African Journal of Pharmaceutical Research and Development
Available online at https://ajopred.com
Vol. 16 No.1; pp. 100-108 (2024)

Original Research Article

PHYSICAL ASSESSMENT AND ATOMIC ABSORPTION SPECTROPHOTOMETRIC ANALYSIS OF CADMIUM AND LEAD IN TWENTY-FIVE BRANDS OF CIPROFLOXACIN TABLETS MARKETED IN LAGOS, NIGERIA

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ABSTRACT

Ciprofloxacin is a second-generation broad-spectrum antibiotic of the fluoroquinolone class, highly effective against many bacteria. Several brands of this drug class are marketed for public consumption; hence, it has placed the public in a confused state about the best brands with suitable physical characteristics and safe oral consumption. Additionally, the adverse effects of heavy metal accumulation in drugs for oral use have made it essential to quantify the amount of such heavy metals present. Evaluating the physical quality, elemental analysis identity, and concentration of cadmium and lead in twenty-five brands of ciprofloxacin tablets marketed in Lagos, Nigeria, is the aim of this study. The physical assessment of the tablets was then methodologically evaluated for these parameters; Uniformity of weight, Hardness, Friability, and Disintegration tests. Determining the amount of Cadmium and Lead with the Atomic Absorption Spectrophotometer (AAS) and evaluating using the Permitted Daily Exposure (PDE). Among all the brands of Ciprofloxacin tablets analyzed, 96 % passed the Uniformity of weight test, 52 % passed the Hardness test, 96 % passed the Friability test, and 96 % passed the disintegration test while 2 % passed the test according to the Permitted Daily Exposure (PDE) to Cadmium. 72 % passed the test according to the Permitted Daily Exposure (PDE) to Lead. The brands that passed the physical tests have good quality and correct physical characteristics. Cadmium and lead are of no benefit to humanity in the body and because they are not easily eliminated from the body, their buildup can put people at risk for mental retardation in children, dementia, kidney damage, nerve damage, infertility, high blood pressure, and cancer at high exposure levels.

ARTICLE INFO

Received 29 January, 2024
Accepted 10 April, 2024
Published 29 April, 2024

KEYWORDS

Ciprofloxacin,
Permitted Daily Exposure,
Physical characteristics,
Atomic Absorption Spectrophotometer,
Cadmium,
Lead

INTRODUCTION

The need to choose one product among several alternatives with same active is an imporatnt stage in ascertaining the chemical and biopharmaceutical equivalence of such drug products [1]. Therefore, the goal of adding generic drug items from various suppliers to the healthcare delivery systems of several developing nations was to improve those systems. The most serious issue is the wide availability of countefeit and inferior drugs, and ascertaining the quality of a drug product

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https://doi.org/10.59493/ajopred/2024.1.11 ISSN: 0794-800X (print); 1596-2431 (online)

involves biopharmaceutical and chemical assay techniques. Chemically and biopharmaceutically equivalent drug products must be similar in quality, strength, purity and the release profile of the active ingredient must be in identical dosage form and route of administration [2]. One pharmaceutical analysis criterion for solid dose formulation quality control is uniformity of content. A proficient analytical method was used to assay the distinct active component content of each capsule or tablet after several were randomly selected. Before using a tablet, hardness testing can help identify its breaking point and structural stability during handling, shipping, and storage [3]. Friability testing is a method used in laboratories to evaluate a tablet's capacity to fragment into smaller pieces while it moves. For quality control purposes, disintegration testers are used to examine how a medicine in pellet form would dissolve in solution, assisting in the analysis of the in-vitro breakdown of powdered substances [4].

Among the fluoroquinolone medication class, ciprofloxacin is a second-generation broad-spectrum antibiotic that is effective against a variety of gram-positive and gram-negative organisms. As a result, it is more frequently given than any other antibiotic for the treatment of nosocomial and community-acquired illnesses. Urinary tract infections caused by certain gram-negative bacteria can be treated with Ciprofloxacin. Ciprofloxacin has *in-vitro* activity against many gram-negative organisms, possessing the most significant antibacterial activity of all quinolones [5]. Ciprofloxacin hydrochloride tablets come in a variety of brands across Nigeria's drug distribution network. Ciprofloxacin tablets are becoming increasingly popular owing to how well they work to treat a variety of bacterial diseases [6] and this study to assess the quality of the different brands sold in Lagos, Nigeria, is required in order to protect Nigerians' health.

Among toxicants, metals are distinct due to their natural occurrence and relative ubiquity in the human environment [7]. The amount of metals in the air, water, soil, and food has changed as a result of human usage of metals. Since metals are elemental species, they cannot be broken down by nature and accumulate through time, which adds to the worry that they may be harmful substances [8]. That notwithstanding, a number of metals have been shown to cause considerable toxicity in humans. Lead and cadmium are examples of primary toxic metals. Other essential and medicinal metals include zinc and copper. Minor toxic metals include metals found in emerging technologies like uranium and indium. Toxic metalloids include arsenic and antimony. Certain non-metallic elemental toxicants include selenium and fluoride. [9].

Anemia is frequently caused by lead toxicity. Lead prevents the synthesis of porphobilinogen and the incorporation of iron into protoporphyrin IX by inhibiting the enzymes ferrochelatase and porphobilinogen synthase. As a result, it stops heme synthesis [8].

Many industrial processes use cadmium, including those that create nickel-cadmium batteries, stabilize polyvinyl chloride (PVC) products, act as a neutron absorber in nuclear power plants, and act as an anticorrosive agent. While it is possible to recycle certain items containing cadmium, the disposal and burning of cadmium-contaminated water accounts for a significant portion of overall cadmium pollution [9]. A recent analysis found that although there is conflicting evidence about the relationship between cadmium and cancers of the liver, kidney, and stomach, there is substantial evidence associating cadmium and lung cancer compared to prostate cancer [10].

Atomic Absorption Spectrophotometry (AAS) is a sensitive analytical method for determining metal concentrations [11].

Evaluating the physical quality and elemental analysis identity and concentration of heavy metals (Cadmium and Lead) in twenty-five brands of Ciprofloxacin tablets marketed in Lagos, Nigeria, is the main aim of this study.

MATERIALS AND METHODS

Sample Collection

The various Twenty-five brands of Ciprofloxacin tablets with the strength of 500 mg and registered by NAFDAC were obtained from different retail pharmacies within Lagos Metropolis, Lagos State, Nigeria.

Apparatus and Instrumentation

Analytical Weighing Balance (Mettler-Toledo® PL203, China); Hardness Tester (Erweka-Apparatebau®, Germany); Friability Tester (Erweka-Apparatebau®-GMBH, serial number, 52970, Heusentamm, Germany); Disintegration Apparatus (Copley® Erweka-Apparatebau, serial number, 065785, Germany); Atomic Absorption Spectrometry, BUCK Scientific Model 210VGP; Fume cupboard Denville KOTTERMAN USA; Q-block wireless controller by Questron Technologist corp attached to a Q-block digester, Year of manufacture: 2015;

Chemicals and Reagents

Analar concentrated Nitric acid, (Oxford laboratory reagent, India, Batch number: 24895, Code number: G8-10168); Milli Q Extra pure water, manufactured by Merck, France;

Standard solutions: Cadmium AAS Standard solution 1000 mg/L (Cadmium in dilute nitric acid-Traceable to National Institute of Standard Technology-NIST), and Lead (ACCU Trace ™ Reference standard), AAS Standard 1000 mg/L, Traceable to NIST Reference materials,123 Market Street, New Heaven CT06513, USA, LOT A1105059, BB:11/21.

Physical Tests Methods

Uniformity of Weight Test

Twenty (20) tablets from each of the 25 brands were weighed singly with an analytical balance (Mettler Toledo), and the individual weights were recorded. The average weight, deviation from the mean, and percentage deviation from each brand were calculated and recorded based on the method specified [12].

Hardness Test

This is an unofficial method of ascertaining the quality of a tablet. Ten (10) tablets of Brands of ciprofloxacin were

positioned vertically between the hardness tester's jaws facing the force application direction. The initial amount of force holding the tablet was recorded. Then the plunger of the hardness tester was screwed until the tablet was crushed, and the final force was recorded. The difference between the final and initial forces taken as the crushing strength of the tablet and the value was recorded [13].

Friability Test

Ten (10) tablets from each of the 25 brands of Ciprofloxacin were weighed together and transferred into a clean, dry friabilator's drum weights were recorded as the initial weight. The cover of the friabilator was correctly closed. The power switch was put on. The drum was allowed to rotate for 4 minutes at 25 rpm (revolution per minute) (subjecting the tablets to rolling and repeated shocks while rotating within the apparatus, falling six inches each time), after which the cover of the friabilator was opened, the ten tablets were carefully removed, de-dusted and re-weighed to obtain a final weight. The ten tablets' weight difference was calculated as the percentage friability [14]. The test was repeated for the twenty-five brands.

Disintegration Test

A disintegration apparatus was used to conduct the disintegration test (Copley Erweka-Apparatebau, Germany). Six (6) tablets of Ciprofloxacin were inserted into the holes in the disintegration basket. A beaker of 800 ml was filled with distilled water (approximately 550 ml) and inserted into the disintegration tank containing water. Afterward, the heater in the water bath was switched on and regulated to a temperature of about 37 ± 0.5 °C. On attaining this temperature, the basket containing these six tablets was attached to a hydraulic hook just above the beaker containing distilled water. The machine was switched on. Then the tablets in the basket were automatically observed as they were dipped and removed from distilled water and operated for 30 minutes in the medium while a split timer was used to monitor the disintegration time of individual tablets. The average time it took all the tablets to disintegrate into granules was noted and recorded [15]. This test was repeated for the twenty-five brands.

Atomic Absorption Spectrometry Method for the Determination of the Amount of Lead and Cadmium in Ciprofloxacin Brands

Sample digestion/preparation

0.500 g of each sample was taken into a 25 ml digester tube, and 10 ml of concentrated HNO_3 (Oxford laboratory reagent G8-10168) was added. The mixture was evaporated using a Q-block wireless controller connected to a Q-block digester in a fume cupboard at a temperature of 150-170 °C for about 45 minutes until the brown vapors vanished and were replaced by white fumes. The samples were allowed to cool down and then made up to 25 ml with deionized water and filtered. The digested samples were stored in universal sample bottles ready for AAS analysis [16].

Standard Preparation/Reference

Sample preparation

The metal ion standard solutions were already prepared from 1000 ppm (Cadmium AAS standard solution-Cd in dilute HNO_3 and Lead Accu Trace™ Reference AAS standard). A working solution of 100 ppm was prepared from the 1000 ppm reference standard (stock solution). The working solution prepared a serial dilution of 0.625 ppm, 1.25 ppm, 2.50 ppm, 5.00 ppm, and 10.00 ppm [16].

Sample Analysis

The AAS method of analysis was used adopting the British pharmacopeia calibration plot method. Buck Scientific model 210VGP atomic absorption spectrophotometer was used to quantify and analyze the metal ions (Lead and Cadmium). Each hollow cathode lamp is element-specific. The samples were aspirated into the flame through a nebulizing system, it was atomized, and the absorbance was recorded. Thus, the function of the flame is to atomize, vaporize, and dissociate from the ground state to the excited state. The standard solution's absorbance was taken, and a calibration graph plotted using Microsoft Excel software. The digested sample solutions were analyzed in duplicates. The concentrations of the sample solutions were calculated from the regression equation of the calibration plot. The average concentration of the metals is displayed in ppm by instrument after exploitation from the standard curve [16].

RESULTS

Uniformity of Weight

Consistency of dose units during compression is guaranteed by uniform weight. There should be as little variance as possible between a tablet's dose and weight. According to USP 2014, not more than two weights should differ from the average weight by more than ± 5%, and no weight shall differ by more than ± 10%. Only 96 % of the brands passed this test (Table 1).

Friability Test

The USP specifies that percentage friability must not be more than 1 % [17]. The percentage of brands that passed was 96 % (Table 1, Figure 2).

Disintegration Test

The ciprofloxacin tablets of the various brands were subjected to a disintegration test, the procedure was carried out using six tablets, and the disintegration time must not exceed 15 minutes [18]. Only 96 % of the brands passed the disintegration test (Table 1, Figure 1). With this method, one may approximate the amount of time needed for all tablets, or all quick-release formulations of a pharmacological dosage form, to dissolve in 37 ± 0.5 °C of water (pH 7.0) [19].

Hardness Test

Oral tablet hardness of 4-10 kgF is the criteria for each of the brands to pass the hardness test [20]. All brands of

Table 1: Results for Uniformity of weight, Friability, Disintegration and Hardness Test

S/N	Samples Code Number	Uniformity Test % Mean deviation	Friability Test (%)	Disintegration Time (min) Mean±SD	Hardness Test (KGF) Mean±SD
1	CIPRO 1	1.32	1.0775	0:80±0:31	6.31±0.48
2	CIPRO 2	1.23	0.1597	1:32±0:08	10.45±0.86
3	CIPRO 3	1.03	0.0160	1:26±0:21	6.40±1.18
4	CIPRO 4	1.07	0.3532	8:66±0:78	7.45±2.95
5	CIPRO 5	2.71	0.1650	1:28±0:05	10.83±0.17
6	CIPRO 6	1.35	0.3200	1:94±0:41	10.93±0.17
7	CIPRO 7	1.35	0.0976	1:32±0:19	11.00±0.00
8	CIPRO 8	1.16	0.1272	6:60±1:27	5.08±1.27
9	CIPRO 9	0.87	0.5945	7:63±1:65	10.93±3.13
10	CIPRO 10	1.76	0.3318	7:50±0:79	9.80±1.02
11	CIPRO 11	1.36	0.3344	3:63±0:95	5.90±0.41
12	CIPRO 12	0.86	0.0000	1:43±0:42	10.58±0.46
13	CIPRO 13	1.71	0.1284	5:58±0:95	8.90±0.49
14	CIPRO 14	1.12	0.0000	3:24±0:69	9.28±1.37
15	CIPRO 15	0.66	0.0970	2:50±0:91	9.13±1.29
16	CIPRO 16	1.67	0.0256	3:23±1:31	11.28±0.32
17	CIPRO 17	1.36	0.1706	1:19±1:29	11.20±0.16
18	CIPRO 18	3.69	0.1802	0:81±0:35	10.25±1.02
19	CIPRO 19	1.95	0.0000	0.00±0.00	10.83±0.55
20	CIPRO 20	2.19	0.2100	1:79±1:19	6.43±2.42
21	CIPRO 21	1.69	0.0681	4:46±0:69	6.78±0.52
22	CIPRO 22	0.14	0.0241	8:83±0:80	11.70±0.92
23	CIPRO 23	0.70	0.0419	1:27±0:03	10.88±0.32
24	CIPRO 24	0.94	0.0510	3:23±1:10	10.48±1.09
25	CIPRO 25	1.053	0.1203	3:37±0:46	9.75±0.26

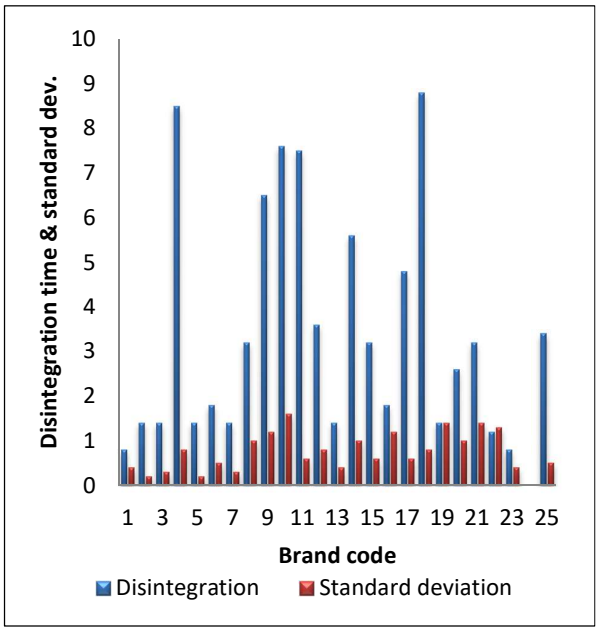

Figure 1: Graph of Disintegration test

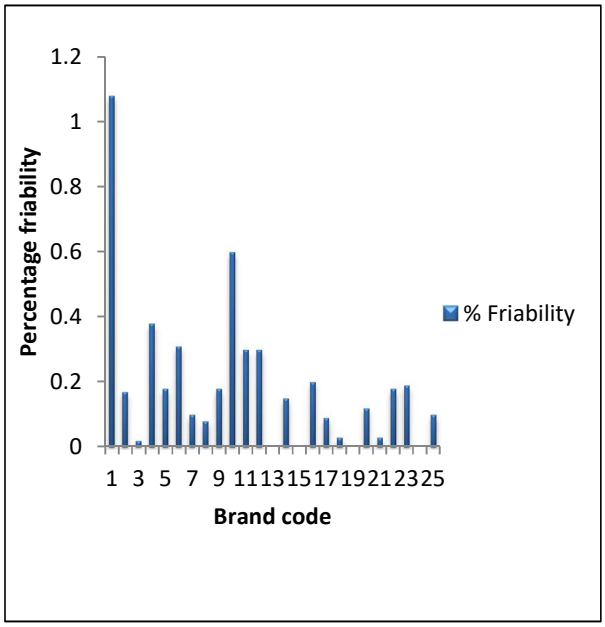

Figure 2: Graph of Friability test

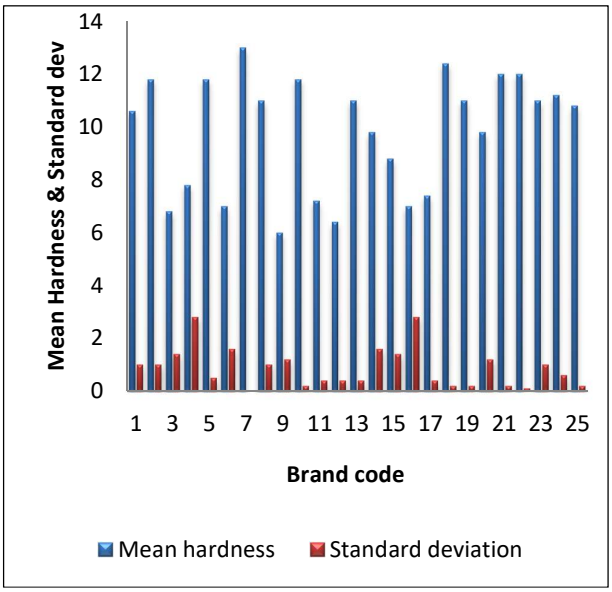

Figure 3: Graph of Hardness test

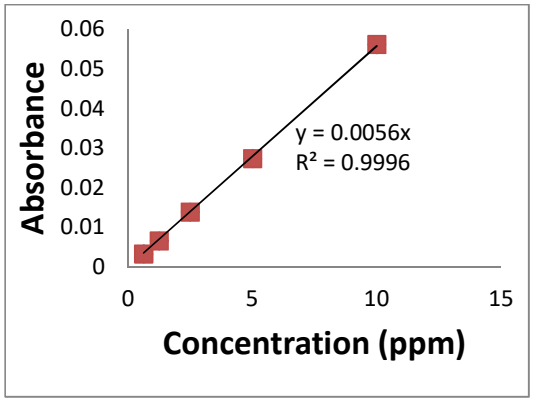

Figure 4: Calibration plot for Cadmium standard at 228.9 nm

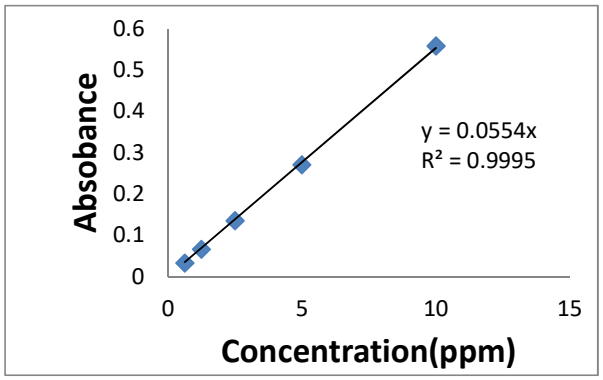

Figure 5: Calibration plot for Lead at standard 217 nm

Table 2: Permitted Daily Exposure for Cadmium and Lead in the Ciprofloxacin brands studied (Ciprofloxacin 500 mg is taken twice daily (12 hourly for five days).

	LEAD					CADMIUM				
Samples Code numbers	Acceptable daily intake (µg/day)	Acceptable intake for 5 days (µg/5 days)	Amount (µg/tablet)	Estimated daily intake (µg/day)	Estimated intake for 5 days (µg/5 days)	Acceptable daily intake (µg/day)	Acceptable intake for five days (µg/5 days)	Amount (µg/tablet)	Estimated daily intake (µg/day)	Estimated intake for five days (µg/5 days)
CIPRO 01	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 02	5	25	11.3	22.6	113	5	25	0.68	1.36	6.8
CIPRO 03	5	25	7.6	15.2	76	5	25	0.68	1.36	6.8
CIPRO 04	5	25	7.5	15	75	5	25	ND	ND	ND
CIPRO 05	5	25	ND	ND	ND	5	25	1.40	2.8	14
CIPRO 06	5	25	ND	ND	ND	5	25	0.59	1.18	5.9
CIPRO 07	5	25	ND	ND	ND	5	25	0.69	1.38	6.9
CIPRO 08	5	25	34.2	68.4	342	5	25	ND	ND	ND
CIPRO 09	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 10	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 11	5	25	ND	ND	ND	5	25	1.34	2.68	5.4
CIPRO 12	5	25	ND	ND	ND	5	25	1.71	3.42	17.1
CIPRO 13	5	25	7.4	14.8	74	5	25	0.67	1.34	6.7
CIPRO 14	5	25	7.5	15	75	5	25	0.68	1.36	6.8
CIPRO 15	5	25	8.8	17.6	88	5	25	1.20	2.40	12
CIPRO 16	5	25	ND	ND	ND	5	25	0.96	1.92	9.6
CIPRO 17	5	25	ND	ND	ND	5	25	0.76	1.52	7.6
CIPRO 18	5	25	ND	ND	ND	5	25	0.67	1.34	6.7
CIPRO 19	5	25	ND	ND	ND	5	25	1.07	2.14	10.7
CIPRO 20	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 21	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 22	5	25	ND	ND	ND	5	25	0.71	1.42	7.1
CIPRO 23	5	25	ND	ND	ND	5	25	1.39	1.39	13.9
CIPRO 24	5	25	ND	ND	ND	5	25	ND	ND	ND
CIPRO 25	5	25	ND	ND	ND	5	25	0.83	1.66	8.3

ciprofloxacin were subjected to hardness testing and from the results obtained, 52% of the brands passed the hardness test (Table 1, Figure 3).

Table 1 shows the results for uniformity of weight, friability, disintegration, and hardness test while a graphical illustration of the results for disintegration, friability, and hardness tests are depicted in Figures 1-3.

Atomic Absorption Spectrometry Test Results with Graphical Representations

The correlation coefficient, r, obtained for the standards cadmium and lead are 0.9995 and 0.9996, respectively, showing a good relationship between absorbance and concentration. The calibration plots for the metals are shown in Figures 4 and 5.

DISCUSSION

Twenty–five different brands of ciprofloxacin tablets marketed in Lagos, Nigeria, were subjected to several tests to assess their physical quality and determine the amount of Cadmium and Lead present. Both the physical and quantitative tests were carried out.

***Physical Assessment Parameters*:** The physical test includes uniform weight, hardness, friability, and disintegration. One in-process test criteria that guarantees dose unit consistency during compression is weight homogeneity. The production of uniform-weight tablets is vital, and it can only be assured by a free granule flow, selecting the appropriate lubricant, and punches with tight working length tolerances. The amount of variation in a tablet's dose and weight needs to be minimized. The Uniformity of weight of tablets is helpful in quality control during production. According to USP 2014, the weight uniformity of 20 uncoated or film-coated tablets, the mean should not be deviated from by more than ±5% for two tablets, and not by ±10% for any tablet. From the results obtained, CIPRO 13, CIPRO 19, CIPRO 21, and CIPRO 22 passed the test as they had one tablet each that deviated more than ± 5 % but none more than ± 10%. In addition, CIPRO 5 and CIPRO 20 passed, as they had two (2) tablets that varied by more than ± 5 % but none more than ± 10 %. However, CIPRO 18 failed the test as more than two tablets (i.e., 4 tablets) deviated from the mean weight by more than ± 5 %. The percentage pass rate of the test was gotten to be 96 %. The hardness of a tablet determines its level of breaking, abrasion, or chipping during transportation, handling and storage prior to use. This test is an unofficial test for the hardness of tablets. Oral tablets should have average hardness values between 4-10 kgF as the criteria for each brand to pass the hardness test [20]. From the results obtained, the percentage pass rate of the test was 52 % as CIPRO 02, CIPRO 05, CIPRO 06, CIPRO 07, CIPRO 09, CIPRO 12, CIPRO 16, CIPRO 17, CIPRO 18, CIPRO 22, CIPRO 23, CIPRO 24 failed the test, only 13 brands were within the specification. Friability is closely related to tablet hardness. A Friability test is done to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. The USP 2014 states that the percentage friability of oral tablets ought to be lower than 1 %. From the results obtained, 96 % of the brands passed the friability test.

All the brands passed the test except CIPRO 01, with a percentage friability value of 1.0775. Thus, twenty-four out of twenty-five brands passed the test as specified in the USP that the percentage friability must not exceed 1 %, which may also mean that the cohesive forces or binders holding the granules of the twenty-four brands together are strong enough to withstand abrasion in packaging, shipping, and handling. Disintegration is need to reduce the surface area of tablets and granules into smaller powder particles of the drugs exposed to gastrointestinal fluids, and it is used to predict how well a dosage form will release its active ingredient. The USP 2014 recommends that immediately released tablets should not have a disintegration time greater than 15 minutes. The results obtained, the percentage pass rate for the test was 96 %. The disintegration time for the twenty-five brands was less than 15 ± 0.5 minutes. All except for CIPRO 19 did not disintegrate and did not pass the test, resulting from a high concentration of binding agents that could affect the drug's bioavailability. This tablet brand will likely take a longer time to elicit pharmacological action when ingested.

***Heavy Metals Quantification*:** The technique of Atomic Absorption Spectrophotometry (AAS) was employed to ascertain the absorbance of Lead and Cadmium metals in the ciprofloxacin tablet brands. The concentrations were extrapolated from the calibration plot. The amount of Lead and Cadmium in the ciprofloxacin tablet brands was calculated and compared to the Permitted Daily Exposure (PDE), which is 5 µg/day [21]. According to the permitted daily exposure of Cadmium, (32 %), 8 brands of the ciprofloxacin tablets are free of Cadmium; this implies that they contain zero permissible quantities of Cadmium, hence, free from its toxicity. However, Cadmium was detected in (68 %) of 17 brands though less than the permitted daily exposure, which implies that there would be an accumulation of this metal in the body of the person taking these brands in case of an overdose, which can lead to kidney, lung and prostate cancer since they are not readily excreted. According to the permitted daily exposure of Lead, (72 %) 18 brands of the ciprofloxacin tablets are free of Lead; this implies that they contain zero permissible quantities of Lead, hence, free from its toxicity (Table 2). However, Lead was detected in (28 %) of 7 brands, with all exceeding the permitted daily exposure of Lead. It shows that the amount of Lead ingested in the body of the person taking these brands would be high.

CONCLUSION

Of all the Ciprofloxacin brands examined for the various physical tests, 96% of the tested brands passed the checks for uniformity of weight, 52% passed the tests for hardness, 96% passed the tests for friability, and 96% passed the tests for disintegration. The percentage passed for Cadmium is 32 %, according to the permitted daily exposure for Cadmium. The percentage passed for Lead is 72 %, and according to the

permitted daily exposure for Lead. The brands that passed the physical tests can be said to be of good quality and correct physical composition, and the amount of Cadmium and Lead detected can benefit humanity and universal use. Cadmium and Lead are of no benefit to humanity in the body. Accumulating Cadmium in the body can predispose humans to deleterious effects.

ACKNOWLEDGEMENTS

We acknowledge the D. K. Olukoya Central Research and Reference Laboratories, University of Lagos, Akoka, Lagos, Nigeria, for the permission granted to carry out this research in its establishment. We also acknowledge the Head of the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Lagos, Nigeria, for providing the physical parameters instrumentation and permission granted to utilize their laboratory.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHORS CONTRIBUTIONS

Adepoju-Bello Aderonke A. (ACEF), Oyawaluja Bamisaye O. (CDEF), Ndugba Augusta C. (BCD);
A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article.

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