



RESEARCH ARTICLE

EVALUATION OF ORO-DISPERSIBLE TABLETS (ARTEMETHER-LUMEFANTRINE AND AMOXICILLIN TRIHYDRATE) USED FOR SOME COMMON CHILDHOOD DISEASES (MALARIA AND PNEUMONIA)

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Abstract

Background: Generic substitution of a brand of medicine for others, with the hope that they have the same therapeutic effect is difficult for health care providers and consumers.

Aim: This study was able to evaluate the authenticity of label claim of eight samples of artemether-lumefantrine and two samples of amoxicillin trihydrate tablets available at Ogige market Nsukka and Ogbete main market, Enugu.

Method: The following tests were carried out; hardness, friability, modified disintegration time, wetting time, water absorption ratio and weight uniformity. The compliance of each sample to the United States Pharmacopoeia (USP) requirements were recorded.

Results: The friability test showed that all the tablets passed the test with less than 1% friability loss. The mean hardness ranged from 1.65±0.47 to 5.35±0.67 kgf for artemether-lumefantrine tablets, while that of amoxicillin trihydrate tablets ranged from 4.00±0.93 to 6.10±0.91 kgf respectively. The tablet diameter and mean thickness of artemether-lumefantrine tablets ranged from 9.00±1.53 to 11.00±1.0 mm and 2.00±1.15 to 4.00±1.53 mm respectively, while that of amoxicillin trihydrate ranged from 8.00±0.9 to 10.00±1.0 mm and 3.00±2.08 to 4.00±1.53 mm respectively. The disintegration time of artemether-lumefantrine tablets ranged from 1.50±0.1 to 3.52±0.01 min and 2.06±0.02 to 3.30±0.03 min for amoxicillin trihydrate respectively.

Conclusion: The study discovered that several generic brands of artemether-lumefantrine and amoxicillin trihydrate tablets in Nigeria could be sub-standard products.

Keywords: Artemether-lumefantrine, amoxicillin trihydrate, oro-dispersible tablets, malaria, pneumonia.

INTRODUCTION

Orodispersible tablet (ODT) is a solid dosage form containing medicinal substances which disintegrates rapidly usually within a second, when placed upon the tongue¹. ODTs are also called orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast disintegrating tablets or fast dissolving tablets. According to European Pharmacopoeia, an orodispersible tablet is an uncoated tablet intended in the mouth where they disperse rapidly before swallowing². Some of the advantages associated with orodispersible tablets include ease of administration to patients who cannot swallow, no water needed, no

chewing gum, they have an acceptable taste and pleasant mouth feeling, suitable for controlled/sustained release drugs, allow high drug loading and cost effective³. Some of the limitations associated with ODTs include: they require special packaging for proper stabilization and insufficient mechanical strength³. Over the years, children have been observed to be suffering and dying of numerous diseases which include tuberculosis, diarrhea, malaria, HIV and pneumonia⁴. Among these diseases, pneumonia, malaria and diarrhea remain the leading cause of morbidity and mortality in children under five years in Africa. In spite of the fact that there are many known interventions available, poor access to qualified

medical attention and effective interventions has remained a major limitation to achieving a decline in morbidity and mortality⁵. Integrated Community Case Management (ICCM) is expected to have provided an increased access to and coverage of treatment particularly for children who lack access to health facilities, its contribution to increased treatment coverage for childhood diseases has been scanty especially in Nigeria⁶. ICCM is a proven equity-focused intervention for extending affordable care to hard to reach communities to reduce deaths among children under 5 years⁷.

Pneumonia has remained a leading cause of global mortality in children under 5 years with an estimated 1.2 million deaths yearly⁸. Studies have shown that prevention and treatment of pneumonia would prevent one million deaths among children every year. Life saving vaccines brought to the developing world have saved many lives. Also effective and low cost treatment for the disease has contributed immensely in fighting pneumonia. A recent study in an attempt to enhance the accessibility of health facilities in the developing countries has shown that treating children at home with oral antibiotics is as effective as treatment at a health facility⁹.

Malaria has remained the leading cause of morbidity and mortality in children under 5 years in Africa. It has continued to cause major public health burden in areas of Africa, Asia and Central America¹⁰. More than half of the population of the world lives in countries where malaria is endemic and imported malaria has been encountered in every country in the world¹¹. More than 70% of the malaria deaths in Africa occurred in children under 5 years of age. Nigeria and Democratic Republic of Congo account for more than 35% of the malaria cases worldwide¹². Amoxicillin is a broad spectrum antibiotic used in the treatment of pneumonia. It is often prescribed to children for the treatment of pneumonia and several other bacterial diseases. Studies have demonstrated greater effectiveness in the treatment of children who have severe cases of pneumonia with amoxicillin compared to co-trimoxazole by 4-15%¹³. Artemisinin combination therapy (ACT) is indicated for the treatment of acute uncomplicated plasmodium falciparum malaria¹³. It has been adopted by the World Health Organization as a first-line treatment and has been proven more effective in treatment and even in reducing its transmission. Due to the widespread use of these drugs, quality control testing was done for the marketed products in order to ensure safety, efficacy and quality. The objective of this work was to evaluate the pharmaceutical quality of eight different brands of Artemether-lumefantrine orodispersible tablets and two different brands of Amoxicillin orodispersible tablets in Enugu, State Nigeria. Counterfeit drugs are a cause of morbidity, mortality and loss of confidence in areas where they are endemic⁹. Substandard or counterfeit drugs may have serious consequences for both patients and global health, such as increased drug resistant species, treatment failure and side effects¹⁰. The evaluation of some commercial available orodispersible artemether-lumefantrine and amoxicillin

tablets are of great importance so as to authenticate manufacturers' claim. This will enhance reduction in morbidity and mortality¹³.

MATERIALS AND METHODS

Artemether-lumefantrine (Sigma Chemical company, USA), Amoxicillin (Wharfedale laboratories, Otley, UK), distilled water (UNN Water Resources, Nsukka, Nigeria), Sodium trioxocarbonate (Paucocyclo, Kwality Pharmaceuticals, India), Sodium nitrate solution, Hydrochloric acid (Schuppen Chondea, chemei, GmbH, Germany). All other reagents used were of analytical grade.

Quality control of tablets

Weight uniformity test.

Twenty (20) tablets were randomly selected from each batch. Using the analytical balance (120-5DM, S. Mettler, Germany), the 20 tablets were weighed together. The mean tablet weight was then calculated. Subsequently the tablets were weighed individually and the weights of the tablets recorded. The variations of individual tablet weights from the mean weight were determined.

Hardness test

Ten (10) tablets were randomly selected from each batch. Using the Monsanto tester, the pointer was fixed at 0 Kgf. One tablet was held and placed with the tester holder and the screw adjusted until the pressure applied cracked the tablet. The hardness of each tablet was determined and recorded¹⁴.

Friability test

Ten (10) tablets were selected at random from each batch. Subsequently, they were dedusted and accurately weighed together in an analytical balance. The dedusted tablets were then placed into the friabilator which was set to rotate at 25 rpm for 4 min. Then the tablets were removed, dedusted and re-weighed. The mean loss in weight and percent friability was then calculated. The friability test was repeated 3 times. The mean and standard deviation were then calculated¹⁴.

Modified disintegration test

There are several limitations associated with the standard procedure for performing disintegration test for orodispersible tablets, and they do not suffice the measurement of very short disintegration time. Hence the need for modification since disintegration is required without water. A petri-dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petri-dish and the time for the tablet to completely disintegrate into fine particles was recorded¹⁵.

Wetting time test

A piece of tissue paper folded twice was placed in a petri dish plate containing 10 ml of water with soluble dye (methyl blue). The tablet was placed on the paper and the time for the blue colour to reach the center of the upper surface of the tablet was measured. All results were reported as mean±SD. A lower wetting time implies a quicker disintegration of the tablet¹⁶.

Water absorption ratio (R)

A piece of tissue paper folded twice was placed in a small petri dish containing 10 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using the following equation¹⁶:

$$R = \frac{W_a}{W_b} \times 100$$

W_b=weight of tablet before water absorption, W_a=weight of tablet after water absorption.

Content of active ingredient

Total 10 tablets from each sample was randomly selected, weighed and finely powdered. An accurately weighed portion of powder equivalent to the average weight of the crushed tablets was transferred into a 100 ml volumetric flask. A 25 ml volume of 1N HCl was added to derivatize the drug and heated on the thermoregulatory water bath at temperature of 80±2°C for 25 min. The solution was allowed to cool at room temperature, filtered and made up to the mark (100 ml) with distilled water. The stock solution was further adjusted to obtain sample solution of concentration within the Beer's plot. The UV spectrophotometer was zeroed using 2.5 ml of 1 N HCl made up to 10 ml. This

process was done in triplicates and repeated for the 8 brands at 255 nm.

Statistical analysis

All the measurements were repeated at least thrice and the data obtained analyzed by Student *t*-test and One-Way Analysis of Variance (ANOVA). Statistical analysis was performed using Statistical Product and Services Solution software (SPSS, version 22.0 Inc., Chicago IL, USA) and Excel Microsoft Office version 2012. The results were presented as mean±SD, and statistical differences between means considered significant at (*p*<0.05).

RESULTS AND DISCUSSION

Friability test

According to USP specification¹⁶, the percentage friability of less than 1 is generally acceptable and any broken or smashed tablets are discarded. As shown in Table 1, all the tablets passed the test since they all had less than 1% friability loss. Laritin[®] by Nemel had the highest friability value of 0.88% with a significant difference (*p*<0.05), while Coartem[®] by Novartis had the least friability of 0.00%.

Table 1: Friability test result for tablets.

| Drug | Brand | Initial weight (g) | Final weight (g) | Loss in weight (g) | Friability (%) | Remark |
|-------------------------|----------|--------------------|------------------|--------------------|----------------|--------|
| Artemether-lumefantrine | Coatal | 2.85±0.01 | 2.84±0.02 | 0.01 | 0.35 | Pass |
| | Ipca | 2.30±0.1 | 2.29±0.02 | 0.01 | 0.43 | Pass |
| | Aflotin | 3.31±0.06 | 3.30±0.20 | 0.01 | 0.30 | Pass |
| | Malanter | 3.13±0.04 | 3.12±0.06 | 0.01 | 0.32 | Pass |
| | Coartem | 2.70±0.02 | 2.70±0.01 | 0.00 | 0.00 | Pass |
| | Laritin | 2.28±0.01 | 2.26±0.02 | 0.02 | 0.88 | Pass |
| | Lokmal | 3.16±0.01 | 3.15±0.02 | 0.01 | 0.32 | Pass |
| | Azmetrin | 3.09±0.02 | 3.07±0.02 | 0.02 | 0.65 | Pass |
| Amoxicillin trihydrate | Nemoxil | 3.57±0.01 | 3.56±0.02 | 0.01 | 0.28 | Pass |
| | Emmox | 5.41±0.1 | 5.39±0.02 | 0.02 | 0.37 | Pass |

Hence, Coartem will be more resistant to stress which can lead to capping, aberration or even breakage during manufacturing, packaging, transportation and storage process before use¹⁷.

Hardness test

Dispersible tablets are produced with a low hardness to enhance fast disintegration and dissolution. Thus there is need to observe careful handling during manufacturing and packaging. The dispersible tablets are very

fragile such that they can break on removal from the blister package. Although there is no official specification for hardness, a range of 4 to 6 kg may be considered good for orodispersible tablets¹⁷.

Laritin had the least hardness of 1.65 kgf, and this could be attributed to a very low compression pressure used by the manufacturers or a low concentration of binder used in the formulation.

Table 2: Hardness test for Artemether-lumefantrine tablets.

| Drug | Brand | Mean hardness (kgf) |
|-------------------------|----------|---------------------|
| Artemether-lumefantrine | Coatal | 3.45±0.52 |
| | Ipca | 4.40±0.46 |
| | Aflotin | 5.35±0.67 |
| | Malanter | 3.70±0.26 |
| | Coartem | 3.80±0.26 |
| | Laritin | 1.65±0.47 |
| | Lokmal | 1.85±0.41 |
| | Azmetrin | 2.85±0.53 |
| Amoxicillin trihydrate | Nemoxil | 6.10±0.91 |
| | Emmox | 4.00±0.93 |

Table 3: Dimensions of tablets.

| Drug | Brand | Mean diameter (mm) | Mean thickness (mm) |
|-------------------------|-----------|--------------------|---------------------|
| Artemether-lumefantrine | Coatal | 10.00±1.0 | 3.00±1.15 |
| | Aflotin | 10.00±0.58 | 4.00±1.0 |
| | Laritin | 9.00±1.53 | 2.00±1.15 |
| | Azmetrine | 10.00±1.53 | 3.00±1.52 |
| | Ipca | 9.00±1.53 | 3.00±1.0 |
| | Malanter | 10.00±1.0 | 4.00±1.53 |
| | Lockmal | 11.00±1.0 | 3.00±2.08 |
| | Coartem | 9.00±1.53 | 4.00±1.0 |
| Amoxicillin trihydrate | Emmox | 8.00±0.9 | 4.00±1.53 |
| | Nemoxil | 10.00±1.0 | 3.00±2.08 |

Aflotin had the highest hardness of 5.35 kgf with a significant difference ($p < 0.05$). This could be as a result of high compression force or a high binder concentration. Lubricants are also known to reduce tablet hardness by forming a physical barrier

interfering with bonding properties. Particle size and shape also affect the tablet hardness or strength¹⁷. Tablet hardness is an important parameter in drug availability because it affects the dissolution rates of drugs and friability. The tablet formulations were within the ranges of 4 to 8 Kgf.

Table 4: Disintegration time of Artemether-lumefantrine tablets.

| Drug | Brand | Disintegration time (min) |
|-------------------------|-----------|---------------------------|
| Artemether-lumefantrine | Coatal | 2.13±0.01 |
| | Aflotin | 2.58 ±0.01 |
| | Laritin | 1.54 ±0.01 |
| | Azmetrine | 1.50±0.1 |
| | Ipca | 3.52 ±0.01 |
| | Malanter | 1.41 ±0.01 |
| | Lockmal | 1.41 ±0.01 |
| | Coartem | 2.48±0.01 |
| Amoxicillin trihydrate | Nemoxil | 2.06±0.02 |
| | Emmox | 3.30±0.03 |

Table 5: Percentage weight deviation of the Artemether-lumefantrine tablets.

| S.N. | Coatal | Aflotin | Laritin | Azmetrine | Ipca | Malanter | Lokmal | Coartem |
|--------------|--------|---------|---------|-----------|-------|----------|--------|---------|
| 1. | 1.43 | 2.94 | 0.63 | 6.61 | 0.42 | 3.64 | 0.44 | 1.48 |
| 2. | 1.83 | 0.00 | 3.40 | 0.85 | 0.42 | 0.59 | 0.44 | 2.31 |
| 3. | 4.53 | 0.00 | 0.63 | 6.61 | 0.42 | 2.29 | 3.29 | 1.48 |
| 4. | 1.83 | 0.00 | 0.63 | 6.61 | 0.42 | 3.64 | 5.78 | 1.48 |
| 5. | 1.83 | 2.78 | 0.63 | 0.85 | 0.42 | 2.29 | 5.78 | 1.48 |
| 6. | 4.53 | 2.94 | 3.40 | 6.72 | 3.60 | 2.29 | 0.44 | 5.00 |
| 7. | 4.53 | 2.78 | 0.63 | 6.61 | 0.42 | 0.59 | 0.44 | 2.31 |
| 8. | 1.83 | 2.78 | 0.63 | 0.85 | 3.60 | 5.00 | 2.58 | 1.48 |
| 9. | 1.83 | 2.78 | 0.63 | 0.50 | 0.42 | 0.59 | 0.44 | 2.31 |
| 10. | 1.83 | 0.00 | 0.63 | 0.85 | 3.60 | 5.00 | 0.44 | 1.48 |
| 11. | 5.34 | 2.94 | 0.63 | 0.50 | 0.42 | 2.29 | 0.44 | 1.48 |
| 12. | 1.83 | 2.94 | 0.63 | 0.85 | 0.42 | 3.64 | 0.44 | 2.31 |
| 13. | 1.83 | 2.94 | 5.00 | 0.50 | 0.42 | 0.59 | 3.29 | 2.31 |
| 14. | 1.43 | 0.00 | 3.40 | 6.72 | 0.42 | 0.59 | 0.44 | 1.48 |
| 15. | 5.34 | 0.00 | 3.40 | 0.50 | 0.42 | 0.59 | 0.44 | 1.48 |
| 16. | 1.43 | 0.00 | 5.00 | 0.50 | 0.42 | 0.59 | 0.44 | 2.31 |
| 17. | 1.83 | 0.00 | 0.63 | 3.71 | 4.78 | 2.29 | 5.78 | 2.31 |
| 18. | 1.83 | 2.78 | 0.63 | 3.71 | 4.78 | 3.64 | 0.44 | 2.31 |
| 19. | 4.53 | 0.00 | 0.63 | 6.72 | 0.42 | 0.59 | 3.29 | 1.48 |
| 20. | 4.53 | 0.00 | 3.40 | 6.72 | 3.60 | 3.64 | 3.29 | 2.31 |
| Average mean | 0.3055 | 0.3500 | 0.2415 | 0.2985 | 0.241 | 0.342 | 0.3385 | 0.2660 |

Tablet dimensions

The diameter of the tablets ranged from 9.00±1.53 (Laritin, Ipca and Coartem) to 11.00±1.0 mm (Lokmal), while their thickness ranged from 2.00±1.15 to 4.00±1.53 mm (Aflotin, Malanter and Coartem). For Amoxicillin trihydrate, the diameter of the tablets ranged from 8.00±0.9 (Emmox) to 10.00±1.0 mm (Nemoxil), while the thickness ranges from 3.00± 2.08

(Nemoxil) to 4.00±1.53 mm (Emmox). Tablet diameter is dependent on the die and punches used in compression. It is also important in quality testing of tablets¹⁷. The thickness and hardness tests are non pharmacopoeia standards used mostly by manufacturers. Tablet thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression¹⁷.

Table 6: Percentage weight deviation of the Amoxicillin trihydrate tablets.

| S/N | Nemoxil | Emmox |
|-----|---------|-------|
| 1 | 1.40 | 0.69 |
| 2 | 1.11 | 1.05 |
| 3 | 1.71 | 1.05 |
| 4 | 4.71 | 1.05 |
| 5 | 1.71 | 1.05 |
| 6 | 4.71 | 1.05 |
| 7 | 4.71 | 1.05 |
| 8 | 1.71 | 2.37 |
| 9 | 1.71 | 1.05 |
| 10 | 1.40 | 1.05 |
| 11 | 1.11 | 0.69 |
| 12 | 4.71 | 0.69 |
| 13 | 1.40 | 2.37 |
| 14 | 1.11 | 1.05 |
| 15 | 1.40 | 0.69 |
| 16 | 1.11 | 0.69 |
| 17 | 1.40 | 0.69 |
| 18 | 1.11 | 1.05 |
| 19 | 1.71 | 1.05 |
| 20 | 1.11 | 2.37 |

Modified disintegration time

In Table 7, the results showed that disintegration time for all the selected artemether-lumefantrine tablets were within the specified limit of less than 3 min¹⁷. Malanter and Lokmal recorded the fastest disintegration time of 1.41 min, while Ipca recorded a disintegration time of 3.52 min. The high disinter-

gration time of Ipca could be attributed to a high concentration of binder and a small concentration of disintegrant used in the formulation¹⁷. Also, a high compression force increases the binding force of the granules therefore making it difficult to break down into smaller particles.

Weight uniformity test

Table 5 shows the result of the weight uniformity test. The weight uniformity test was performed on the tablets to determine its compliance with USP specifications. All the tablets passed the weight uniformity test as the percentage of weight deviation was within the USP limits of $\pm 5\%$ of average weight. The BP stipulates that tablets with an average weight of 250 mg or more should have percentage deviation not greater than 5%¹⁸⁻²⁰. According to BP specification, the tablet passed the test if not more than 2 tablets are outside the percentage limit of ± 7.5 (for tablets weighing between 130-325 mg), and if no tablet differs by more than 2 times the percentage limit, thus all the tablets passed the test.

Wetting time and water absorption ratio test

Superdisintegrants are responsible for the fast disintegration of active ingredient and water absorption of orodispersible tablets. These superdisintegrants act by swelling pressure exerted in the outer direction. This causes the tablet to burst or the accelerated absorption of water leading to an increase in the volume of granules to promote disintegration^{16,21-23}.

Table 7: Wetting time and water absorption ratio for tablets.

| Drug | Brands | Mean wetting time (min) | Water absorption ratio |
|-------------------------|-----------|-------------------------|------------------------|
| Artemether-lumefantrine | Coatal | 0.46 \pm 0.01 | 44.33 \pm 0.01 |
| | Aflotin | 1.43 \pm 0.01 | 121.62 \pm 0.01 |
| | Laritin | 0.23 \pm 0.01 | 68.52 \pm 0.01 |
| | Azmetrine | 0.21 \pm 0.01 | 131.62 \pm 0.04 |
| | Ipca | 4.47 \pm 0.01 | 25.66 \pm 0.01 |
| | Malanter | 0.53 \pm 0.01 | 79.41 \pm 0.01 |
| | Lokmal | 2.40 \pm 0.11 | 89.21 \pm 0.02 |
| | Coartem | 3.12 \pm 0.01 | 126.72 \pm 0.01 |
| Amoxicillin trihydrate | Nemoxil | 1.28 \pm 0.01 | 49.54 \pm 0.02 |
| | Emmox | 10.00 \pm 0.02 | 75.65 \pm 0.03 |

CONCLUSIONS

The aesthetic assessment result of the tablets showed no sign of defects. According to the USP, all the tablets passed the weight uniformity test for tablets weighing between 130-325 mg. The hardness test showed that all the tablets were within the range of 4-6 kgf. The disintegration time was not satisfactory, thus this study came to the conclusion that several generic brands of artemether-lumefantrine and amoxicillin trihydrate in Nigeria could be sub-standard.

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AUTHOR'S CONTRIBUTION

Andrew EC: writing original draft, methodology. **Grace EA:** research design, data collection. **Izuchukwu BC:** statistical analysis, conceptualization. **Chinemerem OE:** editing, methodology. **Onunkwo G:** methodology, investigation. Final manuscript was read and approved by all authors.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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