



Quality attributes of twenty-nine brands of ciprofloxacin: post-marketing *in vitro* analyses, microbiological assay and *in vivo* simulation

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Abstract

Ciprofloxacin is a fluoroquinolone antibiotic employed to treat infections. There are over three hundred registered generic brands of ciprofloxacin in Nigeria. There has been an observed marked variation in therapeutic or clinical outcome with change in brands by health professionals and patients. In a previous study of six (6) brands we had reported a high degree of inequivalence. In this study, twenty-nine (29) brands of ciprofloxacin were extensively evaluated against compendia requirements. Microbial sensitivity against two test organisms was conducted. *In-vitro* drug release and *in-vivo* simulation were established. Analysis of the data generated indicated that all brands passed qualitative test using TLC and disintegration test, six failed hardness test, one failed friability, nine failed antimicrobial assay and six failed percentage content assay. Conclusions drawn from the study for evidence-based clinical decision would include the fact that three brands only were found to be bioequivalent to the innovator brand, Ciproxin; while eight brands were bio-inequivalent using the three models of similarity factor (f_2), and difference factor (f_1) in two media and dissolution efficiency (DE) in pH 4.5. The three brands (Cipro-All, Cifran And Ciprogem) may confidently be used interchangeably with the innovator brand

Keywords: Bioequivalence; Ciprofloxacin Drug quality; Generic substitution; Post-marketing surveillance

INTRODUCTION

Poor quality medicines such as substandard, counterfeit or falsified and degraded products are a global challenge. Poor quality medicines could lead to treatment failure, drug resistance, morbidity and mortality in extreme cases and eventual distrust in the health care system. In Nigeria, poor quality medicines are both locally produced and imported from countries such as China and India. While the regulatory body,

National Agency for Food and Drug Administration and Control (NAFDAC) try to mitigate against poor quality medicines, such medicines still flood the market mainly due to limited resources of the agency, porosity of the borders and corruption. Consequently, quality assurance of medicines from raw materials to administration, requires the involvement of all stakeholders from suppliers to end users. Poor quality medicines should be reported to the National Pharmacovigilance Centre (NPC) at

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NAFDAC, with offices in some health facilities. Drug quality reporting involves all stakeholders especially the health care professionals who observe these medicines when procured and administered. Quality assessments of medicines are usually undertaken by regulatory bodies, designated laboratories, and those in academia. However, availability of data is necessary to ensure public enlightenment and control of procurement and administration of poor-quality drugs. Collation of data by the Pharmacovigilance Centre will facilitate appropriate dissemination to health facilities.

A comprehensive assessment of a solid dose antimicrobial pharmaceutical product should include the evaluation of its attributes such as visual inspection of labelling and packaging, physicochemical properties of uniformity of weight, disintegration and dissolution rates; chemical assays of purity and content of Active Pharmaceutical Ingredient (API); and a compulsory microbiological evaluation. Where interchangeability of products is intended, a dissolution study (*in-vitro* and/or *in-vivo*) becomes necessary.

These product attributes have been the focus of several product evaluations after release into the market [1-4]. Chemical analysis and visual assessment have been used to identify poor-quality drugs prevalent in Asian and sub-Saharan African countries [5, 6]. Nayyar and co-workers [7] reviewed 21 surveys on antimalarial drugs from six classes and from 21 countries in sub-Saharan Africa. The review of the surveys indicated that 35 % of the drugs failed chemical analysis, 36 % failed packaging analysis and 20 % were classified as falsified. WHO [8] states that a drug is said to be falsified when the product is found to be a deliberate or fraudulent misrepresentation of its identity, composition, source or record keeping for traceability, and pretend to have marketing authorization. Those involved in falsified products are in it for profit having a total disregard for public

health and safety. The effects of poor-quality drugs include adverse drug events, treatment failure, prolonged illness, increased cost of treatment, antimicrobial resistance and increased morbidity and mortality. Nigeria has cases of deaths due to poor quality medicines. About four years ago (2016), an estimate of 41.96 % of under-five malaria deaths was associated with administration of poor quality antimalarials [9]. Details on deaths caused by poorly compounded chloroquine, unintentional use of ethylene glycol in paracetamol syrup, fake meningitis vaccines, fake adrenaline, contaminated infusions, diethylene glycol in paracetamol and chlorpheniramine-based teething mixture (My Pikin) are in the public domain.

One underutilized approach to assist in the fight against poor quality of medicines is drug quality reporting. Pharmacovigilance reports regarding quality issues excluding issues relating to adverse drug reactions and medication errors are described as drug quality reporting. A drug quality reporting system (DQRS) receives reports submitted by health professionals and marketing authorization holders voluntarily on observed or suspected defects or quality issues related to marketed drug products [10]. Reporting poor quality drug products may protect the public from treatment failure, antimicrobial resistance, and adverse drug reactions. Such reports should lead to prompt inspections and laboratory analysis.

Ciprofloxacin is one of the most prescribed antibiotics. In Nigeria, it can be obtained without prescription and due to the demand, there are over 300 registered ciprofloxacin brands [11]. Registered medicines must be monitored to ensure they are not re-introduced into the market as substandard or falsified products over time. Antibiotics are one of the targeted classes of medicines for manufacture, importation and distribution of their substandard products and counterfeits due to their high volume of use. As a result, post-

marketing surveillance is vital to sanitize the drug market and protect public health.

Although several studies on ciprofloxacin have been undertaken [1, 12-18], this study was prompted by several observations and reports from some hospitals in North-Eastern Nigeria of varying clinical/therapeutic responses of different brands of Ciprofloxacin 500 mg tablets/caplets. Therapeutic failure often occurred with some brands of Ciprofloxacin 500 mg tablets/caplets making physicians and patients insist on specific brands without a known scientific evidence. Consequently, the study was undertaken to assist the prescribers and pharmacists make evidenced-based choices regarding interchangeability of available generic ciprofloxacin products.

EXPERIMENTAL

Test Products. Twenty-nine (29) different brands of ciprofloxacin 500 mg tablets/caplets available at the time of sampling were procured from Yola and Jos metropolis, capital cities of Adamawa and Plateau states, Nigeria. All test products procured for the study were registered with National Agency for Food Drug Administration and Control (NAFDAC) except the innovator brand, Ciproxin (Bayer, Pakistan, Batch No TRTOE8N) which was sourced abroad. The USP ciprofloxacin standard powder and standard tablets were gifts from a fellow scientist. Details of the twenty-nine (29) brands of ciprofloxacin tablets/caplets were as shown in Table 1. The methods were executed according to USP [19] with slight modifications as indicated in the methods.

Physicochemical tests

Visual inspection. This was undertaken in search of defects on labeling, packaging, and dosage forms. Required information on the package such as shelf-life, manufacturing date, dosage strength, dosage form and dosage description were assessed and documented.

Size, shape, and color were also observed and documented.

Uniformity tests. Laboratory tests such as weight variation and uniformity of thickness and diameter were executed as detailed in the USP [19].

Friability test. Resistance to abrasions and handling was determined as described in the USP [19] using a friabilator (Erweka, JM0004-MG-001, Germany).

Hardness. To assess the tablet hardness, six tablets from each brand were employed using a hardness tester (Monsanto Tablet hardness tester, USA) to obtain the force required to break each tablet.

Disintegration. Six tablets from each brand in 900 mL of 0.1 HCl at $37\pm 0.5^\circ\text{C}$ were also used for the disintegration test (Erweka ZT 720 disintegration tester, Germany). The time at which no particle remained on the mesh was recorded and the average time it took for the six tablets of each brand to disintegrate was determined.

Content assay. Ascertaining the quantity of ciprofloxacin in the tablets of the different brands was undertaken by crushing pre-weighed twenty tablets from each brand. Thereafter, an equivalent weight of 25 mg of ciprofloxacin was dissolved in 25 mL of deionized water. This was further diluted to obtain a stock solution of 100 $\mu\text{g/mL}$. Subsequently, 4 $\mu\text{g/mL}$ was withdrawn from the stock and the absorbance was determined at 275 nm. The percentage content in each brand was calculated after obtaining the equation of best line fit from calibrations carried out with the reference standard of ciprofloxacin.

In vitro drug release. The dissolution apparatus II (LOGANS dissolution system UDT-804, Thailand) was used at 50 rpm in three different media (0.1 N HCl – pH 1.2; acetate buffer pH 4.5 and phosphate buffer pH 6.8). The volume used for each medium was

900 mL equilibrated to $37\pm 0.5^\circ\text{C}$. Six tablets were tested from each brand in the different media. Samples (5 mL) were withdrawn at intervals of 5, 10, 15, 20, 25, 30, 45, 60 min and same volumes were replaced with fresh medium to maintain sink conditions. The samples were filtered and assayed spectrophotometrically at 275 nm.

Impurity profiling of ciprofloxacin brands.

The procedure employed was according to the operation manual of Global Pharma Health Fund (GPHF) Minilab. Thin layer chromatography (TLC) was employed to determine the purity of the ciprofloxacin brands. The mobile phase was prepared comprising 10 mL methanol, 5 mL acetone, 2.5 mL toluene, 5 mL concentrated ammonia solution (25 %), pipetted into the TLC developing chamber. The chamber was tightly closed, and the content mixed thoroughly. The chamber wall was lined with filter paper and left for 5 min; thus, ensuring saturation of the chamber with the solvent vapour. Standard stock solution of ciprofloxacin yielding 5 mg/mL was prepared in water with ciprofloxacin 250 mg standard tablet. Thereafter, 1 mL each was withdrawn from the stock solution to prepare 0.625 mg/mL and 0.5 mg/mL and made up to 10 mL with methanol. Stock sample solutions were prepared with 500 mg tablets from each brand to yield 5 mg/mL. From the stock solutions, 0.625 mg/mL was prepared for each brand. Thereafter, employing a micropipette, 2 μL of working standard and sample solution were spotted at different points (origin line) on the TLC plate. The TLC plates were carefully loaded into the already saturated developing chamber containing the mobile phase. The jar was closed and the chromatoplate was left until the solvent front had moved to three quarter of the length of the plate. The developing time was 22 minutes. The plate was carefully removed, and the solvent front marked, excess solvent was left to evaporate and the chromatoplate was

observed under UV light of 254 nm using a battery driven lamp and the Rf values deduced.

Microbiological assay of ciprofloxacin brands.

Mueller Hinton broth was prepared according to manufacturer's directives and 5 mL of the broth was dispensed into bijou bottles and sterilized in an autoclave at 121°C for 15 min. Similarly, Mueller Hinton agar was prepared according to manufacturer's directives and 20 mL each was dispensed into clean and dried bijou bottles, covered, and sterilized by autoclaving at 121°C for 15 min. The test organisms, *S. aureus* and *P. aeruginosa* were inoculated into the broth, incubated overnight at 37°C . The overnight culture was diluted to 0.5 McFarland standard. The molten sterile agar was cooled to about $40\text{--}45^\circ\text{C}$ and 0.1 mL of standardized inoculum was inoculated into the 20 mL of agar, mixed and poured into a Petri-dish and allowed to solidify. Thereafter, wells were punched into the agar with No 5 cork borer and the wells filled with 0.1 mL solutions of each of the brands and standard. Tests and standards were compared at three concentrations levels - 60, 30, 15 $\mu\text{g/mL}$. The plates were left on the bench for about one hour for pre-diffusion and were incubated for 24 h at 37°C . The zones of inhibition were measured, the log potency ratio was calculated and the percentage content in each brand was determined.

Data analyses and *in vivo* simulation. Basic statistics such as standard deviation was employed to analyse the data obtained. DDSolver as an add-in to Microsoft excel was used to determine difference factor, f_1 , similarity factor f_2 and dissolution efficiency. Microsoft excel and PKSolver were used for simulation of *in vivo* absorption and determination of pharmacokinetic parameters, respectively.

RESULTS AND DISCUSSION

Physicochemical evaluation. Tablets of all the brands were white except those of zibatab (yellow) and ciprotab (one side yellow and the

other white). The tablets of the different brands were of three shape types – round, oval and oblong. Some of the brands had the brand names engraved on the tablets. Table 2 indicates the documented visual inspection of the brands of ciprofloxacin. There was no indication of any degraded tablets on visual inspection.

The outcomes of the physical parameters tested were as shown in Table 3. All brands passed weight variation test except siprosan, cipro-superior and zindocip with percentage deviations of 5.4, 6.6 and 20.1% respectively. These deviations were more than the USP specification for tablets weighing more than 342 mg (not more than 5%). Six brands, ciproheal, rumaxine, ciproall, zindocip, siprosan, and corflox failed hardness test with kilogram force below the required 4 kgF. Of

concern may be the handling and transportation of these brands which may lead to fracture or chipping.

All brands passed the friability test except ciprogem with a percentage friability of 10.8 ± 0.23 . The specification for friability is that tablets should be less than 1% friable. In our previous study, the batch of ciprogem purchased then passed friability test [1]. The manufacturer of ciprogem used to have the franchise and licence agreement to produce ciproxin until 2002. Consequently, one would expect consistency from them. Search for other publications on ciprofloxacin to monitor ciprogem's previous performances yielded limited results as some authors coded the brands [17, 20, 21] while those who did not code did not sample ciprogem [12, 15].

Table 1: Product information of the different brands of Ciprofloxacin

S/N	BRAND	BATCH NO	NAFDAC NO	MFD. DATE	*EXP. DATE	COUNTRY OF ORIGIN
1	Prox	G014020	04–3565	2014/APR	2017/MAR	INDIA
2	Rapidflox	E508	04–3221	2015/MAR	2019/MAR	INDIA
3	Ciproheal	CF4030	04–7436	2014/AUG	2017/JUL	INDIA
4	Rumaxine	O15	A4–9152	2014/APR	2017/MAR	PAKISTAN
5	Cipro-all	5EO25	B4–1551	2015/MAY	2018/APR	INDIA
6	Ciprofax	140615	A4–0482	2014/JUN	2017/JUN	CHINA
7	Cipro-superior	1506020	A4–4889	2015/JUN	2018/JUN	NIGERIA
8	Cipad	4T66004	04–6926	2014/FEB	2017/JAN	INDIA
9	Cipro-Kriss	KP15173	B4–0293	2015/AUG	2016/JUL	NIGERIA
10	Zindocip	60429	B4–2565	2014/JUN	2019/JUN	CYRUS
11	Vitapro	5640626	04–2170	2014/JUL	2017/JUN	NIGERIA
12	Pemcipro	141221	B4–3485	2014/DEC	2017/DEC	CHINA
13	Siprosan	SPS013A	04–2107	2014/AUG	2017/JUL	NIGERIA
14	Cenox	CNXH0160	04–3002	2014/JAN	2017/NOV	INDIA
15	Zyprox	129	04–9612	2015/JUL	2018/JUN	NIGERIA
16	Cyplox	640029	04–3202	2014/JAN	2016/DEC	INDIA
17	Gecip	141112	04–5856	2014/NOV	2017/NOV	CHINA
18	Cipromaxfort	14042001	04–4950	2014/AUG	2017/AUG	CHINA
19	Ciflaxin	100EO1	04–9097	2014/MAY	2018/APR	NIGERIA
20	VPL	140727	B4–0053	2014/JUL	2017/JUL	CHINA
21	Ciprof	GT15010	04–4772	2015/FEB	2019/JAN	INDIA
22	Zibatab	ZXU011402	B4–2220	2014/JUN	2017/MAY	INDIA
23	Corflox	4385	B4–3322	2014/DEC	2017/NOV	INDIA
24	Cifran	2662288	04–4673	2014/DEC	2017/NOV	INDIA
25	Grakkoflox	GK14001	B4–0121	2014/FEB	2017/JAN	INDIA
26	Cipronol	150102	04–6340	2015/FEB	2017/DEC	CHINA
27	Ciproxin	TRTOE8N	NIL	NIL	2019/JUN	PAKISTAN
28	Ciprogem	3641H	04–4699	2015/MAR	2020/FEB	NIGERIA
29	Ciprotab	VG1329	04–0723	2014/JAN	2016/DEC	INDIA

*The study was undertaken from late 2015 to 2016 before the expiry dates of the products.

All brands were within their shelf lives at the time of the study.

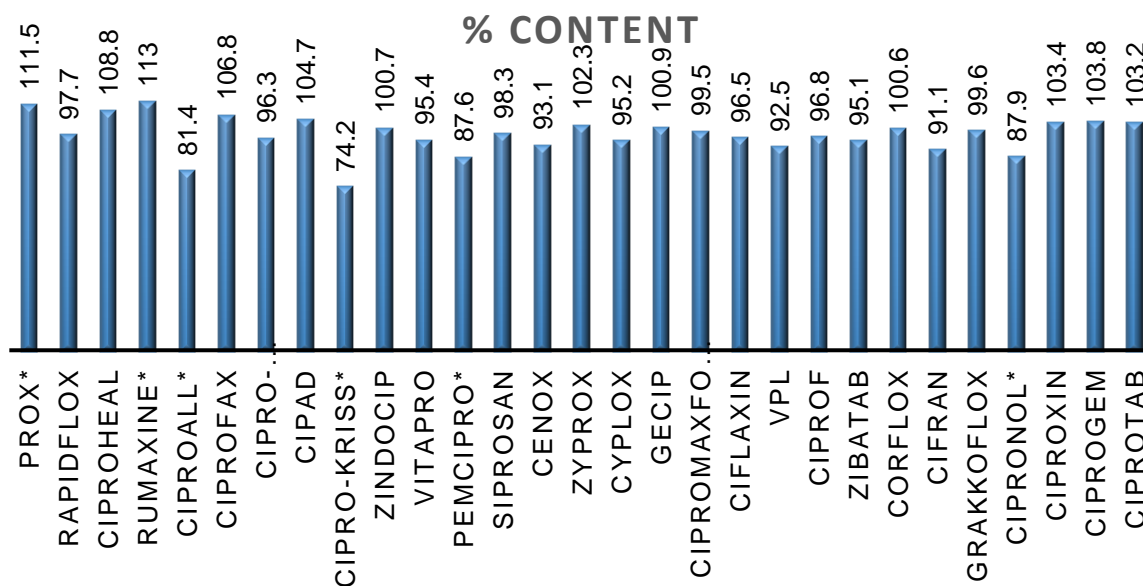
Table 2: Visual assessment of the different brands of ciprofloxacin

S/N	BRAND	Pack size	PACKAGE	DOSAGE FORM	DESCRIPTION
1	Prox	2 x7	Alu/Alu blister*	Film coated caplet	White/ Oblong/ Scored on one side
2	Rapidflox	2 x7	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side and "Rapidflox" engraved on the other side
3	Ciproheal	1 x10	Alu/Pvc blister**	Film coated caplet	White/ Oval/ "Maxheal" engraved on one side and "Ciprof 500" on the other side
4	Rumaxine	2 x7	Alu/Alu blister	Film coated tablet	White/ Round
5	Cipro-all	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side
6	Ciprofax	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side and "Ciprofax 500" engraved on the other side
7	Cipro-sup	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side
8	Cipad	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ Scored on one side and "AD" engraved on the other side
9	Cipro-Kriss	1 x10	Alu/Pvc blister	Film coated caplet	White /Oval/ "Cipro 500" engraved on one side
10	Zindocip	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ Scored on one side with "Zin" and "2" engraved on that side and "500" on the other side
11	Vitapro	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ "Vitapro" engraved on one side
12	Pemcipro	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side and "Pemcipro 500" engraved on the other side
13	Siprosan	2 x7	Alu/Pvc blister	Film coated caplet	White/ Oblong/ Scored on one side and "Tyonex" engraved on the other side
14	Cenox	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ White/ Oblong/ "Cenox" engraved on one side
15	Zyprox	2 x7	Alu/Alu blister	Film coated caplet	White/ Oblong/ "500" engraved on one side and "Zyprox" on the other side
16	Cyplox	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ "Cyplox 500" engraved on one side
17	Gecip	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored and "CP-500" engraved on that side
18	Cipromaxfort	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oval/ "Cipro 500" engraved on one side
19	Ciflaxin	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ "Drugfield" engraved on one side
20	VPL-Cipro	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side and "VPL-C" engraved on the other side
21	Ciprof	1 x10	Alu/Alu blister	Film coated caplet	White /Oblong/ "Ciprof 500" engraved on one side
22	Zibatab	2 x7	Alu/Alu blister	Film coated caplet	Yellow/ Oblong/ Scored on one side
23	Corflox	2 x7	Alu/Alu blister	Film coated caplet	White/ Oblong/ Plain
24	Cifran	1 x10	Alu/Pvc blister	Film coated tablet	White/ Round/ "CFT" engraved on one side and 500 engraved on the other side
25	Grakkoflox	1 x10	Alu/Alu blister	Film coated caplet	White/ Oblong/ Scored on one side
26	Cipronol	1 x10	Alu/Pvc blister	Film coated caplet	White /Oval/ "Cipro 500" engraved on one side
27	Ciproxin	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ Scored on one side with "Cip - 500" engraved on that side and "BAYER" on the other side
28	Ciprogem	1 x10	Alu/Pvc blister	Film coated caplet	White/ Oblong/ Scored on one side with "CIP-500" on that side and "Gemini" engraved on the other side
29	Ciprotab	1 x14	Alu/Pvc blister	Film coated caplet	Yellow on one side and "Ciprotab" written on one side and milky colour on the other side

* Tablets packed with aluminium blister all through. **Tablets packed with aluminium blister on one side and polyvinyl chloride (pvc) plastic on the other side.

Table 3: Physical attributes of ciprofloxacin brands

S/N	Brands	Weight (mg)±SD	% Dev.	Hardness (KgF)±SD	Friability (%)	Disintegration (min) ±SD	Thickness (mm) ±SD	Diameter (mm) ±SD
1	Prox	661±0.007	1.1	8.2±1.1	0.015	9.0±0.6	5.7±0.07	6.6±0.01
2	Rapidflox	631±0.008	1.3	4.5±1.0	0.159	4.0±0.2	5.4±0.08	7.7±0.03
3	Ciproheal	754±0.009	1.2	3.4±0.4	0.108	6.6±0.7	5.8±0.06	9.1±0.02
4	Rumaxine	679±0.018	2.6	3.5±0.3	0.319	4.7±0.5	5.6±0.05	13±0.1
5	Ciproall	659±0.014	2.1	3.8±0.3	0.227	2.9±0.3	5.1±0.02	8.2±0.04
6	Ciprofax	898±0.015	1.7	4.0±0.4	0.232	3.5±0.6	5.4±0.05	9.1±0.01
7	Cipro-Superior	864±0.057	6.6	4.5±0.2	0.106	7.5±2.0	5.3±0.04	9.2±0.01
8	Cipad	721±0.009	1.3	4.7±0.3	0.125	2.9±0.3	5.6±0.04	8.2±0.02
9	Cipro-Kriss	771±0.162	20.1	4.5±0.3	0.063	3.8±0.3	5.3±0.12	9.3±0.02
10	Zindocip	801±0.012	1.5	3.4±0.5	0.137	4.4±0.2	6.4±0.05	8.1±0.02
11	Vitapro	919±0.015	1.7	4.0±0.3	0.032	1.1±0.3	5.3±0.09	9.4±0.02
12	Pemcipro	885±0.027	3.1	4.9±0.7	0.033	11.6±0.9	5.3±0.05	9.2±0.02
13	Siprosan	614±0.033	5.4	3.7±0.3	0.016	3.2±0.2	4.9±0.14	7.6±0.01
14	Cenox	798±0.006	0.7	4.7±0.8	0.012	3.1±0.4	6.3±0.02	8.2±0.03
15	Zyprox	674±0.016	2.3	5.0±1.0	0.084	4.8±1.2	5.5±0.19	9.1±0.07
16	Cyplox	1034±0.02	1.9	6.8±1.5	0.087	2.0±0.3	6.9±0.02	9.8±0.03
17	Gecip	716±0.011	1.5	8.9±1.9	0.015	22.2±1.7	5.9±0.15	8.2±0.01
18	Cipromaxfort	802±0.008	1	11.1±0.3	0.113	4.0±0.3	5.5±0.02	9.2±0.01
19	Ciflaxin	734±0.015	2.1	9.0±0.9	0.082	10.3±0.4	6.3±0.08	7.3±0.04
20	Vpl-Cipro	733±0.004	0.6	10.4±0.9	0.068	3.7±0.4	4.9±0.12	9.1±0.02
21	Ciprof-500	787±0.012	1.6	6.9±1.4	0.405	1.6±0.4	4.9±0.07	9.2±0.09
22	Zibatab	775±0.008	1.1	8.0±1.9	0.065	6.4±0.1	5.9±0.05	8.6±0.01
23	Corflox	707±0.009	1.3	3.6±0.4	0.154	2.1±0.7	4.8±0.09	8.3±0.03
24	Cifran	767±0.007	0.9	7.4±0.8	0	1.3±0.2	4.5±0.05	13.2±0.01
25	Grakkoflox	626±0.011	1.8	6.4±1.0	0.063	10.5±0.4	5.1±0.03	8.4±0.01
26	Cipronol	741±0.007	0.9	9.8±0.2	0.027	2.5±0.5	5.4±0.02	9.1±0.02
27	Ciproxin	759±0.006	0.8	12.2±1.0	0.039	2.5±0.3	5.6±0.07	8.4±0.03
28	Ciprogem	778±0.006	0.8	5.1±1.1	10.8	1.4±0.7	5.5±0.13	8.2±0.02
29	Ciprotab	794±0.012	1.5	SOFTLET	0.025	17.5±1.5	5.9±0.04	7.8±0.05

**Fig. 1.** Percentage content of ciprofloxacin in the various brands of ciprofloxacin hydrochloride.

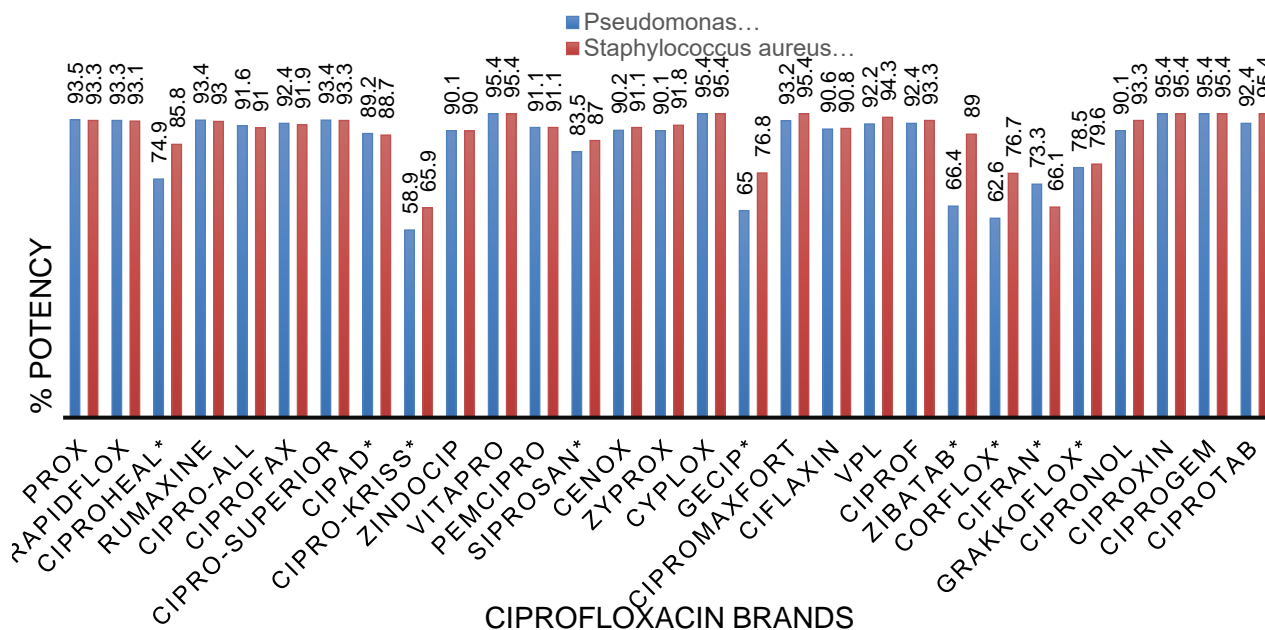


Fig. 2. Percentage potencies of the various brands of ciprofloxacin hydrochloride

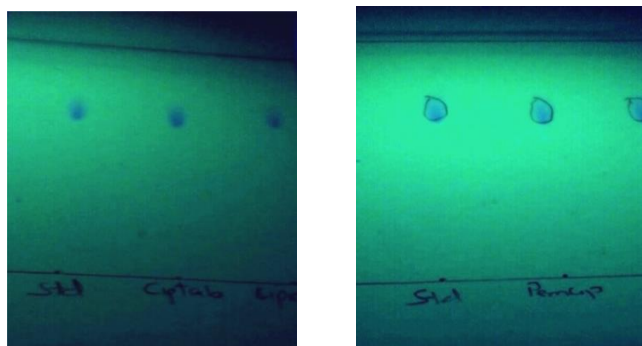


Fig. 3. Sample plates of the impurity testing using TLC

While coding the brands may protect the manufacturers, it does not provide the prescribers, pharmacists, and patients the opportunity to make informed decision on generic substitution. If the failure of the friability test of ciprogem is batch related, then it can be taken as an indication of failure of internal quality control mechanism.

In a previous study, all the brands of ciprofloxacin sampled passed the hardness and only one brand failed friability test [21] while a reverse was observed in another study where all brands passed friability test and two failed hardness test [17]. The degree of hardness of a tablet influences friability,

disintegration, and drug release. It is expected that the harder the tablet, the less friable, the slower the disintegration and rate of drug release. It should not be surprising to see harder tablets disintegrate faster since the intrinsic property of a disintegrant influences rate of disintegration. All brands in this study, passed disintegration time test as the times for disintegration were within 30 min. Vitapro had the least disintegration time of 1.1 ± 0.3 min while Gecip had the longest disintegration time of 22.2 ± 1.7 min. All brands passed the thickness and diameter tests (12.5mm to be $\pm 5\%$ and tablets with diameter up to 15mm to be $\pm 3\%$).

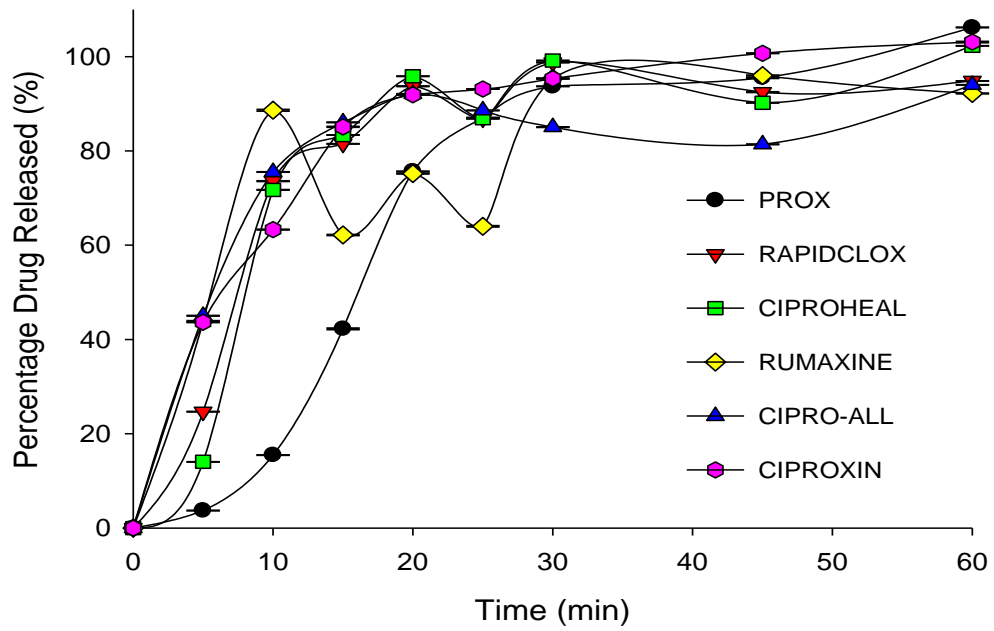


Fig. 4. Percentage Drug Release Profiles of Brands Prox, Rapidflox, Ciproheal, Rumaxine and Cipro-all in 0.1N HCl in comparison with ciproxin

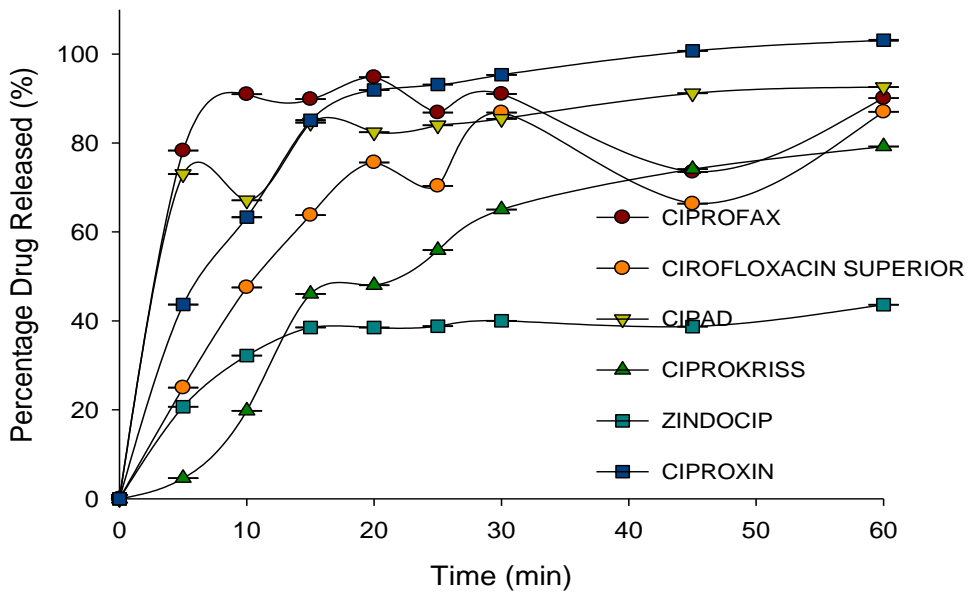


Fig. 5. Percentage Drug Release Profiles of Brands Ciprofax, Ciprofloxacin superior, Cipad, Ciprokriss and Zindocip in 0.1N HCl in comparison with ciproxin

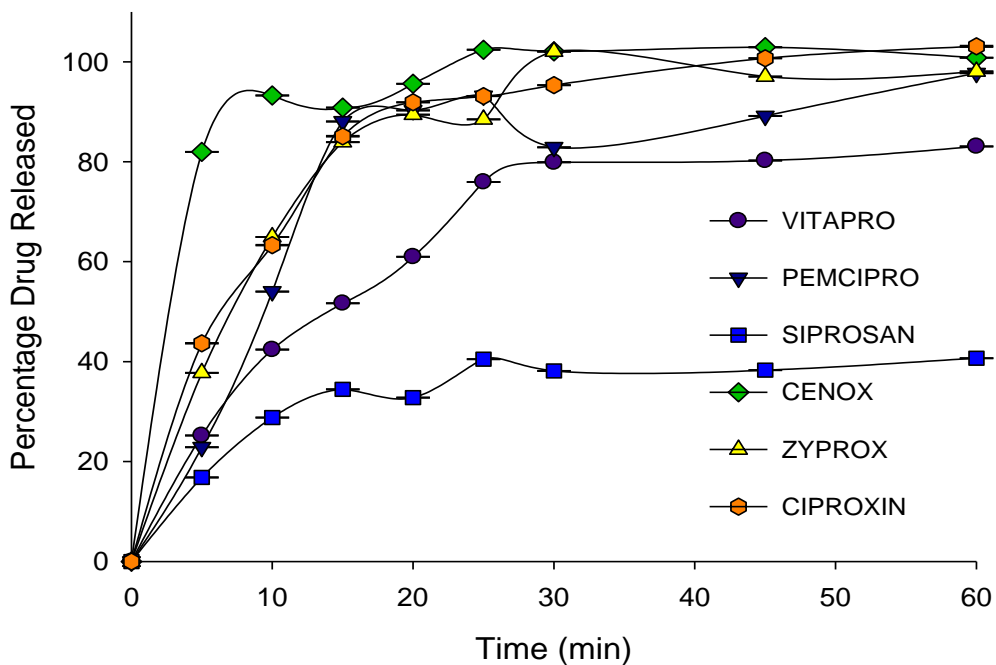


Fig. 6. Percentage Drug Release Profiles of Brands Vitapro, Pencipro, Siprosan, Cenox and Zyprox in 0.1N HCl in comparison with ciproxin

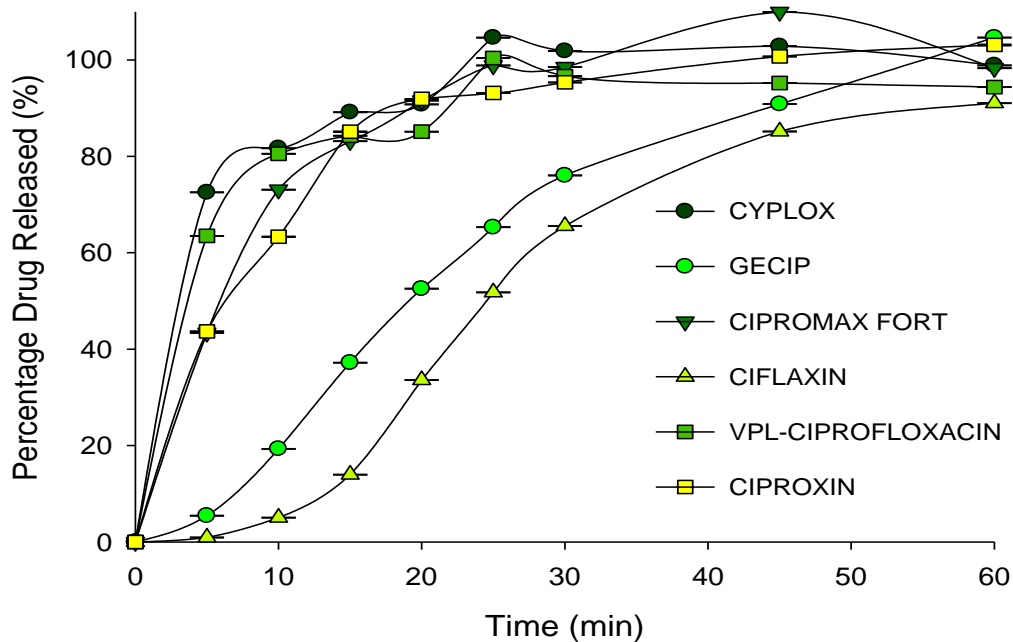


Fig. 7. Percentage Drug Release Profiles of Brands Cyplox, Gecip, Cipromax fort, Ciflaxin and VPL-Ciprofloxacin in 0.1N HCl in comparison with ciproxin

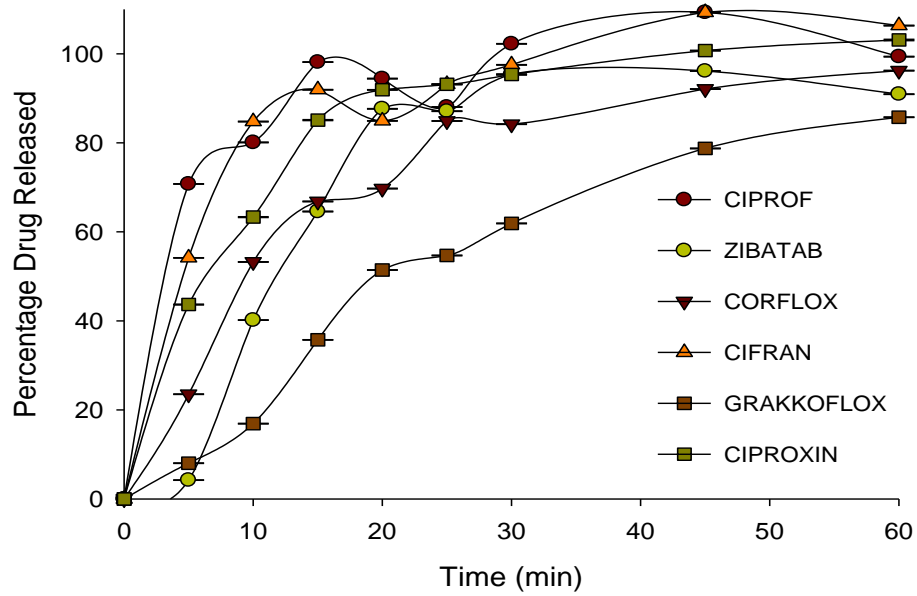


Fig. 8. Percentage Drug Release Profiles of Brands Ciprof, Zibatab, Corflox, Cifran and Grakkoflox in 0.1N HCl in comparison with ciproxin

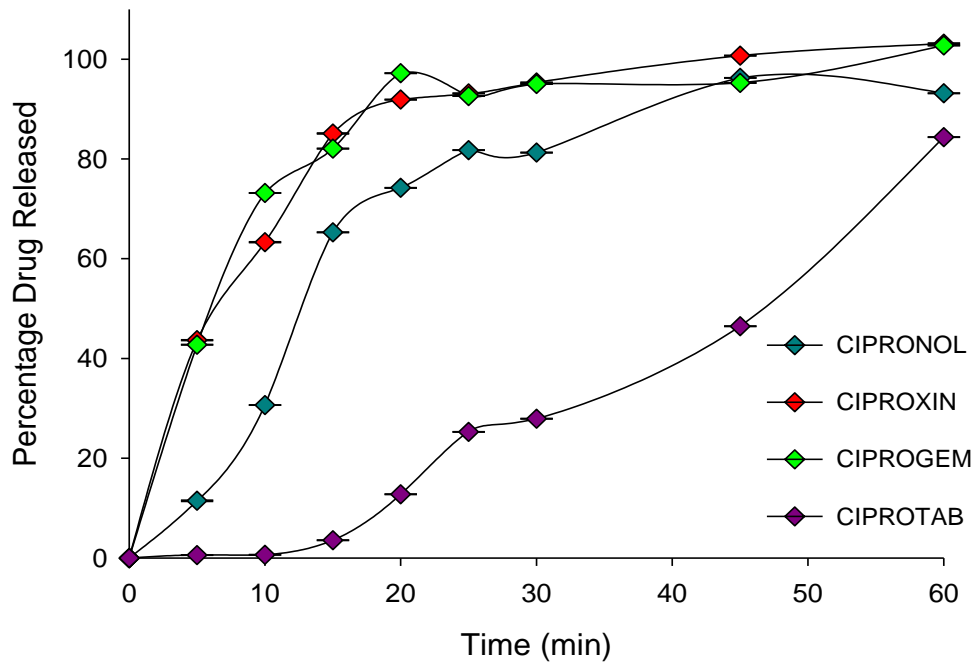


Fig. 9. Percentage Drug Release Profiles of Brands Cipronol, Ciproxin, Ciprogem and Ciprotab in 0.1N HCl in comparison with ciproxin

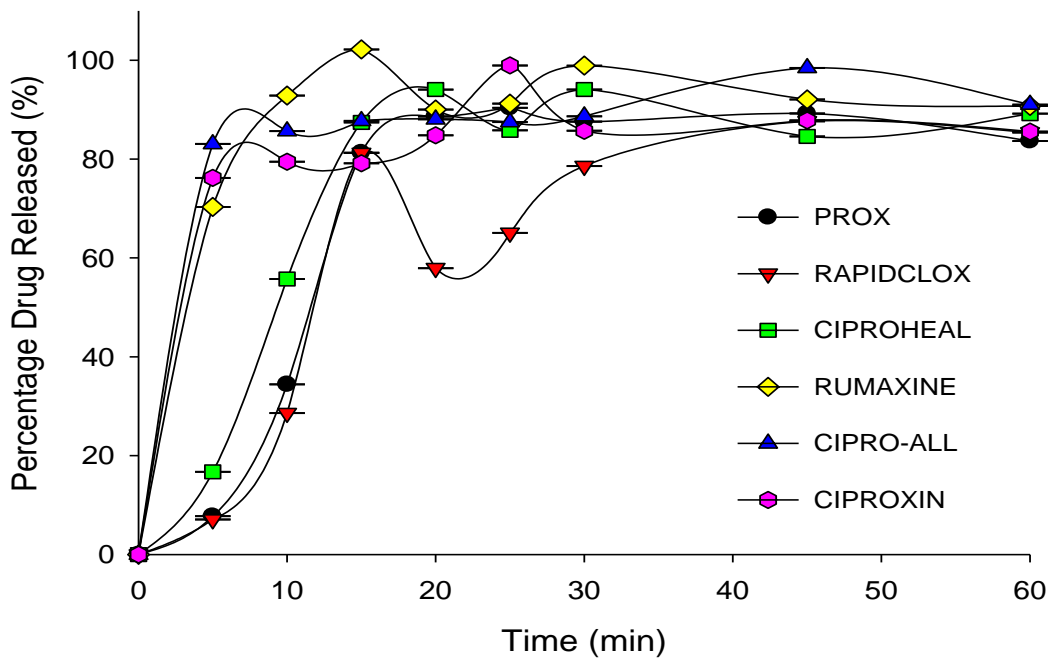


Fig. 10. Percentage Drug Release Profiles with Time of Brands Prox, Rapidflox, Ciproheal, Rumaxine and Cipro-all in Acetate Buffer pH 4.5 in comparison with ciproxin

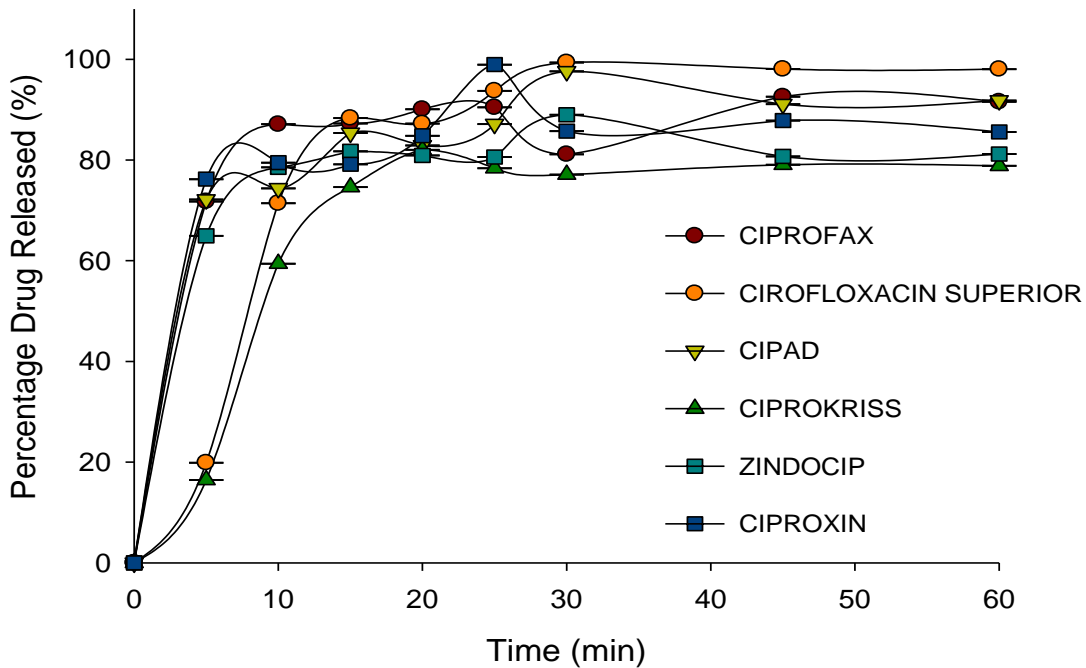


Fig. 11. Percentage Drug Release Profiles of Brands Ciprofax, Ciprofloxacin superior, Cipad, Ciprokriss and Zindocip in Acetate Buffer pH 4.5 in comparison with ciproxin

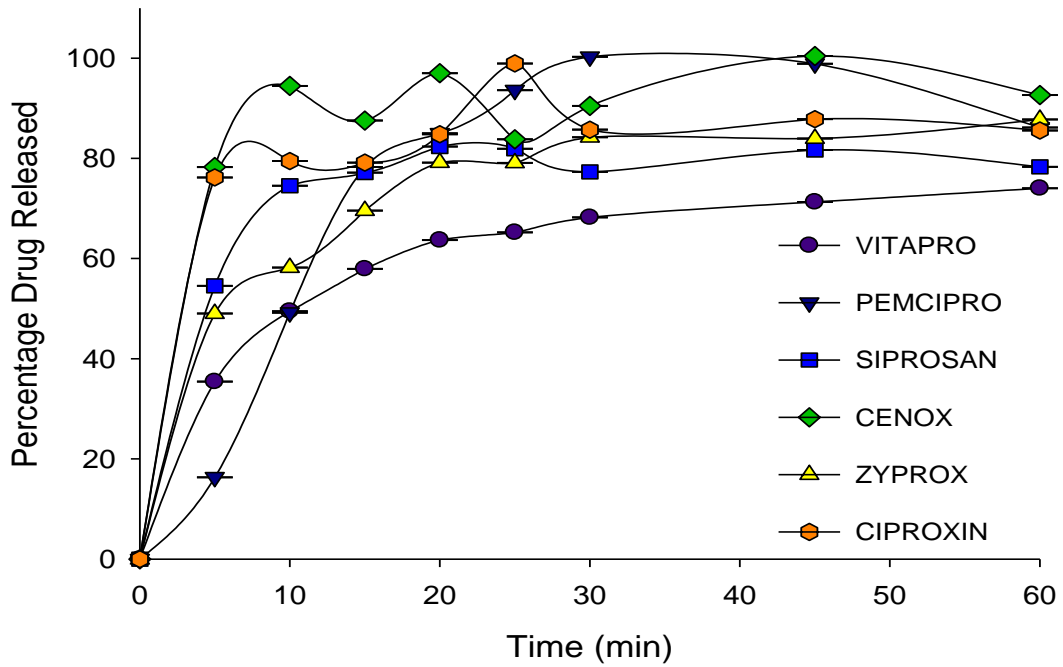


Fig. 12. Percentage Drug Release Profiles of Brands Vitapro, Pemcipro, Siprosan, Cenox and Zyprox in Acetate Buffer pH 4.5 in comparison with ciproxin

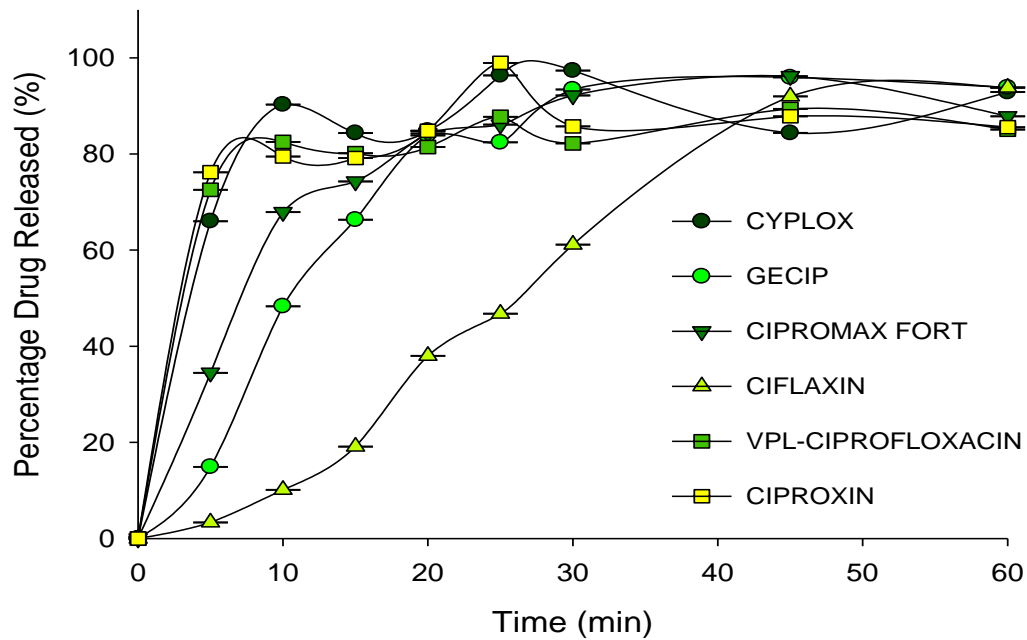


Fig. 13. Percentage Drug Release Profiles of Brands Cyplox, Gecip, Cipromax Fort, Ciflaxin and VPL-Ciprofloxacin in Acetate Buffer pH 4.5 in comparison with ciproxin

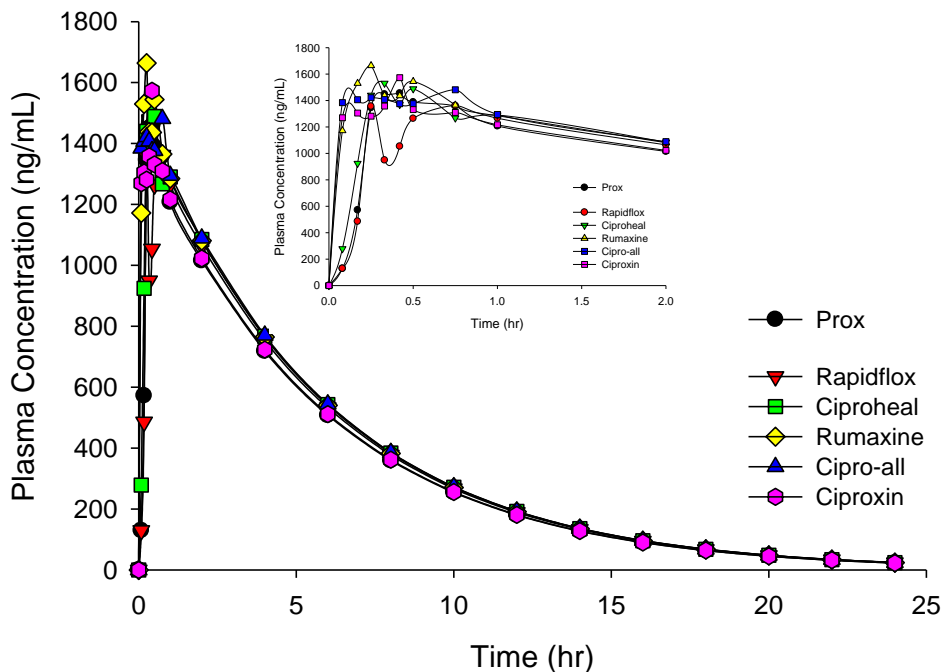


Fig. 16. Predicted plasma concentration time profiles of brands Prox, Rapidflox, Ciproheal, Rumaxine and Cipro-all in in comparison with ciproxin

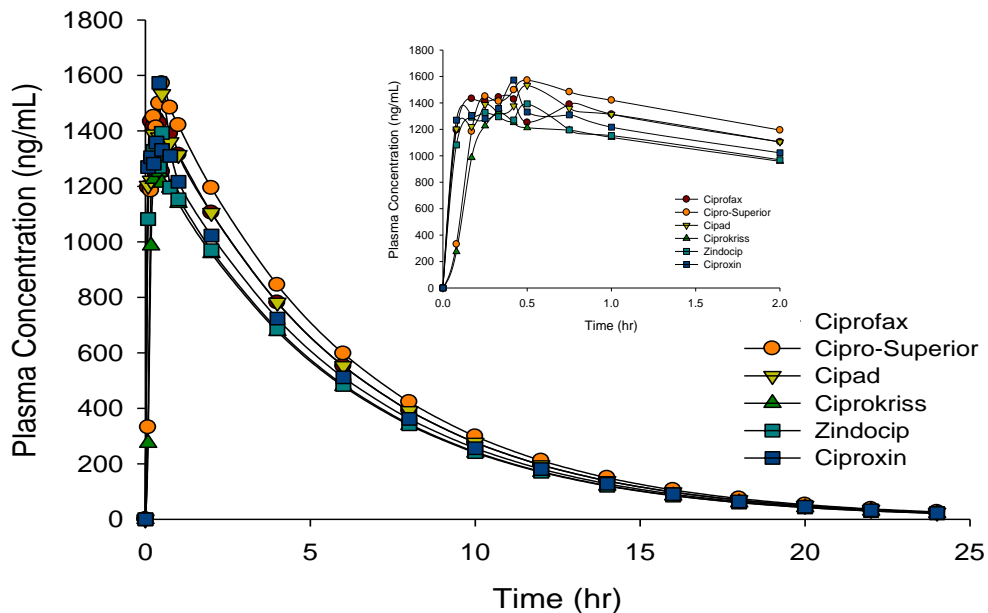


Fig. 17. Predicted plasma concentration time profiles of Brands Ciprofax, Ciprofloxacin superior, Cipad, Ciprokriss and Zindocip in comparison with ciproxin

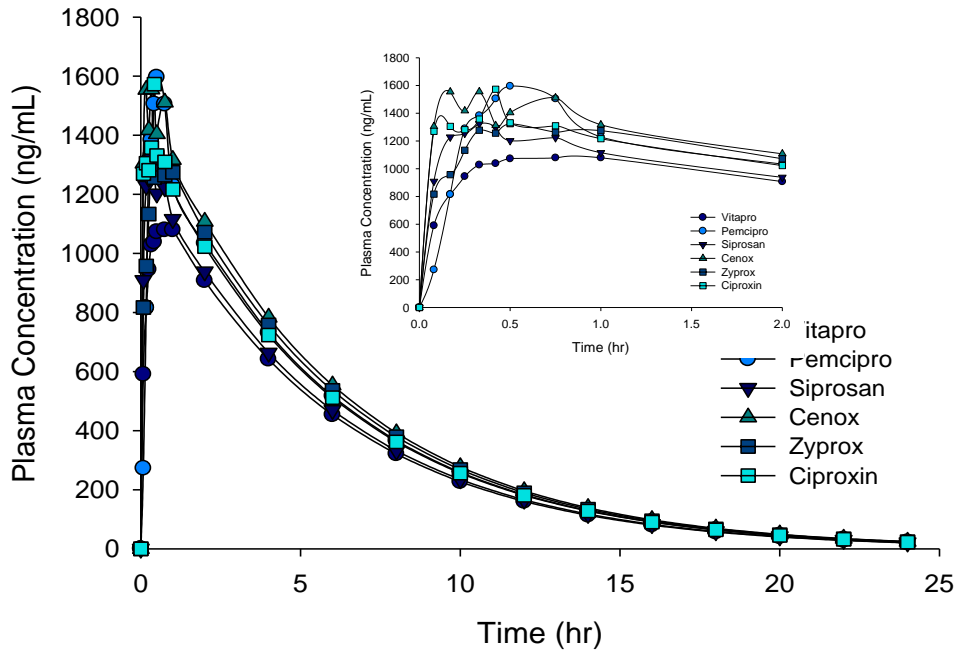


Fig. 18. Predicted plasma concentration time profiles of Brands Vitapro, Pemcipro, Siprosan, Cenox and Zyprox in comparison with ciproxin

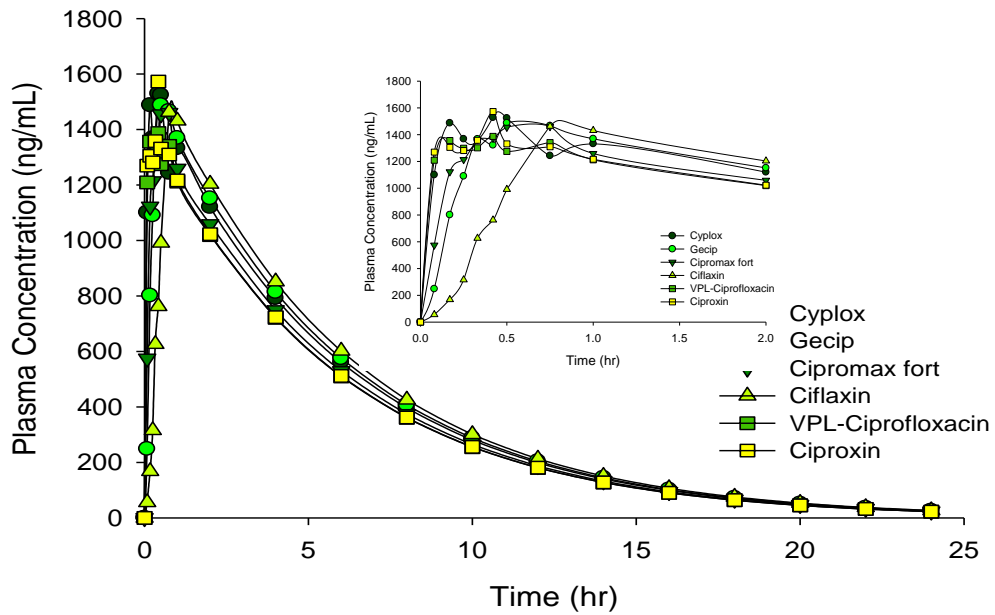


Fig. 19. Predicted plasma concentration time profiles of Brands Cyplex, Gecip, Cipromax Fort, Ciflaxin and VPL-Ciprofloxacin in comparison with ciproxin

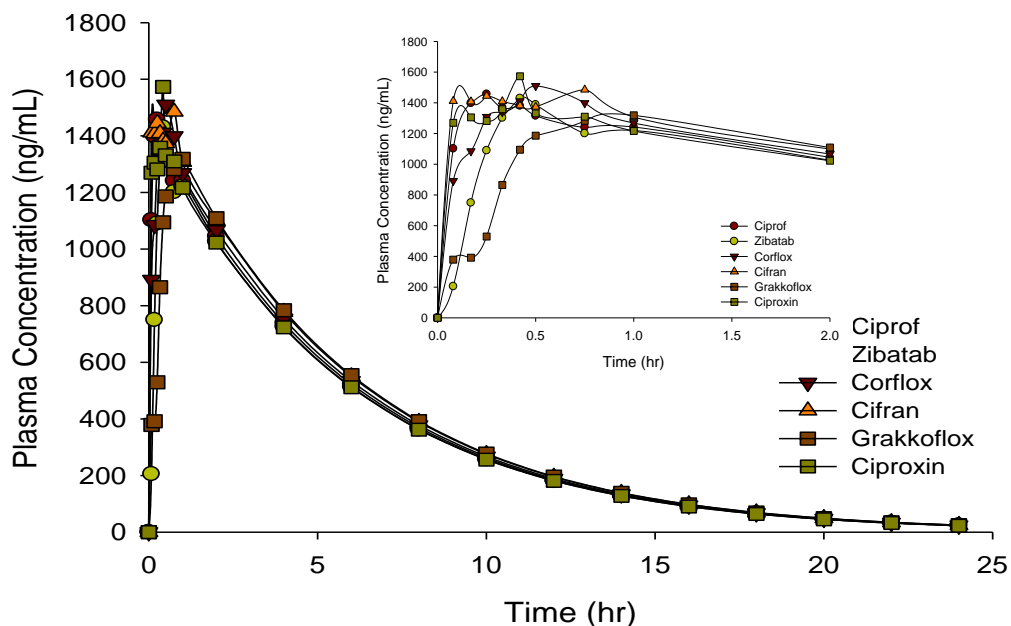


Fig. 20. Predicted plasma concentration time profiles of Brands Ciprof, Zibatab, Corflo, Cifran and Grakkoflox in comparison with ciproxin

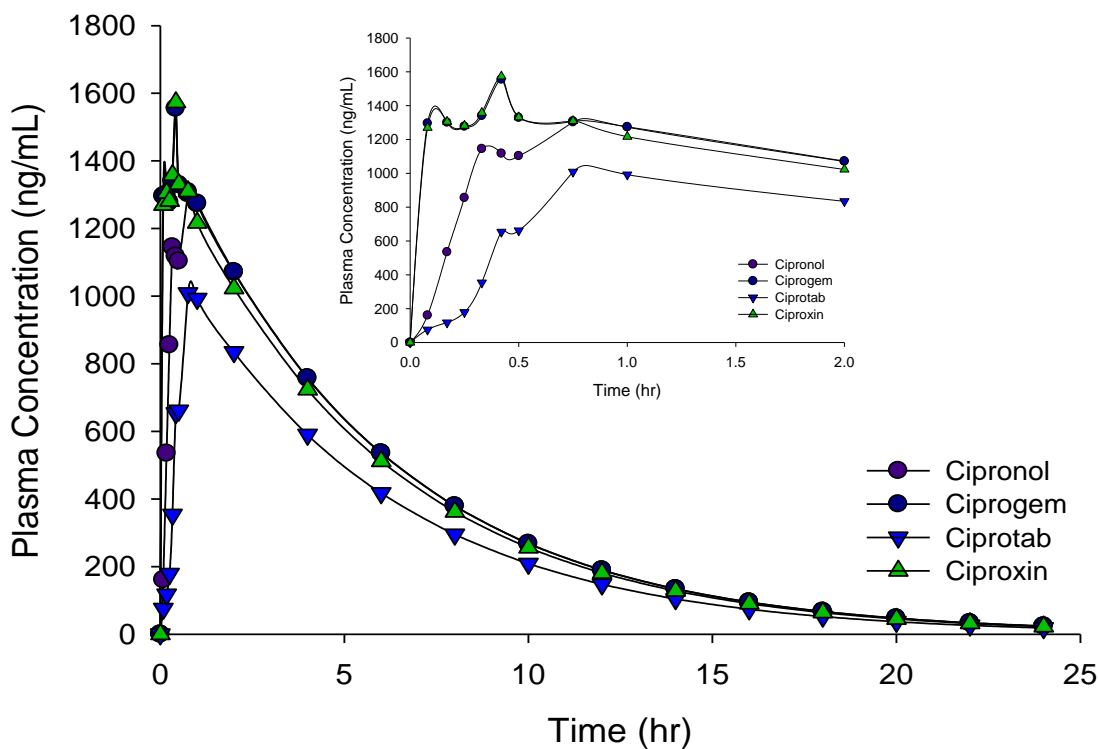


Fig. 21. Predicted plasma concentration time profiles of Brands Cipronol, Ciproxim, Ciprogem and Ciprotab in comparison with ciproxin

Table 4: Similarity Factor f_2 and Difference Factor f_1 for Ciprofloxacin Brands using Ciproxin as the reference brand (0.1N HCl)

S/No	Brands	Similarity factor f_2 (50-100)	Difference factor f_1 (0-15)
1	Prox	29.28	24.08
2	Rapidflox	53.07	9.00
3	Ciproheal	47.44	9.62
4	Rumaxine	39.15	16.26
5	Cipro-All	52.09	8.57
6	Ciprofax	37.02	17.86
7	Ciprofloxacin Superior	35.71	22.73
8	Cipad	45.53	12.15
9	Ciprokriss	23.37	41.92
10	Zindocip	16.38	56.95
11	Vitapro	33.24	26.14
12	Pemcipro	50.55	9.47
13	Siprosan	15.39	60.00
14	Cenox	38.64	14.53
15	Zyprox	68.77	4.62
16	Cyplox	45.25	11.36
17	Gecip	25.63	33.72
18	Cipromax Fort	63.49	5.22
19	Ciflaxin	18.30	48.68
20	Vpl-Ciprofloxacin	49.92	9.98
21	Ciprof	45.48	12.40
22	Zibatab	37.89	16.29
23	Corflox	43.38	15.61
24	Cifran	51.75	8.85
25	Grakkoflox	22.94	41.85
26	Cipronol	36.02	21.03
27	Ciproxin	Ref	Ref
28	Ciprogem	67.81	3.80
29	Ciprotab	11.52	70.19

f_2 = Brands in bold failed the f_2 test. f_1 = Brands in bold failed the f_1 test.

Table 5: Similarity Factor f_2 and Difference Factor f_1 for Ciprofloxacin Brands using Ciproxin as the Reference Brand (Acetate Buffer pH 4.5)

S/No	Brands	Similarity factor f_2 (50-100)	Difference factor f_1 (0-15)
1	Prox	28.01	19.64
2	Rapidflox	24.65	28.09
3	Ciproheal	32.46	19.04
4	Rumaxine	48.23	11.49
5	Cipro-All	57.26	8.17
6	Ciprofax	60.83	7.27
7	Ciprofloxacin Superior	34.34	17.34
8	Cipad	58.17	7.45
9	Ciprokriss	32.22	19.44
10	Zindocip	54.86	7.63
11	Vitapro	30.72	28.39
12	Pemcipro	31.66	18.11
13	Siprosan	49.27	10.31
14	Cenox	49.79	11.39
15	Zyprox	42.85	13.45
16	Cyplox	57.20	7.56
17	Gecip	30.61	21.66
18	Cipromax Fort	40.36	13.07
19	Ciflaxin	16.70	49.89
20	Vpl-Ciprofloxacin	67.22	4.11
21	Ciprof	58.76	6.57
22	Zibatab	30.08	20.34

23	Corflox	49.38	9.96
24	Cifran	55.95	8.74
25	Grakkoflox	23.53	35.17
26	Cipronol	25.28	30.29
27	Ciproxin	Ref	Ref
28	Ciprogem	88.50	1.15
29	Ciprotab	13.66	62.65

Table 6: Dissolution Efficiency for Ciprofloxacin Brands using Ciproxin as the Reference Brand (Acetate Buffer pH 4.5)

S/No	Brands	DE (%)	Difference between DEs of reference and test products*
1	Prox	72.6	9.2
2	Rapidflox	65.7	16.1
3	Ciproheal	76.3	5.5
4	Rumaxine	88.1	- 6.3
5	Cipro-All	86.8	- 5
6	Ciprofax	83.7	- 1.9
7	Ciprofloxacin Superior	83.4	- 1.6
8	Cipad	84.0	- 2.2
9	Ciprokriss	68.4	13.4
10	Zindocip	77.4	4.4
11	Vitapro	61.1	20.7
12	Pemcipro	79.1	2.7
13	Siprosan	74.0	7.8
14	Cenox	88.5	- 6.7
15	Zyprox	73.9	7.9
16	Cyplox	84.1	- 2.3
17	Gecip	69.6	12.2
18	Cipromax Fort	79.3	2.5
19	Ciflaxin	54.7	27.1
20	Vpl-Ciprofloxacin	80.4	1.4
21	Ciprof	80.3	1.5
22	Zibatab	69.3	12.5
23	Corflox	81.3	0.5
24	Cifran	87.2	- 5.4
25	Grakkoflox	60.7	21.1
26	Cipronol	62.8	19
27	Ciproxin	81.8	0.0
28	Ciprogem	82.1	-0.3
29	Ciprotab	37.8	44

*The numbers in bold indicate bio-inequivalence

Content assay. Content assay provides an insight into the identity and quality of drug product when specific analytical methods are employed. Concentration of active ingredient below the specification may predispose patients to treatment failure and when above the specification, may lead to adverse drug events. The USP specification for ciprofloxacin tablets is that the tablets should contain ciprofloxacin hydrochloride equivalent to not less than 90 % and not more than 110 % of the labelled amount of ciprofloxacin (500 mg) [19]. Six (6) brands of ciprofloxacin failed the content assay test as shown in Figure 1. These brands are prox,

rumaxine, cipro-all, cipro-kriss, pemcipro and cipronol.

Regarding antibiotics, the challenge of drug content being outside specification is not just about treatment failure and adverse drug events but also about development of antimicrobial resistance. Providing sub-inhibitory doses of antimicrobial agents facilitate the ability of microorganisms to develop resistance to the antimicrobial agents. Sub-inhibitory concentrations provide an environmental condition that play a vital role in the development and spread of antimicrobial resistance [22].

Table 7: Predicted pharmacokinetic parameters of the brands of ciprofloxacin

S/N	Brands	C _{max} (ng/mL)	T _{max} (h)	T _{1/2} (h)	AUC (ng/mL*h)	MRT (h)	Vz/F (mg)/(mg/mL)	Cl/F (mg)/(ng/mL)/h
1	Prox	1455.48	0.42	4.0	8030.84	5.83	0.35	0.0613
2	Rapidflox	1361.79	0.75	4.0	8275.08	5.92	0.34	0.0595
3	Ciproheal	1530.90	0.33	4.0	8561.01	5.84	0.33	0.0575
4	Rumaxine	1663.83	0.25	4.0	8707.59	5.73	0.33	0.0565
5	Ciproall	1481.22	0.75	4.0	8745.65	5.74	0.33	0.0563
6	Ciprofax	1443.81	0.33	4.0	8810.74	5.78	0.33	0.0559
7	Cipro-Superior	1572.18	0.50	4.0	9418.34	5.85	0.30	0.0522
8	Cipad	1532.78	0.50	4.0	8952.72	5.78	0.32	0.0559
9	Cipro-Kriss	1332.41	0.33	4.0	7577.98	5.83	0.37	0.0649
10	Zindocip	1392.97	0.50	4.0	7788.38	5.74	0.37	0.0632
11	Vitapro	1079.16	1.00	4.0	7119.19	5.87	0.40	0.0691
12	Pemcipro	1595.86	0.50	4.0	8259.30	5.78	0.34	0.0596
13	Siprosan	1324.33	0.33	4.0	7642.62	5.75	0.38	0.0654
14	Cenox	1555.60	0.33	4.0	8900.00	5.74	0.32	0.0553
15	Zyprox	1324.82	0.50	4.0	8434.76	5.85	0.34	0.0583
16	Cyplox	1528.51	0.42	4.0	8916.56	5.79	0.32	0.0552
17	Gecip	1487.66	0.50	4.0	9014.19	5.89	0.32	0.0546
18	Cipromax fort	1460.44	0.75	4.0	8432.90	5.79	0.34	0.0584
19	Ciflaxin	1463.02	0.75	4.0	9050.30	6.11	0.31	0.0543
20	Vpl-Cipro	1387.07	0.42	4.0	8176.68	5.75	0.35	0.0602
21	Ciprof-500	1457.32	0.25	4.0	8344.63	5.77	0.34	0.0589
22	Zibatab	1429.72	0.42	4.0	8056.59	5.87	0.35	0.0610
23	Corflox	1509.99	0.50	4.0	8512.54	5.77	0.33	0.0578
24	Cifran	1485.17	0.75	4.0	8824.43	5.75	0.32	0.0557
25	Grakkoflox	1318.74	1.00	4.0	8491.37	6.00	0.33	0.0579
26	Cipronol	1302.9	0.75	4.0	8260.74	5.96	0.34	0.0595
27	Ciproxin	1572.70	0.42	4.0	8220.19	5.74	0.35	0.0599
28	Ciprogem	1554.69	0.42	4.0	8560.00	5.77	0.33	0.0575
29	Ciprotab	1008.83	0.75	4.0	6270.71	6.10	0.45	0.0784

When microorganisms are exposed to sub-inhibitory concentrations, these have effects on their bacterial physiology and morphology leading to modulation of fitness and pathogenicity traits. The mechanisms of fluoroquinolone resistance include modulation of target, increased efflux (export of a drug out of the microorganism), fluoroquinolone inactivation (by an aminoglycoside N-acetyltransferase), and protection of the target by DNA-binding proteins (known as Qnr) [23]. Assuring quality of antimicrobial agents is one of the strategies that can reduce antimicrobial resistance. Other strategies include patient adherence, removing antimicrobial selective pressure, health promotion and regulation to restrict antimicrobial agents to prescription only drugs.

Microbiological evaluation. A biological or microbiological assay is employed to evaluate both potency and bioactivity of an antimicrobial agent [24]. Quality control of antimicrobial formulations must therefore include antimicrobial potency assay. Agar well diffusion method is a practical and economical method to use. In this study, nine (9) brands of ciprofloxacin failed the potency test (Figure 2) as they were outside the USP specification of content assay (90-110%). These brands were Ciproheal (74.9% and 85.8%), Cipad (89.2% and 88.7%), Cipro-Kriss (58.9% and 65.9%), Siprosan (88.5% and 87.0%), Gecip (65% and 76.8%), Zibatab (66.4% and 89.0%), Corflox (62.6% and 76.7%), Cifran (73.3% and 66.1%) and Grakkoflox (78.5% and 79.6%) indicating % potency against *P. aeruginosa* and *S. aureus*

respectively. This microbiological evaluation provides insight to the antimicrobial activity of these brands of ciprofloxacin. This may confirm the clinical observations of the health professionals in hospitals in North-eastern Nigeria. As the brands varied in % potencies so will their therapeutic efficacies. Indeed, this data may be a guide for the health professionals to make evidence-based decisions on procurement and prescribing. The disparity between the % potency for some brands for the two test organisms as found in brands ciproheal, cipro-kriiss, gecip, zibatab, corflox and cifran ought not to be. The mechanism of action of ciprofloxacin is the same for gram-positive and gram-negative organisms and so the % potency should be same for both organisms. The disparity may be due to actives/metabolites/impurities which may have affected one organism more than the other, giving exaggerated response.

Test for impurities. Any substance in a formulation other than the API and excipients is an impurity. Limiting the quantity of impurities if not ensuring none is a regulatory requirement as some impurities may be toxic and some may affect the efficacy of APIs. As a result, test for purity and impurity profiling are mandatory to establish biological safety [25]. Impurities may emanate from the API as by-products of synthesis, excipients, during formulation process and packaging or degraded products on storage. Figure 3 displayed two images as samples of the outcome of test for impurities using TLC. Single spots were observed in all plates for all brands. All brands had the same Rf values of 0.73 indicating the presence of ciprofloxacin in all the brands. The single spots implied that there were no impurities. While this study indicated no impurities, Kyriacos and co-workers [26] found impurities – ethylenediamine, desfluorociprofloxacin and fluoroquinolonic acid – which were not more than 0.2% and were therefore within limits. This study employed TLC while Kyriacos and

co-workers utilized HPLC. It is worthy to note that HPLC has better sensitivity, selectivity, and resolution. In another study, Trefi and colleagues [27] used ^{19}F and ^1H nuclear magnetic resonance (NMR) and Diffusion-Ordered ^1H NMR Spectroscopy (^1H NMR DOSY) for impurity profiling of generic ciprofloxacin tablets. Four to twelve fluorinated impurities were detected in all brands tested, two non-fluorinated were detected in seven formulations and degradation product of ciprofloxacin was found in all the formulations tested. Consequently, absence of impurities in this study may suggest that there may be no co-active ingredient which may interfere with the efficacy of ciprofloxacin hydrochloride or be toxic to the patient. It may also suggest that a more sensitive and selective instrument should be used to test for impurities.

***In vitro* drug release.** Aesthetic formulations may appeal to the senses of touch, sight, and taste; however, if they are not able to release the drugs to produce the desired therapeutic effects, they are as good as placebo. The rate of liberation from tablet matrix and rate of release determines the rate and extent of absorption. The rate and extent of absorption determine the minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) which influence therapeutic efficacy of antibiotics. Consequently, dissolution testing which assesses the rate of drug release over time can be employed as a surrogate for bioavailability studies. *In vitro* drug release studies can be used to predict *in vivo* absorption giving insight into the liberation and absorption patterns of the formulation. For antibiotics, the optimal dosing should be equal to or greater than the MICs for bacteriostatic drugs and equal to or greater than the MBCs of bactericidal drugs. However, to prevent antimicrobial resistance, bactericidal drugs are preferred. Ciprofloxacin exhibits both bacteriostatic and bactericidal activities depending on concentration the organisms are

exposed to [28]. The study of release of ciprofloxacin from the formulations gives insight into the rate of liberation from tablet matrices, amount released and invariably, plasma concentration that will be expected from each brand.

In this study, employing dissolution medium, 0.1 N HCl, 9 of 29 brands released $\geq 85\%$ of the labelled amount in 15 min. These brands are ciproall (88.8%), ciprofax (88.8%), ciprofloxacin-superior (106%), pemcipro (87%), cenox (89.7%), cyplex (88.2%), ciprof (99.8%), cifran (91%) and ciproxin (85%) while 20 brands that released $\geq 80\%$ of the labelled amount in 30 min are rapidflox (96.9%), prox (92.2%), ciproheal (97.1%), rumaxine (82.8%), ciproall (88.5%), ciprofax (88.5%), ciprofloxacin-superior (85.2%), cipad (83.2%), pemcipro (80%), cenox (99.4%), zyxox (99.9%), cyplex (99.3%), cipromax fort (96.2%), vpl-ciprofloxacin (92.4%), ciprof (99.8%), zibatab (92%), corflox (82.4%), cifran (88.3%), ciproxin (93.1%) and ciprogem (92.8%). However, 9 brands, cipokriss (64%), zindocip (39%), vitapro (78%), siprosan (37%), gecip (74.9%), ciflaxin (64.9%), grakkoflox (60.9%), cipronol (60.9%), and ciprotab (27.6%) failed to release 80 % of the labelled amount in 30 min.

When acetate buffer pH 4.5 was used, 9 brands, ciproall (86.9%), ciprofax (86.3%), ciproheal (86.9%), rumaxine (101.1%), cipad (85%), ciprofloxacin-superior (87.7%), cenox (86.5%), ciprof (88.8%), and cifran (88%) released $\geq 85\%$ of the labelled amount in 15 min. Then, 20 brands, prox (85.8%), ciproheal (92%), rumaxine (96%), ciproall (86%), ciprofloxacin-superior (97.2%), cipad (95.3%), zindocip (86.8%), pemcipro (98%), cenox (87%), zyxox (82%), cyplex (94%), gecip (91%), cipromax fort (90.1%), vpl-ciprofloxacin (85%), ciprof (82%), zibatab (85%), corflox (93%), cifran (86%), ciproxin (83%) and ciprogem (83%) released $\geq 80\%$ of the labelled amount in 30 min. However, cipokriss (75.3%), rapidflox (77.2%),

ciprofax (78%), vitapro (66%), siprosan (75%), ciflaxin (60.1%), grakkoflox (72%), cipronol (68%), and ciprotab (40.3%) failed to release 80 % in 30 min. It may be worthy to note that some brands such as zindocip performed significantly better at higher pH indicating that some formulations may be pH sensitive thereby slightly or significantly modulating the rate of release of ciprofloxacin. Excipients can affect the rate of drug release and invariably, the rate and extent of absorption.

For high solubility active pharmaceutical ingredient formulated as immediate release oral dosage forms, the dissolution criterion is Q (quantity) = 80 % in 30 min [29]. In each medium (pH 1.2 and 4.5), 20 brands met this criterion, however, 7 brands, cipokriss, vitapro, siprosan, ciflaxin, grakkoflox, cipronol and ciprotab failed to meet the dissolution criterion in both media.

FDA Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release (IR) Solid Oral Dosage Forms states that a product is rapidly dissolving when $\geq 85\%$ of the labelled active pharmaceutical ingredient dissolves in 0.1 N HCl, pH 4.5 and pH 6.8 media within 30 min [30]. Eighteen (18) brands (prox, ciproheal, rumaxine, cipro-all, ciprofax, cipro-superior, cipad, pemcipro, cenox, cyplex, cipromax fort, vpl-ciprofloxacin, ciprof, zibatab, corflox, cifran, ciprogem and ciproxin) suggest they are rapidly dissolving as $\geq 85\%$ of the labelled API dissolved in both 0.1 N HCl and pH 4.5 in 30 min. In addition, an IR solid dosage form is very rapidly dissolving when $\geq 85\%$ of the labelled active pharmaceutical ingredient dissolves in 0.1 N HCl, pH 4.5 and pH 6.8 within 15 min. Six (6) brands, rumaxine, cipro-all, ciprofax, cenox, ciprof and cifran suggest rapid dissolution as $\geq 85\%$ of the labelled API dissolved in both 0.1 N HCl and pH 4.5 media in 15 min.

The dissolution profiles in pH 6.8 was not presented as the dissolution of ciprofloxacin in

pH 6.8 was $\leq 35\%$. Oishi and co-workers [31] obtained similar lower drug release (37.17%) in pH 6.8. Fluoroquinolones such as ciprofloxacin are zwitterionic comprising two proton-binding sites and displays a U-shaped pH solubility profile [32]. Ciprofloxacin is highly soluble at pH less than 5 and above 10 with limited solubility close to neutral (pH 7).

Ciprofloxacin has been classified into the 4 classes of Biopharmaceutical Classification System (BCS) by various studies [26, 32-39]. The common class ciprofloxacin is attributed to is Class III (high solubility, low permeability). However, Hansmann and co-workers [37] suggest that ciprofloxacin behaves like a Class I (high solubility, high permeability) drug in vivo. The BCS class changes could be due to the sensitivity of the drug to the excipients used in formulation [39]. Consequently, the FDA biowaiver guidelines advocates that for class III, the test product must contain the same excipients as the reference for a biowaiver to be scientifically justified [30]. This was not the case for all brands.

Mathematical models, similarity and difference factors were employed to determine the bioequivalence between the generic brands and innovator brand, ciproxin. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and measures the similarity in the percent dissolution between the two curves while the difference factor (f_1) is the difference in percentage between two curves at each point and measures the relative error between the two curves [1]. Similarity factor (f_2) is recommended by US Food Drug and Administration, and European Medicines Agency (EMA) for comparing similarity between two or more dissolution profiles and invariably for determining bioequivalence.

Tables 4 and 5 show the data for similarity factor (f_2) and difference factor (f_1) in 0.1 N HCl and pH 4.5, respectively. For a test product to be said to be bioequivalent to the

reference or innovator product, similarity factor (f_2) should be between 50 and 100 and difference factor (f_1) should be between 0 and 15. Dissolution efficiency (DE) was also used to compare similarity and determine bioequivalence in order to have at least three comparison approaches. Dissolution efficiency is described as the area under the dissolution-time curve expressed as a percentage of the dissolution curve at maximum dissolution y_{100} over the same time range. The innovator brand and the generic product can be said to be bioequivalent if the difference between their DEs is within appropriate limits ($\pm 10\%$) [1]. Dissolution efficiency was only calculated using dissolution profiles obtained in medium pH 4.5 because this is the pH closer to the absorption window/site of ciprofloxacin.

In 0.1 N HCl, seven brands, rapidflox, cipro-all, pemcipro, zyprox, cipromax fort, cifran and ciprogem were bioequivalent to the innovator brand, ciproxin using f_1 and f_2 (Table 4). Six brands, ciproheal, cipad, cenox, cyplox, vpl-ciprofloxacin and ciprof were bioequivalent with f_1 and bio-inequivalent with f_2 . In pH 4.5, nine brands, cipro-all, ciprofax, cipad, zindocip, cyplox, vpl-ciprofloxacin, ciprof, cifran and ciprogem were bioequivalent using f_1 and f_2 (Table 5). Six brands, rumaxine, siprosan, cenox, zyprox, cipromax fort and corflox were bioequivalent with f_1 and bio-inequivalent with f_2 . Nineteen brands were bioequivalent to ciproxin using DE alone while rapidflox, ciprokriss, vitapro, gecip, ciflaxin, zibatab, grakkoflox, cipronol and ciprotab were not bioequivalent (Table 6). Eight brands, ciprokriss, vitapro, gecip, ciflaxin, zibatab, grakkoflox, cipronol and ciprotab were bio-inequivalent using the three models, similarity factor (f_2), and difference factor (f_1) in the two media and dissolution efficiency (DE) in pH 4.5. Only three brands, cipro-all, cifran and ciprogem were found to be bioequivalent to the innovator brand, ciproxin using the three models, similarity factor (f_2), and difference factor (f_1) in the two media and dissolution

efficiency in pH 4.5. These three brands may confidently be used interchangeably with the innovator brand, ciproxin. Bio-inequivalence may be caused by excipients or manufacturing process/variables.

Predicted *in vivo* absorption. Dissolution pH data chosen for convolution to determine plasma concentration-time curve (Figures 16 – 21) and pharmacokinetic data was those of pH 4.5 as the main absorption site for ciprofloxacin is the duodenum and jejunum. pH range observed in the duodenum is from 4.20 to 8.20.

The predicted pharmacokinetic parameters for the various brands of ciprofloxacin are shown in Table 7. Maximum plasma concentration, C_{max} for the various brands was from 1008 (ciprotab) to 1663.88 ng/mL (rumaxine); time to maximum plasma concentration, t_{max} was from 0.25 (ciprof-500, rumaxine) to 1 h (grakkoflo, vitapro); $t_{1/2}$ was 4 h for all; area under the concentration time curve, AUC was from 6270.71 (ciprotab) to 9418.34 ng/mL*h and apparent volume of distribution, V_z/F , was from 0.30 (cipro-superior) to 0.45 mg/(mg/mL) (ciprotab). The predicted C_{max} , t_{max} , AUC and V_z/F of innovator brand, ciproxin were 1572.7 ng/mL, 0.4 h, 8220.19 ng/mL*h and 0.35 mg/(mg/mL) respectively. The pharmacokinetic data of some brands indicate that absorption will be rapid, ciprofloxacin will be liberated from the tablets and achieve maximum plasma concentration in ≤ 1 h. Brands such as ciprotab, vitapro, cipronol, grakkflox amongst other may need to be reformulated to produce pharmacokinetic data comparable to that of the innovator brand, ciproxin to ensure bactericidal action.

The *in vivo* studies on ciprofloxacin collaborates with the predicted data in this study such as $t_{1/2}$ range from 3 – 6 h and $t_{max} \leq 1$ h [40-42]. Lubasch and co-workers' [43] *in vivo* study on ciprofloxacin (C_{max} , - 1500 \pm 430 ng/mL; t_{max} , - 0.78 \pm 0.33 h and MRT – 5.8 \pm 0.94) and newer generation quinolones

collaborates with some of the predicted pharmacokinetic data in this study. These *in vivo* studies confirm that pharmacokinetics of drugs can be simulated using *in vitro* drug release data. Predicting *in vivo* absorption (plasma drug concentration-time profiles) from *in vitro* drug release data required inputting known ciprofloxacin parameters – volume of distribution (3 L/Kg), half-life (4 h) and oral bioavailability (0.70) obtained from FDA published data [44]. These parameters are inherent in the drug and are not influenced by the formulation. Predicting *in vivo* absorption from *in vitro* drug release can be used to avert clinical failure as the product developer can have a prior insight into the liberation and absorption of the formulation. Should the formulation not produce the desired plasma concentration and area under the time curve that can elicit therapeutic response, the product developer can reformulate. Consequently, *in vivo* simulation does not only validate the *in vitro* drug release data but also provides some ethical and economic benefits such reduction in cost of product development [45]. The pharmacokinetic parameters were obtained from the non-compartmental analysis of the predicted plasma drug concentration-time profiles using PKsolver, an add-in to Microsoft excel.

Ciprofloxacin is a widely used fluoroquinolones in clinical settings displaying varying clinical success against organisms. The MICs for broad spectrum clinical success against bacteria are from 0.08 to 1.0 ug/mL; higher MICs (0.5 – 1.0 ug/mL) are for species such as *Pseudomonas*, *staphylococcus* and susceptible *S. pneumoniae* [46]. It is envisaged that 500 mg dose should achieve the MIC range. Clinical failure to antibiotics includes factors such as host defences, the bacterium and its susceptibility and the concentration profile of the antibiotic. However, most treatment failures are due to antibiotic concentration dependent outcomes such as MIC and AUC.

The manufacturer or the marketer who receives marketing authorization is responsible for continuous monitoring of the safety of her product(s) in the market, for informing the authorities of possible changes that may affect the marketing authorization and for ensuring the updating of product information in their territories of operation [47]. The clinical pharmacist should report not just adverse drug reactions and medication errors, but also quality issues relating to medicines. Poor quality medicines are a threat to the patients and the health systems. Giving attention to quality issues can prevent adverse drug reactions associated with poor quality medicines and some drug-related problems.

Conclusion. The pharmaceutical integrity of all drugs is of utmost importance, to ensure safe and effective drug therapy. As a result, standardization is necessary to ensure uniformity with compendia such as British pharmacopoeia (B.P), and United States pharmacopoeia (U.S.P) as guides. Pharmaceutical quality assessment of twenty-nine (29) different brands of ciprofloxacin were undertaken. The inability of some of the brands not to meet the specifications of compendia makes the concerns for the study very germane. The varied potencies of the various brands translate to different therapeutic results, hence making generic substitutions inappropriate. The effects of poor pharmaceutical quality ciprofloxacin in the market cannot be over emphasized, as it is one of the most widely used antibiotics capable of decreasing both morbidity and mortality rates in Africa. There is an urgent need to scale up quality control monitoring at the points of manufacturing and importation, as well as post-market surveys. The post-market survey scale-up can be achieved through partnerships with universities and other tertiary institutions, by equipping their laboratories to standards, where these assays can be carried out. In addition, hospitals in the country can be

encouraged to create mini pharmaceutical laboratories within the pharmacy departments for quick quality assessment. This study is a clarion call for all stakeholders to get involved and ensure the safety and potency of drugs in the market.

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