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Full Length Research Paper

Post-market *in vitro* bioequivalence study of six brands of ciprofloxacin tablets/caplets in Jos, Nigeria

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Six brands of ciprofloxacin 500 mg tablets have been evaluated using some quality control tests of uniformity of weight, hardness, friability, assay, disintegration and dissolution with the aim to assess its bioequivalence. The results obtained have been discussed in some details using monographs in the two Pharmacopeia (United States Pharmacopeia, USP and British Pharmacopeia, BP). The results were also subjected to statistical analysis. In particular, the dissolution test results were subjected to further tests to determine significance of ANOVA, significance of Dunnett's test, dissolution efficiency, difference factor (f_1) and similarity factor (f_2). Subsequently the results indicated that 3 of the 6 (50%) brands may not be used interchangeably with the chosen 'innovator' brand.

Keywords: Quality control tests, bioequivalence, ciprofloxacin, dissolution, dissolution efficiency, weight variation, disintegration.

INTRODUCTION

Post-market surveillance or monitoring involves all activeties undertaken to obtain more data and information about a product after it had been granted marketing authorization and made available for public use. The data and information so obtained could be employed for prduct improvement, development of standards and regulations. Regulatory agencies rely on limited information obtained during clinical trials and to some extent scientific literature as guides to granting marketing authorization of medicines for public use. It is therefore imperative to conduct post-market surveillance or monitoring of approved medicines in order to adequately assess the quality, therapeutic effectiveness and safety of medicines for the larger public. Post-market monitoring ought not to be a one off event rather it should be a continuous event throughout the life of a drug product. Activities of post-market monitoring of a drug have been identified to include: review of product's condition of approved study; evaluation and investigation of reported drug complaints; inspection of manufacturer's processes and procedures for production and complaint handling; market surveys of technical and clinical documentation; review of product claims/labelling; public access to information taken and reported to the regulatory agency(ies); and *in vitro* testing of products for compliance
to standards (Hennessy, 1998; Garcia, 2006).

In vitro testing or quality control of drugs is a set of studies or experiments undertaken during production (in process) and occasionally ought to be undertaken post-production by regulatory agencies and researchers. Routine laboratory testing of drugs in the market is crucial to protect public health especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. In Nigeria, several attempts have been made to combat counterfeit and substandard drugs from the Indian sub-continent (Ochekpe et al., 2006a; Raufu, 2003). Counterfeit and substandard medicines are a major cause of morbidity, mortality and loss of public confidence in drugs and health structures (Cockburn et al., 2005).

India happens to be one of the largest exporters of fake and substandard drugs to Nigeria. Other countries are China, Pakistan, Egypt and Indonesia (Raufu, 2003). China and India are known as the leading countries in counterfeit drugs' production and also the bulk active ingredients they produce are used for counterfeiting

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worldwide (Khan and Ghilzai, 2007).

To reduce the cost of medicines especially for the low income group of developing countries, the World Health Organization (WHO) has continuously advocated the use of generic brands (WHO, 2004) but this approach has not provided sufficient evidence for the substitution of one brand for another. The difference in cost between a branded and generic medicine may be as high as 90%. To assist in substitution of branded with generics for affordability and at the same time achieve therapeutic efficacy, bioequivalence studies become paramount. Bioequivalence has been described as the absence of a significant difference in the rate and extent to which the active ingredient or moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action (that is, a significant difference in the bioavailability of the 2 drug products) when they are administered at the same molar dose under similar conditions in an appropriately designed study (FDA, 2003). Two pharmaceutical products are considered to be equivalent when their bioavailability factors (from the same molar dose) are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects (Rani, 2007).

Generic substitution could be considered when a generic copy of a reference drug contains identical amounts of the same active ingredient in the same dose formulation and route of administration as well as meet standards for strength, purity, quality and identity (Meredith, 2003). However evidences over the years indicate that marketed products with the same amount of active ingredient exhibit marked differences in their therapeutic responses (Rani and Pargal, 2004). This may be due to the extent of absorption being dissimilar; perhaps due to different excipients employed. Bioequivalence studies focus on the release of drug from the formulation and subsequent absorption into the system's circulation. Bioequivalence studies may involve both *in vivo* and *in vitro* studies. However, with the introduction of biopharmaceutical classification system (BCS), *in vivo* bioequivalence studies could be waived for immediate release solid oral dosage forms for classes I (high solubility and permeability) and III drugs (high solubility and low permeability) (FDA, 2000; Polli, 2008; Gupta et al., 2006; Yu et al., 2002). Hence only *in vitro* testing may be used to determine bioequivalence for highly soluble and highly permeable drugs (Chen et al., 2001).

Dissolution testing, a surrogate marker for bioequivalence test is indeed a practical and economic approach in developing countries where technology and resources are limited for *in vivo* studies. One of the values of dissolution test is that it can be used to identify bioavail-ability problems and assess the need for *in vivo* bio-availability (Shah, 2001). The release of active pharmaceutical ingredient from drug product, the dissolution of the drug under physiological conditions and the permeability across the gastrointestinal tract determines the drug absorption. Based on this, *in vitro* dissolution may be vital in assessing *in vivo* performance. Dissolution testing also serves as a tool to distinguish between acceptable and unacceptable drug products (Ochekpe et al., 2006b).

The study was undertaken to evaluate the efficacy and justification of generic substitution of ciprofloxacin brands in the Nigerian market. Ciprofloxacin is an antibactericidal agent of the class, fluoroquinolones. It was first sold by Bayer Pharmaceuticals. In the 1990s, there were just a few brands in the Nigerian market but recently many brands of ciprofloxacin have flooded the market. The prices range from Nigerian local currency equivalent of $1.25 to $12.50. There is a growing concern about this situation. How can a patient know if buying a cheaper brand would be cost effective or not? The price of the cheapest is ten times lower than the most expensive. The increase in the number of generics of ciprofloxacin can be attributed to increased prescription of ciprofloxacin. It would appear that for most infections, empirically and sometimes after laboratory investigations, physicians prescribe ciprofloxacin as the first drug of choice. This has resulted in higher demand and the need to increase supply has led to more importation while some indigenous pharmaceutical industries began to produce their own brands of ciprofloxacin. For the health care providers to use these brands interchangeably, the bioequivalence of these brands have to be ascertained. This means that there should be continued post marketing surveillance of the drugs.

MATERIALS AND METHODS

6 different brands of ciprofloxacin as shown in Table 1 were purchased from retail pharmacies in Jos, Nigeria. Pure ciprofloxacin HCl powder was obtained as a gift from a research colleague. The reagents utilized include hydrochloric acid (BDH, UK) and ferric chloride (M and B, Nigeria).

Determination of uniformity of weight

20 tablets from each of the 6 brands were weighed individually with an analytical weighing balance (Ohaus Adventure, USA). The average weights for each brand as well as the percentage deviation from the mean value were obtained.

Assay

A solution of 1% $^{w}/_{v}$ ferric chloride was freshly prepared as well as 100 mcg/ml of pure ciprofloxacin. 5 tablets from each brand were crushed and 100 mg of the powdered samples were weighed, dissolved in 100 ml 0.1N hydrochloric acid (HCl) and further dilution was made to obtain 100 mcg/ml for each brand. To 5 ml of each brand and the pure sample, 1 ml of ferric chloride was added and made up to 50 ml with 0.1N HCl. The absorbance of each sample was taken at 438 nm against the blank reagent (1 ml ferric chloride solution made up to 50 ml with 0.1N HCl) with an ultraviolet spectrophotometer (Jenway, UK). The percentage content was calculated for each brand.

Hardness test

The crushing strength was determined with a tablet hardness tester (Monsanto, UK). 4 tablets were randomly selected from each brand

Table 1. Samples of ciprofloxacin tablets.

Code	Brand name	Dosage form	Country of origin	NAFDAC reg. no
A	Ciproval	Tablets	Nigeria	04-2433
B	Ciprogem	Tablets	Nigeria	04-4699
C	Ciprobon	Caplets	Nigeria	04-4860
D	Cipro-J	Caplets	Nigeria	04-5734
E	Ivacip	Tablets	India	04-5640
F	Vitapro	Tablets	India	04-2170

NAFDAC - National Agency for Food and Drugs Administration and Control; reg – registration.

Table 2. A summary of the quality control test undertaken on the brands of ciprofloxacin.

Code	Average uniformity of weight (g)	% Deviation from average weight	Assay (%)	Average hardness test ($kg/cm^{2)}$	Friability (%)	Average disintegration (min)
A	0.7950	3.46	97	>15	0.2	5.13
B	0.7760	1.39	100	10.7	0.4	1.12
C	0.6820	1.32	90	9.8	1.2	8.23
D	0.5905	2.79	91	11.3	0.7	15.80
E	0.7085	0.93	95	9.3	0.6	1.29
F	0.9610	1.44	91	>15	0.3	23.80

and the pressure at which each tablet crushed was recorded.

Friability test

10 tablets of each brand were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.

Disintegration test

6 tablets from each brand were employed for the test in a freshly prepared medium, 0.1 N HCl at 37℃ using Educational Sciences Disintegration Apparatus (Es Eagle Scientific Limited, Nottingham, UK). The disintegration time was taken to be the time no particle remained on the basket of the system.

Dissolution test

The dissolution test was undertaken using USP apparatus I (basket method) in 6 replicates for each brand. The dissolution medium was 1000 ml 0.1N HCl which was maintained at 37 ± 0.5℃. In all the experiments, 5 ml of dissolution sample was withdrawn at 0, 3, 8, 15, 25, 35, 45 and 60 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by ultraviolet spectrophotometry at 277nm. The concentration of each sample was determined from a calibration curve obtained from pure samples of ciprofloxacin.

Data analysis

The uniformity of weight was analyzed with simple statistics – percentage deviation while the dissolution profiles were analyzed with difference factor (f_1), similarity factor (f_2) and some other approaches such as dissolution efficiency, one way analysis of variance (ANOVA) and Dunnett's test.

RESULTS AND DISCUSSION

A summary of the results of uniformity of weight, assay, hardness test, friability and disintegration are as shown in Table 2.

Uniformity of weight, assay, disintegration and dissolution are compendial standards to assess the quality of tablets while hardness and friability are referred to as non-compendial standards although friability is now included in the United States Pharmacopeia (USP, 1995).

Uniformity of weight does serve as a pointer to good manufacturing practices (GMP) as well as amount of the active pharmaceutical ingredient (API), ciprofloxacin hydrochloride contained in the formulation. All the brands complied with the compendial specification for uniformity of weight which states that for tablets weighing more than 324 mg, weights of not more than 2 tablets should not differ from the average weight by more than 5%.

While all the brands complied with the USP specification for assay, brands C, D and F did not meet British pharmacopoeia (BP) standard. The USP specification is that the content of ciprofloxacin hydrochloride should not be less than 90% and not more than 110% while BP specifies that the content should not be less than 95% and not more than 105%. However, the result ascertains the presence and compendial quantity of ciprofloxacin hydrochloride in all the brands and so could not be judged as

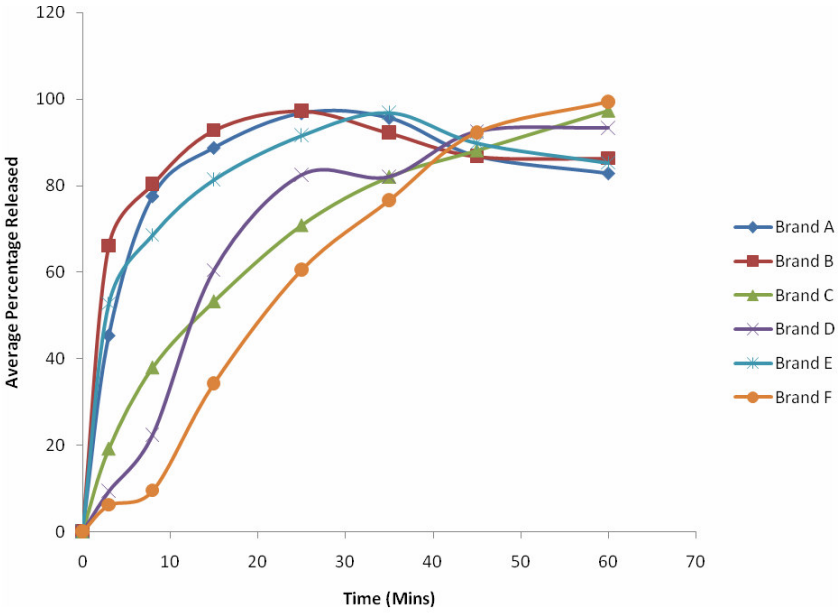

Figure 1. Dissolution profiles of six brands of ciprofloxacin tablets.

counterfeits without APIs.

The hardness or crushing strength assesses the ability of tablets to withstand handling without fracturing or chipping. It can also influence friability and disintegration as can be seen from Table 2. The harder a tablet, the less friable and the more time it takes to disintegrate. Brand C required the least pressure before fracture while brands A and E could not break at 15 kg/cm^2 with Monsanto hardness tester. A force of about 4 kg is the minimum requirement for a satisfactory tablet (Allen et al., 2004). Hence the tablets of all brands were satisfactory for hardness.

The compendial specification for friability is 1%. Friability for all the brands was below 1% except brand C which was 1.2%. Friability test is used to evaluate the tablets resistance to abrasion.

Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. A drug incorporated in a tablet is released rapidly as the tablet disintergrates; a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine. All the brands complied with the compendial specifications for disintegration. The BP specification is that uncoated tablets should disintegrate within 15 min and film coated in 30 min while USP specifies that uncoated and film coated tablets should disintegrate within 30 min. Brands A, C, D and E were uncoated tablets while brands B and F were film coated. However the coating of brand F was thicker than brand B.

The USP and BP specifies that the amount of drug released (dissolution) should not be less than 80% of the labelled amount at 30 min. All brands complied except brand F which had 77% at 35 min as shown in Figure 1.

According to the FDA guidance for the industry, for the dissolution testing of immediate release solid oral dosage forms, the BCS suggests that for class I and in some cases class III drugs 85% dissolution in 0.1 N HCl in 15 min ensures that the bioavailability of the drug is not limited by dissolution (FDA, 1997). Ciprofloxacin is a class III drug (Wu and Benet, 2005; Kasim et al., 2004) and from Figure 1, brand B released as much as 92% at 15 min and so it is envisaged that it will not have any bioavailability problems. The amounts released by the other brands were below 85%, though brands A and E came close to 80 and 81%, respectively.

Brand B made by Gemini Pharmaceutical Nigeria Limited was chosen as a reference product for some reasons. Ciproxin, the original product from Bayer Pharmaceutical was not found in the market. The Ciproxin that used to be in the Nigerian market was made by Gemini Pharmaceuticals which was formerly Bayer pharmaceuticals Nigeria Limited until the 80's when Bayer AG disengaged. With a franchise and licence agreement, Gemini Pharmaceutical continued to manufacture Bayer AG pharmaceutical products until 2002. Afterwards Gemini Pharmaceuticals began to manufacture ciprofloxacin with a new brand name Ciprogem.

The percentage dissolved was tested statistically to ascertain differences among brands using one-way analysis of variance (ANOVA) while Dunnett's test was employed to ascertain where the difference arose. The analyses were undertaken for time points 25 and 35 min. These time points were chosen because at least 3 brands had released over 90% at 25 min while 5 brands had complied with official dissolution specifications by 35 min. The results of ANOVA as shown in Table 3 indicate that the percent dissolved was significantly different at the 2 time points at 0.05 level.

Table 3. Results of analysis of variance at two time points.

Time (min)		Sum of squares	Df	Mean square	F- value	Significance (p)
25	Between groups	6,713.000	5	1,342.600	12.097	0.000
	Within groups	3, 329.450	30	110.982		
	Total	10, 042.450	35			
35	Between groups	2, 125.520	5	425.104	5.750	0.001
	Within groups	2, 217.850	30	73.928		
	Total	4, 343.370	35			

Df - Degree of freedom.

Table 4a. Dunnett's test on the brands at 0.05 level (two-tailed) with critical value 2.66[a].

Time (min)	Pair comparison	Mean difference[b] (% dissolved)	Significance
25	A vs B	-0.6	0.097
	C vs B	-26.4	4.34
	D vs B	-14.9	2.45
	E vs B	-5.7	0.94
	F vs B	-36.8	6.05
35	A vs B	3.4	0.69
	C vs B	-10.1	2.03
	D vs B	-10.2	2.06
	E vs B	4.7	0.95
	F vs B	-15.6	3.15

[a] Critical Value is obtained from a table of Dunnett's test; [b] Mean difference is obtained by substracting mean % dissolved of brand B (reference) from mean % dissolved of other brands (test products).

In order to ascertain the source of the difference, pairwise comparisons of brands A, C, D, E and F against brand B were performed by multiple comparisons using Dunnett's test and the outcome at 0.05 level is as shown in Table 4a and b. Values above the critical value (2.66) indicate that the mean % dissolved difference is significant while values below the critical value indicate that the difference is not significant. Consequently, it can be inferred that the difference in % dissolved for brands C and F at 25 min are significantly different from brand B while brands A, D and E are not significantly different from brand B. At 35 min, brands A, C, D and E are not significantly different from brand B. However brands A and E show the least departure from brand B at the two time points. It is worthy to note that the difference identified by ANOVA and the comparison performed by Dunnett's test are statistical and not pharmaceutical equivalence. Statistical equiva-lence indicates that at 0.05 level, the products are not significantly different while pharmaceutical equivalence means that the dissolution profiles are within dissolution specifications (Anderson et al., 1998).

In order not to conclude based on the results of ANOVA and Dunnett's test, dissolution efficiency (DE) was also employed. This is also due to evidence from literature which purports that no single comparison approach is widely accepted to determine similarity of dissolution profiles (Polli et al., 1997). Dissolution efficiency is the area under the dissolution curve within a time range (t_1 - t_2) expressed as a percentage of the dissolution curve at maximum dissolution y_{100}, over the same time frame (Anderson et al., 1998; Costa and Sousa Lobo, 2001). This was calculated from the equation:

$$\text{Dissolution Efficiency (DE)} = \frac{\int_{t1}^{t2} y.\, dt}{y_{100}\,(t_2 - t_1)} \times 100 \quad (1)$$

where y is the percentage dissolved at time t.

The integral of the numerator which is the area under the curve was calculated using the trapezoidal method:

$$\text{AUC} = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})\,(y_{i-1} + y_i)}{2} \quad (2)$$

The dissolution rates of brands A, B and E came out higher than those of brands C, D and F as shown in Figure 2. Furthermore the dissolution efficiencies also follow the same trend with brands A, B and E having ≥ 80% as compared with brands C, D and F which had ≤ 70%. The reference and the test product can be said to be equivalent if the difference between their dissolution efficiencies is within appropriate limits (± 10%, which is often used) (Anderson et al., 1998).

From Table 5, the differences between the reference brand and the test brands are shown and once again brand A may be said to be bioequivalent to brand B. Brand E may be close to the accepted 10% but exceeded by 1.9%. However, the rest of the brands C, D and F were very much away from the limit. Dissolution efficiency gives an insight into the dissolution behaviour of each brand and is able to assess the individual performance of each brand. To compare the dissolution profiles of the brands, a model independent approach of difference factor f_1 and similarity factor f_2 was employed (FDA, 1997) with the 7 points included in the calculations. Difference factor f_1 is the percentage difference between

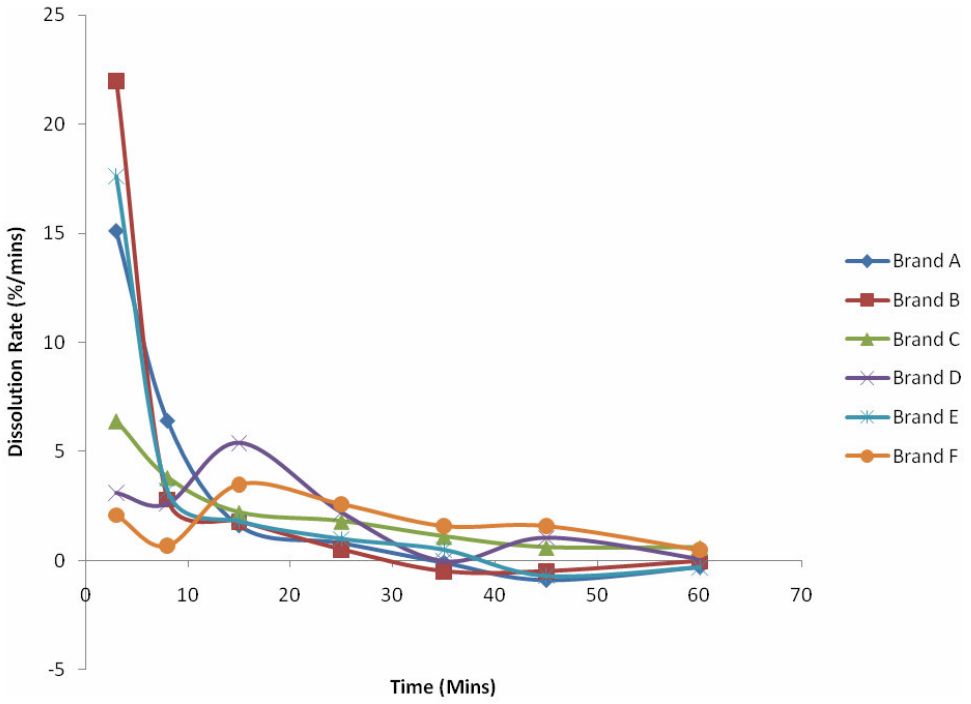

Figure 2. Dissolution rate of six brands of ciprofloxacin tablets.

Table 4b. Dissolution efficiencies (D.E) of the six brands.

Brand code	(D.E, %)	Difference between D.Es of reference and test products
A	85.0	7.0
B	92.0	0.0
C	65.3	26.7
D	66.9	25.1
E	80.1	11.9
F	50.8	41.2

two curves at each point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n}|R_t - T_t|]/[\sum_{t=1}^{n}R_t]\} \bullet 100 \quad (3)$$

where n is the number of time points, R_t is the dissolution value of reference product at time t and T_t is the dissolution value for the test product at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1 + (1/n) \sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\} \quad (4)$$

Similarity factor f_2 has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) by the Committee for Proprietary Medicinal Products (CPMP) as a criterion to compare the similarity of two or more dissolution profiles. Similarity factor f_2 is included by the Centre for Drug Evaluation and Research (CDER) in their guidelines such as guidance on dissolution testing of immediate release solid oral dosage forms (FDA, 1997) and guidance on Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (FDA, 2000). EMEA inclusion can be located in Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (EMEA, 2001). However, scientific analysts and formulation scientists assess similarity factor f_2 as a biased and conservative estimate (Shah et al., 1998) which does not take into account the dissolution differences within the reference product and the test product batches (Gohel et al., 2005). It is also said to be insensitive to the shapes of dissolution profiles and does not put into consideration unequal spacing between sampling time points (Costa, 2001). Despite the disadvantages, similarity factor f_2 is a simple and viable comparison approach to assess bioequivalent between two formulations.

For two dissolution profiles to be considered similar and bioequivalent, f_1 should be between 0 and 15 while f_2 should be between 50 and 100 (FDA, 1997). Therefore, the dissolution profiles of brands C, D and F using the model independent approach of f_1 and f_2 are not similar with brand B and so may probably not be used interchangeably as shown in Table 6. Furthermore, the dissolution profiles of brands A and E are similar and most

Table 5. Dissolution data for the calculation of f_1 and f_2.

Reference (brand B)	Test 1 (brand A)	Test 2 (brand C)	Test 3 (brand D)	Test 4 (brand E)	Test 5 (brand F)
Time mean % SD	Time mean % SD	Time mean % SD	Time mean % SD	Time mean % SD	Time mean % SD
3 66.1 9.4	3 45.3 5.6	3 19.2 1.8	3 9.4 4.2	3 52.7 1.9	3 6.2 0.5
8 80.3 8.0	8 77.5 7.9	8 38.0 5.7	8 22.4 8.3	8 68.6 5.2	8 9.5 2.1
15 92.8 4.5	15 88.7 4.5	15 53.3 8.3	15 60.4 17.2	15 81.4 3.2	15 34.3 12.1
25 97.3 6.7	25 96.7 5.3	25 70.9 10.5	25 82.4 13.6	25 91.6 8.7	25 60.5 14.9
35 92.2 3.5	35 95.6 4.1	35 82.1 13.3	35 82.0 11.3	35 96.9 5.7	35 76.6 8.8
45 86.8 5.6	45 86.8 5.7	45 88.2 10.8	45 92.4 11.1	45 89.9 6.2	45 92.3 7.0
60 86.3 10.1	60 82.8 6.4	60 97.4 4.5	60 93.3 7.4	60 85.3 8.0	60 99.4 1.4
	f_1 = 4.7, f_2 = 53.9	**f_1 = 25.4, f_2 = 25.8**	**f_1 = 26.5, f_2 = 23.5**	**f_1 = 5.9, f_2 = 53.3**	**f_1 = 37.1, f_2 = 17.6**

probably bioequivalent with brand B and so may be used interchangeably.

Conclusion

Post-market monitoring is very crucial for effective clinical outcome and this study has emphasized that chemical equivalence does not indicate bioequivalence. Also one brand substituted on assumption of chemical equivalence with another brand may not give the desired onset of action and subsequent therapeutic effectiveness. Interestingly from this study, it was understood that price may not necessarily indicate the authenticity and effectiveness of a drug product. Brand E is sold at Nigerian equivalent of $1.25 but it is bioequivalent to brand B which is sold at about $12.50. Brands C, D and F are cheaper than brand B but may probably not be given interchangeably with brands A, B or E. However, to conclusively confirm that brands C, D and F may not be used interchangeably with brands A or B or E, in vitro dissolution test in three pH levels and probably in vivo test may be required.

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