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Physicochemical and Bioequivalence Studies on Some Brands of Levofloxacin Tablets Registered in Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author SOO designed the study, performed the statistical analysis and wrote the protocol, author CPA managed the analyses of the study and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study was aimed at comparing the physicochemical and bioavailability profiles of some brands of Levofloxacin 500mg tablets that are registered in Nigeria by her regulatory authority and to examine the feasibility of interchangeability of the brands.
Methodology: The physicochemical equivalence of ten brands of Levofloxacin 500 mg tablets (LEV-1 to LEV-10) were evaluated using both official and unofficial standards including weight variation, hardness, friability test, chemical assay, disintegration, dissolution rate and drug content. Five of the brands were also evaluated for bioavailability profiles using a single dose randomized two period cross–over designs measuring the concentration of drugs in the urine. Urinary samples before dosing and at various appropriate time intervals up to 12 hours were analyzed by validated Double Beam U. V. Spectrophotometer method with 99.8% extraction recovery. Pharmacokinetic parameters for bioequivalence evaluation C_{max}, T_{max} and AUC were determined.
Results: The resultsshowed that 60% of the levofloxacin brands (LEV-2, LEV-4, LEV-5, LEV-7, LEV-8 and LEV-9) failed in at least one of the tested physicochemical parameters. The statistical comparison of the physicochemical parameters showed no difference between the innovator brand (LEV-1) and three of the tested generic brands (LEV-3, LEV-6 and LEV-10). Unlike LEV-5, the results obtained from the reference ratios of the

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parameters from bioavailability studies for the physicochemical equivalent brands were found to be within bioequivalence acceptable range with the reference brand indicating that they are bioequivalent in terms of C_{max} and AUC to the innovator brand.
Conclusion: The study indicates that 60% of the brands may not be used interchangeably with the innovator brand; consequently, the therapeutic substitution of these brands is not advisable. The formulation and/or the manufacturing process affect the weight uniformity, content uniformity, dissolution and thus the bioavailability of the drug products.

Keywords: Levofloxacin; bioequivalence; interchangeability; physicochemical equivalence.

1. INTRODUCTION

Levofloxacin is 6-fluoroquinolone antibacterial agent and is greatly effective against both gram-negative and gram-positive bacteria. It was patented in 1987 and was approved by the United States Food and Drug Administration in 1996 for use in the United States and marketed by Sanofi-Aventis under the trade name "Tavanic®" [1]. Fluoroquinolones inhibit the topoisomerase II ligase domain, leaving the two nuclease domains intact [2]. Levofloxacin, a newer member, is the L- isomer of ofloxacin existing commercially as the hemihydrate. Chemically, it is (-)-(S)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazi-nyl)-7-oxo-7H—pyrido [1,2,3-de]-1,4 benzoxa-zine-6-carboxylic acid, hemihydrate [3].

Bacterial resistance to antibiotics is an emerging public health crisis. The prevalence of pathogens resistant to currently available antibiotics is on the increase. The developing world, being an integral part of a 'global village', is not insulated from this trend. This has resulted in the influx of newer and more potent antibacterial agents, the fluoro-quinolones inclusive, into these countries. About twenty National Agency for Food and Drug Administration and Control (NAFDAC) registered brands of generic versions of levofloxacin tablets are presently available from different manufacturers and from different countries in Nigeria with a wide price margins among them. Generally, the efficacy of pharmaceutical dosage forms depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary [4].

Reducing pharmaceutical care cost with generic drugs while maintaining quality of health care is an important societal goal in developed and developing countries [5]. Health care providers and policy makers also support the practice of prescribing low-cost generic products principally for economic reasons [6]. Generic medicines are those where the original patent has expired and which may now be produced by manufacturers other than the original innovator (patent-holding) company. A generic pharmaceutical is usually intended to be interchangeable with an innovator product, is manufactured without a licence from the innovator company, and is marketed after the expiry date of the patent or other exclusive rights [7]. Generic drugs are less expensive than equivalent innovator brands because generic manufacturers do not have to conduct costly clinical trials to test the safety and effectiveness of a generic version of a drug that has been safely and effectively used for several years [5]. It is therefore important that generics substitutes are analyzed for their chemical and biopharmaceutical equivalence, strength, quality, purity, and releasing profile of active ingredient in comparison to the innovator drug. This is particularly important for developing countries where drug distribution and supply is known to be erratic and the prevalence of substandard/counterfeit medicines is significantly higher [8], and as such, it is

difficult for effective monitoring of the quality of marketed generic drug products [9]. Any substantial variation in these analyses amongst the generics drugs indicates deficiency in the entire drug formulation and the delivery system. As such, the need to establish pharmaceutical equivalence and therapeutic equivalence of generics and innovator drug products cannot be overemphasized. Also, concerns are being raised on the lack of interchangeability between branded and generic drugs in the post-marketing setting. For example, according to Crawford and Campbell [10], switching from branded antiepileptic to generic copies might result in increased risk of therapeutic failure or adverse reactions. Also for generic antibiotics, differences in pharmaceutical properties might result in changes of their pharmacokinetic profiles, with consequent alteration of pharmacokinetic/ pharmacodynamics relationships, leading ultimately to variations in their clinical efficacy with respect to the brand-name counterpart. The assessment of bioequivalence of different drug products is based on the fundamental assumption that two products are equivalent when the rate and extent of absorption of the test drug does not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses [11]. In practice, bioequivalence is indicated when key pharmacokinetic parameters used to establish rate and extent of the test, and reference products fall within a preset confidence interval thus ensuring that the generic drugs will have the same safety, efficacy and therapeutic effect as the innovator product.

Due to the high cost of the innovator brand (Tavanic®), ascertaining the quality of the several brands of levofloxacin has become imperative. The objective of this study is to assess and compare the *in vitro* and *in vivo* performance of generic brands of levofloxacin with the innovator brand and to determine their therapeutic substitution or interchangeability in the post-marketing setting.

2. MATERIALS AND METHODS

2.1 Materials and Reagents

Ten different brands of levofloxacin tablets with labeled strength of 500mg and registered by NAFDAC were randomly obtained from registered pharmacy shops in Lagos, Nigeria. All the tests were performed within product expiry dates. The innovator/reference brand was labeled LEV-1 whereas other nine were designated as LEV 2-LEV-10. The standard levofloxacin powder was kindly donated by May and Baker PLC Nigeria.

All the reagents used are of analytical grade. Freshly deionized distilled water was used throughout the work.

2.2 Methods

2.2.1 Physicochemical Evaluations

2.2.1.1 Weight variation

Twenty tablets of each of the ten brands were weighed individually using a digital analytical balance and the average weight determined. The percentage deviations from the mean weight by each tablet were determined.

2.2.1.2 Friability test

Twenty tablets of each brand were weighed and subjected to a uniform tumbling motion using Erweka friabilator (Heusenstamm, Germany) that revolved at 25rpm for 4 minutes dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were reweighed and the percentage loss in tablet weight determined. The test was carried out in triplicate. The values of <1% are considered to be highly satisfactory evaluation characteristics [12].

2.2.1.3 Hardness test

Ten tablets of each brand were used to evaluate the tablet's hardness. The crushing strength was determined using Monsanto type hardness tester (Pharma-chem, Mumbai, India). The test was carried out in triplicate.

2.2.1.4 Disintegration test

Six tablets from a particular brand were placed in each of the six plastic tubes of Erweka disintegration apparatus (Heusenstamm, Germany). The tablets were monitored for the time taken for the particles to pass through the mesh screen for each of the tablets leaving no residue in the plastic mesh which was kept at 0.1NHCl (simulated gastric fluid) at 37ºC±0.5ºC. The process was repeated for all the brands and was done in triplicate.

2.2.1.5 Drug content in Levofloxacin tablets

Ten tablets of same brand were weighed and pulverized to fine powder. Accurately weighed tablet powder, equivalent to 50mg Levofloxacin hemihydrate from the total weight of tablets pulverized, was transferred into a 100ml volumetric flask. Fifty millilitres of 0.1MHCl was added, shaken for 15 minutes using a vortex mixer and diluted to the 100ml mark with same solvent. It was then filtered to obtain sample stock solution. One millilitre of the filtrate was further diluted to 100ml with 0.1MHCl and then assayed for content of levofloxacin with a solution containing 5µg/ml of pure levofloxacin hemihydrate as standard for comparison. The absorbance of the sample preparation and reference standard solution were taken using 0.1M HCl as blank at 290nm wavelength. The content of anhydrous levofloxacin in the marketed brands was then determined. All analyses were carried out in triplicate.

2.2.1.6 Dissolution rate

Dissolution studies were conducted to determine the release pattern of the drug from the product using dissolution apparatus (Erweka dissolution tester, type DT80, Germany). Three tablets from each brand were tested using dissolution medium of 900mL of 0.1 N HCl, rotating the paddle at 50rpm at 37±0.5ºC. Five millilitres of samples were withdrawn at different time periods or intervals: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 minutes, and the volumes withdrawn, replaced with fresh dissolution medium. These samples collected were filtered into pre-labeled sampling bottles using membrane filter Z(0.45nm) then diluted 1/100 using 0.01N HCL and the absorbance read at 290nm under UV spectrophotometer (Jenway 6405 UV/Vis Spectrophotometer). The concentration and percentage release in each time interval were determined.

2.2.2 Bioavailability studies

Five of the ten brands were used for bioavailability studies. The physicochemical profiles of all the products were considered in choosing the brands for bioavailability studies. The four brands (LEV-1, LEV-3, LEV-6 and LEV-10) that passed all the physicochemical tests were selected for the bioavailability study. An additional brand (LEV-5) that had the most deficient parameters in the physicochemical test was also examined alongside the four brands. The protocol for the urine bioavailability study was conducted in accordance with international conference on harmonization of good clinical practice guidelines. A single-dose randomized two period cross–over study of levofloxacin tablets conducted in fifteen healthy, non-smoking adults with body mass index (BMI) between 18.5-29.9kg/m^2 and normal gastrointestinal functions. The fifteen healthy participants with written consent were recruited before undergoing the study procedure and randomly assigned and divided into five different groups of three participants each and their basal urine collected prior to drug administration. All volunteers were given a single dose of either formulation (innovator and generic brands) with 500ml of water, no food was allowed until five hours after dose administration. The urine collection was carried out in the following schedule, 15, 30, 60, 120, 240, 480, 720 minutes after dosing, and kept in refrigerator before analysis at -4ºC. The urine samples were filtered using membrane filter (0.45µm) and dilutions of 1 in 100 were made (Beer-Lambert law). With reference to calibration standard curve, the amounts of levofloxacin in the samples were determined at wavelength (max) of 290nm using double beam validated UV spectrophotometer and the findings were then analyzed for bioequivalence studies. The area under concentration time curve (AUC) was determined using linear trapezoidal method which generally serves as the indicator for the extent of absorption while peak concentration (C_{max}) and the time of its occurrence (T_{max}) reflects the rate of absorption. These pharmacokinetics parameters generated from the C_{max} and AUC was statistically analyzed. The values of reference/test were compared on the ratio of bioequivalence range of 0.8- 1.25.

3. RESULTS AND DISCUSSION

3.1 Physicochemical Studies

The results of the physicochemical parameters of the ten different brands of levofloxacin tablets are presented in (Table 1).

There were significant differences (P=.05) for the mean tablet weights (593.6mg to 1026.1mg) (Table 1) obtained for various brands of levofloxacin tablets. This result might be attributed to the differences in the percentage concentrations of excipients used in their formulations by different manufacturers. This is similar to the results of wide variation in mean weight reported for nifedipine tablets by Okoye and Iwuagwu [13] and co-trimoxazole tablets by Hailu [14]. However, from the results presented in (Table 2), six of the brands LEV-1 (innovator brand), LEV-2, LEV-3, LEV-6, LEV-7 and LEV-10 passed the test for uniformity of weight while LEV-4, LEV-5, LEV-8 and LEV-9 failed. The British Pharmacopoeia [12] states that not more than two of the individual weights from each sample should deviate from the mean weight by more than ±5% and no tablet by more than ±10%. LEV-5 brand had the highest coefficient of variation which indicates high variation of tablet weight within its batch. Generally, excessive weight variation is attributable to such factors as tooling of the compression machine, flow properties of the powder, improper die filling or presence of air in the powder or granular bed and inconsistent powder or granule

density due to wide range of particle size [15]. The significance of the test is to ensure that tablets in each batch of formulation fall within the appropriate size range as this will affect chemical content directly or indirectly measuring the amount of drug substance in the tablet [16].

The results of friability test showed that all the brands passed the test. The values of <1% are considered to be highly satisfactory evaluation characteristics [12]. LEV-8 had the highest percentage friability of 0.069% while LEV-1, LEV-6 and LEV-4 had the least friability of 0%. The brand most likely to lose particles during manufacturing, handling, packaging and transportation is the LEV-8 brand.

The results of the hardness test (Table 1) showed that all the brands examined had mean crushing strength within the range of 8.15 to 12.25kg/cm^3 which fell between the limit of the specification of 4-15kg/cm^3 [15]. The hardness values correlated with the friability values for all brands i.e. the harder a tablet, the less friable and sometimes the more time it takes to disintegrate [17].

The results of the disintegration time (Table 1) showed that all the brands complied with the compendia specification by disintegrating within 30mins as specified for film coated tablets [12]. Some of the brands' disintegration time varied widely and cannot be predicted from the tablet hardness values. This is not unusual since different manufacturers now adopt different formulation techniques to manipulate the disintegration and release properties of tablets [18]. While tablet crushing strength is not an absolute indication for disintegration, disintegration could be directly related to dissolution and subsequent bioavailability [17]. Rapid disintegration is also attributable to the nature and concentration of the disintegrant used in the formulation as well as the manufacturing process employed [19].

Table 1. Physicochemical parameters of ten different brands of levofloxacin tablets

Samples	Mean weight (mg)	Friability (%)	Drug content (%)	Disintegration time (mins)	Mean Hardness (kgf)
LEV-1	634.62(±4.32)	0	90.42	9.45(±0.63)	13.90(±0.21)
LEV-2	729.30(±12.97)	0.014	79.67	10.19(±0.88)	12.18±0.83
LEV-3	654.04(±4.9)	0.020	93.75	7.4 0(±0.8)	11.58±1.35
LEV-4	593.60(±10.12)	0	98.83	5.49(±0.67)	8.60±0.88
LEV-5	600.78(±19.7)	0.011	79.44	7.05(±1.02)	8.80±1.75
LEV-6	1026.10(±37.7)	0	92.87	7.09(±1.2)	10.67±1.22
LEV-7	726.13(±9.8)	0.012	94.16	24.32(±3.34)	8.50±1.29
LEV-8	967.54(±11.9)	0.069	95.09	8.26(±0.45)	8.15±1.08
LEV-9	694.90(±11.03)	0.009	94.40	5.03(±0.64)	12.25±1.64
LEV-10	661.21(±12.1)	0.046	90.77	6.12±(0.92)	11.85±1.08

Table 2. Weight deviations from mean weights

RANDS	LEV-1	LEV-2	LEV-3	LEV-4	LEV-5	LEV-6	LEV-7	LEV-8	LEV-9	LEV-10
S/no	Mean=635.34mg	Mean=729.25mg	Mean=652.39mg	Mean=593.59mg	Mean=600.78mg	Mean=1026.07mg	Mean=726.13mg	Mean=967.535mg	mean=694.91mg	Mean=661.21mg
1	1.86	1.71	-0.99	-9.49	-12.78	-1.59	1.28	8.27	6.30	-0.55
2	-1.74	1.01	-7.89	3.71	11.82	-4.19	1.08	-6.64	2.60	-1.45
3	1.86	-0.59	3.82	-5.49	0.42	-3.79	1.38	26.87	14.10	1.96
4	-1.74	1.11	1.92	4.11	-5.98	-0.99	2.78	3.47	9.60	5.96
5	-4.44	0.61	3.82	20.11	-8.18	2.32	-0.22	5.97	-5.31	0.46
6	-0.64	-3.19	-0.69	-4.79	-30.88	2.62	-4.62	-9.24	-19.21	-1.75
7	2.36	-1.59	-1.19	-1.49	15.82	-0.99	0.18	-2.84	10.20	-1.65
8	1.56	0.81	-2.09	8.61	-14.28	1.72	0.28	-7.94	-4.31	-2.85
9	0.56	0.71	0.22	2.91	21.82	3.72	-1.92	0.97	-2.31	-2.75
10	2.96	0.31	2.62	-17.39	38.32	-1.92	-0.62	-16.84	-1.91	2.96
11	5.66	-2.29	-0.89	-9.59	-12.68	-0.22	0.88	8.47	6.10	-0.95
12	0.26	1.01	1.52	3.91	12.22	-3.12	1.88	-6.54	2.20	-3.85
13	2.16	-1.29	4.12	-5.69	-5.88	-3.92	0.78	26.27	14.10	2.16
14	-1.94	2.41	2.12	3.81	-8.58	2.12	2.68	2.97	10.10	0.86
15	-3.64	-1.29	-1.89	19.91	-30.68	4.32	2.88	6.47	-24.71	-4.85
16	-0.84	2.11	-1.39	-5.39	-15.48	4.02	1.68	-9.84	-19.01	-0.65
17	3.96	-1.69	-1.79	-1.69	21.02	-5.09	0.68	-2.54	10.30	8.16
18	0.86	-1.79	0.12	8.21	38.42	1.02	-0.92	-0.34	-3.91	-4.75
19	-0.84	2.71	4.92	3.51	-8.28	4.22	-3.82	-17.04	-2.81	-0.95
20	0.76	-0.79	2.62	-17.79	-6.18	0.02	-6.32	-9.94	-2.11	-0.55

The drug content assay revealed that the percentage content of levofloxacin hemihydrate in all the brands ranged from 79.44 to 98.83%w/w, (Table 1). The British Pharmacopoeia [12] states that the content of levofloxacin tablet should not differ from the stated dose by more than ±10% of the labeled amount. LEV-2 and LEV-5 failed the test while others were within the specified rage.

The obtained dissolution profile (Fig. 1) revealed that at 30mins all brands attained more than 80% w/v dissolution except LEV-7. Also the brands studied achieved 85% dissolution of their labeled contents within 60mins except LEV-7. Hence, all brands except LEV-7 complied with the Pharmacopoeia specification [12]. The slower dissolution rate of LEV-7 may be related to its disintegration result in which it had the highest values of 24.30mins. There were no significant differences in the release pattern of all the different brands. Nevertheless, it was evident that LEV-3 and LEV-6 showed faster rate of dissolution having dissolution of above 80% w/v at 10mins among all the brands. Also, 60% of the generic brands dissolved faster than the innovator brand. The differences in the release rate might be attributed to manufacturing process and composition of excipients used by different manufacturers [20,21].

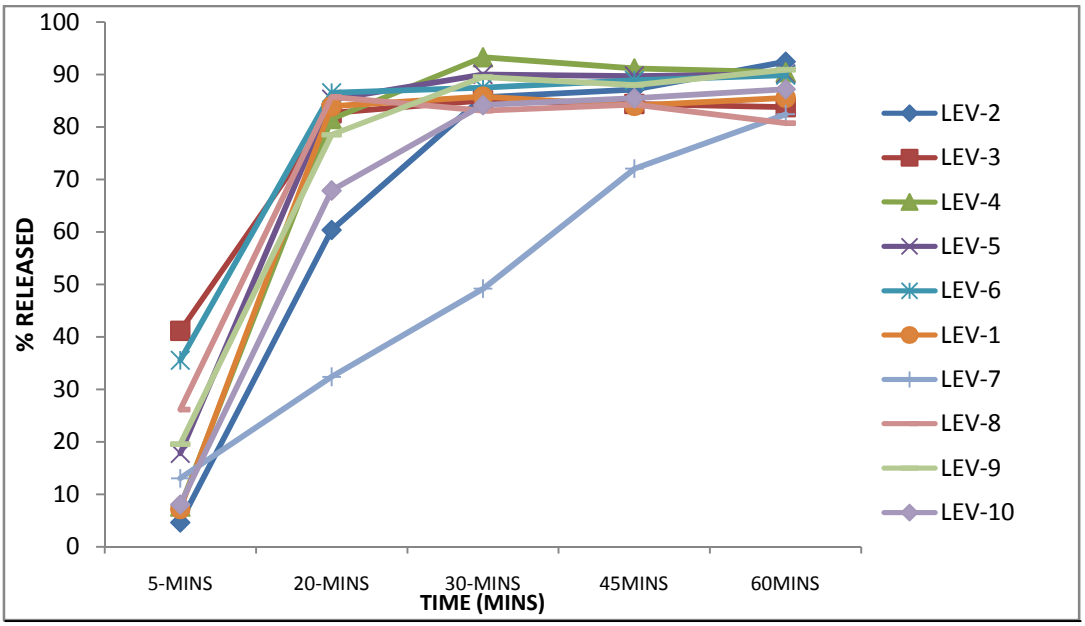

Fig. 1. Dissolution profile of levofloxacin 500mg tablets

3.2 Bioavailability Studies

The parameters from the bioavailability study (Tables 3, 4 and Fig. 2) suggest that the test formulations LEV-3, LEV-6 and LEV-10 are bioequivalent to the innovator brand (LEV-1) as they are within the regulatory bio-equivalent criteria range of 80–125% interval of the FDA guidelines for C_{max} and AUC [22]. The test formulations were rapidly absorbed, based on the mean T_{max} values and AUC test/AUC reference values for the four products (LEV-3, LEV-6, LEV-10 and the innovator brand, LEV-1) showing greater than 80%, suggesting that the duration of sample collection was appropriate, covering greater than 80% of complete drug

profile. As expected, only LEV-5 with C_{max} (0.96±0.17mg/ml), and AUC (8.97±1.19mg/ml/hr), did not comply with standard limits of bioequivalence range. The Lev-5 brand failure to comply with the standard limit of bioequivalence range could be seen to correlate with the drug concentration or its wide weight variation among the batch. This variation implies deficiency in the entire drug production and the delivery system. Also the dissolution result of LEV-5 brand did not correlate with the in-vivo performance, this could be due to wide weight variation, wide drug active content variation and also the complex, variable, and unpredictable *in-vivo* environment compare to that of any *in vitro* test environment, making *in vitro / in vivo* correlations very difficult [23]. Although *in vitro* dissolution testing has been shown to be a valuable predictor of the *in vivo* bioavailability and bioequivalence of oral solid dosage forms [24], the need for an *in-vivo* confirmatory bioequivalent/bioavailability study can never be over-emphasized [25].

Table 3. Mean pharmacokinetics parameters and SEM (n=15)

Parameter	LEV-1	LEV-3	LEV-5	LEV-6	LEV-10
C_{max} (µ/ml)	1.598±0.33	1.486±0.88	0.96±0.17	1.658±0.78	1.636±0.92
AUC $_{0\rightarrow12hrs}$ (mg/ml/hr)	15.2±2.23	13.88±1.90	8.97±1.19	14.55±2.16	15.76±2.27

Table 4. Bioequivalence ratio of reference and test

Test A	**C_{max}**	**AUC**
LEV-1 (INNOVATOR)	1.598	15.2
LEV-10	1.636	15.76
Point estimate of diff of the mean	1.02	1.04
Acceptance range	0.8-1.25	0.8-1.25
Conclusion	Bioequivalent	Bioequivalent
Test B	**C_{max}**	**AUC**
LEV-1 (INNOVATOR)	1.598	15.2
LEV-3	1.486	13.88
Point estimate of diff of the mean	0.93	0.914
Acceptance range	0.8-1.25	0.8-1.25
Conclusion	Bioequivalent	Bioequivalent
Test C	**C_{max}**	**AUC**
LEV-1 (INNOVATOR)	1.598	15.2
LEV-5	0.959	8.97
Point estimate of diff of the mean	0.6	0.57
Acceptance range	0.8-1.25	0.8-1.25
Conclusion	Not-bioequivalent	Not-bioequivalent
Test D	**C_{max}**	**AUC**
LEV-1 (INNOVATOR)	1.598	15.2
LEV-6	1.657	14.55
Point estimate of diff of the mean	1.04	0.96
Acceptance range	0.8-1.25	0.8-1.25
Conclusion	Bioequivalent	Bioequivalent

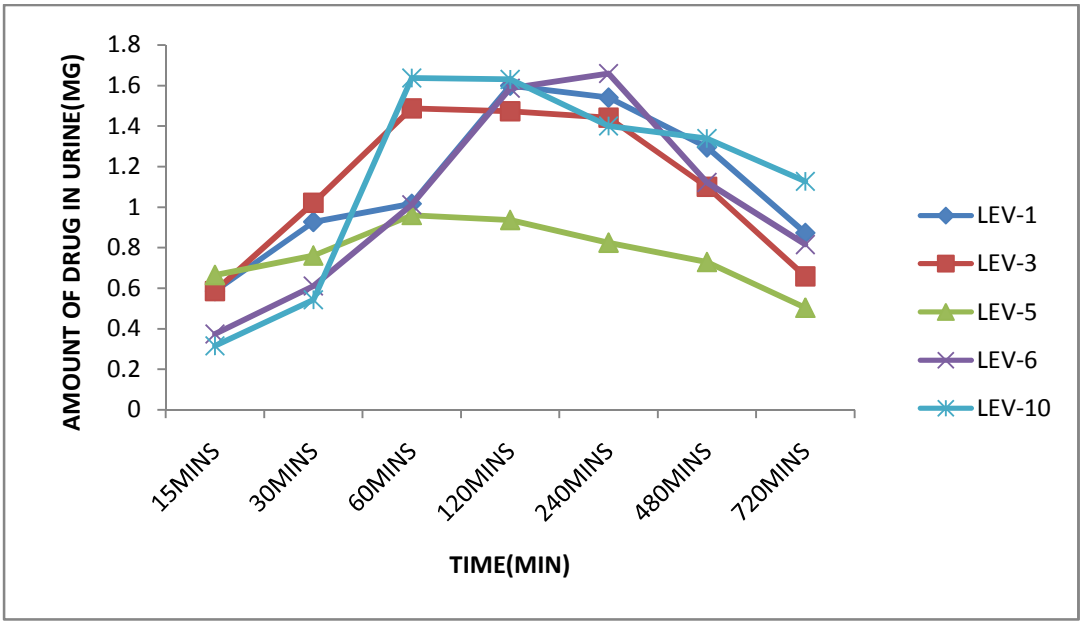

Fig. 2. The mean urinary concentration–time of levofloxacin in five different brands in mg/ml

4. CONCLUSION

Based on this study, 40% of the brands of levofloxacin tablets passed both physicochemical and bioequivalence tests, and are therefore bioequivalent and interchangeable. This study has emphasized that chemical equivalence does not indicate bioequivalence; moreover, the study has highlighted the need to carryout *in vivo* bioavailability studies when studying the interchangeability of generics and innovator drug products. Furthermore, there is urgent need for the regulatory authorities to periodically carryout bioequivalence studies in post marketing setting. There is also need for manufacturers to carryout bioavailability studies periodically especially when there is a change in the quality and concentration of formulation ingredients and manufacturing process.

CONSENT

Volunteers were eligible for participation in the study after voluntarily written informed consent.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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