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QUALITY ASSURANCE AND INTERCHANGEABILITY OF DIFFERENT BRANDS OF ESOMEPRAZOLE MARKETED IN NIGERIA.

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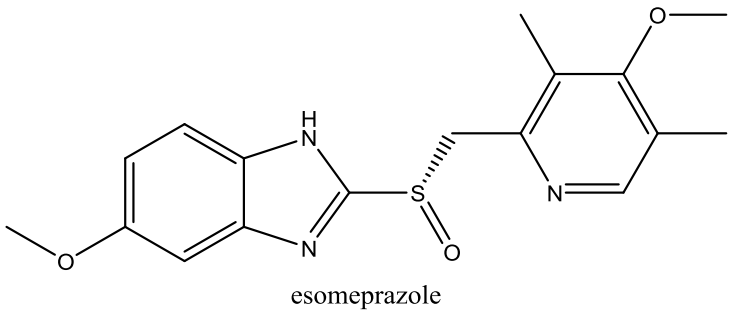
ABSTRACT
Esomeprazole is a highly marketed anti-ulcer drug across Nigeria other sub-Saharan regions. The pharmaceutical quality of the various generics of esomeprazole sold in these regions becomes of utmost importance in ensuring that optimal therapeutic benefits were obtaining after administering any of the available brands in clinical practice. This study was therefore aimed at evaluating the pharmaceutical profile and interchangeability of the different brands of esomeprazole marketed in Nigeria. Six brands of esomeprazole (coded A1-A6) were subjected to official and non-official tests as specified in the USP and BP. These tests were hardness/crushing strength, friability, disintegration time, dissolution and weight uniformity tests. The content of active ingredient was determined using the UV -Visible spectrophotometry at a maximum wavelength of 295 nm. Beer's law was obeyed at a concentration range of 0.2-1.2 µg/ml. Fit factor was calculated to determine *in vitro* bioequivalence of the brands against the innovator brand (A1). The results showed that all the tablet brands (A1-A5) passed the hardness and friability tests, while all the brands (A1-A6) passed the disintegration, dissolution and content uniformity tests according to the USP and BP standards. Only sample A3 failed the weight uniformity test. Also, all the brands showed F_2 values greater than 50, indicating acceptable similarities in their dissolution curves. Hence, these brands could be used interchangeably with one another leading to better availability, patient compliance and overall improvement in therapeutic outcome of esomeprazole products in the country.

KEYWORDS: Esomeprazole, interchangeability, gastro-esophageal reflux disease, spectrophotometer, bioequivalence.

1.0 INTRODUCTION
Esomeprazole is the *S*-isomer of omeprazole used to treat acid related diseases such as peptic ulcer, dyspepsia, gastro-esophageal reflux disease (GERD) and Zollinger-Ellison syndrome.[1] It is a proton pump inhibitor (PPI) which works mainly by inhibiting the formation of gastric acid through the inhibition of the H^+/K^+-ATPase in the parietal cells of the stomach.[2] Esomeprazole plays a role as a histamine antagonist, an EC 3.6.3.10 (H (+)/ K (+)-exchanging ATPase) inhibitor, an anti-ulcer drug and an EC 1.4.3.4 (monoamine oxidase) inhibitor.

Chemically, esomeprazole is known as 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridine-2-yl) methylsulfinyl]-1H-benzimidazole. It has an *S* configuration at the Sulphur atom (Figure 1) and thus an enantiomer of (R)-omeprazole. [3]



esomeprazole

Fig 1: Structure of esomeprazole.

[Formula- $C_{17}H_{19}N_3O_3S$, Molecular weight -345.417 g/mol, Hydrogen bond donor count- 1 and Hydrogen bond acceptor count-6]

Esomeprazole is used generally as its sodium or magnesium salt. It is a solid with melting point of 155 ^oC, very slightly soluble in water and highly soluble in polar solvents (methanol> ethanol> acetone).[4] It is also soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF).

Quality assurance of pharmaceutical products serves a number of purposes. It ensures that the manufacturing processes of pharmaceutical product comply with the required specifications, that each unit dosage form of a drug product contains the right amount of active drug specified on the dosage form, that the drug is stable during storage and that the drug is therapeutically potent in the patient. All these are to ensure that counterfeit and substandard medicines are eradicated from the market.[5] The problem of drug counterfeiting from studies has been shown to be more common in less developed countries where civil laws are either vague or not enforced.[6, 7] Thus, this research work was geared towards assessing the quality assurance and interchangeability of esomeprazole generics marketed in Nigeria. It sought to further study the development of better technologies for protecting the identity of genuine products by pharmaceutical companies thereby curbing this menace.

2.0 MATERIALS AND METHODS

2.1. Collection of samples

Five brands of esomeprazole tablets (coded A1-A5) and one capsule brand (coded A6), marketed by six different manufacturers with labelled contents of 20 mg each were obtained from retail pharmacy outlets in Enugu and Rivers states of Nigeria. A1 was the innovator brand while A2-A6 were other generics of esomeprazole tablets/capsule commonly found in most pharmacies across the country. These were stored under appropriate conditions and tested within their expiration dates.

2.2 Instruments/Reagents used in the study

Laboratory instruments such as dissolution tester (DT 600 High head), Erweka disintegration tester (ZT122, serial No: 125397.Oa96; ZT x 20 series), Jenway 6405 UV/Vis Spectrophotometer, Erweka Friabulator, Monsanto Hardness Tester and Acculab analytical weighing balance were used in this study. Distilled water, Methanol, 5% NaOH, NaOH Pellets and Potassium dihydrogen phosphate were used. All reagents were of analytical grade.

2.3 Preliminary tests

2.3.1 General Appearance

The organoleptic properties which included the shape, colour and coating type of the different brands of Esomeprazole tablets were examined and recorded.

2.3.2 Packaging and labelling inspection

The labelling on the primary and secondary packages of the tablets were properly examined for the following details: name and strength of the active ingredients, batch number, NAFDAC registration number, brand name, manufacturing and expiry dates.

2.4 *In vitro* quality control tests

2.4.1 Weight variation test

Twenty tablets from each brand were weighed individually in a weighing balance. The average weights as well as their standard deviation and standard error of mean were calculated using the following equation: [8]

$$\text{Weight Variation} = \frac{I_w - A_w}{A_w} \times 100\%$$

Where I_w = individual weight of tablets
A_w = average weight of tablets.

2.4.2 Hardness test

The hardness of different brands of esomeprazole tablets was measured using Monsanto hardness tester. The test was repeated ten times for each brand. The acceptable limit of hardness of a tablet is 4-8 Kg/f.[9]

2.4.3 Friability test

Ten tablets of Esomeprazole were selected at random. Each batch of ten tablets was weighed and the respective weights recorded. The tablets were paced in the friabulator and rotated for 4 minutes at 25 revolutions per minute (rpm). The tablets were removed, dedusted and reweighed. The percentage friability was calculated.

2.4.4 Disintegration test

Six tablets from each brand were used for the disintegration test in phosphate buffer (pH 6.8) at 37 ± 2 °C for 1 hour using a disintegration apparatus. The disintegration time was taken to be the time when no particle remained on the basket. Disintegration is the breakdown process of a tablet into smaller particles and is the first step towards dissolution. To be in compliance with USP standards, the tablets should disintegrate and particles must pass through the 3-inch long glass tubes and held against a 10-mesh screen within the time given.[10]

2.4.5 Preparation of standard stock solution

10 tablets of the innovator brand (A1) were crushed in a mortar into a fine powder and extracted using a little quantity of 5% NaOH and Methanol. The mixture was filtered using a suction pump. The filtrate was warmed over a water bath until a dry powder was obtained. The powder containing the active ingredient was dissolved in phosphate buffer of pH 6.8 and was used as a stock solution to obtain a concentration of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 µg/ml of solutions respectively. These concentrations of the standard solution of esomeprazole were each placed in a cuvette to measure the absorbance at 295 nm against a blank (phosphate buffer) for each

solution using UV-vis spectrophotometer. The measured absorbance were plotted against the respective concentrations of the standard solutions to obtain the standard calibration curve.

2.4.6 Preparation and assay of the sample solution

20 tablets from each brand of esomeprazole were weighed and crushed to powder in a mortar. An average weight of the tablets equivalent to 20 mg of esomeprazole was weighed, transferred into a 100 ml volumetric flask and dissolved with 100 ml phosphate buffer (pH 6.8). A 0.05 ml of the solution was measured and transferred to 10 ml volumetric flask separately. Phosphate buffer was added to make up to 10 ml volume. Aliquot volume of the solution was diluted to get a concentration of 20 µg/ml. The average absorbance of the sample solution after two determinations at 295 nm against a blank solvent was recorded. The percentage drug content was calculated for each brand.

2.4.7 Dissolution test

The dissolution test for the different brands of Esomeprazole tablets were carried out according to the United States Pharmacopoeia using Erweka dissolution apparatus (Germany, Paddle type).[9] The dissolution medium was 900 ml of phosphate buffer (pH 6.8) which was maintained at 37 ± 0.5 °C and 75 rpm. In all dissolution experiments, 5 ml of dissolution samples were withdrawn and replaced with equal volume of fresh dissolution medium at regular intervals. Collected dissolution samples were used for determination of released esomeprazole concentrations by using a UV–VIS spectrophotometer against a blank at 295 nm.

2.4.8 DETERMINATION OF FIT/ SIMILARITY FACTOR (F2)

The F_2 (similarity or fit factor) is a logarithm reciprocal square root transformation of the sum of squared error which is a measurement of the similarity in the percent dissolution between two profiles.[11] The F_2 value is equal to 100 when the test and reference profiles are most identical and exponentially decreases as the two profiles become less similar.[12] The FDA recommends that F_2 value of not less than 50 indicates an acceptable similarity between two drug dissolution profiles.[11]

Fit /Similarity factor was calculated using the formula:

$$f_2 = 50 \log\left\{\left(1+\frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right)^{-0.5} X100\right\}$$

Where

n = number of time points,

R_t =dissolution value of reference (innovator) product at time t

T_t =dissolution value for the test product at time t.

3.0 RESULTS AND DISCUSSION

The physical examination of all brands of esomeprazole showed that all the brands were well packaged and appropriately labelled (Tables 1 & 2). All the brands were duly registered with NAFDAC (the Nigerian official drug regulatory agency).

Table 1: Result of the labelling and Inspection Test.

S/N	Brand	Batch No	Label claim	Manufacturing date	Expiry date	Country of origin
1	A1	113/55	20 mg	09/2018	08/2021	Turkey
2	A2	8166	20mg	04/2018	03/2021	India
3	A3	01C	20mg	03/2019	02/2020	Nigeria
4	A4	N-1860	20mg	10/2018	09/ 2021	India
5	A5	BAN20022	20mg	10/2018	09/2020	UK
6	A6	040C150	20mg	07/2018	07/2020	UK

Table 2: Results of the general appearance for the tested brands of esomeprazole.

Product code	Coating type	Colour	Dosage form
A1	Film coated	Light pink	Tablet
A2	Film coated	Light brick red	Tablet
A3	Film coated	Pink	Tablet
A4	Film coated	Cream	Tablet
A5	Film coated	Brown	Tablet
A6	-	Purple	Capsule

Hardness indicates the capability of a tablet to withstand mechanical shocks during handling in manufacturing, packaging and shipping. USP specifies a hardness limit between 4-8 Kg/f for coated tablets.[13] From the result on hardness test, all the tablet samples (A1-A5), passed the test as they all had values within the range of 4-8 Kg/f (Table 3).

Friability test was performed to evaluate the ability of the tablets to withstand abrasion and mechanical shock in packing, handling and transporting. This test indicates the durability and physical strength of tablets.[14] From the analysis made on all brands, it was observed that samples A1, A2, A4 and A5 had a negative value. These negative values indicate the effect of moisture

absorption. Sample A3 gave a positive value but still was within limits (Table 3). All tablet samples passed the friability test as stipulated by the BP.[15]

Table 3: Results of weight variation, hardness, % friability, disintegration and % content.

Sample	Weight variation mean (mg)± SEM	Hardness (Kg/f)	% friability	Disintegration Mean (min)± S/D	% content	F2 (vs A1)
A1	414.2 ± 1.02	7.6	- 0.2	13.49 ± 2.75	97	-
A2	154.8 ± 1.65	5.3	- 0.04	8.24 ± 0.89	103	74.60
A3	210.7 ± 1.91	4.0	0.004	8.22 ± 1.24	97.5	87.20
A4	314.2 ± 1.07	7.9	-0.04	11.18 ± 1.50	95.2	85.70
A5	414.7 ± 0.66	5.3	-0.16	8.47 ± 0.91	96.0	53.40
A6	2.48 ± 0.84	-	-	12.20 ± 1.24	98.5	61.12
Official Specification	≤ 5-7.5 (USP)	4-8 (USP)	<1 (USP)	5-30 (USP)	95-105 (USP)	> 50 (FDA)

The rate of absorption of drugs as well as the therapeutic efficacy is dependent upon the disintegration time. It is also the first step towards dissolution. The onset of action of dosage form of a drug depends on the time to be taken by tablets to release the active ingredient into the sulcus.[16] From the result of the analysis it was found out that the disintegration time of all the brands of esomeprazole were within acceptable limits (5-30 minutes) as specified in the USP (Table 3).[9]

The weight variation of tablets within the compendia limits is a primary indication of its content uniformity and a satisfactory method of determining the drug content uniformity. It also serves as a pointer to good manufacturing practices (GMP) maintained by the manufacturers as well as the amount of active pharmaceutical ingredient (API) contained in the formulation.[16] Therefore, tablets produced to optimal quality should be designed and manufactured to have a high degree of correlation between the weight and content uniformity of the produced tablets.[17] From the outcome of the weight variation analysis, it was observed that all the brands, except sample A3, were within the compendia limits (Table 3). Factors which could be responsible for the failure of weight uniformity test include particle size of the granules, pressure and speed during compression.

For the content of active ingredient, the USP specification for esomeprazole is within the range of 95-105%.[7] All the brands had their values within this range (Table 3).

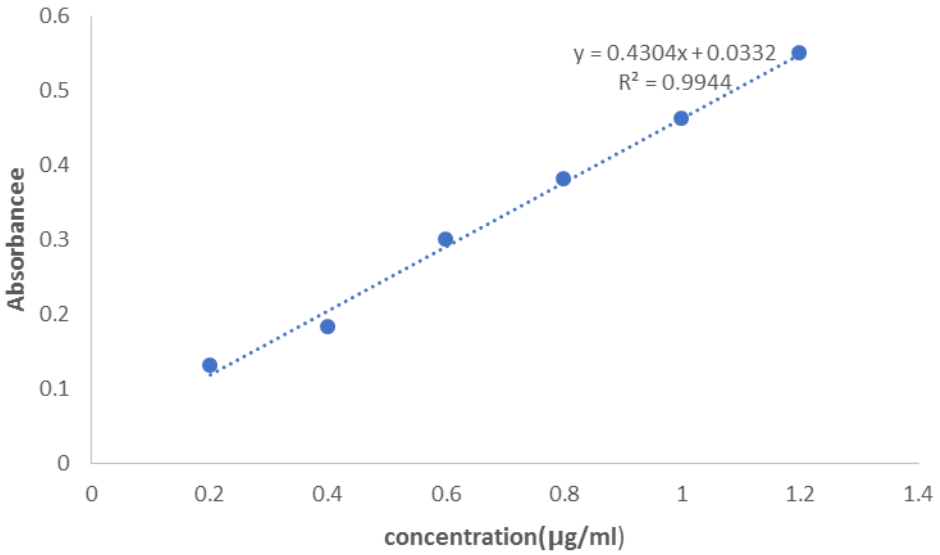


Fig 2: Calibration curve of esomeprazole.

The standard plot for esomeprazole calibration showed that it obeyed Beer-Lambert plot at a concentration of 0.2-1.2 µg/ml (Fig 2). The curve was used in determining the amount of drug released during the dissolution test.

Dissolution is an important factor to be considered in solid dosage formulation as poor dissolution would affect the bioavailability of the drug. The USP specification is that not less than 75% of the labelled amount of

esomeprazole should be released after 45 minutes in phosphate buffer (pH6.8). [16] From the result, samples A1-A6 released more than 75% of its content after 45 minutes. Thus, all the brands passed the dissolution test as they were able to release greater than 75% of their contents after 45 minutes (Fig 3).

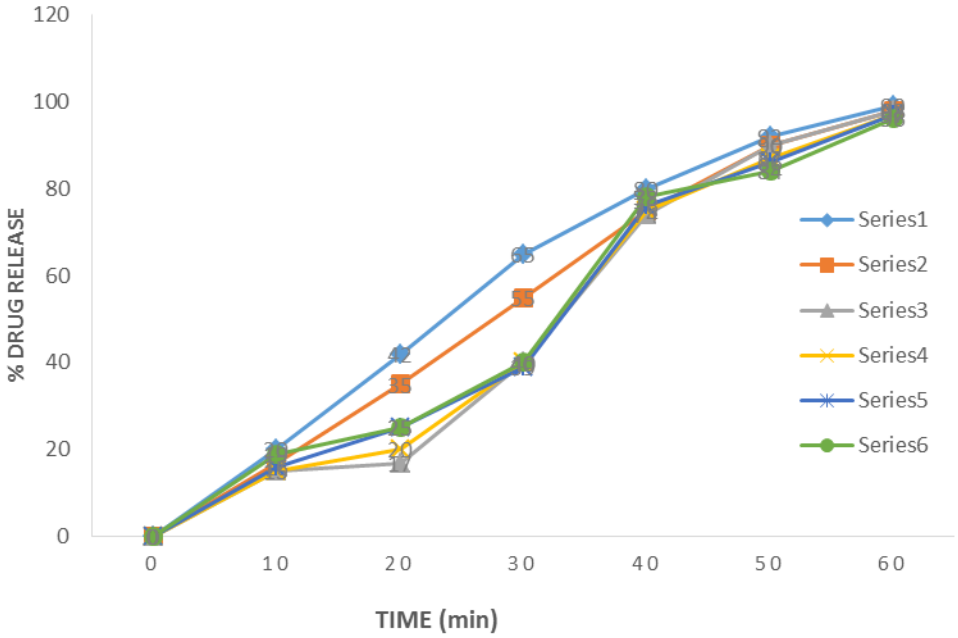


Fig 3: Graph of % drug release vs time (min) of esomeprazole brands.

Fit / similarity factor (F_2) was calculated according to FDA which was used to determine the bioequivalence of the brands against the innovator brand (A1).[11] All the brands of esomeprazole analyzed had a value greater than 50 and so passed the test (Table 3).

4.2 CONCLUSION

The study showed that all the tablet brands (A1-A5) passed the hardness and friability tests, while all the brands (A1-A6) passed the disintegration, dissolution and content uniformity tests according to the USP and BP standards. Only sample A3 failed the weight uniformity test. Also, all the brands analyzed had Fit/ Similarity factor (F_2) values greater than 50, hence could be used interchangeably with the innovator brand A1. Thus, the generic substitution of these bioequivalent brands of esomeprazole would bring about improved patients' compliance and therapeutic efficiency in the clinical application of this agent.

5.0 Conflict of Interests

The authors declare no conflict of interest in the course of this study.

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