



ISSN (E): 2277- 7695  
ISSN (P): 2349-8242  
NAAS Rating: 5.03  
TPI 2018; 7(9): 84-89  
© 2018 TPI  
www.thepharmajournal.com  
Received: 16-07-2018  
Accepted: 18-08-2018

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## Product quality assessment of brands of cefuroxime axetil tablets marketed in southern and western Nigeria

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### Abstract

The study evaluated some brands of cefuroxime axetil tablets (500mg) marketed in both southern and western Nigeria. Seven brands of the drug sourced from different retail outlets were assayed to assess the quality and bioequivalence of the tablets using the in-vitro release study. The brands were subjected to various official tests including uniformity of weight, disintegration and dissolution tests, hardness test and friability test as well as chemical assay. The results obtained revealed that all seven brands passed disintegration, friability and weight uniformity test and assay of active ingredient test. Furthermore, Brands AA, AE and AG failed the hardness test. In-vitro release study revealed that only brands AD and AF can be prescribed as therapeutic substitutes for the innovator brand from the results gotten from the similarity and dissimilarity factors calculation. This study further highlights the need for manufacturers to build quality into their products during manufacture and also maintain the built-in quality from batch to batch in accordance with the principles of c GMP.

**Keywords:** Cefuroxime axetil, quality and bioequivalence, in-vitro study

### Introduction

The essential drug concept emphasizes the availability of good quality drugs to patients at affordable price. Cefuroxime is an orally effective second generation cephalosporin. It acts by inhibiting cell wall synthesis by inhibiting the cross linking of peptidoglycan strands through a trans-peptidation reaction. Various brands of Cefuroxime are available on the Nigerian market. Which brand should be prescribed becomes a problem. Cost of the innovator brand or its irregular availability coupled with the need to adhere to current Drug Prescription Guidelines which emphasizes prescription of generics may demand its use or interchange for other different brands of the product.

When there is significant difference in the pharmacokinetic or even the pharmacodynamics properties of the substitute brands, the therapeutic goal may not be achieved. Several quality control tests, both official and non-official are usually carried out on the different brands of drug products (tablets) in order to assess its quality and thus its efficacy. Such tests include: Dissolution test, disintegration test, content uniformity, hardness test, friability test, tablet diameter and thickness, and organoleptic tests (Ofoefule, 2006) [4].

The different brands of cefuroxime, though containing the same active principle are manufactured differently by different manufacturers and thus the types, concentration and incorporation method of excipients may differ from one manufacturer to another, thereby altering the bioavailability and hence the therapeutic efficacy of the final products. All manufactured drug product must comply with current Good Manufacturing Practice (cGMP), as well as satisfy the standards of quality, efficacy and safety and must meet up to label claims of the manufacturers in order to be interchangeable in clinical practice.

The dissolution profile of a drug product shows the rate and extent of drug release from the dosage form. The rate of dissolution may thus be directly related to the efficacy of the tablet product as well as to the bioavailability differences between formulations.

Two objectives in the development of *in vitro* dissolution tests are to show:

- (1) That the release of the drug from the tablet is as close as possible to 100%
- (2) That the rate of drug release is uniform from batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective (Leon *et al.*, 2009) [3].

It was often assumed that consumers often purchase counterfeit and substandard drugs because

they were cheaper products and may even have attractive packaging (Lai *et al.*, 1999; U.S. Food and Drug Administration, 2007) [2]. However, subjecting the drug products to further re-evaluation from time to time could checkmate sharp practices of drug product counterfeiters, instil confidence in clinicians in their generic drug product choices and also enhance attainment of desired therapeutic end points in practice.

Cefuroxime is a second generation cephalosporin. Oral agent in this group is the axetil ester of cefuroxime. Cefuroxime axetil is the 1-acetoxyethyl ester of Cefuroxime. Chemically, cefuroxime axetil is (RS)-1-hydroxyethyl (6R, 7R)-7-[2-(2-furyl) glyoxyl-amido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo-Oct-2-ene-2-carboxylate, 72-(Z)-(O-me-thyl-xoime), 1-acetate-3-carbamate. Its molecular formula is C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>10</sub>S, and it has a molecular weight of 510.48 (Suthakaran *et al.*, 2013). While, Cefuroxime is chemically (1RS)-1-[(acetyl) oxy] ethyl-(6R, 7R)-3-(carbamoyloxy) methyl]-7-[(Z-2-furan-2yl)-2-(methoxy imino) acetyl] amino]-8-oxo-5-thia-1-aza bicycle-(4,2,0)-oct-ene-2-carboxylate-1-2. (USP & NF, 2000). After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime (Patric, 1995) [5].

## Methods

### Pharmacopoeial Tests

#### Physical Assessment

The packaging and labelling were examined very carefully to check for required information such as manufacturers address, manufacturing dates, batch numbers, expiry date, and amount of active ingredients, National Agency for Food and Drug Administration and Control (NAFDAC) Registration number. Tablet colour, shape, length, thickness, breadth and width were also determined carefully.

#### Tablet Weight Uniformity Test

Twenty tablets from each brand of the tablets were selected at random. The tablets were weighed together and the average weight of a tablet determined. The tablets were weighed individually and the deviations of the weights of each tablet from the average weight of a tablet were calculated. The percentage deviation of each tablet from the average tablet weight was calculated and the results compared to the standards in the BP.

#### Tablet Friability Test

Ten tablets were selected at random from each brand and an Erweka friability tester was used to carry out the friability test. These tablets were first de-dusted, weighed and subjected to a well-defined level of agitation in a fixed geometry closed chamber. After 4 minutes at 25rpm, the tablets were de-dusted and weighed and the difference between their original and final Weights was obtained. The percentage loss was calculated which is equal to the percentage friability and should not be more than 1 % which is acceptable for most tablets. Same was repeated for all other brands. Tablet friability was calculated using the formula below:

$$F = \frac{W_o - W_f}{W_o} \times \frac{100}{1}$$

Where W<sub>o</sub> = Initial weight of tablets, F = Percentage friability, and W<sub>f</sub> = Final weight of tablets

### Tablet Hardness Test

Ten tablets for each brand were randomly chosen. The hardness was singly determined using the Erweka hardness tester and the average hardness and standard deviations calculated. Tablet hardness of 9-15 kgf was considered acceptable for film coated tablets.

### Tablet Disintegration Test

Six tablets were taken from each brand and one tablet placed in each of the six cylindrical tubes whose lower ends were closed by a screen of 2mm nominal aperture. The bottom of the disintegration basket was at least 15mm below the surface of the water and the apparatus was made to operate. The time taken for each tablet to disintegrate was recorded and compared with the standard specified for coated tablets in the BP. The disintegration media used was 500ml of 0.1N HCl maintained at 37 ± 1<sup>o</sup> C and at 50 revolutions per minute.

### Dissolution Test

#### Preparation of Media Simulated Gastric Fluid.

Simulated gastric fluid (SGF) without enzymes was prepared by adding 8.5ml of concentrated hydrochloric acid to 1 litre of distilled water. In the dissolution test, the paddle method was used. The *in vitro* dissolution test was performed in simulated gastric fluid (SGF) without enzymes. 900ml of the media was used to ensure sink condition. Temperature was maintained at 37°C ± 1°C. One tablet of each brand was randomly chosen for evaluation. The tablet was placed in the dissolution media and 5ml sample withdrawn at intervals of 10, 20, 30, 40, 50 and 60 minutes respectively. 5ml of fresh dissolution medium was used to replace each of the withdrawn samples immediately. The withdrawn samples were filtered and absorbance determined using UV-Vis Spectrophotometer at 290nm wavelength.

#### Dissolution Efficiency (DE) and Predicted Availability Equivalent (PAE)

Dissolution Efficiency is an efficient method of evaluating drug release from a dosage form. It can be theoretically related to *in vivo* data, if it is assumed that the degree of absorption of a drug *in vivo* is proportional to the concentration of the drug in solution and the time this solution is in contact with a suitable absorptive region of the gastrointestinal tract.

Predicted Availability Equivalent is a modification of dissolution efficiency used to assess the *in vitro* performance of tablets (Osadebe *et al*; 2003).

Mathematically,

$$\text{Dissolution efficiency} = \frac{\text{Area under curve (AUC)}_{\text{brandx}}}{\text{Area under the curve (AUC)}_{\text{total time}}} \times \frac{100}{1}$$

$$\text{Predicted availability equivalent} = \frac{\text{AUC}_{\text{brandx}}}{\text{AUC}_{\text{innovator brand}}} \times \frac{100}{1}$$

#### Evaluation of Dissolution Rate

AUC is calculated using the trapezoid rule,

$$(\text{AUC}_{t_n - 1}) = \frac{C_{n-1} + C_n (t_n - t_{n-1})}{2}$$

Where t = time, C<sub>n</sub> = concentration at time t<sub>n</sub> and C<sub>n-1</sub> = concentration at time t<sub>n-1</sub>

$$\%PAE = \frac{AUC_{brand}}{AUC_{standard}} \times \frac{100}{1}$$

Where PAE = Predicted availability equivalence.

**Comparison of Dissolution Data:**

Difference factor (f<sub>1</sub>), similarity factor (f<sub>2</sub>) and dissolution efficiency (%DE) were calculated to compare the dissolution profile. Difference factor is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves.

The similarity factor 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. The following equations were used to calculate f<sub>1</sub> and f<sub>2</sub>.

$$f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \times 100$$

$$f_2 = 50 \log \left\{ \left( 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

Where n = number of time points, R<sub>t</sub> =dissolution value of reference product at time t and T<sub>t</sub> =dissolution value for the test product at time t. Similarity factor has been adopted by FDA (1997) [10], and the European Agency for the Evaluation of Medicinal Products (EMA, 2001) by the Committee for Proprietary Medicinal Products (CPMP) to compare

dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f<sub>1</sub> is between 0 and 15 and f<sub>2</sub> is between 50 and 100 (FDA, 1997) [10].

**Table 1:** Weight Uniformity of the Sampled Cefuroxime Axetil Tablet Brands

S/N	Brands	Brand code	Mean weight(mg) ± sd Sem	Standard deviation	% deviation	Remark
1	Kadnat®	AA	869.05 ±4.77	21.37	2.45	Passed
2	Spizef®	AB	937.45 ±1.75	7.84	0.83	Passed
3	Zinnat®	AC	916.10 ±1.76	7.89	0.86	Passed
4	Sefzital®	AD	1031.6 ±3.15	14.09	1.36	Passed
5	Microcef-500	AE	820.8 ±2.57	11.50	1.40	Passed
6	Axacef®	AF	870.80 ±6.02	26.96	3.09	Passed
7	Donacef-500	AG	1042.60±2.83	12.65	1.21	Passed

\*International Pharmacopoeia, 2007 specifies %deviation less than 5 for tablets that weigh 250mg or more.

**Friability Test of the Sampled Cefuroxime Axetil Tablet Brands**

All the seven brands demonstrated the acceptable % friability of less than 1% as specified by the British Pharmacopoeia 2009

**Hardness Test of the Sampled Cefuroxime Axetil Tablet Brands**

The Mean Hardness(KgF) of the different brands were as follows:

**Preparation of Cefuroxime Solutions for Calibration Curve**

Cefuroxime axetil Stock reference solution (1mg/ml) was freshly prepared from pure sample of cefuroxime axetil by dissolving 50mg in 50ml of methanol. For selection of analytical wavelengths, from stock solutions working solution of cefuroxime axetil 10mcg/ml where prepared in 0.1N HCl. (Game *et al.*, 2010) [1].

**Plotting of Calibration Curve**

Different aliquots of stock reference solution (1mg/ml) from 0.2-1ml were transferred into a series of 10ml standard flasks. The solutions were made up to volume with 0.1N HCl. The absorbance of each solution was measured at 290nm against the reagent blank. The calibration graph was constructed by plotting the absorbance versus concentration of the drug. The concentration of the unknown was computed from the regression equation (Game *et al.*, 2010) [1].

**Procedure for Analysis of Commercial Tablets**

Ten tablets were weighed accurately and milled into a fine powder. An amount of the powered tablet equivalent to 50mg of Cefuroxime axetil was weighed and transferred into a 50ml volumetric flask, 30ml of methanol solvent was added and sonicated for 15minutes and filtered using a Whatman filter paper. Then the volume was made up to the mark with the solvent. The assay of the tablets was carried out according to the general procedure (Game *et al.*, 2010) [1].

**Results and Discussion**

**Physical Assessment**

Physical assessment of the brands revealed that only one, (Donacef) was orange in colour. Others were white in colour, all film coated in blister packs with NAFDAC No. and Manufacturing and Expiry dates as would be expected

AA- 8.60; AB- 13.25; AC- 10.44; AD- 9.43; AE- 8.35; AF- 10.26 and AG- 16.49 meaning that AA, AE and AG failed the hardness test (BP 2009 specifies 9 – 15KgF as acceptable mean hardness for coated tablets).

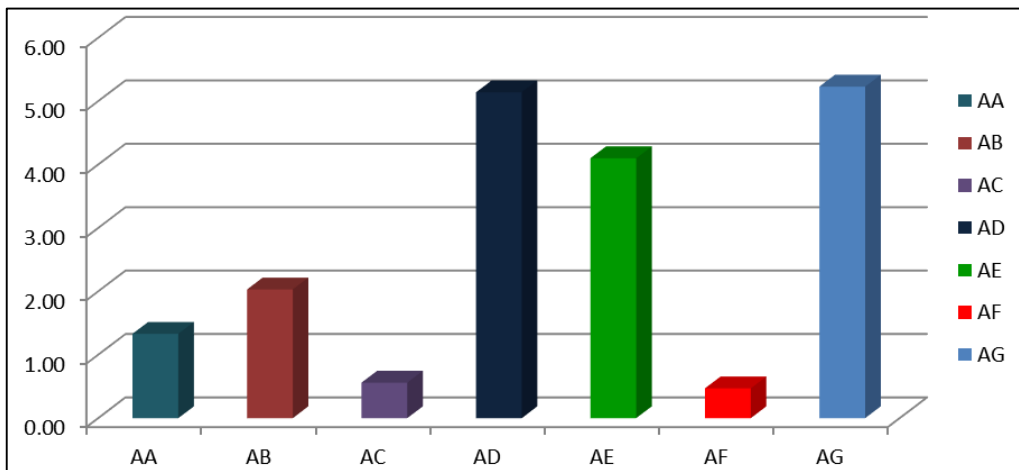


Fig: Mean disintegration time (Min) of the different brands

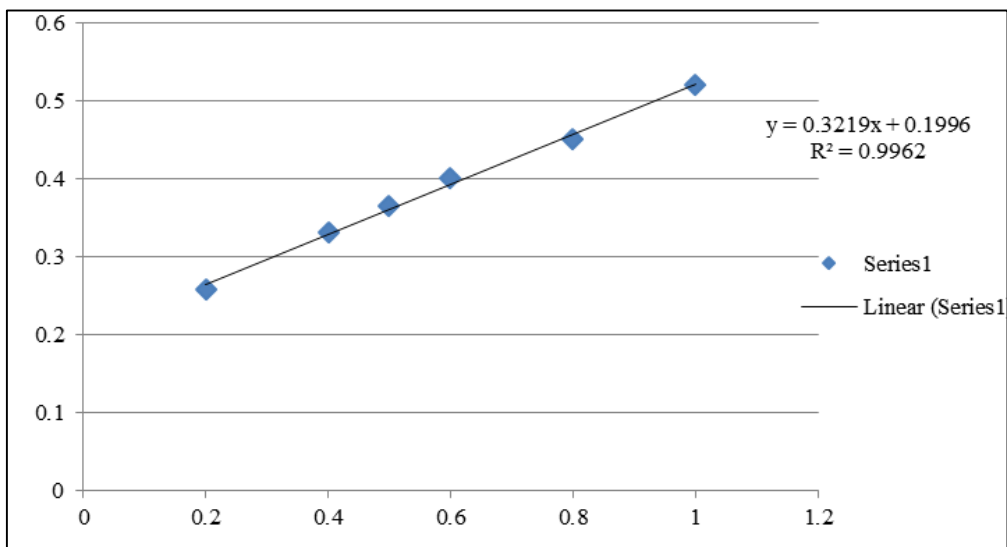


Fig 2: Calibration curve of Cefuroxime Axetil in 0.1N

**HCl Assay of Active Ingredients in 0.1N HCl**

Maximum wavelength of pure sample of Cefuroxime axetil in 0.1N HCl=290nm

From calibration curve,  
 $Y = 0.3219x + 0.1996$

Where Y = absorbance, X = concentration,  $K = 0.3219$  = slope. And Intercept = 0.1996

$$\text{Concentration} = \frac{\text{Absorbance} - \text{Intercept}}{K}$$

Content of drug in each tablet = concentration/label claim X 100

**Dissolution Profile in Simulated Gastric Fluid**

$$\text{Concentration} = \frac{\text{Absorbance}}{K}$$

$$Y = 0.3219x + 0.1996$$

$$K = 0.3219$$

Table 2: Concentration of drug dissolved in 0.1N HCl

Time(Minutes)	AA	AB	AC	AD	AE	AF	AG
10	0.052	0.055	0.053	0.052	0.160	0.062	0.104
20	0.313	0.277	0.289	0.285	0.214	0.283	0.207
30	0.365	0.332	0.368	0.337	0.294	0.335	0.311
40	0.406	0.431	0.399	0.373	0.427	0.335	0.363
50	0.350	0.434	0.534	0.462	0.419	0.515	0.403
60	0.521	0.553	0.525	0.518	0.534	0.515	0.518

Table 3: Percentage of Drug Released in Simulated Gastric Fluid (SGF)

Time(Mins)	AA	AB	AC	AD	AE	AF	AG
10	9.98	9.95	10.10	10.03	29.96	12.04	20.07
20	60.08	50.09	55.05	55.02	40.07	54.95	39.96
30	70.06	60.04	70.09	65.06	55.06	65.05	60.04
40	77.93	77.94	76.00	72.01	79.96	65.05	70.07
50	67.18	78.48	101.71	89.19	78.46	100	77.79
60	100	100	100	100	100	100	100

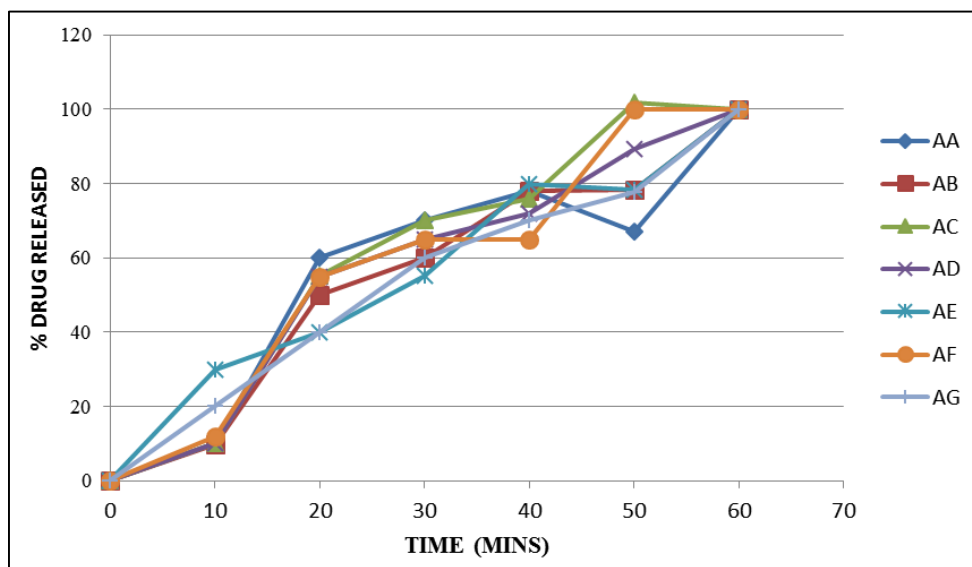


Fig 3: Dissolution Efficiency and % Predicted Availability Equivalent

Table 4: Fit Factor comparison

Pair Comparison	F <sub>1</sub>	F <sub>2</sub>
AC V AA	10.08	42.23
AC V AB	9.77	48.72
AC V AD	5.24	61.71
AC V AE	18.66	40.75
AC V AF	4.78	64.49
AC V AG	15.73	44.01

**Discussion**

Physical assessment of the different brands of cefuroxime axetil showed that all the brands sampled were white in colour, except for brand AG (Donacef-500) which was orange. The tablets all have manufacturer’s trade markings on their surfaces and were all oblong in shape. All the brands were also well packaged in blisters and properly labelled, with labels containing NAFDAC registration numbers, batch number, manufacturing date, expiry date and quantity of active ingredients written on both the primary and secondary packaging materials. The tablets of all seven brands were also found to be film coated. All the brands showed uniform shape with uniformity in their length, breadth and thickness.

The uniformity of weight test showed that the weight of each of the seven brands were within acceptable limits with slight deviation, less than ± 5% with brand AB having the best weight uniformity with standard deviation of 7.84 and percentage deviation being 0.83% and mean weight of 937.45mg.

The standard specification (USP NF: 2009) states that for tablets having an average weight ≤ 80mg; percentage deviation is ± 10%, tablets having an average weight > 80-250mg; percentage deviation is ± 7.5%, and those having an average weight of ≥ 250mg have percentage deviation to be ± 5%. The seven brands had different mean weights because the quantities and types of excipients used by the various manufacturing companies were different with the smallest being brand AE 820.80mg and the highest being brand AG 1042.60mg.

Tablet hardness affects the bioavailability of the active ingredient and thus affecting the overall therapeutic efficacy of the particular drug. If the tablet is too hard or is above the specified limits, it may not disintegrate in the required period of time and this affects the active ingredient bioavailability as

its release and absorption is not accomplished. The tablet may also be passed out in the faeces un- dissolved. And if the tablet is too soft, it will not withstand the handling during subsequent packaging and shipping causing breaking of tablet parts resulting in decreased amount of active ingredient formulated.

The hardness test though not an official test was also within acceptable limits for film coated tablets which is between 9-15kgf with the exception of brand AE having a mean hardness of 8.35kgf, brand AA mean hardness of 8.60kgf and brand AG mean hardness 16.49kgf.

The difference in hardness between the different brands could be attributed to the type and amount of binders, compressional force and the method of granulation used by the different companies during production. (Ofoefule, 2006) [4].

Friability is a property that is related to the hardness of the tablet and indicates the ability of the tablets to withstand agitation and also chipping or breakage during transportation. All the seven brands were within the acceptable limit for friability test which is ≤ 1% (BP, 2009). This implies there was no compromise with standard.

The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles. The British Pharmacopoeia (2009), disintegration test for coated tablets requires that tablets should disintegrate within 30 minutes. For tablets to pass the tablet disintegration test, six tablets selected at random from a batch of tablets should disintegrate within 30 minutes. All the brands disintegrated within 30 minutes and hence passed the disintegration test.

There was however a marked difference in the disintegration time of the tablets from the different brands. Tablets from brand AG had the highest disintegration time of 5.23 minutes and those from brand AF had the shortest disintegration time of 0.47 minute. The differences could be attributed to differences in excipients used in the manufacture of the tablets as well as differences in the manufacturing process.

According to the USP NF 2009, cefuroxime tablets labelled to contain the equivalent of 500mg of cefuroxime, not less than 50% of the labelled amount of cefuroxime axetil should be dissolved in 15minutes and not less than 70% dissolved in 45minutes. In view of this, only brand AA did not release up to 70% of its active ingredient in 50 minutes. This could be

attributed to the quantity and quality of excipients used in its production.

For comparison of *in-vitro* dissolution profiles, similarity and difference factors are emphasized by US FDA. As the name implies, similarity factor ( $f_2$ ) stresses on the comparison of closeness of two comparative formulations. The  $f_2$  parameter is commonly used to establish similarity of two dissolution profiles. Dissimilarity factor focuses on the difference in percent dissolved between reference and test at various time intervals.  $F_1$  factor is used to calculate the approximate % error in drug release profile. Hence  $f_2$  factor was used as a tool to compare the dissolution profiles and  $f_1$  the difference factor. As per the US FDA the  $f_2$  values were achieved at 61.71% and 64.49% and the difference factor of about 5.24 and 4.78 which is closer to zero were achieved. This however shows that brands AD and AF lie within acceptable range. From the fit factor (Table 4),  $f_1$  was found to be 5.24 and 4.78 for brands AD and AF indicating that they both do not vary much from the innovator brand (Zinnat). Similarly the  $f_2$  was found to be 61.71 and 64.49 which indicate that the test brands are similar to the reference innovator brand. Thus it can be inferred that the dissolution profiles of both brands AD, AF and the innovator brand are similar.

According to the United State Pharmacopoeia, cefuroxime axetil tablets should contain not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime (as cefuroxime axetil). Uniformity in the content of cefuroxime axetil tablets is to ensure a constant dose between individual tablets, hence a predictable bioavailability. Results showed that all the brands of cefuroxime axetil tablets contained amounts of cefuroxime that conformed to the required amounts as stated in the USP 32/ NF 27. The brands AA, AB, AC, AD, AE, AF, and AG had their percentage contents of cefuroxime of 103.68%, 101.80%, 99.92%, 101.80%, 106.16%, 104.92%, and 102.43% respectively. This indicates that they can be efficacious against microorganisms susceptible to cefuroxime.

### Conclusion

This work was able to assess the tablet properties of seven commercial brands of cefuroxime (as cefuroxime axetil, 500mg) tablets. They all conformed to the friability test, disintegration time test and weight uniformity test but not all conformed to the hardness test. All the brands were found within acceptable limit for cefuroxime in the assay of the labelled claim of their active ingredients. However, only brands AD (Sefzital) and AF (Axacef) could be considered bioequivalent with the innovator brand (AC, Zinnat) meaning that only these two brands can be used interchangeably in clinical setting with Zinnat amongst the brands studied.

### Recommendation

Other Cefuroxime axetil 500mg brands not covered in this study could as well undergo similar evaluation. Further *in-vivo* bioequivalence study after an *in-vitro* release study on cefuroxime tablets in healthy individuals would add more scientific value to the investigation.

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