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Quality Assesment/ *in Vitro* Bioequivalence Consideration of Some Sustained Release Diclofenac Sodium Tablets in the North Central Senatorial Zone of Nigeria

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Abstract

There is need for cross-substitution of sustained release diclofenac sodium tablets in Nigeria for better patient compliance. The *in vitro* bioequivalence of these products could be probed through determination and comparison of their drug release profiles and mechanisms/ kinetics of drug release which is the aim of this study. Five brands of sustained release diclofenac sodium tablets were purchased from the North Central Senatorial Zone of Nigeria. The tablets were evaluated for batch number, NAFDAC number, expiration date, weight uniformity, hardness, drug content, drug release profile and *in vitro* drug release mechanisms / kinetics. All the tablets had batch numbers, NAFDAC numbers and had not expired. Brands A, B and E tablets complied with the compendia standards for weight uniformity while brands C and D failed. The five brands had hardness values ranging from 4.1 – 5.4 Kgf. The friability of all the tablets were less than or equal to unity except for brand D tablets that had friability of 2.4 %. Brand A tablets released up to 100 % of drug content at 6 hours and brands B, C and D had 50 – 60% drug release after seven hours while brand E tablets released 100% of drug content within 30 minutes. The release profiles of the tablets were dominated by the Higuchian release kinetic which is diffusion controlled except brand E tablets whose drug release kinetic is anomalous. The mechanism of drug release for all the brands was dominated by the super case II transport with *n*-value greater than 0.89. The f_2 similarity determination of drug release profiles revealed that brand B drug release profile is similar to that of brand C and brand C is similar to brand D. The above results strongly suggest a possible bioequivalence between brand B, C and D tablets and so, they could be interchanged during therapy.

Keywords: *Diclofenac Sodium, Sustained Release, in Vitro Bioequivalence, Pharmaceutical Equivalence.*

I. INTRODUCTION

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID), which is very effective in the management of pain, inflammation and stiffness caused by many conditions such as osteoarthritis, rheumatoid arthritis, abdominal cramps associated with menstruation, and ankylosing spondylitis.[1] Norvartis Pharmaceutical Company is the innovator company that introduced Cataflam® (diclofenac potassium) and Voltaren® (diclofenac sodium) into the market. Years later, many generics containing diclofenac became available which were cheaper than the innovator brands and also provided prescribers and users with many alternatives. However, different clinical responses to these generics from different manufacturers have been documented. [2] These responses may be due to some differences in active ingredients, excipients (such as binders and disintegrants), and formulation process, packaging and storage conditions. Varied clinical responses in products of the same drug are also dependent on the level of in-process quality control observed by the manufacturers from the point of raw material purchase to when the tablets are packaged and distributed.[3] [4]

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Diclofenac sodium tablets are of different types which include the following; the conventional tablets, the prolonged/slow/sustained release tablets (or retard tablets) and delayed release tablets. The sustained release diclofenac sodium tablets containing 75mg or 100mg are administered as once daily to guarantee less frequent dosing and diminished occurrence of gastro-intestinal side effects. [5] Different types of diclofenac sodium tablets have different release mechanisms and kinetics. The factors that influence drug release from sustained release matrix systems include drug-related factors such as drug solubility, dose/drug content, molecular weight and size, drug particle size and shape and polymer-related factors such as polymer type, polymer viscosity grade, polymer proportion, polymer combination and polymer particle properties. [6]

Many generic versions of diclofenac sodium tablets by different manufacturers and from different countries exist today in Nigeria therefore there is need to investigate their compliance to the required standards as specified in the pharmacopoeia. [4] For a tablet to be considered satisfactory, it must pass certain test as contained in the pharmacopoeia. These tests include uniformity of weight, uniformity of drug content, hardness, friability, dissolution and disintegration time. [7] The aim of this work is therefore to investigate the conformation of different brands of sustained release enteric coated diclofenac sodium tablets to stipulated official test and determine whether the brands are pharmaceutically equivalent (through *In vitro* bioequivalence test) and interchangeable. The interchangeability between different brands of a drug is based on the concept of therapeutic equivalence between them, usually provided by evidence of pharmaceutical equivalence. [8][9]

II. MATERIALS AND METHOD

➢ *Materials*

One hundred tablets of each of the five brands of sustained release diclofenac sodium tablets.

➢ *Method*

- *Hardness Test*

The hardness of 10 tablets chosen at random from each of the batches after storing at ambient temperature for 24 hours was determined in a hardness tester (Erweka, Model TBH - 28). The mean hardness was calculated. [10]

- *Frialbility*

Previously weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rotations per minute (rpm) for 4 minutes. Then the tablets were dusted and reweighed and the percentage of powder eroded (percentage loss) during 4 minutes was calculated using the formula below. [10]

$$\text{Friability} = \left[\frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}}\right] \text{x100}$$

- *Uniformity of Weight*

Twenty tablets were randomly selected and weighed individually, as well as together. The total weight of the 20 tablets was then divided by 20 to calculate the average tablet weight. The percent weight deviation for each tablet was calculated following the official method. [10]

- *Drug Content of the Tablets*

Five tablets were ground into a fine powder using a mortar. An amount of the powder equivalent to 50 mg of the drug was placed in a 100 ml round-bottom flask, and 20 ml of phosphate buffer (pH 7.0) was added for extraction over 30 minutes. Appropriate dilutions were made, and the absorbance was measured at 262 nm against a blank solution. [7]

- *Dissolution Test*

A 900 ml volume of phosphate buffer (pH 6.8) was prepared as the dissolution medium. The specified volume of the medium, ensuring it was free of dissolved air, was added to the apparatus vessel. The dissolution medium was then heated to a temperature between 36.5°C and 37.5°C. The tablet was allowed to settle at the bottom of the vessel before the paddle started rotating. A wire helix was used to ensure the tablet remained horizontal, preventing it from floating. Air bubbles on the tablet's surface were removed. A sample was taken from the surface of the dissolution medium, and its absorbance was measured using a spectrophotometer, as outlined in the standard monograph. This procedure was repeated five times, and the percentage of the dissolved active ingredient in the solution was calculated based on the initial amount. [7]

- *Comparison of Drug Release Profiles*

The $\boldsymbol{f_2}$ similarity factor values were used to compare the drug release profiles of the various batches of diclofenac sodium sustained release tablets with that of the reference standard (voltaren) and with each other. The $\boldsymbol{f_2}$ values for the comparison were obtained by using the formula:

$$\boldsymbol{f_2} = 50 \text{ Log } \{ [1 + (\tfrac{1}{n})] \textstyle\sum_{t=1}^{n} [(R_t - T_t)^2]^{-1/2} \times 100\}$$

Where $\boldsymbol{f_2}$ = Similarity and $\boldsymbol{f_2}$ values of 50 – 100 shows similarity

n = Number of time points or samplings.

R_t = Cumulative percentage drug release of the reference product at time (t).

T_t = Cumulative percentage drug release at time (t).

➢ *Determination of Drug Release Kinetics*

- *Zero-Order Release Kinetics*

The zero-order kinetic model was represented using the equation:

$$Q = Q_0 + K_0 t$$

where Q is the amount of drug released or dissolved (assuming rapid release following dissolution), Q_0 is the initial drug concentration in solution (typically zero), and K_0 is the zero-order release constant. [11]

For zero-order kinetics, plotting the amount of drug released against time produces a straight-line graph.

- *First-Order Release Kinetics*

The first-order kinetic model was described using the equation:

$$dC/dt = k (Cs – Ct)$$

where dC/dt represents the rate of concentration change over time, and k is the rate constant. The integrated form of the equation is:

$$\ln [Cs / (Cs – Ct)] = kt$$

or

$$\text{Log } C = \text{Log } C_0 – (kt / 2.303)$$

where C_0 is the initial drug concentration, and k is the first-order rate constant. [11]

- *Hixson-Crowell Cube-Root Model*

The Hixson-Crowell model was applied using the following equation:

$$Q_0^{\wedge} (1/3) – Q_t^{\wedge} (1/3) = K\_HC\ t$$

where Q_t represents the amount of drug released at time t, Q_0 is the initial drug content in the tablet, and K_HC is the rate constant for the Hixson-Crowell equation. A graph of the cube root of the percentage of the drug remaining in the matrix against time was plotted. [12]

- *Higuchi Model*

The Higuchi model was analyzed using the equation:

$$\text{Log } Q = \log K\_H + (1/2) \log t$$

where Q is the amount of drug released per unit area at time t, C is the initial drug concentration, C_s is the drug solubility in the matrix medium, and K_H represents the Higuchi dissolution constant. [13]

- *Korsmeyer-Peppas Model*

The Korsmeyer-Peppas model was expressed using the equation:

$$\mathbf{M_t / M\infty = Kt^n}$$

where $\mathbf{M_t / M\infty}$ is the fraction of the drug released at time **t**, **K** is the rate constant, and **n** is the release exponent. The **n** value helps characterize different drug release mechanisms. [14]

- *Data Analysis*

The collected data were analyzed by calculating the mean, standard deviations, and percentage deviations.

III. RESULTS

➢ *Identification Properties of Brands A – E*

The different identification requirements of the different brands of diclofenac sodium tablets are represented in table 1 below.

Table 1 Identification Properties of Five Brands of Sustained Release Diclofenac Sodium Tablets

Brand Code	Strength (mg)	Brand name	Batch number	Mfg. date	Expiry date	NAFDAC Reg. No
A	100	Voltaren	S0159	10/2015	09/2020	04-0033
B	100	Clofenac	BG07529	01/07/2016	30/06/2019	04-3211
C	100	Bentren SR	N-1172	02/2015	01/2018	04-3712
D	100	B-fenac	DBK 16101	03/2016	02/2019	B4-2140
E	100	Betaren dexcel	1312039	12/2013	12/2018	04-38877

NAFDAC - National Agency for Food and Drug Administration and Control
Reg. No – Registration Number, Mfg. date – Date of Manufacture.

Table 2 Weight Uniformity

Brand Code	Mean weight(mg)± standard deviation	No. of tablets within the BP range	No. of tablets outside the BP range
A	300.40±2.70	19	1
B	211.25±2.90	19	1
C	326.10±9.31	12	8
D	358.00±5.44	14	6
E	332.50 ±4.73	18	2

Table 3 Hardness and Friability

Brand name	Hardness (Kgf)	Friability (%)
A	5.44±0.27	0.067
B	4.87±0.38	0.680
C	4.1±0.41	0.560
D	4.16±0.44	2.400
E	4.72±0.39	0.093

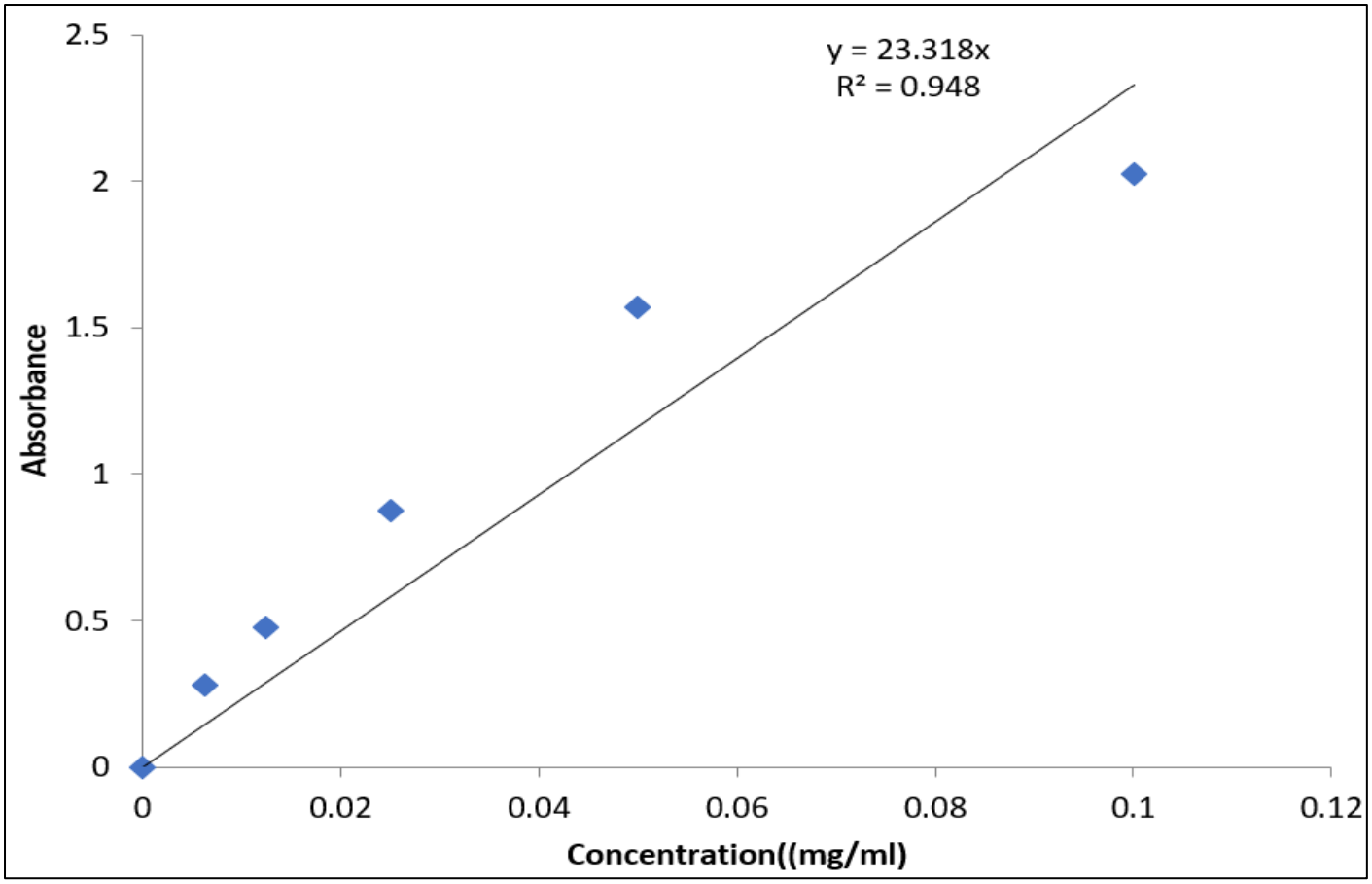

Fig 1 Beer Lambert's Plot of Diclofenac Sodium in Phosphate Buffer of Ph 7

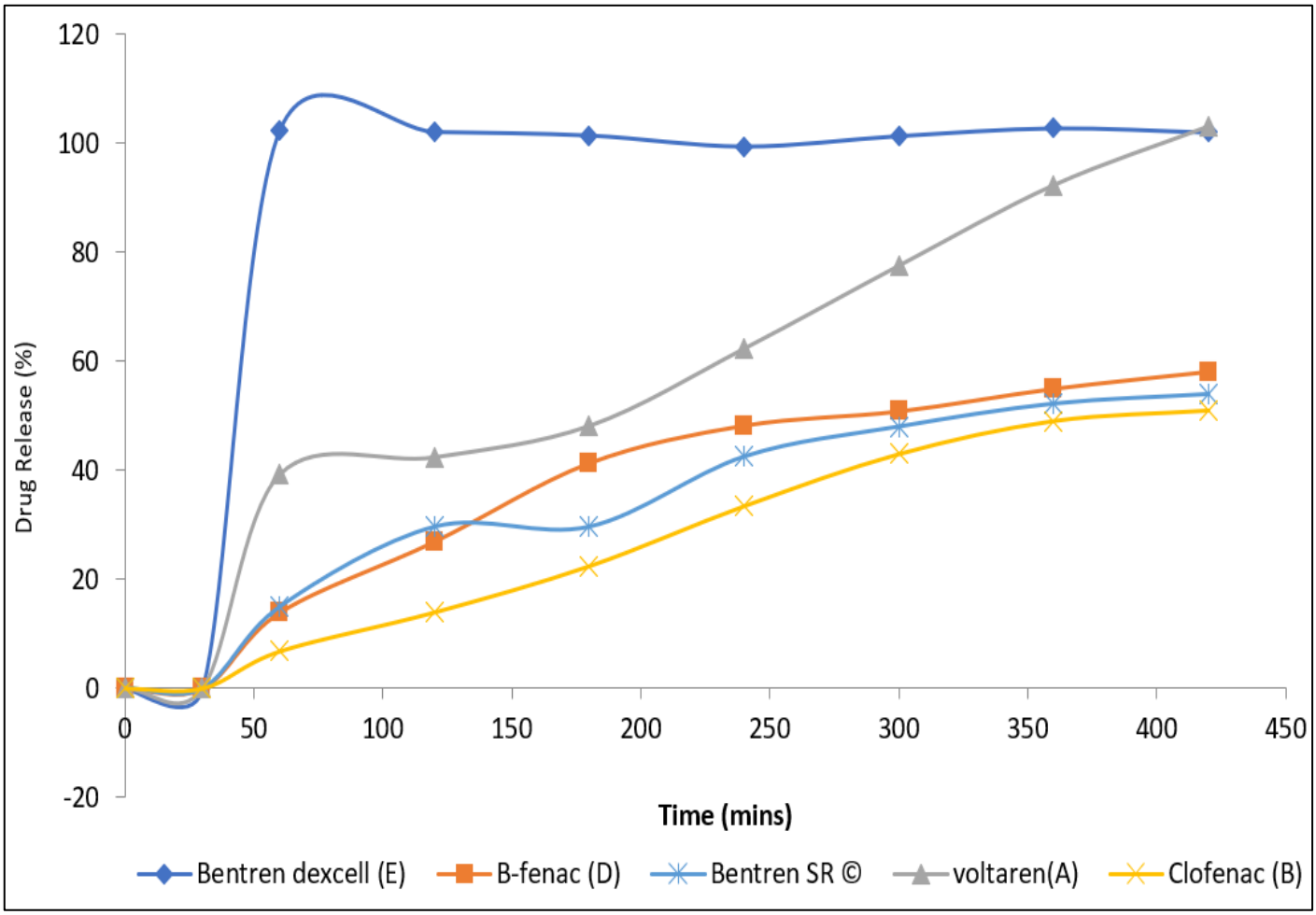

Fig 2 Comparative Dissolution Profile for All Five Brands of Sustained Release Diclofenac Sodium Tablets

➢ *In Vitro Drug Release Kinetic Modeling of the Dissolution Profiles of Diclofenac Sodium from Brands A – E*

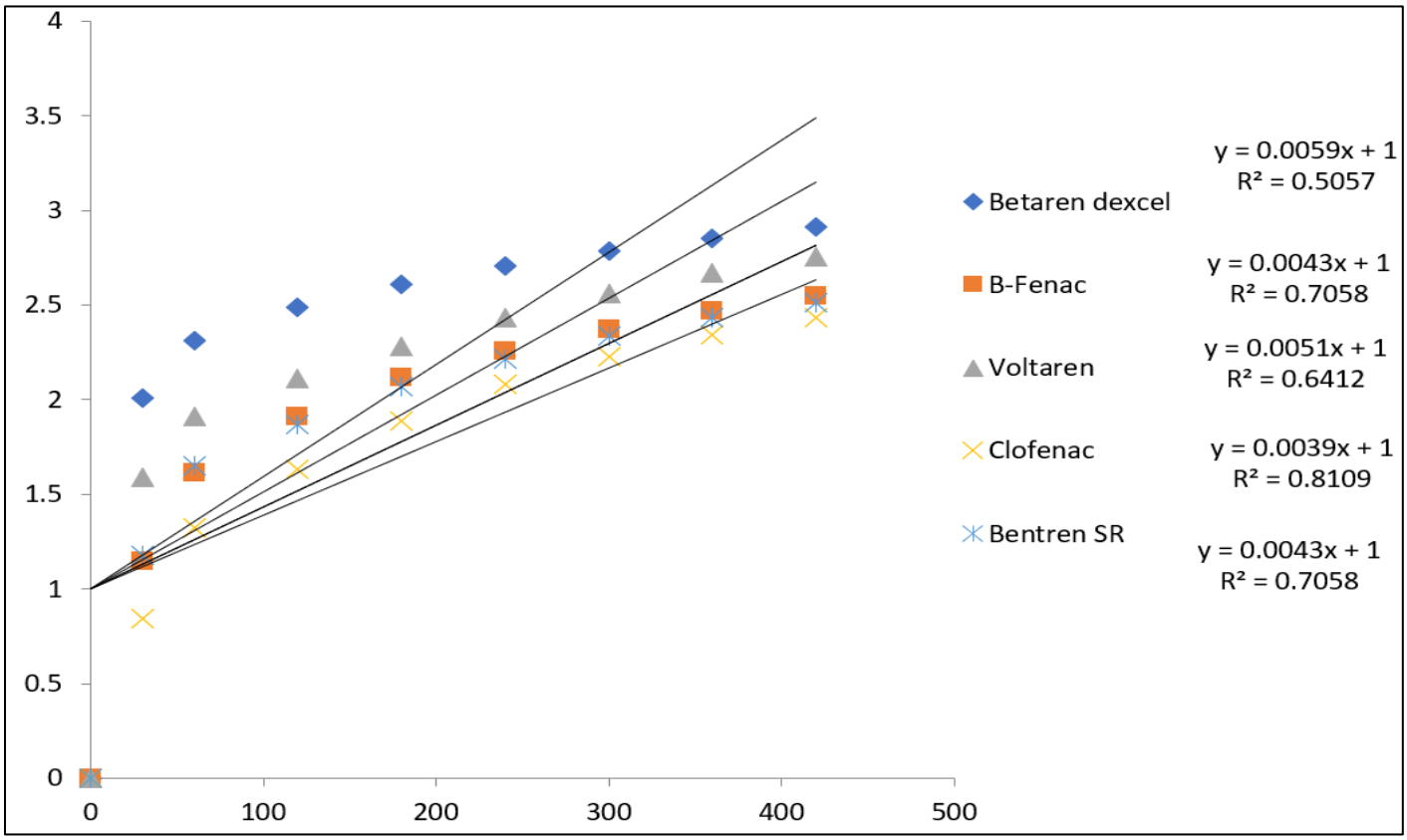

Fig 3 First Order Drug Release for Brands A-E

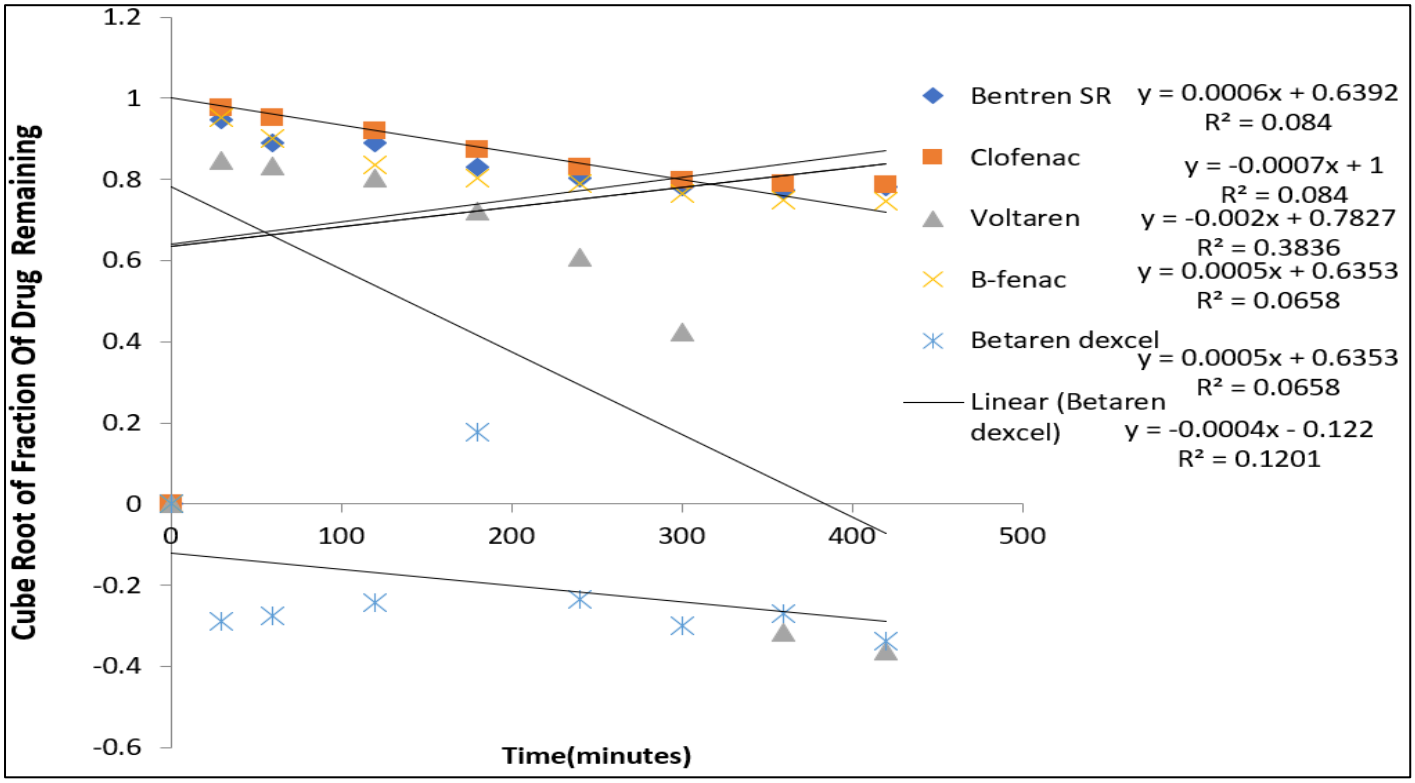

Fig 4 Hixon-Crowell Cube Root Plot for Brands A-E

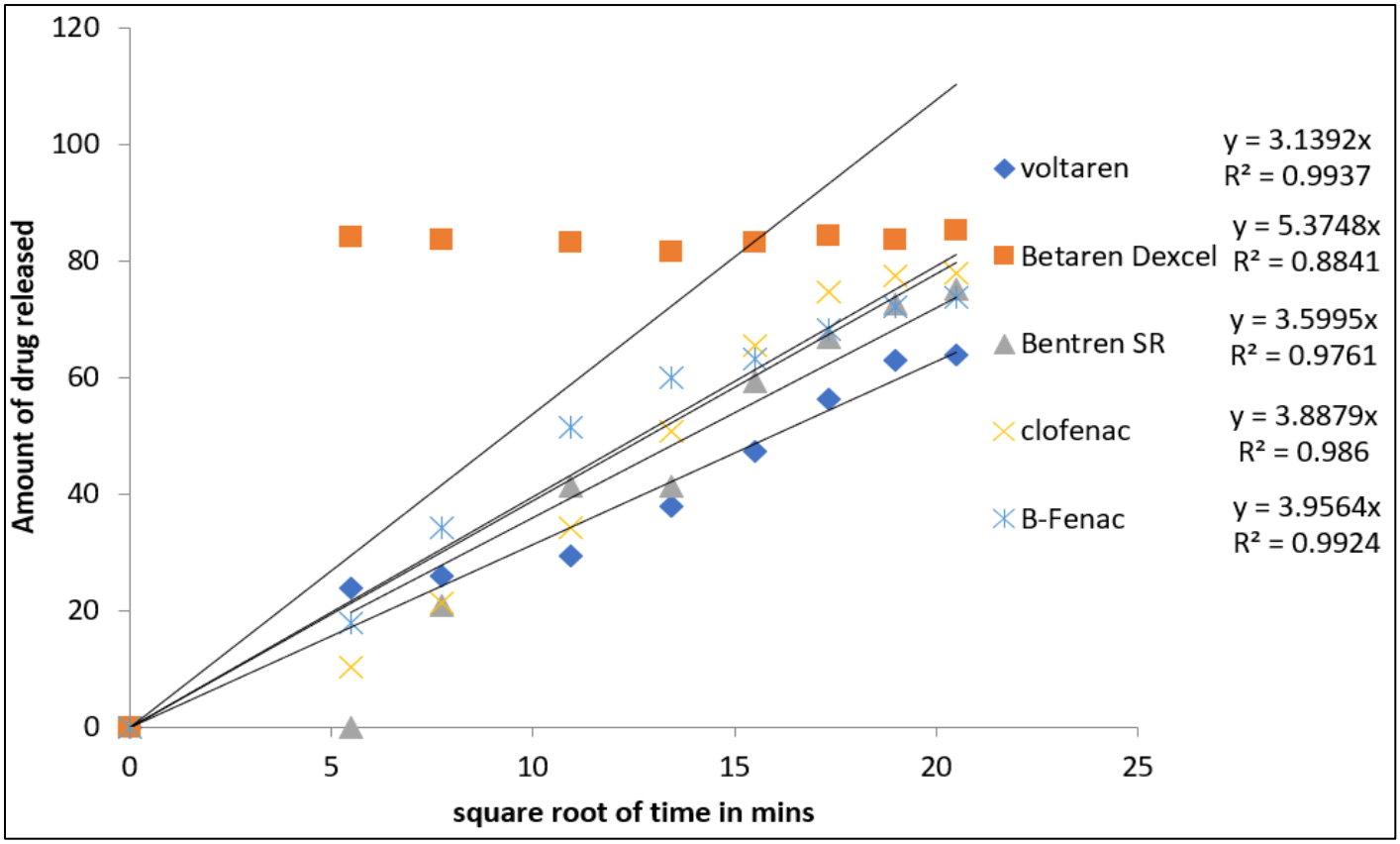

Fig 5 Higuchi's Plot for Brands A-E

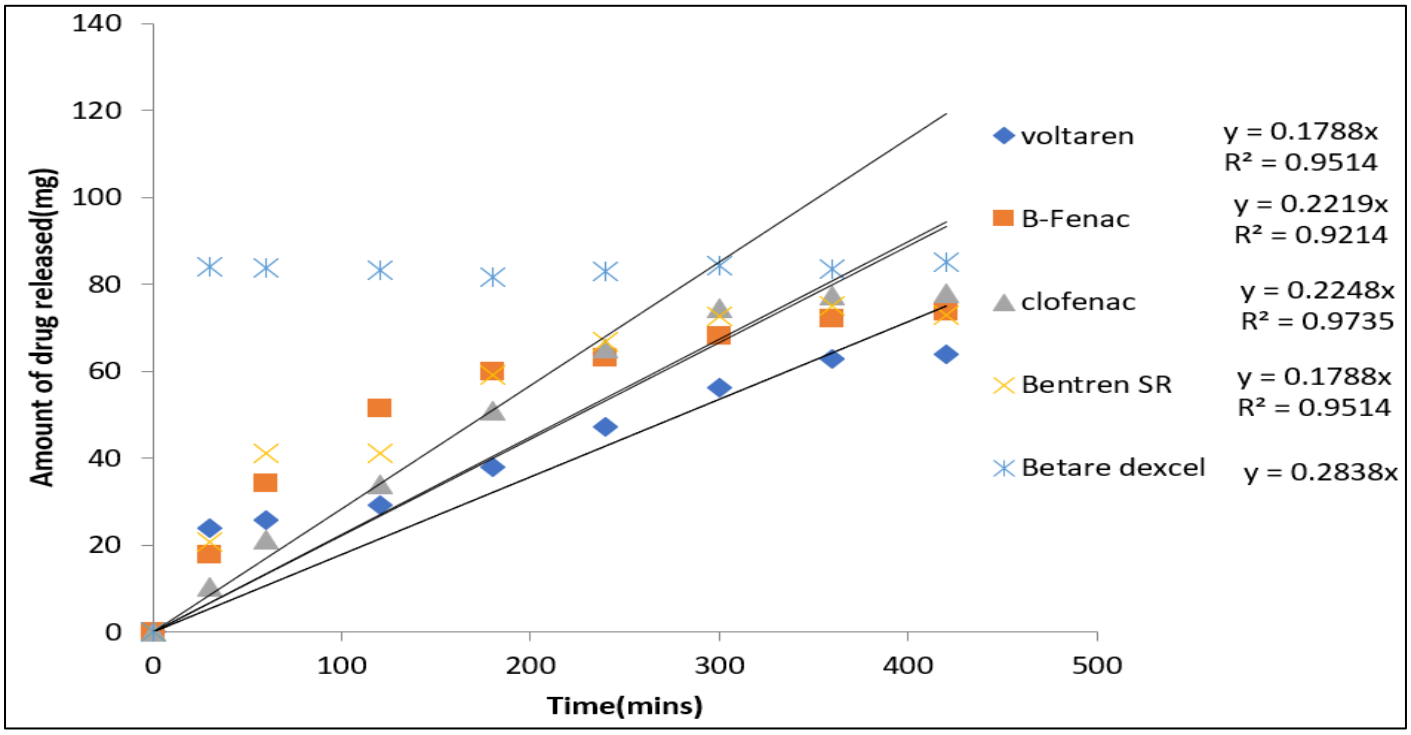

Fig 6 Zero Order Plot for Brands A-E

Table 4 Kinetics of Drug Release for Brands A-E

Batch (Brand)/ Models	Zero order kinetics		First order kinetics		Higuchi kinetics		Hixson-Crowell kinetics		Korsemeyer Peppa's (power law) Plot	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	*n*-value
A	0.768	0.178	0.251	0.002	0.970	3.193	0.305	-0.002	0.997	1.027
B	0.905	0.224	0.173	0.001	0.950	3.887	-.042	-0.000	0.950	0.947
C	0.600	0.226	0.705	0.004	0.952	4.027	-0.55	-0.000	0.979	0.975
D	0.608	0.221	0.097	0.001	0.962	3.956	-0.60	-0.000	0.988	0.985
E	-1.44	0.283	0.000	1E-05	-0.04	5.374	-17.2	-0.004	0.975	1.085

Table 5 Analysis of Dissolution Profile (Similarity, f_2)

DETERMINATION	f_2 VALUE
A/B	21.34
A/C	24.53
A/D	26.92
A/E	20.94
B/C	55.03
B/D	47.44
B/E	8.35
C/D	62.27
C/E	10.75
D/E	11.92

IV. DISCUSSION

➢ *Product Identification and Documentation*

The sustained-release diclofenac sodium tablet brands listed were properly labeled with batch numbers, manufacturing and expiration dates, NAFDAC registration numbers, and manufacturer details. This confirms the authenticity and traceability of these products.

➢ *Weight Uniformity*

Weight uniformity serves as an indicator of good manufacturing practices (GMP) and ensures consistent levels of the active ingredient, diclofenac sodium, in each tablet. According to B.P. 2010 guidelines [7], tablets weighing over 250 mg should not deviate from the average weight by more than ±5% for more than two tablets, and no single tablet should exceed ±10%. As shown in Table 2, only brands A, B, and E met this requirement. Brands C and D did not comply, with six and eight tablets, respectively, falling outside the acceptable weight range (321-331 mg and 353-363 mg).

➢ *Hardness*

Tablet hardness assesses a tablet's ability to withstand handling without breaking or chipping and influences properties such as friability, disintegration, and dissolution. A minimum force of 4 kg is considered acceptable for tablet hardness. The results (Table 3) show that all brands had hardness values above this threshold. Brand C had the lowest hardness (4.1 kg), while Brand A had the highest (5.438 kg), as determined by the Monsanto hardness tester. Therefore, all brands met the BP requirements for hardness. [7]

➢ *Friability*

Friability testing evaluates a tablet's resistance to abrasion, with the BP standard specifying a maximum friability of 1%. All tested brands had friability values within or below this limit, except Brand D, which recorded a friability of 2.4% (Table 3). This suggests that brands A, B, C, and E complied with the standard, whereas Brand D failed. The high friability of Brand D may be attributed to inadequate binder concentration or low compression pressure during manufacturing, leading to weak inter-particle bonding.[4]

➢ *Active Ingredient Content*

The assay results indicated that none of the brands met the BP and USP specifications for drug content, which require the active ingredient concentration to be within 90%–110% of the labeled amount. Consequently, these diclofenac sodium sustained-release tablets did not comply with official pharmaceutical standards wih regards to content of active ingredient.

➢ *Dissolution Studies of Diclofenac Sodium in Brands A–E*

The dissolution test determines the rate at which a drug is released in a given medium over time. Results (Figure 2) showed that Brand A achieved complete drug release (100%) at 420 minutes. Brands B, C, and D exhibited similar dissolution profiles, with drug release rates of 51%, 52%, and 55% after seven hours (420 minutes). However, Brand E displayed 100% drug release at 30 minutes, suggesting it is more likely an immediate-release formulation rather than a sustained-release tablet, contrary to its labeling. Further analysis using the model-independent f_2 similarity factor confirmed that the dissolution profiles of Brands B and C were similar, as well as those of Brands C and D. The dissolution profile of Brand B also closely resembled that of Brand D, with an f_2 value of 47 (Table 5). [7] It is also amazing that none of the brands had dissolution profile similar to that of the innovator which could be a pointer to differences in formulation materials and processes.

Comparing the *In vitro* dissolution data with *In vivo* drug therapeutic serum levels, it is worthy to note that the therapeutic serum level of diclofenac sodium in humans ranges from 0.5 to 2 μg/ml reaching peak plasma levels within 1-2 hours after oral administration. The dissolution data revealed that all the tablet batches released between 6.81mg to 100mg (6,810 – 100,000μg) within 60 minutes. If there is complete *In vivo* drug absorption and considering an adult blood volume of 6 liters (6,000 ml), the diclofenac sodium will achieve a serum blood concentration of 1.14 to 16.70 μg/ml. Remembering that the serum toxic levels for diclofenac sodium is >10 μg/ml, it implies that brand E which will generate such serum drug level may not be very safe. But we must remember that this dose will be released over one-hour wih attendant metabolism and excretion by the body and so, it may be difficult to reach toxic serum level. That not withstanding, diclofenac sodium is 99.7% protein bound, primarily binding to albumin The remaining drug in the tablet matrix serve to maintaining therapeutic serum levels for effective pain control. Based on the above *In vitro - In vivo* correlation, it can be said that all the

brands would be very suitable for immediate and sustained pain management. [15]

➢ *In Vitro Drug Release Kinetics*

Drug release kinetics analysis showed that Brands A and B primarily followed the Higuchi diffusion-based model, with some correlation to the zero-order kinetic model. This suggests that drug release is largely diffusion-controlled but it could be said that the rate of diffusion is fairly uniform. Similarly, Brands C and D followed the Higuchi model but also exhibited traces of zero-order and first-order kinetics (for Brand C) and only zero-order kinetics (for Brand D). The coexistence of multiple kinetic models may be due to differences in tablet matrix structure and composition, making them heterogeneous systems. Across all brands, drug release was predominantly governed by the Super Case II transport mechanism, characterized by an *n*-value greater than 0.89. Additionally, none of the brands followed the Hixson-Crowell cube root law, which is based on erosion-controlled drug release. [14] Brand E has no defined release kinetic since the release profile was more of immediate release tablet.

V. CONCLUSION

Brands A, B, and E complied with the compendial standards for weight uniformity, whereas Brands C and D did not. All brands exhibited satisfactory hardness, while only Brands A, B, C, and E met the friability standard, with Brand D failing. The dissolution profile of the tablets was primarily governed by the Higuchi diffusion model, except for Brand E, which demonstrated an unexpected release pattern. The dominant drug release mechanism across all brands was Super Case II transport. The f_2 similarity analysis revealed that the dissolution profiles of Brands B, C, and D were comparable, indicating potential bioequivalence. As a result, these brands may be interchangeable in clinical therapy.

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