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# Comparative Assessment of the Quality and Interchangeability of Some Brands of Dihydroartemisinin/Piperaquine Tablets Marketed in Niger Delta Region of Nigeria

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author MBB designed the study while author EOA wrote the protocol. Author IUM managed the literature searches and took part in all the bench works with author EOA. The statistical analysis was performed by authors MBB and IUM. Authors MBB and EOA wrote the first draft of the manuscript while the final manuscript was read and approved by all authors.*

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## ABSTRACT

The research work was carried out to ascertain the quality and suitability for substitution in clinical practice of some brands of Dihydroartemisinin/Piperaquine phosphate (40 mg/320 mg) tablets marketed in Niger Delta Region of Nigeria. Ten different brands (A to J) of the drug were used. The tablets were subjected to various Official and non-Official test as specified by the Pharmacopoeias. All the brands under review passed the test of physical assessment, the weight uniformity test and friability test. Brands A, B, C, F and G passed the hardness test while samples D, E, H, I and J failed the test. The disintegration time for all the brands were within the acceptable limit with the innovator brand (C) showing the shortest disintegration time of 0.75 minutes, while brand I, had the

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highest disintegration time of 7 minute. Samples B and D were pharmaceutically bioequivalent to the sample C (innovator brand) for Dihydroartemisinin. While samples B, H, and J were pharmaceutically bioequivalent to innovator product (sample C) for Piperaquine phosphate. Therefore, this study implies that only sample B is both pharmaceutically and therapeutically equivalent to the innovator brand, and thus they can be used interchangeably in clinical settings.

*Keywords: Dihydroartemisinin/piperaquine; interchangeability; similarity factor and difference factor.*

## 1. INTRODUCTION

The therapeutic efficacy of a drug in clinical practice partly depends on the rate and extent of its availability in the systemic circulation. The dissolution rate of poorly water-soluble drugs is often a rate-limiting step in their absorption from the GI tract. Such drugs suffer limited oral bioavailability and are often associated with high intra subject and inter subject variability [1]. Therefore, constant surveillance on marketed poorly water soluble drugs by relevant agencies, individual researchers and research bodies is necessary to ensure that only quality drugs of certified therapeutic efficacy are made available for use in clinical practice [1]. Malaria is endemic in Nigeria, with a steady transmission rate throughout the year which comprises of a distinctive rainy and dry season [2]. Nigeria is made up of several hundreds of communities and settlements with their own indigenous people, microclimate, topography, population densities, cultural practices and general way of life. These parameters greatly influence the transmission intensity and management of the disease [3].

Malaria is caused by parasitic protozoa of the genus *Plasmodium* and it is transmitted to humans by the female Anopheles mosquitoes, which are present in almost all tropical and sub-tropical countries. There are approximately 380 Anopheles species, but only about 60 transmit malaria [4].

Dihydroartemisinin (DHA), is a derivative of artemisinin, a naturally occurring antimalarial. Artemisinin (also known as qinghaosu) comes from the Chinese wormwood *Artemisia annua* L [5]. This sesquiterpene lactone endoperoxide is extremely potent against chloroquine and Sulphadoxine-pyrimethamine resistant *P. falciparum in-vitro* and *in-vivo* and can produce faster parasite clearance and fever resolution times than any other licensed antimalarial, including quinine [6]. Piperaquine, on the other hand, is a bisquinoline antimalarial drug which was synthesized by the Shanghai Research Institute of Pharmaceutical industry in 1966 [7]. It was highly effective against chloroquine-resistant *P. falciparum* and *P. vivax* malaria in many areas of China and it replaced chloroquine as the first line treatment in 1978. Recently, it has been in a combination drug with artemisinin derivatives. These drugs have a high affinity for hemozoin, a stage form of hemin, which is retained by the parasite after digestion of hemoglobin, leading to a highly selective accumulation of the drug by the parasite. This results in changes in membrane integrity and depression of protein synthesis resulting ultimately in cytotoxicity, phagocytosis, and clearance by most leucocytes [8].

The incidence of fake, counterfeit and adulterated drug is now a worldwide problem moreover, the issue of affordability of the medicine is taking its toll on humanity. Thus the current study research was carried out to ascertain the quality and suitability for substitution in clinical practice of some brands of Dihydroartemisinin/Piperaquine phosphate tablets marketed in Niger Delta Region of Nigeria.

## 2. MATERIALS AND METHODS

All the samples were obtained from registered Pharmacies. The Pure sample of Dihydroartemisinin/Piperaquine was a kind donation by Kunimed Pharmaceutical, Lagos, Nigeria.

**Chemicals:** Methanol, Concentrated hydrochloric acid, Distilled water, 0.001 M HCl, etc.

**Instruments:** Analytical balance (Adventure, China), Friabilator (Erweka, Germany), Disintegration apparatus (D 63150, Germany), Dissolution apparatus (Erweka DT,600, Germany), UV, Vis Spectrophotometer (6405UV, Jenway), Hardness tester (Erweka, Germany), Volumetric flasks, Conical flasks, Measuring cylinders, Beakers, Graduated pipettes (1 ml, 5 ml, 10 ml), Glass funnel, Filter papers, Round bottom flasks, Fume cupboard.

## 2.1 METHODS

### 2.1.1 Pharmacopoeia tests

*2.1.1.1 Physical assessment*

The packaging and labeling for each of the brands were carefully checked for information such as; Manufacturer's address, manufacturing dates of the drugs, expiry dates, batch numbers, amount of active ingredients and the National Agency for Food, Drug, Administration, and Control (NAFDAC) registration numbers. Also, the color and appearance of the tablets were checked.

*2.1.1.2 Tablet weight uniformity test*

Twenty tablets (20) from each of the brands were weighed using Analytical balance. The average weights were calculated and their percentage deviation from the mean value was determined.

*2.1.1.3 Hardness test*

The Erweka hardness tester was used to check the hardness of ten (10) tablets from each of the brands under study. The mean hardness and standard deviation for each of the brands were calculated. Tablet hardness of 9-15 kg was considered acceptable for film-coated tablets.

*2.1.1.4 Tablet friability test*

Ten (10) tablets were selected at random from each of the brands. The tablets were first dusted, weighed and subjected to agitation in a Roche Friabilator. After four (4) minutes at 25 rpm, the tablets were de-dusted again and re-weighed. The difference between their original and final weight was obtained. The percentage loss was calculated. The percentage friability should not be more than 1% which is acceptable for most tablets. The same thing was done for all the brands.

*2.1.1.5 Tablet disintegration test*

Three tablets were randomly selected from each brand and placed in each of the cylindrical of the disintegrator apparatus tubes were put into operation. The time taken for each tablet to disintegrate was recorded and compared with the standard specified for coated tablets in the B.P. The disintegration media used was 500 mL of distilled water maintained at 37 ± 1°C while the equipment was operated at 50 revolutions per minute.

*2.1.1.6 Dissolution test*

The paddle method was used in the dissolution test. The *in-vitro* dissolution test was performed in a simulated gastric fluid without enzymes. 900 ml of the media was used. The temperature was maintained at $37 \pm 1$ºC. One tablet randomly selected from each of the brands was placed in the dissolution media and 5 ml sample withdrawn at the intervals of 5, 10, 15 and 20 minutes for dihydroartemisinin and 5, 10, 15, 20, 25 and 30 minutes for piperaquine phosphate. 5 ml of the fresh dissolution medium was used to replace each of the withdrawn samples immediately.

The withdrawn samples were filtered and their absorbance was determined at maximum UV-Vis Spectrophotometer. The absorbance of Dihydroartemisinin in the sample was determined at 260 nm while that of Piperaquine phosphate was determined was determined at 350 nm.

*2.1.1.7 Preparation of calibration curves*

Preparation of Piperaquine phosphate pure sample solution for calibration curve.

Piperaquine phosphate stock solution (200 µg/ml) was freshly prepared by dissolving 10 mg in 50 ml volumetric flasks, a pure sample of Piperaquine phosphate. A 25 ml volume of distilled water was added to the solution and was shaken for 10 minutes and topped up to 50 ml with distilled water.

*2.1.1.8 Plotting of calibration curve*

Different aliquot of stock reference solution (200 µg/ml) from 1 ml to 5 ml were transferred into 10 ml standard volumetric flasks. The solutions were topped up to the required volume with distilled water. The absorbance of each concentration was taken at 350 nm against the reagent blank.

*2.1.1.9 Assay of piperaquine containing tablets*

An amount of powdered tablet "A" containing 0.4581 g of Piperaquine phosphate was dissolved in 100 ml of 0.001 M HCl solution and filtered. About 20 ml of the first filtrate was discarded and 1 ml was pipetted from the rest and topped up to 10 ml with 0.001 M HCl (stock solution). The absorbance was taken at 350 nm and the percentage content of Piperaquine

phosphate was calculated. The above procedure was repeated for samples B-J.

## 2.2 Preparation of Calibration Curve for Dihydroartemisinin

The calibration curve for Dihydroartemisinin in combination tablet was prepared using an established and validated method but slightly modified. Thus, Dihydroartemisinin stock reference solution was prepared by dissolving 13 mg of pure Dihydroartemisinin sample (260 µg/ml) in 50 ml volumetric flask. A 25 ml of methanol was added to the volumetric flask. This was shaken for 15 minutes and was topped up to 50 ml with methanol.

## 2.3 Plotting of Calibration Curve for Dihydroartemisinin Pure Sample

Different aliquots of stock reference solution (260 µg/ml) from 1 ml to 5 ml were transferred into 10 ml standard volumetric flasks. The solutions were topped up to the required volume with methanol. Their absorbances were checked at 260 nm against the reagent blank.

### 2.3.1 Assay of dihydroartemisinin containing tablets

An amount of powdered tablet "A" containing 0.4581 g of Dihydroartemisinin was dissolved in 100 ml of 0.001M HCl solution and filtered. About 20 ml of the first filtrate was discarded and 1 ml was pipetted from the rest (80 ml) and topped up to 10 ml with 0.001M HCl (stock solution). The absorbance was taken at 260 nm and the percentage content of Dihydroartemisinin was calculated. The above procedure was repeated for samples B-J.

## 3. RESULTS AND ANALYSIS

The study regarding interchangeability of few drugs (Dihydroartemisinin/Piperaquine) show response depending upon their usability, is that, there are segregated patterns of efficacy are observed which can be treated as the base line for defense mechanism. All are showed in the table and its interference.

The Table above shows that all the brands with codes A – J has manufacturing and expiry dates with their respective NAFDAC registration number (NRN). Four of the brands (G, H, I and J) had India as their country of manufacture, two brands (B and D) were made in China, Brands A and E had Nigeria as their source. The mean weight/ tablet was least (466.5±0.010) with Arthelad® (Brand A) and highest (694.6±0.015) with Falcidin® (Brand F). The mean disintegration time was least (0.75 min) with Eurartesin® (brand C) and highest (7.89 min) with Terocan® (the brand I). Brand D had the highest % friability of 0.93 however, much lower percentage friability was found within the range, 0.0043 – 0.0089 for brands F, B and G. Apart from Waipa® (Brand E) that has the least drug content both for Dihydroartemisinin(DHT) 31.5 g and Piperaquine (243.86 g), others had considerable drug contents ranging from 37.0 – 53.0 g for DHT and 289.76 – 358.62 g for Piperaquine

The above Table describes the percentage drug release by Dihydroartemisinin after 5, 10, 15 and 20 minutes in a solvent. At 20 minutes in a solvent, drug brands F, B, D, and C had 97.66, 98.75, 101.56 and 102% respectively. Others had relatively lower percentage drug release ranging from 75.16 for Brand E to 88.6 for brands I and J after 20 minutes in a solvent. This means that these latter group will require a longer time for an acceptable drug release.

Table 3 describes the percentage drug release of Piperaquine phosphate after 5, 10, 15, 20, 25 and 30 minutes in the appropriate solvent. Brand E had the least percentage drug release of 68.85 after 30 minutes in an appropriate solvent. The next lower percentage drug release was recorded for brands I and D that respectively had 85.74 and 92.13% drug release after 30 minutes in a solvent. The rest brands had above 95% drug release after 30 minutes in a solvent.

Table 4 describes the Similarity factor (F2) and dissimilarity factor (F1) between the innovator brand (Brand C) and other brands with respect to the dissolution profiles of Dihydroartemisinin and Piperaquine phosphate in each brand. Only Brand B with a value of 96.448 as F2 for Piperaquine and 53.86 as F2 for Dihydroartemisinin falls within the Similarity factor (F2) range of 50 – 100 acceptable by US FDA. Brand D had F2 of 67.49 for Dihydroartemisinin but failed for Piperaquine with the value of 43.016 which is lower than the acceptable lower limit of 50.0 recommended by US FDA. Brands H (F2=56.99) and J (F2=63.63) met the FDA Similarity factor criteria Piperaquine but both failed for Dihydroartemisinin with 27.57 and 33.8 respectively. Other brands failed for both drug contents.

**Table 1. General description of different brands of dihydroartemisinin/piperaquine used in this study**

| Brand | Code | MFD | EXP | Source | Mean weight/ tablet | Mean Disinte. time (min.) | Mean hardness Kgf | % Friability | Drug content (DHT) | Drug content (Piperaquine) | NRN |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Arthelad® | A | 01/16 | 12/18 | Nigeria | 466.5±0.010 | 1.63 | 4.85 | 0.0330 | 41.0 | 313.16 | A4-9416 |
| Codisin plus® | B | 07/15 | 07/18 | China | 689.5±0.087 | 4.22 | 4.95 | 0.0072 | 37.2 | 309.84 | A4-4917 |
| Eurartesin® | C | 09/15 | 08/17 | Italy | 539.8±0.006 | 0.75 | 7.50 | 0.1100 | 40.0 | 321.04 | B4-2348 |
| D-Artepp® | D | 06/15 | 06/17 | China | 504.3±0.009 | 1.63 | 3.65 | 0.9300 | 53.0 | 315.58 | A4-5745 |
| Waipa® | E | 12/14 | 12/18 | Nigeria | 553.2±0.015 | 1.26 | 0.95 | 0.0930 | 31.5 | 243.86 | 04-7913 |
| Falcidin® | F | 07/15 | 07/18 | Vietnam | 694.6±0.015 | 3.56 | 7.50 | 0.0043 | 41.7 | 358.62 | A4-2683 |
| P.Alaxin® | G | 12/14 | 11/17 | India | 559.9±0.008 | 4.76 | 5.00 | 0.0089 | 42.9 | 309.84 | 04-9495 |
| P.Mal® | H | 01/16 | 12/18 | India | 632.6±0.014 | 1.49 | 1.60 | 0.0350 | 40.9 | 289.76 | B4-2199 |
| Terocan® | I | 01/15 | 12/17 | India | 582.4±0.008 | 7.89 | 3.40 | 0.0190 | 44.7 | 318.44 | A4-7204 |
| Sivophate® | J | 07/14 | 06/17 | India | 635.9±0.014 | 1.26 | 2.30 | 0.0510 | 37.0 | 292.62 | B4-0382 |

**Table 2. Percentage drug released by dihydroartemisinin**

| Time (minute) | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 1.95 | 5.61 | 10.28 | 4.58 | 4.66 | 3.42 | 9.53 | 6.89 | 4.17 | 4.17 |
| 10 | 56.88 | 80.94 | 90.78 | 84.37 | 70.00 | 63.44 | 60.16 | 47.19 | 57.97 | 57.97 |
| 15 | 73.90 | 85.00 | 96.88 | 95.94 | 73.44 | 83.13 | 71.41 | 66.41 | 75.47 | 75.47 |
| 20 | 79.22 | 98.75 | 102. | 101.56 | 75.16 | 97.66 | 83.75 | 85.16 | 88.60 | 88.60 |

**Table 3. Percentage drug released by piperaquine phosphate**

| Time (minute) | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 11.48 | 89.23 | 90.49 | 63.77 | 34.75 | 44.75 | 8.36 | 80.82 | 6.23 | 84.10 |
| 10 | 22.29 | 95.58 | 95.74 | 82.13 | 56.88 | 93.28 | 23.77 | 84.43 | 10.98 | 89.34 |
| 15 | 40.16 | 96.72 | 96.56 | 86.88 | 60.0 | 94.10 | 81.31 | 91.48 | 42.95 | 98.89 |
| 20 | 55.74 | 97.05 | 97.05 | 91.48 | 63.28 | 95.08 | 87.87 | 92.13 | 73.77 | 101.97 |
| 25 | 67.21 | 97.71 | 98.53 | 91.48 | 64.26 | 101.64 | 93.28 | 93.44 | 78.53 | 103.97 |
| 30 | 98.69 | 100 | 100 | 92.13 | 68.85 | 105.08 | 96.56 | 96.56 | 85.74 | 105.58 |

**Table 4. Fit factors**

| Pair comparison | Piperaquine phosphate | | Dihydroartemisinin | |
|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_1$ | $F_2$ |
| C Vs A | 2.981 | 13.369 | 1.650 | 30.97 |
| C Vs B | 0.026 | 96.448 | 0.725 | 53.86 |
| C Vs D | 0.745 | 43.016 | 0.647 | 67.49 |
| C Vs E | 2.408 | 20.303 | 1.286 | 33.78 |
| C Vs F | 0.659 | 36.144 | 1.601 | 39.89 |
| C Vs G | 1.196 | 17.220 | 0.858 | 32.77 |
| C Vs H | 0.414 | 56.990 | 1.296 | 27.57 |
| C Vs I | 2.957 | 12.870 | 1.456 | 30.39 |
| C Vs J | 0.316 | 63.630 | 1.312 | 33.80 |

**Table 5. Dissolution efficiency (D.E)**

| S/N | Code | Piperaquine phosphate | | Dihydroartemisinin | |
|---|---|---|---|---|---|
| | | AUC | D.E (%) | AUC | D.E (%) |
| 1 | A | 19.595 | 45.52 | 5.719 | 69.3 |
| 2 | B | 43.640 | 99.60 | 7.330 | 88.8 |
| 3 | C | 43.850 | 100 | 8.252 | 100 |
| 4 | D | 38.259 | 87.20 | 7.844 | 95.1 |
| 5 | E | 26.028 | 59.30 | 6.162 | 74.7 |
| 6 | F | 39.95 | 91.10 | 6.599 | 80.0 |
| 7 | G | 22.951 | 52.30 | 6.116 | 74.1 |
| 8 | H | 40.716 | 92.80 | 5.414 | 65.6 |
| 9 | I | 21.190 | 48.30 | 5.683 | 69.0 |
| 10 | J | 44.000 | 100.3 | 6.039 | 73.2 |

## 4. DISCUSSION AND CONCLUSION

Physical assessment of different brands of commercially available Dihydroartemisinin/ Piperaquine tablets used in this study were all registered by National Agency for Food, Drug, Administration, and Control (NAFDAC) with batch numbers, manufacturing dates as well as expiry dates (Table 1). Physically, samples A and B were light green oblong scored tablets, while samples E, H, and J were off-white round tablets though sample F is a scored, pink colored tablet and sample G is blue oblong scored tablet. All the brands had different mean weights due to the variation in the quantity and type of excipients used in their formulation. The sample with the

least mean weight (466.5 mg) was brand A While F had the highest mean weight (694.6 mg). None of the samples deviate more than 5%, thus indicating that all the samples studied fall within the specified standard. Friability is a property that is related to the hardness of the tablets and indicates the ability of the tablets to withstand agitation and chipping or breakage during transportation and at the same time easily break down in the gastro-intestinal tract for easy absorption. All the brands under this study passed the friability test as their percentage friability were within the acceptable limit [9], thus all the samples are presumed to able to withstand abrasion, stress due to transportation, packaging, shipment, and handling prior to when it gets to the end user. Tablet hardness affects the bioavailability of the active ingredient and thus the therapeutic efficacy of the particular drug. Hardness Test is measured in terms of load/pressure required to crush a tablet when placed on its edge. Although it is a non-official test but it is believed that tablets with crushing strength of more than or equal to 4 kg should be considered acceptable [10]. From the test result (Table 1), only samples A, B, C, F and G passed the test with kgf values of 4.85, 4.95, 7.5, 7.5 and 5 respectively while samples D, E, H, I and J failed the test. This implies that those samples that failed the test may not have enough binders or compressional force, and even the method of granulation used by the manufacturing companies during production may not be the right one [10]. In general, tablets should be hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The label claimed for Piperaquine phosphate is 320 mg while the label claimed for Dihydroartemisinin is 40 mg. Sample E had the least percentage drug content (76%) and sample F (112.1%) had the highest percentage drug content (Table 1) for the former while sample E had the least drug content (78.8%) and D had the highest drug content (132.5%) for the later. Interestingly sample E had the lowest percentage drug content in both Dihydroartemisinin and Piperaquine phosphate (76% and 78%). However, only sample C contained the exact percentage drug content and concentration of 40 mg and 320 mg respectively. Uncoated tablets should disintegrate within 30 minutes while coated tablets may take up to 120 minutes. All the samples passed disintegration test with the shortest disintegration time recorded for sample C (1.25 min), while sample D had the highest disintegration time of 5.15 mins. Tablet disintegration takes place before its dissolution in the gastrointestinal tract. All the tablets passed the test of disintegration time [11]. However, a number of formulation and manufacturing factors account for the variation in the disintegration time of a tablet. These include; particle size of the drug substance, solubility, and hygroscopy of the formulation, type and concentration of the disintegrants, binders, lubricant, manufacturing method particularly the compactness of the granulation and compressional force used in the tableting. For comparison of *in-vitro* dissolution properties, the difference and similarity factors ($f_1$ and $f_2$) were emphasized by US FDA. As the name implies, similarity factor ($f_2$) emphasize on the comparison of the relative closeness of generic to innovator brand of the drug product. The $f_2$ parameter is commonly used to establish similarity of two dissolution profiles of a generic and innovator brand and by extension the bioequivalence of the products. On the contrary, the dissimilarity factor ($f_1$) focuses on the difference in the percentage of the drug that dissolved between the reference and test products at various time intervals, which indicates the therapeutic equivalence of the products. Therefore, In terms of bio-equivalency, samples B and D are similar and bioequivalent to the sample C (innovator brand) in terms of Dihydroartemisinin. While samples B, H, and J are also similar and bioequivalent to sample C in terms of Piperaquine phosphate. The implication of the above observation is that only sample B is both pharmaceutically and therapeutically equivalent to the innovator brand among the 10 brands randomly used in this study and thus can be interchanged for the innovator brand in clinical settings.

### 4.1 Conclusion

This study concludes that all the 10 brands evaluated passed the physical assessment test, friability test, weight uniformity test as well as disintegration test. However, only Brand B is both pharmaceutically and therapeutically equivalent to the innovator brand and thus, may be interchanged in a clinical setting.

## 5. RECOMMENDATIONS

1. Regulatory agencies in Nigeria should strengthen their post-marketing surveillance.
2. Hospitals, Clinics, Pharmacies should make a deliberate effort to access research findings so as to take an informed decision in terms of generic substitution.

3. Finally, sample E can further be re-assessed by the regulatory agency (NAFDAC) for its percentage drug content.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

We are not indented to harm any company profile or manufacturing units, as this particular study in only done with the agenda of public concern and interest.

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