 40% in developed countries. Analgesics and antipyretics (6%), antimalarial (7%), antiasthma and antiallergy (8%), antibiotics (28%), hormones and steroids (18%), and other therapeutic categories (33%) were among the counterfeit pharmaceuticals detected by WHO between 1999 and 2002 (Kahsay et al., 2007; Uddin et al., 2017). Studies that deal with comparative in vitro quality evaluation of different drug tablets in different countries have been published. The bioavailability of amoxicillin formulations has been observed to vary greatly in the literature. One study conducted to analyze amoxicillin capsules in many Arab countries showed that 56 % of them did not meet USP standards. Another study showed variations in dissolution patterns among amoxicillin brands in the Estonian and Brazilian markets. On the other hand, based on in vivo investigations in the Italian and Thai markets showed that some generic amoxicillin capsules were not bioequivalent to the innovator product (Hailu, Gutema, Hishe, Ali, & Asfaw, 2013). Some studies in Ethiopia have also proved the existence of substandard drugs in the country. A national survey conducted in Ethiopia on the quality of mebendazole, albendazole, and tinidazole medicines found that 45.3% of the samples did not fulfil pharmacopoeia quality specifications. Similarly, another study revealed that two out of 10 brands of norfloxacin brands did not meet the specified USP dissolution requirement. The dissolution profiles of two brands of norfloxacin tablets (25%) were found to be identical to the comparator product in the study (Abebe, Ketema, & Kassahun, 2020). Also, another study conducted in Ethiopia revealed that 28.3%, 31.7%, and 6.8% of antimalarial medicines (chloroquine phosphate and quinine sulfate tablets) had failed to comply with the pharmacopoeia quality standards for visual inspection, hardness and weight variation tests, respectively. Additionally, a few other studies conducted in Ethiopia on comparative in vitro bioequivalence evaluation of different drug brands reported that 62.5% of brands of amoxicillin capsules were not interchangeable with the innovator, only one out of five amoxicillin capsule had a similar dissolution profile with the innovator and can be considered bioequivalent and interchangeable (Abebe et al., 2020; Abraham, Abuye, Kebede, & Suleman, 2021). Also, some studies were conducted between different brands of Glibenclamide (antidiabetic agent). One of the studies conducted in Jordan on five generics of Glibenclamide tablets available in the Jordanian market revealed that the five generics demonstrated dissolution profiles that were significantly different from each other and from that of the innovator. Another study on the same drug conducted in Libya evaluated three brands of Glibenclamide tablets available in the Libyan market and reported that all products were within the British Pharmacopeia (BP) specifications. Also, in Ethiopia, a study confirmed that five brands of Glibenclamide tablets complied with the official specification for hardness, friability, assay, and disintegration. Thus, in clinical practice, any of the Glibenclamide products might be

substituted for the innovator medication (Kassahun, Asres, & Ashenef, 2018). A quality assessment study of eleven different brands of prednisolone (glucocorticoid) in Nigeria concluded that most prednisolone tablets marketed in the Abuja metropolis of Nigeria meet all USP specifications. (17) Whereas, another quality assessment study in Nigeria on eight different brands of Metformin (antidiabetic agent) revealed that only four brands had complied with the pharmacopoeia limit tests and their dissolution curves were similar (Olusola, Adekoya, & Olanrewaju, 2012). Since there are no data regarding the quality assessment of ciprofloxacin hydrochloride 500 mg or any other medication in Iraq, this study was conducted in order to increase awareness among the health practitioners and medicine control authority so that they force pharmaceutical companies to provide high-quality drugs. The study aimed to assess the quality of five different brands of ciprofloxacin tablets available in Iraq. Also, to Investigate the relationship between the price and quality of the tablets.

METHODS

Collections of the samples

All brands of ciprofloxacin tablets with a label claiming 500 mg of ciprofloxacin as ciprofloxacin hydrochloride (HCl) had been obtained from various retail pharmacies in Kirkuk City in Iraq. The brands were named Brand A, B, C, D, and E. The experimental part was conducted in Pioneer Company for pharmaceutical industries.

Table (1): Shows brand information.

Brand Code	Manufacture country	Price (IQD)
Brand A	Switzerland	15,000
Brand B	Germany	13,000
Brand C	Iraq	5,000
Brand D	Jordan	4,000
Brand E	Turkey	3,000
***IQD = Iraqi dinar**		

Instruments:

Analytical balance, printer, Dr. Schleuniger Pharmatron tablet hardness tester, disintegration apparatus.

Weight variation test

The test is conducted by weighing 20 for each brand separately by using an analytical balance, then calculating the average weight of the tablet and comparing the individual tablet weights to the average. Weight variation is calculated by using the following formula:

Weight variation = (Iw − Aw)/Aw × 100%

Where,

Iw = Individual weight of the tablet

Aw = Average weight of the tablet

The tablet met the requirement of the weight (wt.) variation test according to the USPNF if not more than 2 of the individual weights deviate from the average weight by more than 5%

(Alyahawi & Abdulmajed, 2018; Uddin et al., 2017).

Hardness test

This test measures the pressure required to break diametrically placed tablets by applying pressure with coiled springs. Ten tablets from each brand are selected to measure their hardness by Dr Schleuniger Tablet Hardness Tester; after breaking the tablet, the pressure is recorded from the instrument. In general, in order to comply with hardness test specifications, the tablet must have a hardness > 50 Newton (N)(Alyahawi & Abdulmajed, 2018; Hambisa, Belew, & Suleman, 2019; Uddin et al., 2017).

Diameter and thickness test

The thickness and diameter of each brand were determined by using (Dr Schleuniger Pharmatron tablet hardness tester), and their average and standard deviation values were determined. Tablet thickness should be within ±5% variation from the standard value depending on the size of the tablet (Gad, 2008; Jaman et al., 2015).

Disintegration test

The basket rack was positioned in a 1000 ml vessel holding 900 ml of water maintained at 37.2 °C so that the tablets remained 2.5 cm below the surface of the liquid on their upward movement and descent not closer than 2.5 cm from the bottom of the beaker. A typical motor-driven device was utilized to move the basket assembly carrying the tablets up and down at a frequency of 28–32 cycles per minute across a distance of 5–6 cm. 6 tablets from each brand was used for this test by placing one tablet in each vessel.

To meet USP-NF requirements for the disintegration time (DT) test, the tablets must disintegrate within 30 minutes, and all particles must pass through a 10-mesh screen. If there is any residue left, it must be a soft mass with no obvious firm core (Uddin et al., 2017).

Statistical Analysis

The results were expressed as mean ± standard deviation. The results were analyzed by (SPSS) software version 20. (ANOVA) test was used to analyze the results. A probability of $P < 0.05$ was considered as significant.

RESULTS

The results of the five quality assessment tests for the five ciprofloxacin brands are illustrated in the following table. Results are expressed as mean ± standard deviation (SD) (Table 2).

Table (2): Quality assessment results of the five ciprofloxacin brands.

Brand code	Weight variation (g) Mean±SD	Hardness (kp) Mean±SD	Thickness (mm) Mean±SD	Diameter (mm) Mean±SD	Disintegration time
A	0.7716 ± 0.01309	28.2 ± 2.62382	5.344 ± 0.04719	19.149 ± 0.01595	0:04:46
B	0.7319 ± 0.02205	28 ± 2.21359	6.071 ± 0.08346	17.177 ± 0.02111	0:02:38
C	0.7673 ± 0.00845	25.23 ± 1.42287	6.297 ± 0.01889	18.403 ± 0.00949	0:04:00
D	0.77265 ± 0.01371	24.63 ± 2.66669	5.289 ± 0.03247	18.088 ± 0.01687	0:03:00
E	0.76265 ± 0.00704	15.59 ± 2.98569	5.855 ± 0.05061	19.279 ± 0.01524	0:03:20

Weight variation test

All five brands (except Brand B) had complied with the compendial specification for the weight variation test according to the United States Pharmacopeia (USP), which stated that not more than 2 of the individual weights deviate by more than 5% from the average weight of the tablets (Figure 1).

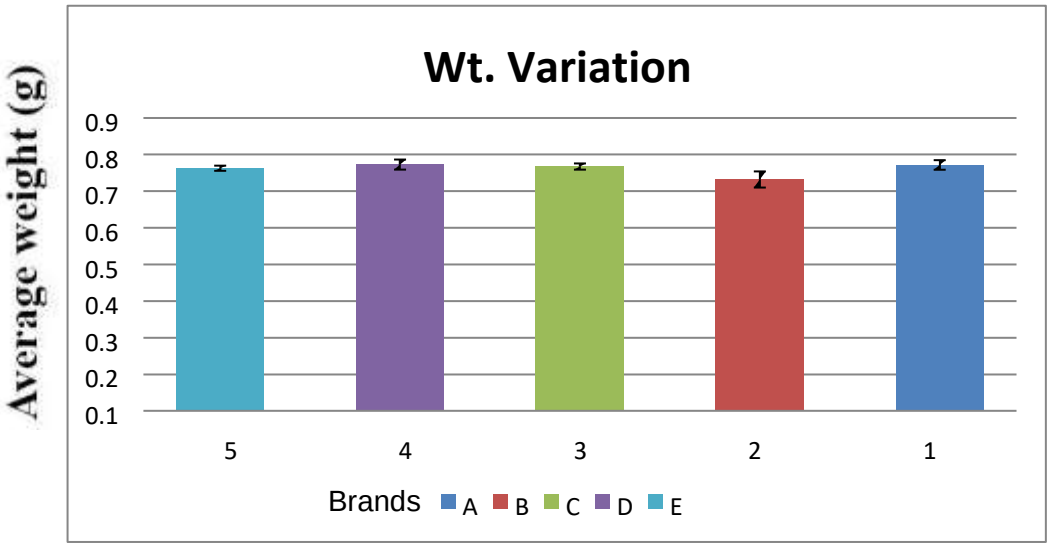

Figure (1): Results of the five brands' weight variation (g) test. Results are expressed as mean ± SD.

Hardness test

The mean hardness results of the five brands (Figure 2) were obtained in the following order: Brand E (15.59 kp) or (152.886 N) < Brand D (24.63 kp) or (241.538 N) < Brand C (25.23 kp) or (247.422 N) < Brand B (28 kp) or (274.586) N < Brand A (28.2 kp) or (276.548 N). Among the five brands, (Brand A) had the highest mean hardness value (28.2 kp), and (Brand E) had the lowest mean hardness value (15.59 kp). Since all the brands had hardness values of more than 50 N, all five brands fulfilled the requirement of the hardness test.

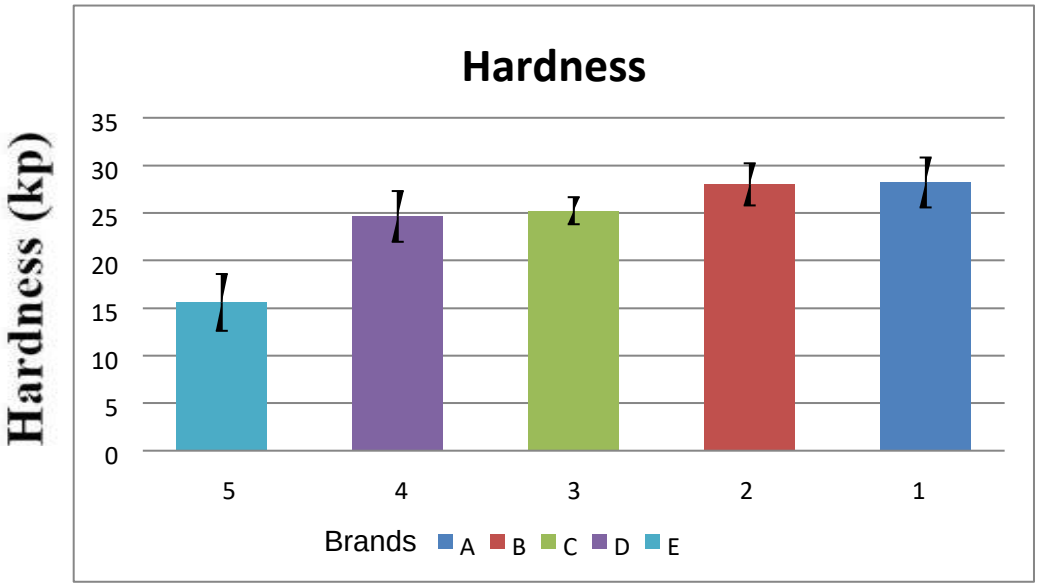

Figure (2): Results of the five brands' hardness test (kp). Results are expressed as mean ± SD.

Diameter test

The mean diameter and standard deviation of the five brands were obtained. Since all five brands showed a small deviation from the average value (Figure 3), thus, all five brands comply with the requirements of the diameter test. Among the five, (Brand B) had the highest deviation from the mean (0.02111 mm), whereas (Brand C) had the lowest deviation from the mean (0.00949 mm).

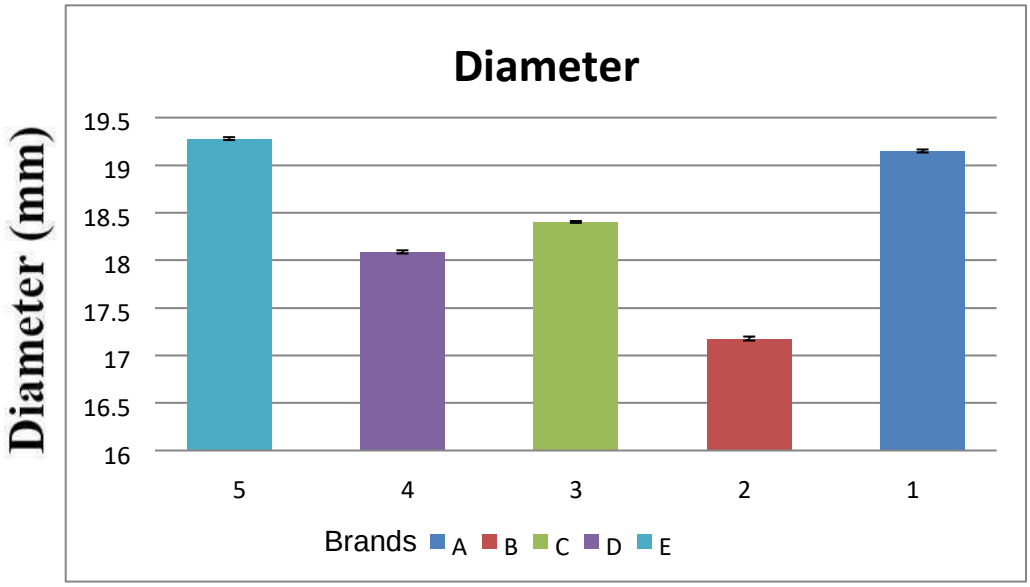

Figure (3): Results of the five brands' diameter test (mm). Results are expressed as mean ± SD.

Thickness test

The mean thickness and standard deviation of the five brands were obtained. Since all five brands showed a small deviation from the average value (Figure 4), thus, all five brands comply with the requirements of the thickness test. Among the five, (Brand B) had the highest deviation from the mean (0.08346 mm), whereas (Brand C) had the lowest deviation from the mean (0.01889 mm) (Gad, 2008).

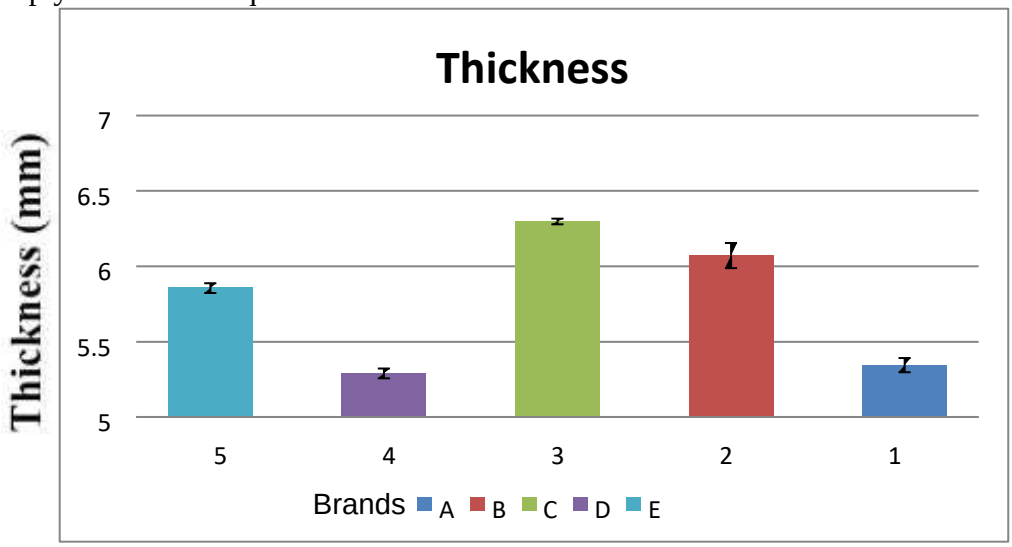

Figure (4): Results of thickness test (mm) of the five brands. Results expressed as mean ± SD.

Disintegration test

The DT of the five brands was obtained in the following order: Brand B (2.38 min) < Brand D (3 min) < Brand E (3.20 min) < Brand C (4 min) < Brand A (4.46 min). Since all the tablets from the five brands had disintegrated within 30 minutes, thus, all five brands complied with the USP-NF requirements for the DT test. Among the five brands, the highest DT recorded is that of Brand A (4.46 min), whereas the lowest DT recorded is of Brand B (2.38 min) (Uddin et al., 2017) (Figure 5).

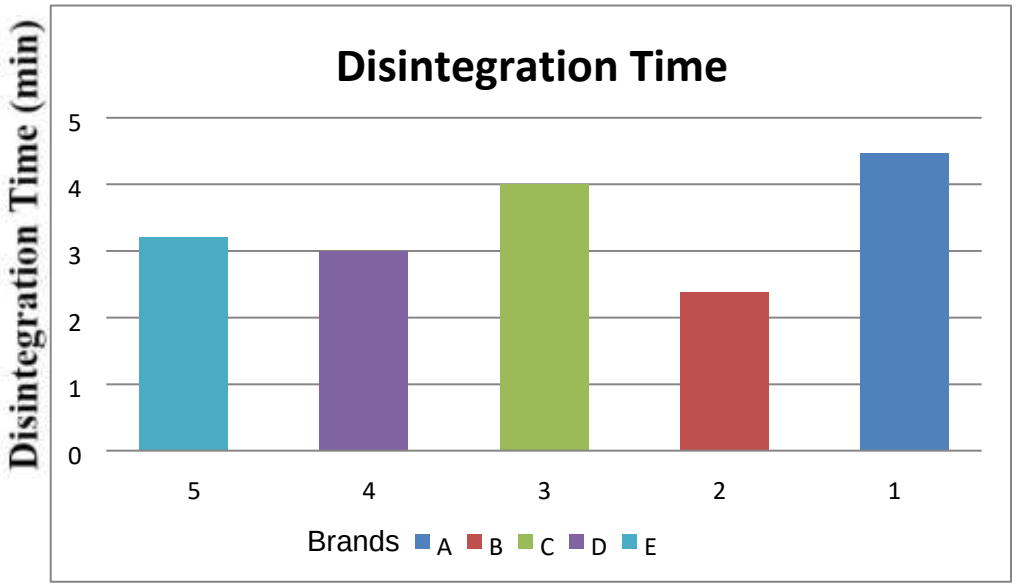

Figure (5): Results of the five brands' DT test (min). Results are expressed as mean ± SD.

DISCUSSION

Quality assessment is essential in tablet evaluation and exposing counterfeit products. Various assessment tests were performed to compare between five different brands of ciprofloxacin HCl 500 mg tablets, which are available in Iraq. All five brands were subjected to weight variation, hardness test, thickness, diameter, and disintegration tests. Weight uniformity serves as a marker for the amount of the active pharmaceutical ingredient (API) present in the tablet and the content uniformity of the formulation, especially if the API constitutes the most weight of the tablet. Thus, it serves as an indicator of good manufacturing practices (GMP) (Alyahawi & Abdulmajed, 2018; Jaman et al., 2015; Kahsay, 2010). All the brands except (Brand B) comply with the USP compendial specification for this test which states that not more than 2 of the individual weights deviate by more than 5% from the average weight of the tablets. Brands (A, C, D, and E) had a standard deviation between 0.00845 - 0.01371 (Table 2 and Figure 1) and had a weight deviation percentage below 5% from the average weight of tablets of each brand, while (Brand B) had a standard deviation of (0.02205) and had four individual tablets that deviated by more than 5% from the average weight. The highest deviation among the five brands was found in (Brand B) and the lowest deviation in (Brand E), indicating more consistency regarding tablet weight in Brand E. The standard deviation results of the five brands were obtained in the following order: (Brand B > Brand D > Brand A > Brand C > Brand E). The weight variations may have been related to the pharmaceutical manufacturers' formulation process, such as improper blending of granules, abnormal uniform mixing of all excipients, or improper drying. However, to ensure uniform tablet

weight, a smaller granular size is preferable with a narrow size distribution (Bhowmik, Duraivel, An, & Kumar, 2014). The hardness test is a non-compendial test that is used to assess the ability of the tablets to withstand consumer handling and the different conditions of manufacturing, storage, and transportation without fracturing or chipping. Additionally, tablet hardness must provide suitable disintegration and dissolution results. If the tablet is too hard, it may not give satisfactory DT, hence dissolution, whereas if the tablet is too soft, it may not withstand handling in subsequent manufacturing processes such as coating, packaging, or shipping. Hardness is also called crushing strength (Alyahawi & Abdulmajed, 2018; Jaman et al., 2015; Uddin et al., 2017). The mean results of the hardness test (Table 2 and Figure 2) for the five brands were obtained in the following order: (Brand A > Brand B > Brand C > Brand D > Brand E). Brand A and B had similar average hardness values and standard deviation. The highest deviation from the standard value was found in Brand E (2.98569), and the lowest standard deviation was found in (Brand C), indicating more consistency in pharmaceutical manufacturing in Brand C and the opposite in Brand C E. However, all five brands comply with the requirement of the hardness test, which states that the tablet must have a hardness value of > 50 N, which suggests a good quality indication in terms of resisting mechanical shocks during manufacturing, packaging, storage, shipping, and consumer handling. Tablet hardness could be related to the different types of excipients used in the manufacturing of the different brands, alterations in the machine operating speed, and changes in the particle size distribution of the granulation mix. Additionally, during the procedure of hardness testing, tablet size, shape, and orientation in the tester can also affect the value of measured hardness for a given formulation (Bibi, Naqvi, Shoaib, & Rahim, 2011; Uddin et al., 2017). The variation in the tablet's hardness could be due to due to weight variation in granules filled in die or the space between lower and upper punches; to avoid such a problem, proper tooling of the machines is indicated (Bhowmik et al., 2014). The thickness and diameter of the tablet serve as a marker for the uniformity of the size and shape of the tablets(Jaman et al., 2015). The mean results (Table 2 and Figure 3) of the diameter test of the five brands were obtained in the following order: (Brand E > Brand A > Brand C > Brand D > Brand B). The average results ranged between (17.177 mm - 19.279 mm), which indicates variation among the five brands in terms of tablet diameter. Deviation from the mean ranged between (0.00949 mm - 0.02111), which indicates a small difference between the tablets' diameter in each brand. The highest deviation was shown in (Brand B) and the lowest in (Brand C). The mean results (Table 2 and Figure 4) of the thickness test of the five brands were obtained in the following order: (Brand C > Brand B > Brand E > Brand A > Brand D). The average results ranged between (5.289 mm - 6.297 mm), indicating variation among the five brands regarding tablet thickness. Deviation from the mean ranged between (0.01889 - 0.08346). The highest deviation was shown in (Brand B) and the lowest in (Brand C). However, all five brands fulfilled the thickness test requirement, which states that tablets should be within ±5% variation from the standard value depending on the size of the tablet. From the results of the thickness and diameter test, we can conclude that (Brand C) has the highest size and shape uniformity among the five brands, and (Brand B) has the lowest size and shape uniformity in terms of the thickness and diameter of the tablet. Disintegration time is one of the essential physicochemical parameters in solid dosage forms (i.e., tablets). The disintegration test measures the time required for the tablet to disintegrate into particles, which is an important process to prepare the tablet for the dissolution and absorption step. Thus, tablet disintegration affects the drug's bioavailability and its

therapeutic efficacy (Alyahawi & Abdulmajed, 2018; Ngwuluka, Lawal, Olorunfemi, & Ochekpe, 2009). The DT results (Table 2 and Figure 5) of the five brands were obtained in the following order: (Brand A > Brand C > Brand E > Brand D > Brand B). The DT results ranged between (2.38 min - 4.46 min), suggesting small differences between the disintegration of the five brands. Brand B had the lowest DT indicating a relatively faster onset of action than other brands. However, all five brands complied with the USP-NF requirements for this test, which states that the tablets must disintegrate within 30 minutes. The rapid disintegration exhibited by all brands and the slight differences between them could be attributed to the amount and type of disintegrant used (Kassahun et al., 2018). From the previous discussion regarding the five quality parameters (weight variation, hardness, thickness, diameter, DT), we could conclude that in terms of weight variation, all the brands (except Brand B), including the expensive Brand A and the less expensive Brand C and Brand D and the cheapest Brand E (Table 1) had complied with weight variation test requirement of the USP. This indicates no superiority between the brands (A, C, D, E) regarding weight variation. Also, all the brands fulfil the test requirements in terms of tablet hardness and DT. Also, the same applies to tablet thickness and diameter since they all exhibited uniform shape and size. Thus, there is no obvious relation between the price and quality of the tablets regarding these five quality parameters. Further studies on larger sample scales and more quality parameters could establish a relationship between the price and tablet quality. The local Brand C complied with the requirements of all five tests and showed the best result regarding tablet size and shape uniformity (thickness and diameter test). Also, Brand C showed the DT results (Table 2 and Figure 5) better than Brand A. Thus, the local Brand C showed very good quality results compared to its imported counterparts.

CONCLUSION

From the present study, we can conclude that all five brands of ciprofloxacin HCl tablets have complied with the specifications of *in vitro* quality assessment tests of weight variation test, hardness test, thickness test, diameter test, and disintegration test except for the weight variation of Brand B. Additionally, we also concluded that the price of the brand does not necessarily reflect the drug's authenticity, superiority, and effectiveness. Also, the local Brand C met all the specifications regarding the five quality tests and showed very good results compared to its imported counterparts.
Finally, quality assessment studies and bioequivalence studies are essential and should be performed on a regular basis for all types of medicines, especially in developing countries, where the risk of counterfeit and substandard products is much higher, in order to ensure the safety and efficacy of the drug products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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