

Evaluation of Pharmaceutical and Chemical Equivalence of Selected Brands of Diclofenac Sodium Tablets

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There is the need to subject different brands of the same drug to physicochemical tests to determine their pharmaceutical and chemical equivalence and the possibility of substituting brands and generics, while achieving the same therapeutic effect. Hence, this work was done to determine the variations in the properties of five brands of enteric coated slow release diclofenac sodium tablets. The brands were subjected to standard physicochemical tests. The results from the generics were compared to those of the innovator brand with reference to official standards. All the brands passed the chemical tests for drug content with a range of 98.1 to 100.76% w/w diclofenac sodium content. The innovator brand passed all the other tests, while the generics passed some tests but failed others. There were significant differences ($p < 0.05$) in the values obtained for uniformity of weight and friability tests for all the brands. No significant differences were observed for crushing strength and disintegration tests. The results showed that the brands are chemically but not physically equivalent. The generic brands could neither be substituted for each other nor for the innovator brand to achieve the same therapeutic effects.

Key words: Tablet release properties, pharmaceutical equivalence, diclofenac

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. Novartis Pharmaceutical Company is the innovator company that introduced Cataflam[®] (diclofenac potassium) and voltarol[®] (diclofenac sodium) into the market. Some years later, many generics containing diclofenac became available, which were much cheaper than the innovator brands and also provided prescribers and users with many alternatives. However, variable clinical responses to these drug products from different manufacturers have been documented [1]. These responses may be due to some differences in active ingredients, excipients (such as binders and disintegrants), 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.

Many generic versions of diclofenac tablets by different manufacturers and from different countries exist today in Nigeria and hence the need to investigate their compliance to the required standards as specified in the pharmacopoeia. For a tablet to be considered satisfactory, it is not enough for it to be elegant and firm to withstand handling; it must pass certain tests as contained in the pharmacopoeia. These tests include uniformity of weight, uniformity of drug content, hardness, friability, dissolution and disintegration time [2].

The aim of this work is therefore to investigate the conformation of different brands of slow release enteric coated diclofenac sodium tablets to stipulated official tests and determine whether the brands are pharmaceutically equivalent.

MATERIALS

One hundred (100) tablets of each of five different brands of slow release enteric-coated

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diclofenac sodium (100 mg) tablets were used for the study. The drugs were purchased from Lagos and Shagamu, located in South-West area of Nigeria. Product information is documented in Table 1.

EXPERIMENTAL

Identification test

Identification test was carried out for all the brands using the procedure stated in British Pharmacopoeia [2].

Determination of uniformity of weight

Twenty tablets (20) were selected randomly from each brand and weighed on an analytical top-loading balance (FA 2104A). The weight variation of each brand was determined using the average weight of the 20 tablets. The standard deviation for each brand was determined.

Determination of uniformity of content

Twenty (20) tablets from each brand were randomly selected, weighed on the analytical balance and then crushed into powder in a ceramic mortar and pestle. A 0.25 g aliquot of the powder was weighed and dissolved in 30 ml glacial acetic acid. This was titrated with 0.1 M perchloric acid with crystal violet as the indicator and the end point determined potentiometrically [2].

Crushing strength

The crushing strength of tablets was determined at room temperature by diametrical compression [3] using a tablet hardness tester (Model EH01, DBK Instrument, Mumbai, India). The tablet was placed between the platen of the tester and the adjustable knob was screwed, to make contact with the tablet. Enough pressure was applied to cause tablet breakage. Results were taken only from tablets which split cleanly into two halves without any sign of lamination. Ten (10) tablets

from each brand were tested and all measurements were made in quadruplicate.

Determination of tablet friability

Ten (10) tablets from each brand were weighed and carefully placed in a friabilator (DBK Instrument, England, 40 FTA01). The friabilator was operated at a rate of 25 revolutions per minute for 4 min, with the tablets falling through a height of 6 inches at each turn. The tablets were dusted, final weight taken, and the percentage loss in weight calculated.

Tablet disintegration test

Disintegration test apparatus (DBK Instrument, England, 40 TDA01) containing 0.1 M HCl and thermostatically maintained at $37\pm 0.5^{\circ}\text{C}$ was used. Six (6) tablets from each brand, placing one per tube, were tested at a time. The time taken for each of the six tablets to disintegrate was recorded and the mean disintegration time of each brand was calculated.

Determination of tablet dissolution

Dissolution rate of the tablets was determined using the USP dissolution test apparatus. The flask was maintained at 37 ± 0.5 by a constant temperature bath. The motor was adjusted to 50 rpm. A tablet from each selected brand was placed in a flask containing phosphate buffer pH 6.8 (disodium hydrogen orthophosphate and potassium dihydrogen) and the five flasks were rotated. A 10 ml sample of fluid of each brand was withdrawn at 5 min intervals using a pipette.

This was filtered, and 2 ml was withdrawn and diluted with 10 ml phosphate buffer. The amount of diclofenac sodium in solution was determined using UV spectrophotometer (276 nm). Ten millilitres of phosphate buffer was added immediately after each sampling to keep the volume of the medium constant at 900ml. Test time of 45 min was used to determine compliance with pharmacopoeia specification of not less than 70% dissolution in 45 min. Determinations were done in quintuplicate.

Table 1: Documentation of five brands of diclofenac sodium tablets

Brand code	Country of manufacture	Batch number	Manufacture date	Expiry date	NAFDAC Registration Number
A	India	MP-001	05-2009	04-2012	04-4669
B	Israel	11294	12-2009	12-2013	04-3877
C	Korea	L5002M050125	09-2010	08-2013	04-3568
D	Switzerland	AF10536	11-2010	10-2013	04-3211
E	Japan	189050	02-2009	01-2013	04-1514

Table 2: Physicochemical properties of five brands of diclofenac sodium tablets

Brand	Uniformity of weight, g (mean \pm sd)	Friability, % loss (mean \pm sd)	Crushing strength, KgF (mean \pm sd)	Crushing strength friability ratio (CSFR)	Disintegration time, min. (mean \pm sd)	Crushing strength-friability /disintegration time ratio (CSFR/DT)	Drug content % w/w (mean \pm sd)
A	0.304 \pm 0.02 (6.61%)*	1.89 \pm 0.2	2.58 \pm 0.37	1.37	23.39 \pm 3.60	0.06	98.91 \pm 0.21
B	0.325 \pm 0.05 (15.88)*	0.59 \pm 0.2	8.77 \pm 1.58	10.85	71.29 \pm 3.33	0.21	97.39 \pm 0.19
C	0.374 \pm 0.03 (7.58)*	1.05 \pm 0.1	5.33 \pm 1.03	5.08	27.59 \pm 8.24	0.18	100.76 \pm 0.18
D	0.222 \pm 0.01 (2.77)*	0.82 \pm 0.3	8.90 \pm 1.33	14.86	51.46 \pm 0.87	0.15	99.31 \pm 0.09
E	0.308 \pm 0.05 (17.46)*	1.86 \pm 0.2	6.50 \pm 0.55	3.49	58.24 \pm 3.54	0.06	98.12 \pm 0.18

*% Coefficient of weight variation

Table 3: Parameters obtained from Kitazawa analysis

Brand	K ₁	K ₂	t ₁ (min)
A	0.011±0.001	-	-
B	0.017±0.001	-	-
C	0.221±0.001	0.170±0.001	20±1.200
D	0.024±0.002	-	-
E	0.005±0.000	-	-

Kitazawa analysis:

The result obtained from the dissolution test was further subjected to Kitazawa analysis [4].

Data analysis

The results obtained were analyzed as mean ± standard deviation. The statistical differences in the physicochemical parameters were further analyzed using t-test.

RESULTS**Product documentation**

Table 1 shows information on the five brands used for the tests. All the brands had been validated by product regulatory body, the National Agency for Food Drugs Administration and Control (NAFDAC). None of the products had expired as at the time of the tests.

Product properties

Physicochemical properties comprising weight uniformity, friability, crushing strength, and disintegration time tests, CSFR, CSFR/DT, and drug content for the five brands are presented in Table 2.

Kitazawa equation

Dissolution rate constants for the products are shown in Table 2. Brand C exhibited diphasic dissolution with K₁ value being lower than K₂.

Other brands had monophasic dissolution with lower K₁ values than Brand C.

DISCUSSION**Drug content uniformity**

Identification test revealed that all the five brands contained diclofenac sodium as their active ingredient. The percentage content ranged from 98.12% w/w to 100.76% w/w (Table 2). BP [2] stipulates 95 – 100% drug content for diclofenac sodium tablets. The results indicate that all the brands had high and acceptable contents of the active ingredient. It is essential for tablet formulations to pass the drug content test because even good mechanical properties of tablets cannot make up for insufficient drug content [5].

Uniformity of weight

The significance of this test is to ensure that tablets in each batch of formulation fall within the appropriate size range as this will affect chemical content. The B.P. [2], states that for tablets having mean weight of greater than 250mg, not more than 2 tablets are permitted to deviate from the mean by greater than ± 5% and no tablet by more than ±10%. From the results (Table 2), only the innovator brand (D) passed the test for uniformity of weight. Brand E had the highest coefficient of variation which indicates high variation of tablet weight within the batch. Generally, excessive weight variation is attributable to poor granule flow during

compression, improper die filling or presence of air in the powder/granule bed.

Crushing strength

Crushing strength of 40 – 150N is recommended satisfactory for tablets [2,6]. The values of crushing strength varied significantly ($p < 0.05$) among the brands. Brand A failed the test with a value of 25.8N, while other brands had values within the acceptable limits (Table 2). Poor crushing strength as seen in Brand A may result from poor choice of binding agent, low binder concentration, wrong method of binder incorporation, inadequately dried granules, and low compression force. The crushing strength measures the ability of the tablet to withstand mechanical shock in handling, manufacture, packaging and shipping. Such properties of tablets like crushing strength and friability are

prerequisites for consumer acceptance [7].

Friability

Friability is a disruptive force used to evaluate the ability of tablets to withstand chipping and breakage during use. A maximum weight loss of 1% is usually acceptable for tablets. Brands B and D passed the friability test while brands A, C and E failed (Table 2). Failure to meet specification of friability test may be due to low binder concentration, resulting in loose interparticulate bonding or the use of low compression pressure in the tablet machine. There were significant differences ($p < 0.05$) in the friability values of the brands. Crushing strength was found to be inversely related to percent friability of tablets; brands with low crushing strength had high percent friability.

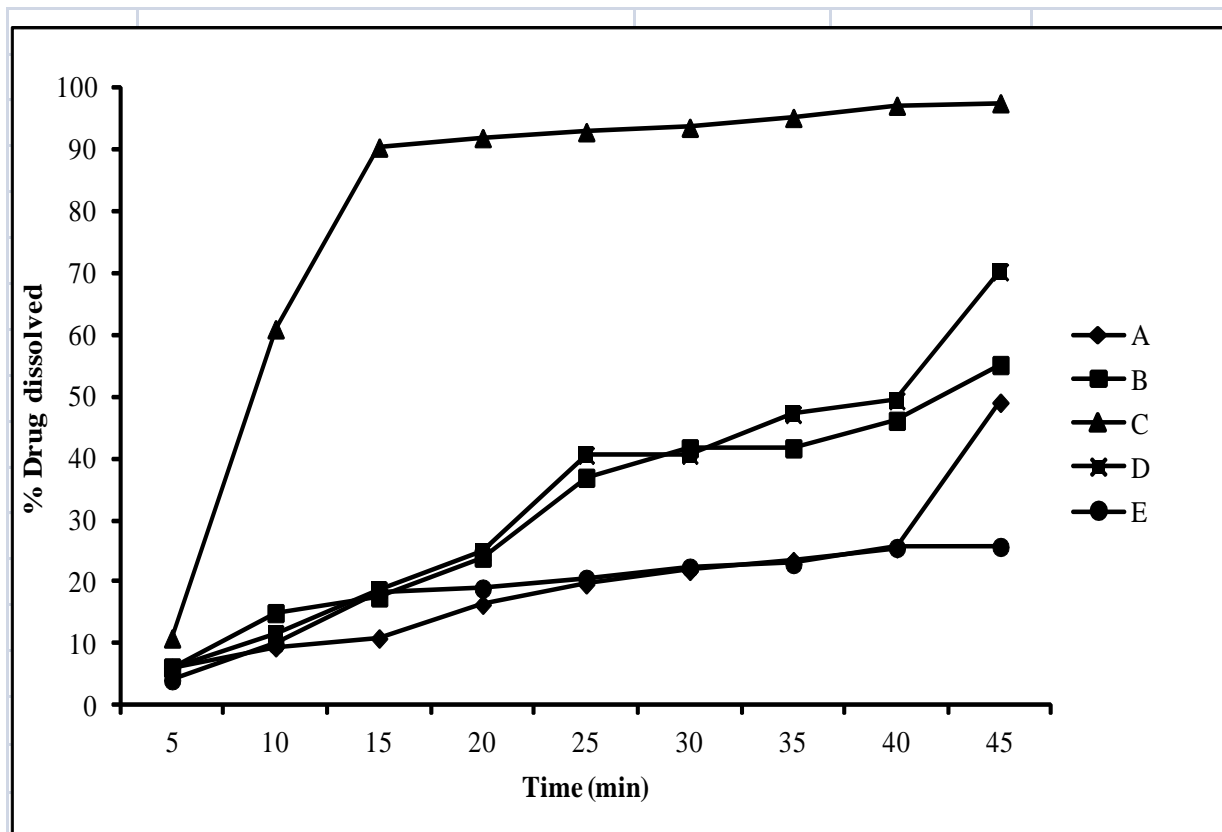


Figure 1. Plots of percent drug dissolved against time for five brands of diclofenac sodium tablets to determine compliance with official specifications.

Disintegration time

Tablet disintegration has been described as the net outcome of adhesive and disintegrating forces which are activated when the tablet is subjected to the aqueous environment [8]. Disintegration time is usually a necessary step for dissolution and could be the rate determining step in the process of drug absorption. For enteric coated tablets, B.P. [2] stipulates maximum disintegration time of 60 min. From the results obtained, brands A, C, D and E passed the test while brand B failed, having a high value of 71.29 min (Table 2). There was correlation between disintegration time and crushing strength; brands A and C (with low values of crushing strength) disintegrated most rapidly. The value of crushing strength may be expected to give some indication of the disintegration of the tablet. However, it must be noted that tablet crushing strength is not an absolute indicator of strength as some tablet formulations when compressed under high pressures to produce very hard tablet, tend to laminate or “cap” [9]. Rapid disintegration is also attributable to the nature and concentration of disintegrant used in the formulation as well as the manufacturing process employed. High compression speed has been found to lead to production of tablets with low mechanical strength [10].

Crushing strength friability ratio (CSFR)

A parameter, CSFR is obtainable from the crushing strength and friability tests. The innovator brand had the highest value (Table 2). CSFR provides a measure of tablet strength and weakness and has been described as a useful index for tablet quality [8]. Also, Bamiro *et al.* [5], reported that the higher the value of this index, the stronger the tablet. Results of this parameter shows the superior quality of the innovator brand over the generic brands.

CSFR/Disintegration time (Dt)

Another parameter derived is the ratio of CSFR to disintegration time (Dt). It is a good index of tablet quality because it measures tablet strength (CS) and weakness (friability), which are

indicators of the bond strength, and simultaneously evaluate any negative effect of these parameters on disintegration time, which is an indicator of disruption of bonds [11]. High value indicates good balance between binding and disintegration properties [5]. The values obtained for all the brands were generally low. This suggests the need for improvement in the selection of binding agent and/or disintegrant in the formulation of enteric coated diclofenac sodium tablets.

Dissolution test

The British Pharmacopoeia [2] stipulates that not less than 70% of diclofenac sodium must be dissolved in 45 min. Figure 1 shows the plots of percent diclofenac sodium dissolved with time. At 45 min, brands C and D had more than 70% drug dissolved while brand A, B and E failed the drug release test having less than 60% drug dissolved at this time. Low percent drug dissolved will result in poor bioavailability of the drug thereby leading to therapeutic failure. All the drugs may still dissolve from the tablets, but coming after 45 min may not be acceptable.

Kitazawa analysis

Kitazawa plot analysis involves the use of integrated form of Noyes-Whitney equation:

$$\ln\{C_s/C_s - C\} = Kt$$

Where C_s is the concentration of the solute at saturation, C , the concentration at time t and K is the dissolution rate constant. Slope of the plots of $\ln C$ against $(C_s - C)$ gives the value of K .

Table 2 shows the parameters obtained from Kitazawa plots for the five brands. Plots for brands A, B, D and E showed monophasic dissolution with single regression lines and low values of K_1 (Table 2). This indicates that the brands released the drug rapidly over the test time of 45 min. The values of K for brands A, B and D were not significantly different ($p > 0.05$), while that of E was very low and significantly different ($p < 0.05$). This analysis further suggests that brand E might result in poor bioavailability as a result of very slow rate of

drug release. The plot for brand C showed two phases of dissolution with higher values of K_1 and K_2 . The time at which the two lines intersect is denoted as t_1 . K_1 was found to be higher than K_2 , showing that dissolution was faster before t_1 . This suggests that the onset of dissolution is rapid and the rate decreased after 20 min (Figure 1).

CONCLUSION

One (innovator brand) out of the five brands subjected to the tests conformed to almost all the official specifications. There were significant differences among the brands in the measured parameters, showing that the brands, though chemically equivalent, are not pharmaceutically equivalent and hence could not be substituted for each other. All the brands had the required regulatory agency's approval; it is therefore important for the regulatory body to be more stringent in product evaluation before giving approval for sale and use. Further, there is need for periodic assessment of pharmaceutical products. Companies involved in production of generics need to properly consider all the physicochemical properties of the drug and carefully select appropriate excipients in the right proportion so that pharmaceutical equivalence which is needed for the desired therapeutic effect can be achieved.

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