ASSESSMENT OF QUALITY OF COMMERCIALLY AVAILABLE ARTEMETHER–LUMEFANTRINE TABLETS IN RIVERS STATE, NIGERIA

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ABSTRACT

Background: The war against fake and counterfeit medicines is one that the National Agency for Food, Drug Administration and Control has fought for several years. Malaria is a major public health problem in Nigeria and accounts for an estimated 225,000 deaths annually. Artemether-lumefantrine combination, one of the artemether-combination therapy (ACT), is currently WHO recommended first line treatment for malaria. Numerous brands of these medicines manufactured in various countries are commercially available in Nigeria. Objective of study: This study aimed to assess the quality of these various brands of artemether-lumefantrine, and to determine if these products contain the level of active ingredient claimed on the label, and are in conformity with specified requirements in the Pharmacopoeia. Method: Physical assessment studies and Pharmacopoeial tests (weight uniformity, hardness, disintegration, and friability tests) were carried out on the various brands of artemether–lumefantrine tablets. Dissolution test was carried out using paddle method in simulated gastric fluid, and the dissolution efficiency/percentage predicated availability equivalence estimated, and percentage content of the active ingredients obtained. Obtained data were analyzed with SSPS software. Result: The physical assessment tests showed that all the artemether-lumefantrine brands conformed to NAFDAC stipulations for packaging and labeling. All the brands passed weight uniformity
test, disintegration, and friability tests, while 50% of the sampled brands failed the hardness test. Dissolution test showed that the brands had dissolution efficiency (DE) at AUC 120mins ranged 29% - 44% with percentage Predicated Availability Equivalent (%PAE) above 80% for all the brands. Assay of active ingredients showed that only 30% of the brands met the International Pharmacopoeial percentage content requirement of 90% - 110% for both artemether and lumefantrine. **Conclusion:** The need to continuously assess the quality of commercially available medicines remains very crucial.

**KEYWORDS:** Artemether- lumefantrine artemether-lumefantrine,; dissolution efficiency; %PAE.

**INTRODUCTION**

Nigeria, like other developing countries has been plagued by counterfeit and poor quality medicines for years. The degree of this scourge was captured in World Health Organization report in 2002 which stated that 70% of drugs in Nigeria were fake or substandard.[1] Since then National Agency for Food and Drug Administration and Control (NAFDAC) took up the challenge of combating the menace of counterfeit medicines starting from baseline estimate of 41% of drugs in the country being counterfeit.[2, 3] Some other studies[4, 5] agreed with NAFDAC estimated value of amount of fake medicines in the country.

The effect of fake and substandard drugs in both economic terms and in lives lost remained very high as typified in a case of one hundred and nine children in Nigeria who died after being administered with fake paracetamol.[6] Reports of growing resistance to common first line antimalarials likely driven by both irrational drug use, and prevalence of substandard medicines, was also noted.[7]

Under the then NAFDAC Director General, Dora Akunyili a lot of effort yielded great improvement via re-invigorated policing and prosecution of counterfeiters that by 2006, the number of substandard and counterfeit medicines circulating in Nigeria market had fallen to about 16%, reported by NAFDAC, and Nigerians were consistently ranking NAFDAC among the most effective Nigeria’s government agencies.[8] However, problems remained. Over 30% of samples of anti-malarial drugs collected from pharmacies in Lagos area in September 2007, as part of the study of six African countries, failed thin layer chromatography and/or disintegration tests.[1] Furthermore, eight– four children reportedly died between late 2008 and early 2009 from diethylene glycol contaminated teething
medicine “My Pikin Baby Teething Mixture” distributed by NAFDAC-licensed Barewa Pharmaceuticals.\textsuperscript{[9]} In Africa, the availability of substandard and possibly counterfeit artemisinin-based anti-malarials has been reported in several countries,\textsuperscript{[10, 11, 12, 13]} A study in Nigeria reported significant differences in the dissolution profiles of nine brands of artesunate tablets, with one brand having particularly low dissolution rate which was likely to cause poor bioavailability of the product.\textsuperscript{[14]} Studies in six towns (three urban and three rural) in Anambra, Southeast Nigeria, assessed the quality of 225 samples of antimalarials including artesunate, dihydroartemisinin, sulphadoxine-pyrimethamine, quinine and chloroquine, which were either purchased or collected from randomly selected providers, reported that over one third of the antimalarials tested did not meet the United States Pharmacopoeia (USP) specifications for the amount of active ingredients required.\textsuperscript{[15]} In order to counteract the problems of fake and substandard drugs, it has become absolutely necessary that all drugs put out for sale and use in Nigeria must undergo stringent tests to confirm their identity, purity, and safety for human consumption.\textsuperscript{[16]}

Malaria is a major public health challenge in Nigeria where it accounts for more clinical cases and death than in any other country in the world. Malaria contributes to an estimated 11\% of maternal mortality.\textsuperscript{[17]} It accounts for 60\% outpatient visits and 30\% of hospitalizations among children under five years of age in Nigeria and it is responsible for an estimated 225,000 deaths annually.\textsuperscript{[18]}

Drug quality assurance is very important in the fight against malaria. Lack of quality drugs for malaria treatment can result in many dire consequences which can range from therapeutic failure to death of patient. Another consequence is development of resistance to antimalarial medication by \textit{Plasmodium species} which has led to the ineffectiveness of some important antimalarial like chloroquine. Poor quality ACT, along with poor prescribing and poor adherence would destroy the renewed hope for malaria control and provide fertile ground or environment for the spread of artemisinin–resistant parasites. Artemether-lumefantrine is a fixed dose regimen and most adopted ACT for malaria treatment.

This study aimed to assess the quality of various brands of artemether- lumefantrine antimalarial tablets commercially available in Rivers State, South –South Nigeria.

\textbf{MATERIALS AND METHOD}
A total of ten different brands of artemether- lumefantrine antimalarial combination tablets (20mg/120mg) purchased across pharmacies within Rivers State, were analyzed. The samples were designated A, B, C, D, E, F, G, H, I, J. (Table 1).

Standard Pharmacopoeial tests were carried out on the samples and results compared with official compendia. Dissolution rate profile of the samples was evaluated and percentage content of active ingredients determined. All the brands were assayed within the shelf life of the drug. Pure samples of artemether and pure sample of lumefantrine were obtained from Evans Pharmaceutical, Nigeria limited.

UV –visible spectrophotometer (model UNICO 2012, USA), Monsanto tablet hardness tester, Monsanto–Stokes hardness tester, (UK), UC Disintegration apparatus (England), Roche Friabilator, GallenKamp (England), Electronic balance, Adventeur (China), were all used for the study. All the solvents used were of analar grade.

Pharmacopoeial Tests

Physical Assessment
The packaging and labeling on the sample packets were carefully examined to check for required information and they include: manufacturer’s name, address, manufacturing date/expiration date, batch number, NAFDAC registration number, tablet content, and strength, and country of origin. Results are shown in Table 1.

Uniformity of Weight
Ten (10) tablets from each brand of the samples were selected at random. The tablets were weighed together and the average weight of a tablet determined. The tablets were weighed individually and the deviation of the weight of each tablet from the average weight of a tablet was calculated. The percentage deviation of each tablet from the average tablet weight was obtained and the result compared to the standard in the official compendium, United States Pharmacopoeia (USP).

Tablet Disintegration Test
Six tablets were randomly taken from each brand of the artemether-lumefantrine tablets samples. A tablet was placed in each of the cylindrical tubes in the UC disintegration basket. The bottom of the disintegration basket was at least 15mm below the surface of the water,
and the apparatus was switched on. The time taken for each tablet to disintegrate was recorded. The exercise was repeated 3 times and the mean value obtained.

**Friability Test**

Ten tablets of artemether-lumefantrine were randomly selected from each brand of the samples, and Roche Friabilator was used to carry out the friability test. The ten tablets were first weighed together before placing them in the friabilator. The tablets were rotated in the friabilator for 4mins at 25rpm, then dusted and re-weighed. The difference between the original weight and the final weight was calculated. The percentage loss was determined which is equal to the percentage friability and should not be more than 1% as stipulated in the official compendium, calculated as:

\[
F = \frac{Wo - Wf}{Wo} \times 100
\]

(where \( F \) = % friability, \( Wo \) = initial weight’ \( Wf \) = final weight).

**Hardness Test**

Ten (10) tablets were randomly selected from each brand of the samples. The Monsanto-Stokes hardness tester was used to determine the crushing strength of each tablet. The mean value for each brand was determined. The test was repeated 3 times for each sample and the mean value obtained.

**Authentication of Artemether and Lumefantrine**

The presence of artemether in artemether –lumefantrine tablet samples was determined using basic official tests (International Pharmacopoeia, 2003, Monographs for antimalarial drugs).

**Test A:** To a quantity of powdered artemether –lumefantrine tablets equivalent to 80mg of artemether, 40ml of dehydrated ethanol was added. Half of the filtrate was evaporated to about 1ml, and 100mg of potassium iodide was added and heated on a water bath for about 5mins. A yellow coloration signifies presence of artemether.

**Test B:** The remainder of the filtrate was evaporated to about 5ml, then few drops of this solution were placed on a white porcelain dish and 1 drop of vanilla/sulphuric acid was added. Development of pink colour signifies the presence of artemether. The same test was carried out with pure artemether sample.
The qualitative analysis of lumefantrine in artemether–lumefantrine tablet samples was carried out using basic identity tests (International Pharmacopoeia, 2003). To a quantity of powdered tablets of artemether–lumefantrine equivalent of 10mg lumefantrine in a test tube was added 5ml ethyl acetate. Few drops of 1M HCl solution were added. The solution was stirred, warmed and filtered. To a portion of the test solution a drop of Dragendoff’s reagent was added. Formation of an orange precipitate shows the presence of alkaloid. To another sample of powdered tablets equivalent to 10mg of lumefantrine, 5ml of methanol was added and shaken well to dissolve. To the solution 20mg of potassium permanganate was added and boiled for about 1 minute. The solution was filtered, and a few drops of 2, 4-dinitrophenylhydrazine solution (Brady’s reagent) was added and shaken. Production of an orange precipitate signifies positive test for lumefantrine. The same test was done with pure lumefantrine sample.

**DISSOLUTION RATE TEST**

Simulated gastric fluid (SGF) without enzyme was prepared based on official standard (British Pharmacopoeia, 2009).

Serial diluted solutions of 5, 10, 20, 30, 40, 50, 60 mg/ml of pure artemether were prepared from a stock solution of 200mg w/v in SGF. Absorbance readings were taken at 254nm against blank SGF solution, using UV spectrophotometer. A calibration curve of absorbance versus concentration was plotted from which the regression equation was obtained.

\[ y = 0.0336x + 0.0839, \quad r^2 = 0.998 \]

Similarly serial diluted solutions of 0.01, 0.02, 0.04, 0.06, 0.08, 0.1 mg w/v of pure lumefantrine were prepared from stock solution of 20mg w/v in SGF. Absorbances of these concentrations were taken at 335nm against blank SGF. A calibration curve was plotted from which the regression equation was obtained.

\[ y = 0.1288x + 0.0534, \quad r^2 = 0.999 \]

The dissolution test for sample of each brand was determined using the paddle method according to US Pharmacopoeia guidelines, operated at 100rpm in a dissolution bath containing 900ml of SGF, with sink condition maintained at a temperature of 37°C ±1°C. One tablet from each brand was randomly chosen for the assay. The chosen tablet was placed into the basket suspended in the dissolution medium. 2ml sample was withdrawn at intervals of 20, 40, 60, 80, 100, 120 minutes. At each withdrawal, 2ml of fresh dissolution medium was
used to replace the withdrawn sample. Each withdrawn sample was filtered, diluted and the absorbance reading determined for both artemether and lumefantrine at 254nm and 335nm respectively, against blank SGF. The concentrations were estimated from the equations of the calibration curves for pure artemether and pure lumefantrine.

**Dissolution Efficiency (DE) and Predicated Availability Equivalence (PAE)**

Dissolution efficiency can be used to evaluate drug release from dosage form and can be theoretically related to *in vivo* data, if it is assumed that the degree of absorption of a drug in solution is proportional to the concentration of the drug in solution and the time this solution is in contact with a suitable absorptive region of the gastrointestinal tract.

Predicated Availability Equivalence is a modification of dissolution efficiency used to assess the in vitro performance of tablets.[19]

\[
\text{DE} (\%) = \frac{\text{AUC (of brand X)}}{\text{AUC (over the entire time curve)}} \times 100
\]

\[
\% \text{ PAE} = \frac{\text{AUC (brand X)}}{\text{AUC (innovator brand)}} \times 100
\]

AUC is calculated using trapezoidal rule.

\[
\text{AUC (t}_{n-1}) = \frac{C_{(n-1)} + C_n (t_n - t_{n-1})}{2}
\]

Where \( C_n = \) concentration at time \( t_n; \) \( C_{n-1} = \) concentration at \( t_{n-1} \)

\[
\% \text{ PAE} = \frac{\text{AUC (of brand X)}}{\text{AUC (of standard/innovator brand)}} \times 100
\]

**Determination of percentage content of artemether and percentage content of lumefantrine in sample brands**

400mg of pure artemether was accurately weighed and dissolved in methanol to give 100ml solution. The solution was filtered using sintered glass crucible. Concentrations of 0.4, 0.8, 1.2, 2.4, 7.2% w/v were prepared from the stock solution by serial dilution. To 2ml of each resulting solution, 2ml of HCl was added. The test tubes were stoppered and allowed to stand for 25mins in a water bath set at 30°C±1°. Each of the resulting solution was diluted with
methanol to 50ml. Absorbance readings were taken at 254nm against blank methanolic HCl. A calibration curve was plotted and the regression equation obtained.

\[ y = 0.0002619 + 0.398x, \quad r^2 = 0.989 \]

Then 40mg of powdered commercial artemether–lumefantrine tablets was accurately weighed and dissolved in 100ml methanol. The above procedure was repeated. Absorbance reading was taken at 245nm against blank methanolic HCl. The artemether content was obtained from the regression equation for pure artemether and the percentage content calculated.

For lumefantrine, 20mg of pure lumefantrine was accurately weighed out and dissolved with 200ml methanolic HCl. From the stock solution, concentrations of 0.005, 0.01, 0.015, 0.02, 0.025%w/v were prepared by serial dilution. The absorbance readings of these solutions obtained at 335nm against 0.1M methanolic HCl as blank were used to plot a calibration curve and the regression equation obtained.

\[ y = 0.02445 + 0.02953x, \quad 0.998 \]

To assay the content of lumefantrine, 20mg of powdered tablets was weighed and dissolved with 200ml 0.1M methanolic HCl. The solution was filtered. From the filtered solution a concentration of 0.0016%w/v was prepared. The absorbance reading was taken at 335nm against 0.1M methanolic HCl as blank. The content of lumefantrine was determined from the regression equation of pure lumefantrine and the percentage content calculated.

**RESULTS**

The result of physical assessment of the packaging of all the sample brands of artemether–lumefantrine (A – J) shown in Table 1 shows that all the brands complied with NAFDAC labeling requirements. Of all the brands studied, 80% originated from India and only 10% is from Nigeria.

<table>
<thead>
<tr>
<th>Brand</th>
<th>NAFDAC reg. no</th>
<th>Manf. &amp; Exp. date</th>
<th>Quty. of active drug</th>
<th>Batch no</th>
<th>colour</th>
<th>packaging</th>
<th>Country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (coartem) ®</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yellow</td>
<td>Blisters</td>
<td>China</td>
</tr>
<tr>
<td>B (amatem) ®</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yellow</td>
<td>Blisters</td>
<td>India</td>
</tr>
<tr>
<td>C (ATCpro) ®</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yellow</td>
<td>Blisters</td>
<td>Nigeria</td>
</tr>
<tr>
<td>D (MaliCare) ®</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yellow</td>
<td>Blisters</td>
<td>India</td>
</tr>
</tbody>
</table>
The results of the Pharmacopoeial tests for the studied samples are shown in Table 2. All the artemether-lumefantrine brands passed the British Pharmacopoeial stipulation for weight uniformity with brand E having the highest % weight deviation of 2.48% and brand G with the least percentage weight deviation of 0.11%. Official compendia (International Pharmacopoeia, 2007; British Pharmacopoeia 2009) stipulate percentage weight deviation of less than 10% for tablets that weigh less than 130mg or less.

Again the BP 2009 stipulates that uncoated tablets should disintegrate in less than 30mins. All the studied brands passed the specification with brand H having the highest disintegration time of 22.7mins and brand F having the least disintegration time of 0.42 minutes. 50% of the commercial samples of the brands of artemether-lumefantrine tablets studied passed the hardness test. Brands B, C, D, E and F failed the crushing strength test. They had suboptimal crushing strength that ranged between 1.65 ± 0.05 kgf to 3.68 ±0.11. The brands that passed (A, G, H, I, and J) had crushing strength within the British Pharmacopoeia specification for uncoated tablet which is 4 – 8kgf.

The British Pharmacopoeia specifies a percentage friability of less than 1% to be acceptable. All the artemether–lumefantrine brands passed the %friability test. The obtained results ranged from 0 – 0.4%, with brands C and I having the least % friability of 0.00, and brand E having the highest % friability of 0.4%. (Table 2)

Table 2 Pharmacopoeial Tests results of artemether-lumefantrine brands studied

<table>
<thead>
<tr>
<th>Brand</th>
<th>Mean tablet weight ±SEM (gm)</th>
<th>% weight deviation</th>
<th>Mean disintegration time (minutes) ±SEM</th>
<th>Mean hardness ±SEM (kgf)</th>
<th>%violation hardness requirement lower range to upper range</th>
<th>% friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.24 ± 0.003</td>
<td>0.35</td>
<td>3.42 ± 0.05</td>
<td>6.45 ± 0.14</td>
<td>None</td>
<td>0.082</td>
</tr>
<tr>
<td>B</td>
<td>0.33 ± 0.001</td>
<td>1.59</td>
<td>2.47 ± 0.01</td>
<td>2.42 ± 0.05</td>
<td>60.5 – 30.25</td>
<td>0.061</td>
</tr>
<tr>
<td>C</td>
<td>0.29 ± 0.002</td>
<td>2.52</td>
<td>3.49 ± 0.00</td>
<td>2.87 ± 0.15</td>
<td>71.75 – 35.87</td>
<td>0.000</td>
</tr>
<tr>
<td>D</td>
<td>0.21 ± 0.0001</td>
<td>0.78</td>
<td>10.17 ± 0.00</td>
<td>3.09 ± 0.04</td>
<td>77.25 – 38.62</td>
<td>0.140</td>
</tr>
<tr>
<td>E</td>
<td>0.35 ± 0.002</td>
<td>2.48</td>
<td>4.40 ± 0.02</td>
<td>3.68 ± 0.11</td>
<td>92.00 – 46.00</td>
<td>0.457</td>
</tr>
<tr>
<td>F</td>
<td>0.29 ± 0.002</td>
<td>1.92</td>
<td>0.42 ± 0.00</td>
<td>1.65 ± 0.05</td>
<td>41.25 – 20.62</td>
<td>0.302</td>
</tr>
</tbody>
</table>
### Qualitative Test to authenticate the presence of artemether and presence of lumefantrine in samples of artemether-lumefantrine tablets

Colorimetric tests on the samples of the different artemether–lumefantrine tablet samples yielded colored products of varying intensity. The development of pink colour in the Test B confirmed the presence of artemether. Formation of orange precipitate indicated the presence of lumefantrine. All the artemether-lumefantrine tablet brands studied indicated presence of artemether and lumfantrine.

The dissolution profiles of artemether and lumefantrine in artemether–lumefantrine tablet samples are shown in Fig. 1 and Fig. 2.

The result shows a similar pattern of drug release among all the brands artemether-lumefantrine tablets studied. The concentration of drug released increased with increase in time with sample I having the highest release at 100 minutes and sample A the least release for artemether.

![Dissolution Profile of Artemether in samples of Artemether - Lumefantrine Tablets.](image)

Sample F and G showed highest released at 60 minutes for lumefantrine and sample A showed the least release at 20 mins.

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.36 ± 0.001</td>
<td>0.29 ± 0.001</td>
<td>0.25 ± 0.000</td>
<td>0.24 ± 0.000</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>1.49</td>
<td>0.99</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>4.32 ± 0.01</td>
<td>22.71 ± 0.09</td>
<td>6.31 ± 0.01</td>
<td>5.20 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>4.15 ± 0.09</td>
<td>4.42 ± 0.11</td>
<td>4.52 ± 0.11</td>
<td>4.69 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>0.252</td>
<td>0.41</td>
<td>0.000</td>
<td>0.080</td>
</tr>
</tbody>
</table>

![Graph showing dissolution profile](image)
The estimated percentage dissolution efficiency (%DE) of the samples of artemether-lumefantrine tablets at 120 minutes in SGF is shown in Table 3.

**Table 3: Estimated AUC; %DE (120 mins) and %Predicated Availability Equivalence.**

<table>
<thead>
<tr>
<th>Brand</th>
<th>AUC</th>
<th>%DE</th>
<th>%PAE</th>
<th>Brand</th>
<th>AUC</th>
<th>%DE</th>
<th>%PAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>379.27</td>
<td>35.5</td>
<td>100</td>
<td>F</td>
<td>426.03</td>
<td>42.06</td>
<td>112.33</td>
</tr>
<tr>
<td>B</td>
<td>356.2</td>
<td>36.3</td>
<td>93.92</td>
<td>G</td>
<td>368.90</td>
<td>29.82</td>
<td>97.26</td>
</tr>
<tr>
<td>C</td>
<td>368.06</td>
<td>32.45</td>
<td>97.04</td>
<td>H</td>
<td>326.56</td>
<td>33.74</td>
<td>86.10</td>
</tr>
<tr>
<td>D</td>
<td>385.57</td>
<td>44.0</td>
<td>101.66</td>
<td>I</td>
<td>345.64</td>
<td>32.40</td>
<td>91.13</td>
</tr>
<tr>
<td>E</td>
<td>373.89</td>
<td>32.18</td>
<td>98.58</td>
<td>J</td>
<td>343.78</td>
<td>37.98</td>
<td>90.64</td>
</tr>
</tbody>
</table>

The result showed sample H exhibiting the least percentage availability equivalence with the innovator product sample A having 100% PAE. The dissolution efficiency ranged from 29% - 44% at 120 minutes.

**Table 4: Percentage content of Artemether and Lumefantrine in tablets of brands of samples of artemether –lumefantrine.**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Concentration of artemether (mg)</th>
<th>% w/w content of artemether</th>
<th>Remark</th>
<th>Concentration of lumefantrine (mg)</th>
<th>% w/w content of lumefantrine</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>26.6</td>
<td>134</td>
<td>Fail</td>
<td>114.3</td>
<td>95.25</td>
<td>Pass</td>
</tr>
<tr>
<td>B</td>
<td>20.06</td>
<td>100.3</td>
<td>Pass</td>
<td>137.54</td>
<td>114.58</td>
<td>Fail</td>
</tr>
<tr>
<td>C</td>
<td>32.75</td>
<td>165.75</td>
<td>Fail</td>
<td>121.42</td>
<td>100.35</td>
<td>Pass</td>
</tr>
<tr>
<td>D</td>
<td>19.26</td>
<td>96.3</td>
<td>Pass</td>
<td>107.06</td>
<td>89.22</td>
<td>Fail</td>
</tr>
<tr>
<td>E</td>
<td>18.76</td>
<td>93.8</td>
<td>Pass</td>
<td>116.20</td>
<td>96.83</td>
<td>Pass</td>
</tr>
</tbody>
</table>


<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>20.59</td>
<td>102.95</td>
<td>Pass</td>
<td>116.75</td>
<td>97.29</td>
<td>Pass</td>
</tr>
<tr>
<td>G</td>
<td>17.76</td>
<td>88.8</td>
<td>Fail</td>
<td>120.90</td>
<td>100.75</td>
<td>Pass</td>
</tr>
<tr>
<td>H</td>
<td>21.33</td>
<td>106.65</td>
<td>Pass</td>
<td>121.69</td>
<td>101.40</td>
<td>Pass</td>
</tr>
<tr>
<td>I</td>
<td>22.43</td>
<td>11.15</td>
<td>Fail</td>
<td>120.68</td>
<td>100.56</td>
<td>Pass</td>
</tr>
<tr>
<td>J</td>
<td>9.28</td>
<td>46.4</td>
<td>Fail</td>
<td>126.19</td>
<td>105.15</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Samples A, C and I contained more than 110% w/w of artemether, while samples G and J contained less than 90% w/w of artemether and thus failed official specifications for percentage content for artemether in artemether-lumefantrine tablets. Sample J contained as low as 46% w/w. Meanwhile sample B failed the percentage content for lumefantrine as the sample contain more than 110% w/w and sample D had less than 90% w/w lumefantrine in the tablet. International Pharmacopoeia, 2009 specifies that the acceptable percentage content of artemether and lumefantrine is 90% - 110% w/w.

**DISCUSSION**

The production and distribution of substandard and counterfeit drugs including artemisinin based combination therapy (ACT) is a huge problem particularly in Africa where post marketing surveillance and Pharmacovigilance is severely limited. Adulterated medicines contain little or no active ingredients, thus leading to therapeutic failure, drug resistance, and consequently death of patient. Failure to comply with good manufacturing practice (GMP) can equally lead to non-bioavailability of the active ingredient in the systemic system thus leading to similar consequences. Therefore, there is need to assess the quality of antimalarial products available in Nigeria market. Physical assessment of all the samples studied showed a good compliance to NAFDAC registration and labeling requirements. This may be attributed to the recent re-invigorated NAFDAC efforts under Dora Akunyili through reactivated regulation and policing drug importation and distribution in the Nigeria, even as 90% of the ACT samples studied were imported into Nigeria. This, however, is another area of concern for the Nigerian drug manufacturing industry.

Appearance itself has low specificity and predictive value as concerns health implications, thus the picture of samples’ quality in this study was based on the results of the laboratory tests. An oral dosage form is normally composed of the active drug substance and excipients; the proportion between them, the type of excipients, and the manufacturing method of the final product taken as a whole gives each product certain biopharmaceutical characteristics. Variations were observed in the results of disintegration time and hardness tests among the sample brands. However, the disintegration times of all the sample brands fell within the
International Pharmacopoeial stipulation of less than 30 minutes for uncoated tablets with sample H having the highest disintegration time of 22.7 minutes. Disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate to particles. The difference in crushing strength and disintegration times, among the different sample brands could be as a result of the type and quantity of binders, disintegrants, lubricants, and compressional force used by the different companies during production (20). In this study, sample brands B, C, D, E and F failed the BP 2009 hardness test specification for uncoated tablets. The percentage violation of hardness requirements for the failed brands ranged from 41% - 92% for the lower range and 20% - 46% for the upper range with sample E showing the highest percentage violation. Tablet hardness affects disintegration time and invariably the dissolution and then the bioavailability of the active ingredient and consequently affect overall therapeutic efficacy of a particular drug. If a tablet is too hard or above specified limit, it may not disintegrate at the required period of time and thus affect bioavailability of the active ingredient. Worse still the tablet may be passed out in the feaces undissolved. Hence, there is a strong correlation between disintegration time and the rate of dissolution.\[21\] If the tablet is too soft, it will not withstand the handling during subsequent packaging and shipping thereby causing breakage or chipping of tablet parts resulting in decreased amount of active ingredients in the formulated drug product. Friability is another property that is related to hardness of the tablet and it indicates the ability of the tablets to withstand agitation and chippings or breakage during transportation. In this study, all the brand samples exhibited % friability within the official specifications of British Pharmacopoeia 2009.

Dissolution of drug from oral solid dosage forms is an important aspect of drug bioavailability, i.e. drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed. As such dissolution testing of solid drug product has emerged as one of the most important control tests for assuring product uniformity and batch to batch equivalence.\[22, 23\] Dissolution test is a measure of amount of the active ingredient(s) released from a solid dosage form using a known volume of dissolution medium within a predetermined length of time. The release pattern or dissolution profile of tablet dosage form could be directly related to the rate of absorption and efficacy of the drug product.\[24\] The US Pharmacopoeia, 2003, specified minimum required percentage release for artemether and lumefantrine as 45% in 1 hr, and 60% in 45 minutes of the labeled amount of claim respectively. In this study, the dissolution profile for artemether (Fig.1) and that of
lumefantrine (Fig 2) for the studied samples, indicate that all the samples complied with the official standard. The points of intersection or overlaps observed on these figures were points at which these samples exhibited similar release rates. Dissolution efficiency variation known as predicated availability equivalence (PAE) is used to predict the likely in vivo bioavailability. The implication of the PAE is to express the relative ease of release and predictive release pattern of drugs in vivo.[25] The dissolution efficiencies of the various sample brands ranged from 29% - 44% with sample G exhibiting the least % dissolution efficiency. The % PAE estimated for the different sample brands showed that all the samples had %PAE above 90% except sample H with 86%.

The International Pharmacopoeia, 2003 specifies that atemether-lumefantrine tablets containing atemether and lumefantrine, must contain 90% - 110% of the amount of the two active ingredients stated on the label. This study showed that 50% of the samples failed the official specification for atemether and 20% failed specification for lumefantrine. In a similar study reported in Ghana all the brands of atemether-lumefantrine tablets analyzed contained more than 110% of lumfantrine.[26] An overdose of lumefantrine is undesirable and can result to toxicity which can worsen the potentially serious adverse effect of lumefantrine like QT interval prolongation which can lead to arrhythmia and still worse in patients with cardiac conditions. On the other hand, under-dose can result to therapeutic failure with undesirable consequences as well.

Substandard antimalarials are caused by poor local regulation of the pharmaceutical industry as well as poor compliance by Pharmaceutical industry to WHO good manufacturing practices (GMPs) in resource poor countries especially those in developing countries.[27, 28]

**CONCLUSION**

This study assessed the quality of 10 brands of atemether- lumefantrine tablets available in the market in Port Harcourt. The study established a good conformation to some of the official specifications and requirements. However, 50% of the samples fell short of specification in their percentage content of active ingredients. Thus the need for assessment of quality of antimalarial products available for use by the populace cannot be over emphasized due to safety reasons.
REFERENCES


