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IN-VITRO COMPARATIVE QUALITY ASSESSMENT OF DIFFERENT BRANDS OF DICLOFENAC SUPPOSITORIES AVAILABLE IN THE KUMASI METROPOLIS, GHANA

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Diclofenac, Suppository, Quality, Assessment, Sub-standard

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ABSTRACT: Drugs play a vital role in maintaining and promoting health. The safety, efficacy, and quality of the drugs must be assessed to protect the health of the user. Diclofenac is a cyclooxygenase inhibitor and one of the most useful, effective commercially available NSAIDs used in the management of pain. Many different brands and dosage forms (tablets, oral powder, and suppositories) of diclofenac are available on the market. This study sought to determine the quality as well as the physicochemical equivalence of 10 diclofenac suppositories brands. The sampled suppository brands had their registration status verified from the FDA. They were subjected to *in-vitro* tests associated with the quality of suppository dosage form, and the tests were conducted according to the United States Pharmacopeia and British Pharmacopeia standards. Two of the brands had an expired registration, whiles two (2) also had not been registered. All except two of the brands complied with the USP for uniformity of weight; they all passed the disintegration test. The FTIR identification test proved the presence of diclofenac in all the brands. The percentage content of diclofenac in the various brands ranged from 99.3 to 115.7%, 6 of the brands had active contents above the acceptable criteria (95-105.0%), whiles 4 were within this stipulated range. Five brands failed the percentage release (70% of their contents within 45 min) test. The physicochemical evaluation showed that not all the diclofenac brands met the quality specification with respect to uniformity of weight, hardness, disintegration, and content assay.

INTRODUCTION: There is documentation of variable experimental outcomes to generic drugs 1-5. These responses may be due to poor-quality medicines that reach the market through substandard production or deliberate fraudulent practices. Sub-standard drugs are genuine drug products produced legitimately but do not conform to quality standards due to poor standard manufacturing process [3, 6, 7].

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This may emerge from unintentional use of inferior or incorrect active or non-active ingredients, inaccurate measurement of drug quantity, manufacturing processes that may introduce contaminants or do not adequately ensure sterility, substandard packaging design or quality, and ineffectual quality-control measures. Counterfeit drugs, on the other hand, are drugs whose source or identity has deliberate or fraudulently being mislabeled [7-9]. Some substandard drugs may contain active overdose ingredients than stated [10] and, this is likely to increase the prevalence of any adverse effects.

Diclofenac is an inhibitor of cyclooxygenase (COX). It is amongst the most successful and 11-13 commercially available non-steroidal anti-

inflammatory drugs with potent analgesic, antipyretic and anti-inflammatory activity. It is famously formulated for oral use in tablets; however, it is also available AS a suppository for rectal use.

Suppositories have the advantage of potentially preventing irritation to the stomach and small intestine, which is likely to be associated with some orally administered drugs [14-16], especially when there is a manufacturing defect in enteric-coated tablets. Unlike oral dosages, emesis in nauseousness and vomiting are prevented when drugs are rectally administered. Suppositories are usually the alternatives, especially in pediatric and geriatric patients and in situations in which the oral dosage route is not practicable, for example, in conditions such as convulsion, difficulty in swallowing, and gastric irritation [17, 18]. Contrary to oral dosage forms, suppositories can be given to patients in emergency and unconscious conditions. However, the upsurge in various generics of diclofenac suppositories on the Ghanaian market stimulates the need to assess their quality and determine their compliance to official standards. This project also seeks to augments the activities of regulators in the country.

MATERIALS AND METHODS:

Collection of Samples: Ten (10) brands of diclofenac suppositories, each with a label claim of 100 mg, were purchased from licensed drug retail and wholesale outlets located in Kumasi Metropolis, Ghana. A convenience sampling technique was used for sample collection sites, while overt sampling technique was considered for sample collection according to WHO Guidelines on the Conduct of Surveys of the Quality of Medicines [19, 20]. The samples were transported by cooler bags to the site of work. The experimental part of the work was undertaken at Danadams Pharmaceutical limited drug quality laboratory and the study was performed before product expiration dates. The products were coded randomly for purposes of the research. Product information is presented in **Table 1**.

Chemicals and Reagents: HPLC grade methanol (Fisher Scientific UK Limited), potassium hydroxide (BDH), potassium dihydrogen phosphate (BDH), and The USP standard pure diclofenac sodium was obtained as a kind donation from Danadams Pharmaceutical Industry limited.

TABLE 1: PRODUCT INFORMATION FOR THE VARIOUS SUPPOSITORIES

Brand	Manufacturer	Marketing Authorization	Base	Primary Package	Batch No.
S1	Meridian Enterprises Pvt. Ltd. India	Pharmanova Ltd. Ghana	Water-soluble	–	CQ1607
S2	Kar Labs Private Ltd. India	Kojach Ltd. Ghana	–	–	160303
S3	Haupt Pharma Wulfing GmbH. Germany	Denk Pharma GmbH Co. Germany	Hard fat	–	19872
S4	–	Ronak Exim Pvt. Ltd. India	–	–	1405114
S5	World Medicine Ilac San. Ve Tic. A. S. Turkey	World Medicine Ilac San. Ve Tic. A. S. Turkey	Hard fat (Witepsol S55)	Polyvinyl chloride/polyethylene strip	002036
S6	Bliss Gvs Pharma Ltd. India	–	Polyethylene glycol	–	F2ABE014
S7	Walter Ritter Gmbh Co. Kg. Germany	–	Hard fat	–	15112
S8	–	Nauketan Pharma Pvt. Ltd. India	Polyethylene glycol	–	GS-18
S9	R. P. Scherer. Germany	Acino. Switzerland	Hard fat, Polyethylene glycol	Aluminium foil blister	1450698
S10	Ciron Drugs and Pharmaceuticals Pvt. Ltd. India	–	–	Aluminium foil strip	6ES01001 6ES03003

Methods: The quality of the Diclofenac suppositories was assessed according to procedures outlined in the BP, USP, and literature. Similarly, the following *in-vitro* quality control parameters were considered for the sampled products under the investigation.

Physical Assessment of Suppositories: The packaging was checked for correct and legible labeling of active ingredients and strength, expiration date, batch number, manufacturer and country of origin. Color and surface texture was observed in the intact dosage unit, whiles pitting, sedimentation and the migration of the active ingredients were observed by splitting the suppository vertically.

Weight Variation Test: Twenty (20) suppositories selected randomly from each brand were weighed to obtain the average weight using Sartorius (BS223S) analytical balance. The percentage weight deviation of the individual suppository was deduced from the mean weight of the 20 suppositories. Then, the percentage deviation from the average was calculated using the following formula.

$$\text{Deviation (D)} = \text{Supp. weight} - \text{Average weight} \quad \text{.....Eq. 1}$$

$$D\% = D/(\text{Average weight}) \times 100 \quad \text{.....Eq. 2}$$

As stated in the BP 2018, the weight of two suppositories may not differ by more than ±5% from the mean weight, and none may differ by more than ±10% from the average (BP, 2018).

Diclofenac Identification Test: A Perkin Elmer Spectrum Two™ FT-IR with a deuterated triglycine sulfate (DTGS) detector was used to scan and measure all infrared spectra from 4000 cm-1 to 400 cm-1. The diamond crystal of the UATR was cleaned with isopropanol, and the instrument background was run. A small portion of the sample was put directly on the diamond crystal, and force was applied on the sample. The force was applied until the strongest spectra bands were measured. Perkin Elmer Spectrum 10™ software was used to record and process all spectra data.

Disintegration Test: Six suppositories were sampled from each brand, and a dosage unit was placed in each of the six tubes of the basket rack, and a disc was added. The apparatus was operated using distilled water, maintained at 37±2 °C. The time duration taken for each of the suppositories to disintegrate was recorded, and the mean was calculated.

Assay of Active Ingredients: The Chromatographic system Agilent HPLC equipped with a UV detector set at 283nm and a C8 column packed with a stationary phase of 5-µm particle size was used. A mixture of filtered and degassed methanol and water (70:30) was employed as a mobile phase. Column preconditioning was performed for 8 hours. The flow rate for the assay was 1mL/minute, and the injection volume 20 µL.

Preparation of Samples: Five suppositories of each diclofenac sodium brand were randomly sampled, weighed, mashed and mixed. An accurate portion of the suppository mass, equivalent to 20mg of the diclofenac sodium, was weighed and transferred into a 100ml volumetric flask. It was then partly filled with the solvent. This was completely dissolved by sonication and intermittent shaking for at least 20 minutes. It was left to cool and filled to the 100ml mark with the solvent. The solution was then filtered using a 0.45µ nylon filter. Suppositories of the fatty base were sonicated again and warm filtered. The filtrate was collected and in an HPLC vial after discarding the first 2 ml of filtrate (0.2 mg/ml of diclofenac sodium). On the other hand, a 20mg diclofenac sodium WS was accurately weighed using an analytical balance into a 100 ml volumetric flask and dissolved with some quantity of the solvent, and subsequently sonicated for at least 20 min. It was then made up to the volume and allowed to cool. The solution was then filtered using a 0.45µm nylon filter and collected in an HPLC vial after discarding the first 2 ml of the filtrate to obtain an RS solution with a known concentration of about 0.2 mg/ml diclofenac sodium solution**.** Both water-miscible and fat-soluble suppositories were prepared and dissolved for assay in 100 percent methanol. However, miscellaneous base suppositories (suppository base containing both hard fat and Polyethylene glycol) were dissolved in 50:50 water and methanol.

Calibration Curve for API Content Determination: Solutions of concentrations (50, 100, 150, 200, and 300 µg/ml diclofenac sodium were prepared in mobile phase, and their respective peak areas were determined chromatographically at a wavelength of 283nm. Then, concentrations of diclofenac sodium against peak areas were plotted to obtain the calibration curve.

Calibration Curve for Dissolution Test Method: A stock solution of 1mg/ml was prepared by accurately weighing 50mg of diclofenac sodium

working standard into a 50ml volumetric flask, 5ml of 0.1M NaOH was added and diluted with water to the mark and mixed. Solutions of concentrations (25, 20, 15 10, and 5 µg/mL) were prepared from the stock solution by measuring the required amount of stock solution and making up to the required volume with the buffer, and their respective absorbance was determined at a wavelength of 265nm using UV-vis spectrophotometer. Using the equation obtained from the calibration curve, the percentage release values of samples taken at times 5, 10, 15, 20, 30, 35, 45, and 60 min were calculated.

Procedure of Dissolution Test: This was conducted using the USP dissolution apparatus 1 (basket method). The phosphate buffer (pH 7.3) medium was maintained at 37±0.5 ºC temperature, and the basket speed was set to 50rpm. A suppository each was placed into each of the six baskets, and the baskets were descended into position before rotation. The baskets were immediately rotated, and at the different time intervals (5, 10, 15, 20, 30, 45, and 60 min.), 10mL of the dissolution medium was withdrawn from the vessels. The withdrawn sample was filtered into a flask, and a quantity of the filtrate was diluted with the phosphate buffer. The sampled vessel was immediately replaced with the same quantity of phosphate buffer. This was repeated in sextuplicate.

The absorbance of the diluted samples was read at 265 nm, 7.3pH phosphate buffer as blank with UV-vis spectrophotometer.

Drug Release Kinetics: The mechanism and kinetics of drug release from the suppositories were deduced using some of the commonly used mathematical models' dependent approaches such as zero order, first order, Higuchi, Hixon- Crowell and Korsmeyer- Peppas.

The different kinetics equations are given:

Zero Order:

$$Q_t = Q_o + K_{ot} \quad \text{Eqn 3}$$

Where Q_t is the amount of drug released in the time t, Q_o is the initial amount of drug in solution, and k_o is the zero-order release constant.

First Order Kinetics:

$$\text{Log } Q_t = \text{Log } Q_o - kt / 2.303 \quad \text{Eqn 4}$$

Where Q_t is the amount of drug released in the time t, Q_o is the initial amount of drug in solution, and k is the first-order release constant

Higuchi Kinetics:

$$Q_t = K_h t^{1/2}$$

Where Q_t is the amount of drug released in the time and K_h is the Higuchi dissolution constant

Kosmeyer-Peppas:

$$M_t/M_\infty = Kt^n \quad \text{Eqn 5}$$

Where M_t/M_∞ is the fraction of drug released at the time t, k is the release rate constant, and n is the release exponent

Hixson Cromwell:

$$\sqrt[3]{Q_o} - \sqrt[3]{Q_t} = k_s t \quad \text{Eqn 6}$$

Where Qo is the initial amount of drug, Qt is the remaining amount of DCF at time t, and k_s is the Hixson-Crowell constant describing surface volume relation [21, 22]

RESULTS AND DISCUSSION:

Physical Assessment: In assessing the quality of the various brands of suppositories, the product information, including the product manufacturer, marketing authorization, primary packaging material, and batch number, were observed and recorded in **Table 1**. The registration status of the various suppositories brands was inquired from the Ghana Foods and Drugs Authority as at the period the study was conducted, and as shown in **Table 2**, eight of the brands were duly registered, but two of them had an expired license; however, two brands were not registered at all.

The suppositories were observed and assessed for their shape, color and appearance, and texture. These were conducted both in the intact unit and in longitudinally sectioned form. Almost all the suppositories were white to off-white except S8 and S9, which were orange and color RGB (255,159,159), respectively.

Most of the suppositories were also smooth in texture and torpedo in shape **Table 2**. None of the suppositories had sedimentation; however, suppositories S2, S5, S6, and S8 had cavities in them after longitudinal sectioning **Fig. 1** and **Table 2**.

TABLE 2: PHYSICAL ASSESSMENT OF VARIOUS SAMPLES OF SUPPOSITORIES

Brand (code)	Shape	Color and Appearance	Texture	Holes	Sedimentation	Registration status
S1	Bullet	White to off-white and opaque	Tacky	Absent	Negative	Registered
S2	Torpedo	White to off-white and opaque	Smooth	Negative	Negative	Not Registered
S3	Torpedo	Ivory colored	Smooth	Negative	Negative	Registered
S4	Torpedo	Yellowish white	Smooth	Positive	Negative	Registration expired
S5	Torpedo	White	Smooth oily	Positive	Negative	Not Registered
S6	Torpedo	Titanium dioxide	Tacky	Positive	Negative	Registered
S7	Torpedo	White	Smooth	Negative	Negative	Registered
S8	Conical	Orange	Smooth and tacky	Positive	Negative	Registration expired
S9	Capsule	RGB value is (255,159,159)	Smooth	Negative	Negative	Registered
S10	Bullet	White to off-white	Smooth	Negative	Negative	Registered

FIG. 1: CAVITIES IN THE LONGITUDINAL SECTION OF ONE OF THE SAMPLES

Weight Variation: This test evaluates how much the sampled dosage units are dispersed about the mean weight and shows how the uniformity of content of the suppository. The British Pharmacopoeia states that the weight of at most two suppositories may not differ by more than ±5% from the mean weight and none may differ by more than ±10% from the average (BP, 2007). From the results in **Table 3** all the brands passed the test except S2 and S8. Generally, deviation from the permitted level may be due to extreme low or high weight of some of the suppositories, and this may occur in insufficiently filled mould, air bubbles due to poorly adjusted mechanical stirring, or presence of adverse surfactant and if scraping during production is not appropriately done.

TABLE 3: PERCENTAGE CONTENT, WEIGHT VARIATION, AND DISINTEGRATION TIME FOR THE VARIOUS SUPPOSITORIES

Brand Code	Uniformity of weight			Disintegration time (min) Mean ± SD	% Active content uniformity Mean ± SD
	Weight variation (g) (Mean ± SD)	Number of supp. with weight variation >5%	Number of supp. with weight variation >10%		
S1	1.246±0.020	None	None	12.10±0.028	100.3±0.124
S2	0.981±0.53	None	3*	7.06±0.071	114.1±0.793
S3	2.151±0.013	None	None	8.36±0.170	113.2±0.201
S4	1.893±0.016	None	None	6.26±0.903	110.7±0.142
S5	2.011±0.004	None	None	6.50±0.134	99.3±0.310
S6	1.840±0.015	None	None	13.14±0.092	100.8±0.179
S7	2.169±0.002	None	None	7.09±0.014	115.7±0.988
S8	1.028±0.053	8*	None	9.15±0.042	100.8±0.179
S9	1.358±0.015	None	None	17.44±0.085	106.7±0.030
S10	1.003±0.009	None	None	14.04±0.382	111.0±0.109

*Samples with deviations from compendial requirements

Disintegration Time: With reference to the BP 2007, disintegration in the suppository is considered to be achieved; when melted fatty substances are collected on the surface of the

medium and soluble constituents dissolve; and when softening of the suppository is associated with a significant change of shape without necessarily complete separation of the components, and the softening is such that it does not have a solid core offering resistance to pressure of a glass rod. The disintegration should take place in at most 30 minutes for fat-based suppositories and not more than 60 minutes for water-soluble suppositories. All the brands of suppositories disintegrated within the required and stipulated time. S4 had the lowest disintegration (6.26±0.903 min), whiles S9 had the highest disintegration time (17.44±0.085) among the ten brands of suppositories **Table 3**. Disintegration is significant in the dissolution process since it influences the surface area of contact between the solid drug and the bodily fluid. Low disintegration time helps in quicker dissolution, absorption, and pharmacological action.

Assay of Active Ingredients: The value of correlation coefficient (r^2) of 0.9993 obtained after plotting the calibration curve indicates a good linear correlation between the concentration of the test sample and the response (peak area). The content assay test ensures that the dosage units contain the quantity of drug substance within the acceptable range as specified by the standard literature. The percentage drug content of the suppositories ranged from 99.3-115.7% **Table 3**. S5 had the lowest percentage content of active ingredient of 99.3%, whiles S7 had the highest of 115.7%. The percentage drug content of S1, S5, S6, and S8, were found to comply with the official compendia requirement for content assay (95–105.0% of the prescribed content).

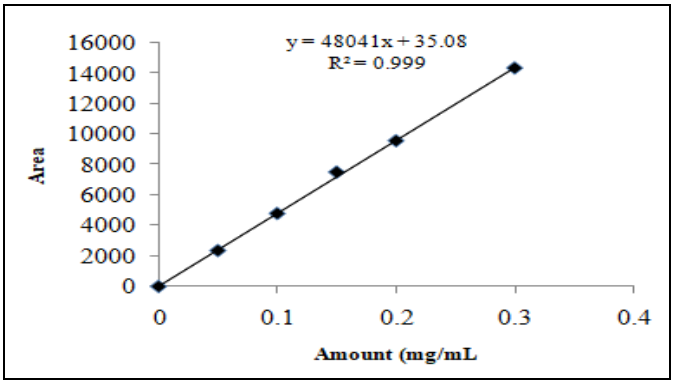

FIG. 2: CALIBRATION CURVE OF DICLOFENAC SODIUM IN MOBILE PHASE

Contrary S2, S3, S4, S7, S9, and S10 respectively recorded over-range percentage drug content against that of the compendia acceptable range. Therefore, not all brands of the diclofenac suppository showed assay results within the compendial requirement. Statistically, the one-way ANOVA analysis done for the mean difference of the drug content revealed that with a 95% CI, there was a significant difference in the drug content among the brands ($p<0.05$).

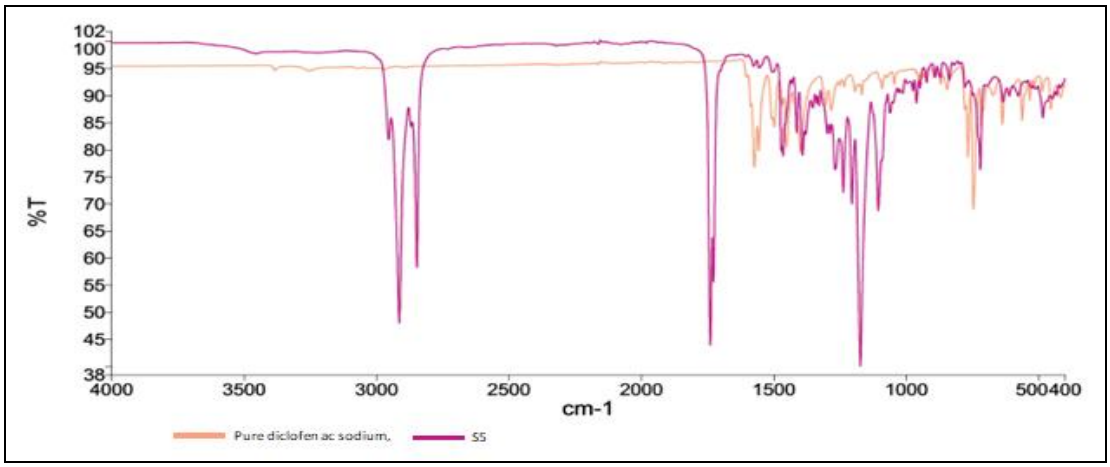

FIG. 3: IR SPECTRUM OF PURE DICLOFENAC SODIUM AND S5

IR Identification of Diclofenac in Samples and Nature of Bases used in the Formulation: The IR spectra are shown in **Fig. 4** and **5**. The IR spectrum of pure drug diclofenac sodium shows a characteristic peak at 3386 cm^{-1} due to the N-H stretching frequency of secondary amine. The absorption bands at 1304 and 1282 cm^{-1} resulted from C-N stretching and the peaks at 1556 and 1573 cm^{-1} due to C=C stretching and C=O stretching of carboxylate group, respectively. The

C-Cl stretching characteristic peak was observed at 745 cm^{-1}. All these characteristics peaks were present in all the samples confirming the presence of diclofenac. Samples whose bases were indicated by the manufacturers had their spectra compared to samples whose bases were not indicated. It could be deduced through comparative spectral analysis that samples S2, S3, S4, S5, S7, S9 and S10 **Fig. 4** were made from fatty bases whilst S1, S8 and S6 **Fig. 5** were made from water-soluble base precisely Polyethylene glycol.

Dissolution Studies and Release Kinetics: A calibration curve showing the relationship between concentration and absorbance was plotted and the equation and correlation values of the curve were generated from the scatter plot. As revealed on the calibration curve **Fig. 5**, a linear regression equation is y = 27.12x+0.0098, where y is the absorbance and x is the concentration in µg/mL with an R^2 value of 0.9975, indicating good linearity.

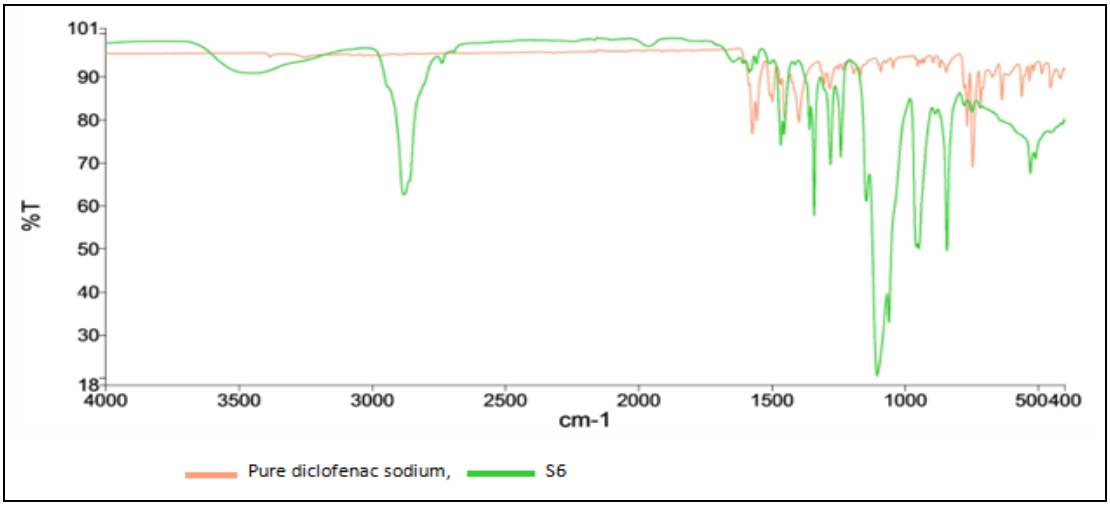

FIG. 4: IR SPECTRUM OF PURE DICLOFENAC SODIUM AND S6

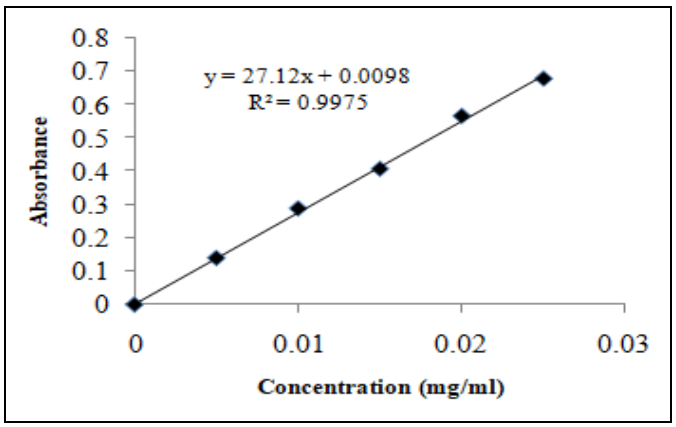

FIG. 5: CALIBRATION CURVE OF DICLOFENAC SODIUM IN BUFFER

The extent and rate at which the active ingredient in a solid-state is transferred into solution is dissolution. This test is done in *in-vitro* to predict the *in-vivo* performance of pharmaceutical solid dosage forms. The test can also serve as a surrogate for bioavailability and bioequivalence. The results for the dissolution studies are presented graphically in **Fig. 6**. As per the BP specification, not less than 70 percent of the active ingredient must be released within 45 min under required test conditions in conventional release dosage forms [23] S (BP, 2013). The present study revealed that, sample S1, S6 and S8 which are purported to be made with water soluble bases released 70% or above of their content in 45 min. Among the fatty base suppositories, only S7 and S9 were within the acceptable criteria of drug release as stated above. This implies that, all the samples that did not pass the test may not release a significant amount of drug absorption into systemic circulation.

Though most the samples were made from fatty acid bases, only two were able to meet the required standard. This difference can be attributed to formulation excipients that were used, the processing and formulation variables. Since the drug release from the fatty bases are also variable, the release difference may be from the type of fat from which the base was derived be it coconut or palm kernel.

In this present work, different kinetic models were fitted into the dissolution data in order to explain the overall release of the drug from the dosage

form. The model that gives the highest correlation after fitting the models to the individual unit of dissolution data is considered the best fit. From the modelling data, as seen in table 4, S7 and S9 zero-order release best fitted, S3, first order, S5, S8 and S10 Higuchi model and S1, S2, S4, S6 Korsmeyer-Peppas. It can therefore be concluded that all the brands under investigation showed different kinds of release mechanisms.

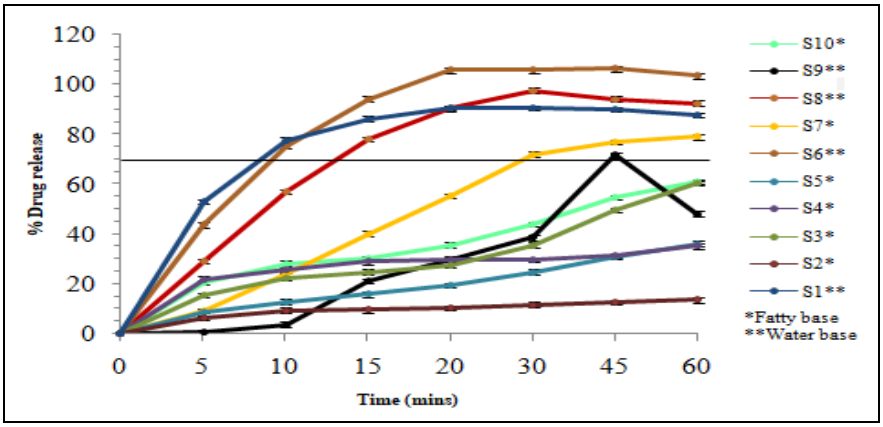

FIG. 6: DISSOLUTION PROFILES OF SUPPOSITORY SAMPLES S1-S10

TABLE 4: DETERMINATION OF CORRELATION COEFFICIENTS OF DIFFERENT RELEASE KINETICS MODELS FOR THE VARIOUS SUPPOSITORY BRANDS

Brand	Coefficient of determination (r^2)				
	Zero Order	First Order	Higuchi	Hixson- Crowell	Korsmeyer- Peppas
S1	0.5996	0.4753	0.6911	0.4542	0.8738*
S2	0.818	0.6733	0.8976	0.6665	0.9841*
S3	0.9481	0.9828*	0.9771	0.9789	0.7891
S4	0.6704	0.5624	0.7852	0.5439	0.9334*
S5	0.9866	0.9694	0.9941*	0.9611	0.8849
S6	0.7372	0.6696	0.7838	0.6686	0.839*
S7	0.969*	0.9145	0.9231	0.8907	0.8154
S8	0.8094	0.5905	0.8235*	0.628	0.7483
S9	0.8261*	0.6542	0.7672	0.7022	0.5357
S10	0.9539	0.9629	0.9951*	0.9428	0.8838

*Highest value of r^2 value for each sample

CONCLUSION: This study attempted to assess the quality and physicochemical equivalence of various brands of suppositories. The test showed that not all the suppositories met the quality specification for uniformity of weight and assay. They all met the quality specification for disintegration. Also, among all the brands evaluated for dissolution, five brands failed to fulfill the pharmacopeial dissolution test requirement. This study finding highlights the need for post-marketing evaluation of pharmaceutical products circulating in the market regularly.

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