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Quality and *In Vitro* Pharmaceutical Equivalence of Ciprofloxacin Tablets Brands in Kenya

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The quality and *in vitro* pharmaceutical equivalence of nineteen generic products of ciprofloxacin tablets with marketing authorization in Kenya are reported. The tablets were assessed for compliance with pharmacopoeial specifications for identity, uniformity of weight, disintegration, drug content and dissolution. All the evaluated generic brands complied with the compendial specifications for identity, uniformity of weight, disintegration and drug content. However, five (26.3%) of the evaluated generic brands were non-compliant in the dissolution test at pH 1.2. *In vitro* pharmaceutical equivalence analysis showed that ten (52.6%) generic ciprofloxacin tablets brands exhibited similar dissolution profiles as the innovator Cipro® brand at pH 1.2 and pH 4.5, while the other nine (47.4%) had significantly variable dissolution profiles. Therefore only 10 of the 19 generic ciprofloxacin tablets brands evaluated in this study may be regarded as pharmaceutically equivalent to the innovator Cipro® brand.

Key words: Ciprofloxacin tablets, quality parameters, pharmaceutical equivalence

INTRODUCTION

Ciprofloxacin is a synthetic second-generation 6-fluoroquinolone broad-spectrum antibacterial commonly used in the treatment of a wide range of bacterial infections affecting the urinary tract, respiratory tract, gastrointestinal, musculoskeletal, skin and soft tissues, and is included in the World Health Organization (WHO) List of Essential Medicines [1]. Since its launch as innovator brand Cipro® by Bayer Pharmaceuticals in 1987, several ciprofloxacin generic brands have entered clinical use. Although the generics are cheaper and therefore affordable to a greater patient population, variable therapeutic responses to ciprofloxacin from various manufacturers have been documented [2]. The variation in therapeutic responses may be due to differences in the content of active pharmaceutical ingredient (API), excipients, formulation design, packaging and storage conditions.

The interchangeability between innovator brands and generic equivalents is strongly encouraged by the WHO and medicines regulatory authorities and advocated by consumer lobby groups to improve healthcare access [3]. A generic drug product is assumed to be bioequivalent to the innovator brand if there is no statistically significant difference in the rate and extent of absorption of the API when administered at similar dose [3]. The *in vitro* dissolution testing has been adopted as a surrogate indicator of bioequivalence for certain drugs with good dissolution and membrane

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permeability [4, 5]. Additionally, for a tablet to be considered satisfactory, it must comply with pharmacopoeial specifications that include test for identity, uniformity of weight, disintegration and drug content [6, 7].

The number of ciprofloxacin tablets brands in the Kenyan market has steadily increased over the years such that as of 2014 when this study was carried out, there were 88 different brands authorized for marketing by the Pharmacy and Poisons Board. The high number of generic drug products from multiple sources places enormous pressure on prescribers, pharmacists and consumers who have to choose one brand from among several seemingly pharmaceutically equivalent products. Further, high number of equivalent products poses control challenge on the regulatory agencies that may inadvertently pave way for the influx of counterfeits and substandard products. The availability and use of substandard ciprofloxacin products of spurious quality has been associated with increased risk of treatment failure and development of antibacterial resistance [8].

The high number of generic ciprofloxacin tablets brands in the Kenyan market creates a compelling need for regular evaluation of pharmaceutical equivalence of the generic products relative to the innovator brand so as to ascertain assumption of therapeutic equivalence [9]. This study evaluated pharmaceutical parameters of selected generic brands of film coated ciprofloxacin tablets to determine their compliance with compendial specifications and assess their comparative *in vitro* pharmaceutical equivalence to the innovator Cipro® brand.

EXPERIMENTAL

Materials

Nineteen generic products of ciprofloxacin (500 mg) tablets registered for marketing in Kenya and the innovator Cipro® brand were used in the study. The tablets were purchased randomly from licensed retail pharmacy outlets in Nairobi Central Business District in November 2013. The drug samples were purchased in their original package as supplied by the manufacturers, coded, stored appropriately and all tests performed within the products expiration dates. Ciprofloxacin HCl working standards of potencies 93.7% and 93.3% from Pharmathen Pharmaceutical Industry (Athens, Greece) and Saluntas Pharma (GmbH, Germany) were a kind donation from the National Quality Control Laboratory (NQCL), Nairobi, Kenya.

Reagents

Analytical grade sodium hydroxide, glacial acetic acid, sodium acetate and triethylamine were from RFCL Ltd (New Delhi, India) while potassium chloride and potassium dihydrogen orthophosphate were from Merck Pvt. Ltd. (Guateng, South Africa) and BDH Laboratory Supplies (Poole, England), respectively. Hydrochloric acid was from Loba Chemie Pvt. Ltd. (Mumbai, India) while phosphoric acid was from Sigma-Aldrich Co. (Steinheim, Germany). Acetonitrile (Avantor Performance Materials Ltd., Haryana, India) was of HPLC grade. Purified water was prepared by distillation on an Arium® laboratory water system (Sartorius Stedim Biotech GmbH, Doettigen, Germany) that consists of reverse osmosis and ultrafiltration modules with UV irradiation.

Equipment

A Shimadzu AUW220D electronic semi-micro analytical weighing balance (Shimadzu Corp., Kyoto, Japan) with a sensitivity/readability of ±0.1 mg was used for all weighings. A 2E/205 electronic tablet hardness tester (Dr. Schleuniger Pharmatron, Solothurn, Switzerland) was used to determine crushing strength while disintegration was carried out on an Erweka ZT3-1 disintegration test apparatus (Erweka GmbH, Heusenstamm, Germany).

A Labindia DS 800 dissolution tester (Labindia Instruments Pvt. Ltd, Mumbai, India) fitted with a high precision multichannel pump and an automated sample collector was used for dissolution studies. The dissolution media were U.S.P. 0.01N hydrochloric acid solution (pH 1.2), sodium acetate buffer (pH 4.5), and phosphate buffer (pH 6.8). The dissolution media were maintained at 37±0.5°C in a thermostated water-bath and the paddles rotated at 50 rpm. The drug concentration in sampled dissolution media was determined by ultra-violet (UV) light spectroscopy on a double beam T90+ UV/VIS spectrophotometer (PG Instruments, Leicestershire, UK) at 278 nm using 1 cm path length quartz cuvettes and supported by the UV-WIN software Version 5.2.0.

The content of ciprofloxacin HCl in the test tablets was determined on an Agilent 1200 infinity series high performance liquid chromatographic (HPLC) system (Agilent Technologies, Deutschland, Germany) fitted with a 5 µm C18 Symmetry® column 4.6 × 250 mm (Waters Corp., Massachusetts, U.S.A.) and supported by OpenLab software Version A.01.03. The system was equipped with an Agilent 1260 Infinity Variable wavelength UV detector at 278 nm, Agilent 1260 Infinity quaternary pump, autosampler, and thermostated column compartment at 30±1°C. All the mobile phase preparations were degassed using a DC-200H MRC Ultrasonic Cleaner (MRC Lab Ltd, Holon, Israel).

Test for identity

The identity of ciprofloxacin HCl in the test tablets was confirmed by retention time (t_R) on HPLC as per the pharmacopoeial specifications [7].

Uniformity of weight

For each of the 19 ciprofloxacin tablets brands, 20 tablets were taken at random, dusted using a soft brush and weighed individually. The average weight of the tablets for each brand and the percentage deviation from the mean value were then calculated.

Test for hardness

For each brand, six tablets were randomly selected. The tablets were placed between the jaws of the tablet hardness tester and oriented in the same way with respect to the direction of application of the force. The pressure at which each tablet crushed was recorded.

Disintegration test

Six tablets were individually placed in the disintegration basket and lowered into a 1 L basket containing distilled water thermostated at 37±0.5°C. The disintegration time was recorded as the time taken for the tablets to go completely into solution through the sieve with no particles remaining in the disintegration basket.

Assay

Drug content in each of the test ciprofloxacin tablets brands was determined by HPLC in accordance with the procedure outlined in the ciprofloxacin tablets monograph of the United States Pharmacopeia [7]. Tablets powder equivalent to 50 mg of ciprofloxacin HCl was dissolved in 50 mL of the mobile phase and the solution sonicated and filtered. A 10 mL aliquot of the filtrate was pipetted into a second 50 mL volumetric flask and made to volume with the mobile phase to give a working test solution nominally containing 0.2 mg/mL ciprofloxacin HCl. A 0.2 mg/mL solution of the standard ciprofloxacin HCl was prepared by dissolving 10 mg of standard ciprofloxacin HCl in 50 mL mobile phase. The injection volumes were 10 µL. Acetonitrile–0.025 M phosphoric acid adjusted with triethylamine to pH 3.0±0.1, (87:13 % v/v), was used as the mobile phase at a flow rate of 1.5 mL/min. The assay was carried out in triplicate.

Dissolution test and *in vitro* pharmaceutical equivalence

The dissolution vessels were filled with 900.0 mL of the dissolution medium and the test ciprofloxacin tablets immersed. In all the experiments, 5.0 mL aliquots of the dissolution medium were withdrawn from the vessels at 0, 5, 10, 15, 20, 30 and 45 min and replaced with equal volumes of fresh dissolution medium to maintain sink conditions. The samples were filtered and assayed by UV spectrophotometry. A 1.0 mL aliquot of each sample was pipetted into a 100.0 mL volumetric flask and made to volume using the dissolution medium to obtain a nominal concentration of 0.005 mg/mL that was compared to the same concentration of the standard solution. Absorbances of the samples and the standard were determined and the percentage amount of drug released calculated. The dissolution profiles of the different brands of ciprofloxacin tablets were generated from the graph of the amount of ciprofloxacin HCl released versus time.

Data analysis

The results of uniformity of weight, hardness, disintegration, dissolution and assay were tabulated and the dissolution profiles graphically presented. All the dissolution data obtained were based on the actual drug content of the tablets as calculated from the assay results. A model independent approach of difference factor f_1 and similarity factor f_2 was employed for comparative *in vitro* pharmaceutical equivalence [10].

RESULTS AND DISCUSSION

Quality parameters

As shown in Table 1, all evaluated ciprofloxacin tablets brands complied with the compendial specifications for identity, weight uniformity, disintegration and assay, as well as the non-compendial test for hardness. The test for identity is necessary to ensure that the product contains the requisite API. The t_R of ciprofloxacin HCl in all the samples was 5.1–5.2 min and closely corresponded to the t_R of the ciprofloxacin HCl reference standard (5.2 min). The test for weight uniformity serves as a pointer to good manufacturing practice and to assure that the drug content in each unit dose is distributed within a narrow range around the label strength [4].

Table 1: Quality parameters of ciprofloxacin tablets brands

Brand code	Retention time (min)	Uniformity of weight (mg) ± SD	% Deviation from the mean weight	Hardness (N) (average ± SD)	Disintegration time (min)	Assay (%) (RSD)
IB	5.2	762.5 ± 4.4	-1.4 – 1.2	176.7 ± 9.3	0.5	98.6 (0.3)
C001	5.2	777.2 ± 7.3	-2.1 – 2.2	141.8 ± 13.2	1.5	96.8 (0.8)
C002	5.2	899.1 ± 24.4	-4.7 – 6.1	188.3 ± 10.7	12.0	98.4 (1.5)
C003	5.1	770.8 ±10.2	-2.0 – 3.2	176.7 ± 19.2	0.8	94.8 (1.1)
C004	5.2	743.6 ± 11.3	-2.7 – 1.9	193.2 ± 6.9	1.5	97.3 (0.4)
C005	5.2	635.8 ± 5.9	-1.2 – 2.6	119.3 ± 16.8	3.0	98.2 (0.4)
C006	5.2	739.5 ± 14.3	-5.1 – 3.7	187.7 ± 9.0	2.2	95.9 (0.6)
C007	5.1	783.1 ± 7.9	-1.7 – 1.8	180.2 ± 6.7	0.5	97.3 (0.5)
C008	5.1	740.9 ± 9.9	-3.0 – 1.9	190.5 ± 5.9	2.7	97.2 (0.3)
C009	5.1	694.7 ± 6.7	-1.5 – 1.6	145.8 ± 16.6	2.3	99.4 (0.7)
C010	5.2	679.7 ± 6.0	-2.0 – 1.5	164.5 ± 19.9	1.2	98.8 (0.2)
C011	5.2	969.8 ± 9.6	-1.9 – 1.6	158.2 ± 12.2	1.2	97.0 (0.8)
C012	5.2	643.0 ± 10.5	-2.4 – 4.7	148.0 ± 23.4	6.0	94.4 (0.4)
C013	5.1	823.0 ± 15.6	-4.1 – 3.2	109.2 ± 7.6	23.5	104.6 (0.6)
C014	5.1	827.1 ± 5.4	-1.3 – 1.2	189.0 ± 8.1	3.5	99.6 (1.8)
C015	5.2	1033.8 ± 19.8	-7.2 – 2.4	166.2 ± 13.4	3.2	99.2 (0.6)
C016	5.2	1064.3 ± 25.5	-2.7 – 4.9	144.2 ± 6.8	1.0	95.5 (0.4)
C017	5.2	745.4 ± 10.4	-3.0 – 1.8	186.7 ± 8.4	1.3	98.6 (1.7)
C018	5.1	692.2 ± 24.1	-6.7 – 5.9	62.0 ± 14.8	6.5	90.4 (1.5)
C019	5.2	730.6 ± 8.6	-5.1 – 3.7	142.3 ± 5.3	1.3	95.0 (1.1)

Key: IB = Innovator brand; SD = Standard deviation; RSD = Relative standard deviation.

Hardness is a non-compendial test which assesses the ability of tablets to withstand handling during packaging, transportation and usage without fracturing or chipping. It can also influence other parameters such as friability and disintegration [11]. The harder a tablet, the less friable and the more time it takes to disintegrate. A force of about 40 N is the minimum requirement for a satisfactory tablet [12]. Brand C018 required the least amount of pressure (62 N) to break as shown in Table 1. The disintegration test measures the time required for a tablet to disintegrate into particles when in contact with gastrointestinal fluids, and different formulation factors are known to affect it. There was a wide inter-brand variation in the disintegration time. However, all evaluated brands complied with the pharmacopoeial specification which stipulates a disintegration time of not more than 30 min for film coated tablets [4]. There was no direct correlation between tablet hardness and disintegration time.

The aim of the assay specification is to assure the presence of the API in requisite amount. Significant variations in the amounts of API could lead to ineffective therapeutic drug levels or overdosing that may cause toxicity [13]. Compendial specifications require that ciprofloxacin tablets should contain not less than 90.0% and not more than 110.0% of the stated amount [7]. The highest percentage content was obtained for brand C013 (104.6%), while the least drug content was obtained for brand C018 (90.4%). Statistical comparison for drug content indicated that within 95% confidence interval, there was no significant difference in the drug content among the different brands ($p < 0.05$).

Dissolution test

The results obtained in the dissolution study are summarized in Table 2. Products containing the same API but differently formulated may have different dissolution profiles or drug-release characteristics and therefore exhibit variable bioavailability. For ciprofloxacin tablets, the USP specifies that the amount of ciprofloxacin HCl released within 30 min at pH 1.2 is not less than 85% of the stated amount [7]. Fourteen (73.7%) of the studied ciprofloxacin tablets generic products released more than 85% of the drug within 30 min at pH 1.2, while the remaining five (26.3%) released less than the specified amounts (Figure 1).

The dissolution profile at pH 4.5 is graphically depicted in Figure 2. At pH 4.5, most of the generic brands released more that 85% of ciprofloxacin HCl within 30 min except brand C013, C015 and C016, which released 73.7, 80.4 and 81.6%, respectively. However, all the products including the innovator brand Cipro® had very poor release characteristics at pH 6.8. This observation is consistent with the solubility of ciprofloxacin which exhibits a "U" shaped pH–solubility profile with high solubility at pH values below 5 and above 10, and low solubility near the isoelectric point (pH 7) [14, 15].

Table 2: Dissolution of ciprofloxacin tablets brands at 30 minutes

Brand Code	% Dissolution at 30 min (RSD)			Compliance at pH 1.2
	pH 1.2	pH 4.5	pH 6.8	
IB	91.5 (1.3)	94.8 (2.3)	35.3 (25.0)	Complies
C001	95.8 (3.6)	96.6 (2.1)	32.1 (35.0)	Complies
C002	90.7 (2.1)	88.0 (2.9)	4.4 (56.5)	Complies
C003	92.2 (2.5)	93.2 (3.2)	5.0 (68.6)	Complies
C004	82.5 (8.6)	94.4 (1.7)	47.4 (12.4)	Does not comply
C005	91.0 (5.2)	94.8 (1.5)	38.3 (3.8)	Complies
C006	93.4 (2.5)	97.0 (1.4)	51.5 (44.5)	Complies
C007	83.5 (2.0)	96.5 (2.6)	55.4 (15.0)	Does not comply
C008	98.4 (2.8)	97.2 (1.8)	47.7 (15.7)	Complies
C009	94.7 (1.0)	97.5 (1.7)	29.2 (11.1)	Complies
C010	88.8 (3.6)	96.2 (0.9)	46.1 (17.6)	Complies
C011	97.2 (1.0)	91.4 (3.5)	10.5 (17.6)	Complies
C012	77.7 (6.2)	94.3 (2.3)	7.1 (45.3)	Does not comply
C013	101.4 (2.6)	73.7 (4.2)	1.6 (43.4)	Complies
C014	94.0 (1.5)	95.7 (2.2)	1.8 (30.6)	Complies
C015	52.8 (12.4)	80.4 (10.4)	7.1 (32.6)	Does not comply
C016	79.3 (17.4)	81.6 (8.1)	21.4 (33.1)	Does not comply
C017	85.0 (3.4)	94.5 (0.6)	59.0 (11.7)	Complies
C018	88.6 (3.4)	88.2 (5.3)	7.6 (82.5)	Complies
C019	91.3 (3.2)	95.4 (1.5)	43.4 (3.2)	Complies

IB = Innovator brand; RSD = Relative standard deviation, n = 6.

In vitro pharmaceutical equivalence

A model independent approach of the difference factor f_1 and similarity factor f_2 was employed in comparative *in vitro* pharmaceutical equivalence [10]. Six sampling time points (5, 10, 15, 20, 30 and 45 min) were used. Table 3 shows calculated f_1 and f_2 values of the different brands in respect to the innovator brand at pH 1.2 and pH 4.5. In the f_2 calculation, only one measurement is generally considered after the comparator product has reached 85% dissolution as observed in 0.01N hydrochloric acid (pH 1.2) and acetate buffer (pH 4.5). At pH 1.2, the f_2 values of 12 generic products namely C002, C003, C004, C005, C006, C007, C009, C010, C011, C016, C017 and C019, are more than 50 while the corresponding f_1 values are all below 15 suggesting likelihood for pharmaceutical equivalence to the innovator brand.

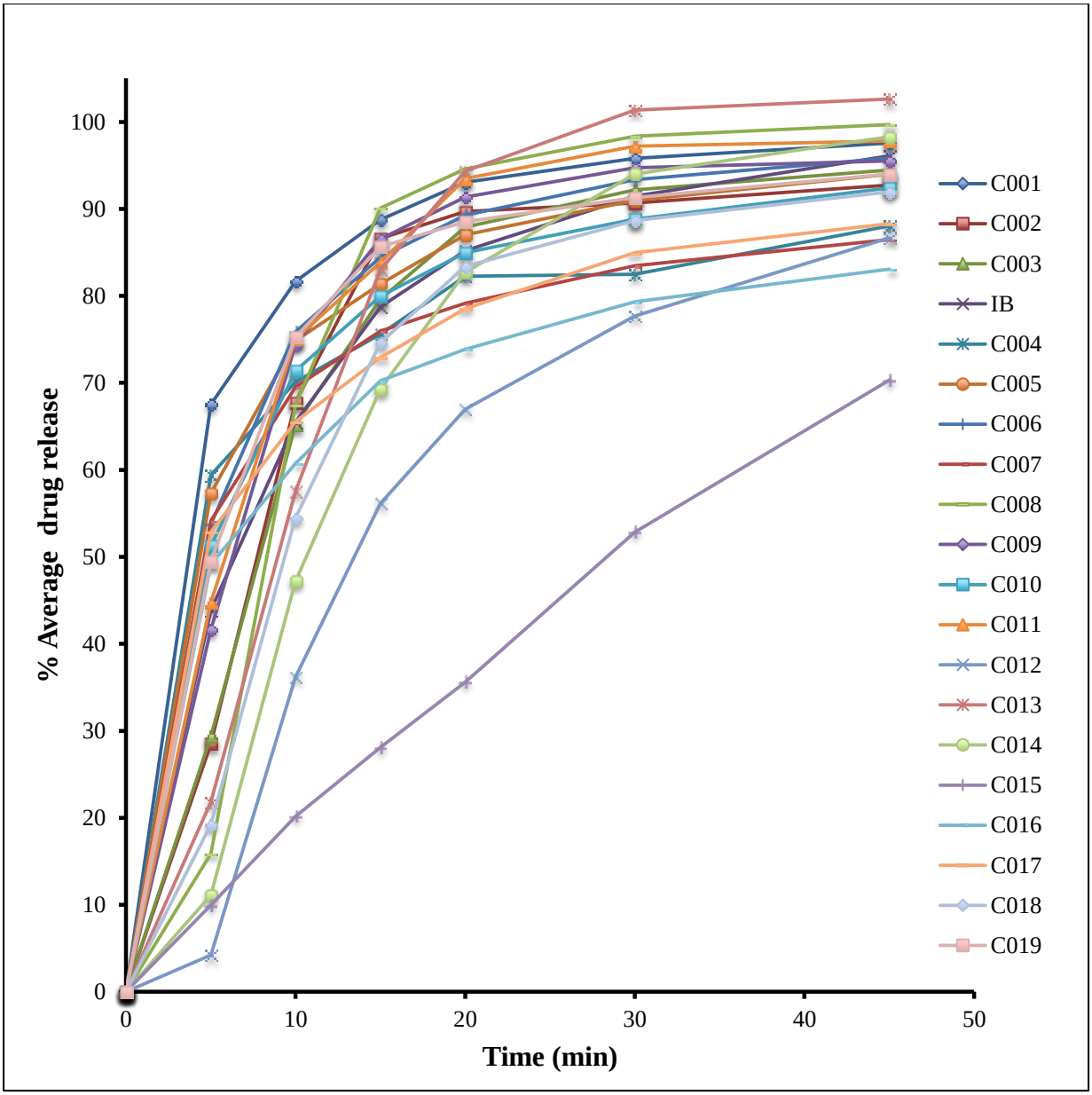

Figure 1: Dissolution profiles of the innovator and generic ciprofloxacin tablets brands at pH 1.2. IB = innovator brand.

At pH 4.5, the f_2 values of 12 generic products namely C001, C002, C003, C004, C005, C006, C007, C008, C009, C010, C017 and C019, are above 50 while the corresponding f_1 values are all below 15, implying their likelihood for pharmaceutical equivalence to the innovator brand. Overall, the f_2 and f_1 values of ten generic products, i.e., C002, C003, C004, C005, C006, C007, C009, C010, C017 and C019 at both pH 1.2 and pH 4.5 are above 50 and below 15, and may therefore be considered pharmaceutically equivalent to the innovator brand. At pH 6.8, the amount of ciprofloxacin HCl released for all the brands and the IB was below 85% within 45 min. Therefore the difference factor f_1 and similarity factor f_2 are not applicable for the dissolution data obtained at pH 6.8 due to low drug release. The low drug release at pH 6.8 even for the IB is expected given the pH-dependent solubility of ciprofloxacin that is lowest at neutral pH.

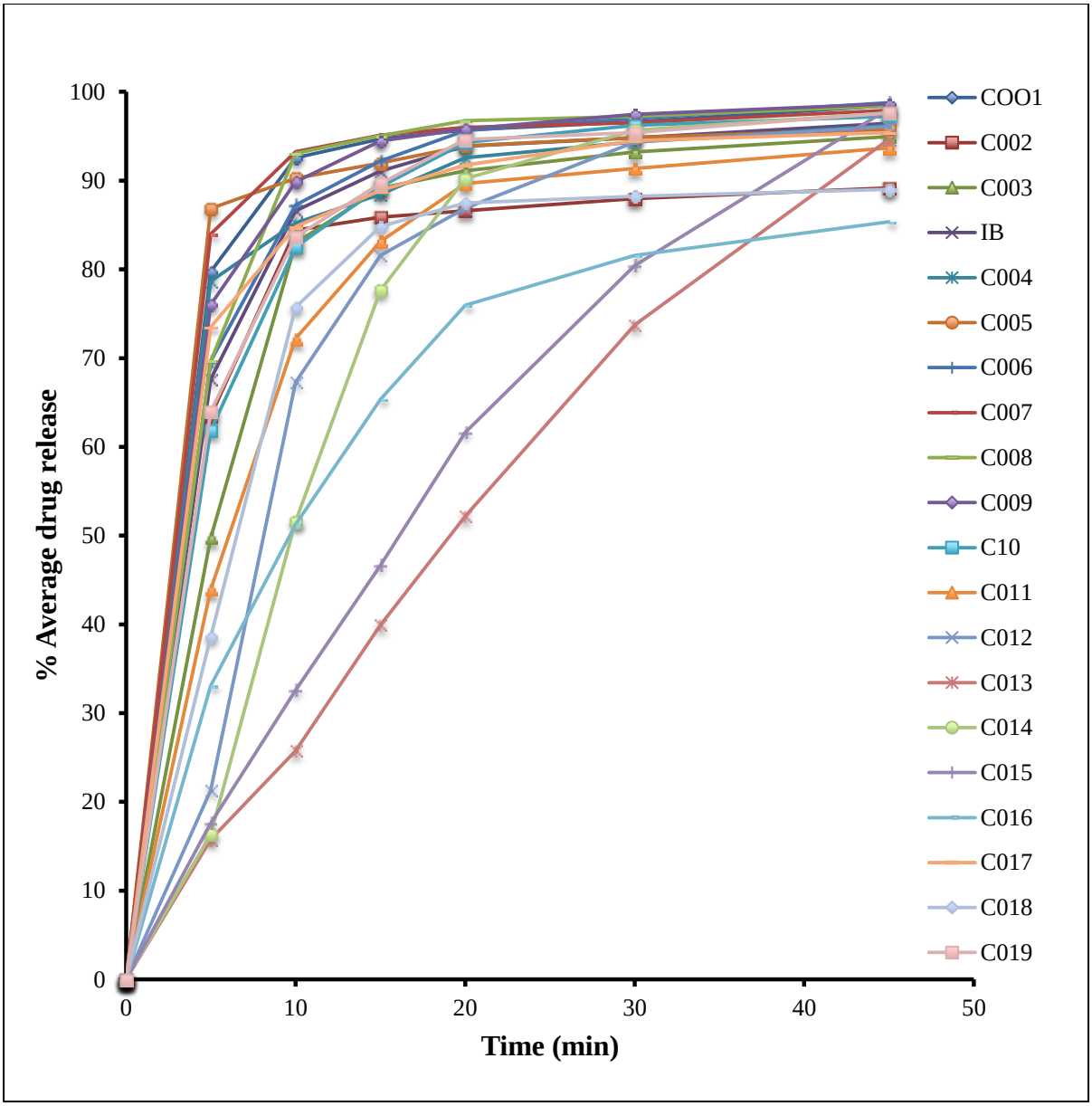

Figure 2: Dissolution profiles of the innovator and generic ciprofloxacin tablets brands at pH 4.5. IB = innovator brand.

The f_1 and f_2 values obtained in this study implied that nine (47.4%) of the 19 generic ciprofloxacin tablets brands studied may not be pharmaceutically equivalent to the innovator Cipro® brand. The results of the current study are comparable with findings of a similar study carried out in Nigeria, where three (50%) of the six studied ciprofloxacin tablets brands were deemed pharmaceutically non-equivalent to the innovator Cipro® brand [16].

Table 3: The difference factor (f_1) and similarity factor (f_2) of the generic ciprofloxacin tablets brands

Brand Code	pH 1.2		pH 4.5	
	f_1	f_2	f_1	f_2
C001	13.8	44.3	5.2	61.3
C002	1.0	56.2	6.2	61.5
C003	2.6	60.6	5.5	55.7
C004	0.6	53.5	1.0	65.9
C005	5.3	57.9	4.4	54.7
C006	6.9	58.9	1.9	84.5
C007	2.6	56.5	6.6	55.7
C008	1.7	42.9	3.7	71.1
C009	5.1	61.9	4.1	68.0
C010	1.7	67.7	1.7	74.6
C011	6.8	60.5	10.6	45.9
C012	28.9	30.7	15.6	33.8
C013	0.0	46.9	43.1	18.2
C014	12.6	39.9	19.1	29.2
C015	52.9	19.0	36.5	21.0
C016	9.6	50.5	26.0	30.2
C017	3.8	58.7	0.3	76.1
C018	10.5	47.2	12.6	43.0
C019	5.1	62.1	1.0	81.8

CONCLUSION

All the 19 evaluated generic ciprofloxacin tablets brands complied with the pharmacopoeial specifications for identity, uniformity of weight, disintegration and assay prescribed in the B.P. (2012) and U.S.P. (2014), as well as the non-compendial test for hardness. Approximately three-quarters (73.7%) of the evaluated generic products complied with the dissolution test. There was no direct correlation between tablet hardness, disintegration time and dissolution. In general, there were observable differences in the *in vitro* drug release characteristics among the 19 ciprofloxacin tablets brands implying potential differences in their bioavailability. However, since *in vitro* pharmaceutical equivalence is only a predictor of *in vivo* therapeutic equivalence of drug products, the obtained data may not exclusively indicate the *in vivo* performance of the tested ciprofloxacin tablets generic products [18, 19]. From the calculated difference factor f_1 and similarity factor f_2 values, 10 (52.6 %) of the 19 ciprofloxacin generic products can be considered pharmaceutically equivalent to the innovator Cipro® brand and may therefore be therapeutically interchanged.

REFERENCES

[1] World Health Organ. WHO Model Lists of Essential Medicines. Available online at http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed 12 August 2015.

[2] R.B. Taylor, O. Shakoor, R.H. Behrens, M. Everard, A.S. Low, J. Wangboonskul, R.G. Reid and J.A. Kolawole. The Lancet 2001, 357 (9272), 1933–1936.

[3] C.A. Rodriguez, M. Agudelo, A.F. Zuluaga and O. Vesga. Antimicrob. Agents Chemother. 2015, 59(1), 53–58. DOI:10.1128/AAC.03633-14.

[4] J.E. Polli. AAPS Jour. 2008, 10(2), 289–299.

[5] G.L. Amidon, H. Lennernas, V.P. Shah and J.R. Crison. Pharm. Res. 1995, 12(3), 413–420.

[6] The British Pharmacopoeia Commission. British Pharmacopoeia. The Pharmaceutical Press, Her

Majesty Stationery Office, London, Vol. 1, 2012.

[7] The United States Pharmacopeial Convention, Inc. United States Pharmacopeia and National Formulary USP 37/NF 32. Twinbrook Parkway, Rockville, MD, 2014.

[8] R.E. Weir, F.H. Zaidi, D.G. Charteris, C. Bunce, M. Soltani and A.M. Lovering. Br. J. Ophthalmol. 2005, 89, 1094–1096. DOI: 10.1136/bjo.2004.059519.

[9] A.F. Zuluaga, M. Agudelo, C.A. Rodriguez and O. Vesga. BMC Clin. Pharmacol. 2009, 9(1), 1–11. DOI: 10.1186/1472-6904-9-1.

[10] US Food and Drug Administration (1997). Center for Drug Evaluation and Research. Guidance for industry: Dissolution testing of immediate release solid oral dosage forms. Available online at http://www.fda.Gov/cder/guidance/1713bp1.pdf. Accessed 17 November 2015.

[11] J. Muaz, L.K. Gazali, G.U. Sadiq and G.M. Tom. Niger. J. Pharm. Sci. 2009, 8, 102–106.

[12] T.S. Oishi, A. Haque, I. Dewan and S.M.A. Islam. Int. J. Pharm. Sci. Res. 2011, 2, 3129–3135.

[13] L.V. Allen, N.G. Popovich and H.C. Ansel. Pharmaceutical dosage forms and drug delivery systems, Lippincott Williams & Wilkins, Philadelphia, 2004, Edition 8, pp. 236.

[14] M.K. Khan, M.F. Khan, H. Khan and G. Mustafa. Pak. J. Pharm. Sci. 2009, 22(3), 329–334.

[15] M. Jaman, A.A. Chowdhury, A.A. Rana, S.M. Masum, T. Ferdous, M.A. Rashid and M.M. Karim. Bangladesh J. Sci. Ind. Res. 2015, 50, 251–256.

[16] M.E. Olivera, R.H. Manzo, H.E. Junginger, K.K. Milha, V.P. Shah, S. Stavchansky, J.B. Dressman and D. M. Barends. J. Pharmaceut. Sci. 2011, 100, 22–23.

[17] N.C. Ngwuluka, K. Lawal, P.O. Olorunfemi and N.A. Ochekpe. Scientific Res. Essay 2009, 4(4), 298–305.

[18] O. Vesga, M. Agudelo, B.E. Salazar, C.A. Rodriguez and A.F. Zuluaga. Antimicrob. Agents Chemother. 2010, 54, 3271–3279.

[19] M. Agudelo and O. Vesga. Antimicrob. Agents Chemother. 2012, 56, 2659–2665.