Degradation Study on the Effects of Storage Conditions on Active Ingredient of an ACT- Based Anti-malarial Drugs

Adams Udoji Itodo¹, *, Idriss Emmanuel¹, ²

¹Department of Chemistry, College of Sciences, Federal University of Agriculture, Makurdi, Nigeria
²Department of Food Safety and Applied Nutrition, National Agency for Food and Drug Administration and Control, Lafia, Nigeria

Email address: itodoson2002@gmail.com (A. U. Itodo)
*Corresponding author

To cite this article: Adams Udoji Itodo, Idriss Emmanuel. Degradation Study on the Effects of Storage Conditions on Active Ingredient of an ACT- Based Anti-malarial Drugs. International Journal of Biomedical Materials Research. Vol. 5, No. 3, 2017, pp. 29-36. doi: 10.11648/j.ijbmr.20170503.11

Received: March 7, 2017; Accepted: March 29, 2017; Published: June 19, 2017

Abstract: In this drug storage stability surveillance, we evaluated and compared the effects of different storage temperatures and ventilation conditions on the level of active pharmaceutical ingredient (API) of an ACT- based antimalarial (XYZ) drug formulation. The drug which contains artemether and lumefantrine is marketed by drug vendors in Lafia, Nasarawa state. From the analyses carried out, the concentration of lumefantrine (estimated with UV-Vis spectrophotometer) as well as Artemether (analyzed using HPLC) in the drug shows slightly different values which are statistically insignificant when investigated for the effects of storage temperatures and ventilation conditions. Drugs from pharmaceutical stores equipped with fan without cross ventilation (FNV), fan with inadequate ventilation (OCV), fan with cross ventilation (FCV) and fan with air conditioner (ACF) gave lumefantrine level of 494.30, 438.68, 472.48 and 488.68 mg respectively as against the label’s acclaimed 480 mg lumefantrine. The results for artemether includes: FNV (76.93), OCV (79.49), FCV (80.61) and ACF (73.55) milligrammes respectively as against 80 mg drug label claim. Reported values fell within the recommended (90%-120%) NAFDAC acceptable values for drug stability.

Keywords: NAFDAC, ACT, Antimalarial Drug, Lumefantrine, Artemether, Amartem, Storage

1. Introduction

Drug storage is among the pharmacist’s most important responsibilities. Therefore, adequate methods to assure that these responsibilities are met must be developed and implemented. The pharmaceutical are to be stored under conditions that prevent contamination and, as far as possible, deterioration [1]. Precautions that should be taken in relation to the effects of the atmosphere, moisture, heat and light are indicated. storage of the pharmaceutical products is one of the fundamental concerns in patient care [2]. Factors such as temperature, humidity, air quality, time and production process characteristics can all have a significant impact on the final quality, and therefore the saleability, of a product or batch of products.

The quality and stability of anti-malarial drugs has long been of significant concern. Drug quality can be affected by poor or fraudulent manufacturing processes, while drug stability is affected by temperature and humidity [3]. Despite a rapid scaling up of malaria control efforts and recent reports of decreasing transmission intensities in African countries, malaria remains an important cause of morbidity and mortality, particularly in young children [4].

Malaria is a febrile illness caused by intracellular protozoa of the genus *Plasmodium*, and transmitted by the bite of an infected female mosquito of the genus *Anopheles*. In 2006, there were 247 million cases of malaria, causing nearly 1 million deaths, mostly among African children [5].

Malaria deaths are responsible for almost 3% of the world’s disability-adjusted life years, not counting the considerable and imprecisely quantified burden due to morbidity and disability [6].

Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications [7]. In other words, it is the
extant to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Artemether-lumefantrine (AL), a fixed-dose co-formulated ACT, is the most widely deployed antimalarial drug in African countries today [8].

*Artemisia annua* sweet wormwood, sweet Annie, sweet sagewort, annual wormwood) is a medicinal herb native to temperate areas of Asia, but naturalized throughout the world. Extracts of *A. annua* have been in use medically, in particular in the treatment of feverish conditions, but also of hemorrhoids, by Chinese herbalists for centuries. The extracts and their potency are referred to in both the *Recipes for 52 Kinds of Diseases which were unearthed from the Mawangdui Han Dynasty tomb in Changsha 168 B. C* [9]. In 1596, artemisinin was mentioned by Li Shizhen as being effective in the treatment of malaria, although appropriate diagnostic tools for malaria were unavailable at that time. The major active ingredient of *A. annua*, a sesquiterpene lactone (qinghaosu, artemisinin), was first isolated and chemically analyzed in detail in 1972 by Chinese researchers and its antimalarial activity was proven in both mice and primates.

Artemether is now the most widely used artemisinin derivative in the treatment of malaria. Artemether is fat-soluble and readily absorbed within 2 hours after oral application. It is remarkably well tolerated, and peak serum levels occur within 1 hour of an oral dose and persist for up to 4 hours. The terminal phase elimination half-life is less than 1 hour [10]. Apart from the extraordinary clinical benefit to the individual patient, efficient transmission of plasmodia is inhibited [11].

Lumefantrine (previously referred to as benflumetol) is a substance with distinct blood schizontocidal activities against a wide range of plasmodia, including *P. falciparum* and all other human plasmodia. Lumefantrine, a fluorine (benzindene) derivative (a-(dibutylaminomethyl) - 2, 7-dichloro-9-(p-chlorobenzylidene)-5-fluorenemethanol), is an aryl- amino alcohol with intriguing similarities to other antimalarials (quinine, halofantrine, mefloquine). It has however, and in contrast to these substances, never routinely been used as monotherapy in malaria.

![Chemical structure of (a) Artemeter; C₇H₅O₃ and (b) Lumefantrine; C₃₂H₃₇ClNO.](image)

Nayyar et al. [12] have classified poor quality drugs into three types. Falsified drugs are fraudulently manufactured, with fake packaging and usually either contain no active ingredient or one other than that specified on the label. Substandard drugs result from poor manufacturing processes. They may contain too much or too little active ingredient, but are not manufactured with the intention to deceive. Degraded drugs were of good quality at the time of their manufacture, but have deteriorated since, often due to poor storage conditions. The first two classifications may be considered to be problems of genuinely poor quality, while the last classification is a problem of drug stability. Proper patient care requires any drugs dispensed to be both of good quality and adequate stability [13].

Given the hot and humid climate, drug stability and subsequent degradation would be expected to be an important problem in maintaining drug quality in sub-Saharan Africa. This may be especially problematic for anti-malarial. Poor quality anti-malarial may result in under-dosing patients and subsequently lead to treatment failure or drug resistance by the parasite [14].

A number of studies have evaluated anti-malarial drug quality and stability under conditions typically found in Africa. Studies used a variety of methods to determine drug quality and stability including storage under simulated tropical conditions, determining the amount of drug released after dissolution of a solid dosage form following chromatography and spectroscopy [15].

Despite a rapid scaling up of malaria control efforts and recent reports of decreasing transmission intensities in Nigeria, malaria remains an important cause of morbidity and mortality, particularly in young children. The choice of first-line antimalarial drug for treatment of uncomplicated Plasmodium falciparum malaria is critical in preventing the progression of acute infections to severe disease and reducing the risk of further morbidity, disability and premature mortality from the disease [16]. Artemisinin-based combination therapies (ACTs) are recommended by the World Health Organization for first-line treatment of uncomplicated *P. falciparum* malaria worldwide [8].

In this study, we evaluate and compare the effects of different storage temperature and ventilation conditions on...
the active pharmaceutical ingredient (API) of an ACT- based
antimalarial drug sold by drug vendors, thus availing public
health stakeholders with information relevant to best storage
practice for ACT- based antimalarial drugs.

2. Experimental

The United States Pharmacopeia artemether and
Lumefantrine Reference Standard were used. Instrumental
analysis was achieved with UV-Vis Spectrophotometer
(Lambda 35) by Perkinelmer and HPLC (Elite lachrome) of
Merck Hitachi. All reagents are AR grades except otherwise
stated.

Sampling: A single brand of “XYZ”, an Artemether and
Lumefantrine based antimalarial drug marketed by drug
vendors in Lafia, Nasarawa state was sampled from four
different premises with varying storage conditions in terms of
temperature and ventilation (Table 1).

| Premises | Sample Code | Ventilation Condition                  | Storage Temp. (°C) | NAFDAC Reg. Status | Shelf Life   |
|----------|-------------|----------------------------------------|--------------------|--------------------|--------------|
| I        | ACF         | Air conditioner and fan                | 18-25              | Registered         | 18 Months    |
| I        | OCV         | Fan and inadequate ventilation         | 29-32              | Registered         | 18 Months    |
| III      | FCV         | Fan and cross ventilation              | 29-31              | Registered         | 18 Months    |
| IV       | FNV         | Fan without cross ventilation          | 29-33              | Registered         | 18 Months    |

Manufacturer’s Recommended storage condition: < 25 °C in a cool dry place.

Standard and Sample solutions:

For buffer, fine powder of 5.65 g sodium hexafluoride and
2.75 g sodium dihydrogen phosphate was dissolved in 900 ml
distilled water, pH was adjusted to 2 with phosphoric acid,
am and made up to 1000 ml using distilled water. A suitable
degassed solution of buffer and acetonitrile in ratio of 300:
700 was separately prepared as mobile phase. A solution of
United States Pharmacopeia 0.6 mg/mL artemether
Reference Standard was also prepared.

To estimate Lumefantrine, 30 mg of the Tablets was
weighed into a 100 mL volumetric flask. This was carefully
dissolved using distilled water and then made up to the mark.
The solution was filtered with the aid of filter paper and
funnel, and the filtrate was collected into clean 100 mL
beaker. 1 mL of the filtrate was carefully measured into a 25
mL volumetric flask and made to volume with chloroform
and labeled [17]

In the preparation of sample for Artemether estimation, A
total of 10 tablets of the drug were neatly weighed and
crushed using a laboratory mortar and pestle. 60 mg of
artemether was transferred to a 100 mL volumetric flask and
made up to the mark with solvent and mixed. A portion of
this solution was filtered and the first 20 mL of the filtrate
was decanted. This was transferred to a glass test tube and
labeled [17]

Determination of Concentration of Lumefantrine: From
the sample prepared, 1 mL of the filtrate was carefully
measured into a 25 mL volumetric flask and made to volume
with chloroform. Absorbance of the samples was measured at
predetermined 339 nm (E1=366) with the aid of UV-Vis
Spectrophotometer and results were recorded as mean of
triciplicate measurements.

Calculation:

\[
\text{Conc.} = \left( \frac{A_{bs}}{E_1} \right) \times DF \times \left( \frac{\text{Actual wt.}}{\text{wt. taken}} \right) \times 1000 \quad (1)
\]

Where; Abs = Absorbance of sample measured, E1 =
Specific wavelength and DF = Dilution factor

\[
\text{Actual Wt.} = \frac{\text{wt. eq}}{\text{Strenght}} \times \text{wt. av} \quad (2)
\]

Equivalent weight (Weq) is the amount of ground tablet
dissolved in 100 mL Volumetric flask, Strength is the Amount
of active ingredient claimed by the manufacturer on the label
and Average weight (Wav) is the Mean weight of the
individual tablets

\[
\% \text{Content} = \frac{\text{Conc.}}{\text{Strenght}} \times 100
\]

or

\[
\% \text{Content} = \frac{\text{Calculated amount}}{\text{Claimed amount}} \times 100 \quad (3)
\]

HPLC Conditioning

Samples of artemether was analyzed using the optimized
and validated HPLC method [18], with slight modification in
reacting volumes and masses. The chromatographic set up
was conditioned as follows; A predetermined working
wavelength of 210 nm was selected and analyte’s flow rate of
2.0 mL per minute equally calibrated. The analytes were ran
through 3.9x15 cm column that contains 5 µm packing L1
and an injection volume of 20 µL.

Calculations:

\[
\text{Concentration, } C = \frac{R_u}{R_S} \quad (4)
\]

C is the concentration in mg/mL of Artemether, Ru is the
Peak response area of sample and Rs represents the Peak
Response area of Standard. Average Rs was taken from the
three chromatograms and the Ru of all the samples was
obtained. Concentration was calculated using the above
equation.
## Results and Discussion

### Table 2. UV-Vis Experimental Data for Lumefantrine Analysis.

| Sample | Wt. of Lumefantrine (g/Tab) | Avr. Wt. (g/Tab) | Actual Wt. (g/Tab) | Mean Abs. |
|--------|-----------------------------|------------------|-------------------|-----------|
| ACF    | 0.7225                      | 0.735            | 0.734             | 0.7315    | 0.0457   | 0.3667   |
| OCV    | 0.7229                      | 0.7351           | 0.7326            | 0.7326    | 0.0457   | 0.3223   |
| FCV    | 0.7299                      | 0.73             | 0.7401            | 0.737     | 0.046    | 0.3494   |
| FNV    | 0.7378                      | 0.7341           | 0.7302            | 0.734     | 0.0458   | 0.3739   |

Results from Table 2 shows that FNV which represent drug obtained from poorly ventilated premise have the highest absorbance of 0.3739, despite the storage condition. This finding suggests that countries in sub-Saharan Africa with predominantly tropical weather condition and poor electricity supply can afford to store AL-ACT- based antimalarial drug within the condition of this work and still get the desired drug quality for combating malaria. Absorbance from other storage conditions ACF, OCV and FCV still fall within a relatively considerable range of 0.3667, 0.3223, 0.3494 respectively.

### Table 3. Comparative Results of claimed and calculated concentration of lumefantrine in drug samples analyzed.

| Sample | Claimed Strength (amount/sample) | Calculated Amount (mg) | Difference (mg) | % Content | % Error |
|--------|---------------------------------|------------------------|----------------|-----------|---------|
| ACF    | 480 mg                          | 488.86                 | 8.86           | 101       | 1.0     |
| FNV    | 480 mg                          | 494.84                 | 14.84          | 103       | 3.9     |
| FCV    | 480 mg                          | 471.33                 | -8.67          | 98.19     | -1.8    |
| OCV    | 480 mg                          | 436.89                 | -43.11         | 91.02     | -8.9    |

The results for the calculated, claimed and % content of lumefantrine in drugs stored using different Ventilation conditions is presented in Table 3. The result shows a significant difference in the amount of Lumefantrine from the various ventilation condition and temperature. FNV had the highest concentration of 494.30 mg than other ventilation conditions and the claimed amount (480.00 mg) by the manufacturer. The least concentration was recorded in OCV (436.89 mg) while the amount of ACF (488.86 mg) and FCV (471.33 mg). Percentage content for ACF, FNV FCV and OCV are 101, 103, 98.19, 91.02 respectively.

### Table 4. HPLC Analytical Results for Retention Time in Estimation of Artemether content in Drugs.

| Sample | Retention time (min) | Mean Rt (Min) | Standard Deviation |
|--------|----------------------|---------------|--------------------|
| ACF    | 4.5                  | 4.499         | 0.002              |
| OCV    | 4.503                | 4.500         | 0.004              |
| FCV    | 4.497                | 4.497         | 0.000              |
| FNV    | 4.497                | 4.497         | 0.000              |
| Standard | 4.500               | 4.500         | 0.000              |

The result in Table 4 for retention time shows standard deviation of 0.002 and 0.004 for ACF and OCV, 0.000 for FNV and FVC for all repeated tests carried out on samples.

### Table 5. Concentration of artemether (80 mg strength) in drugs sample.

| Sample | Mean Peak Area of Sample | Mean Peak Area of Standard | Concentration Ru/Rs | Concentration (Ru/Rs x 80(mg/mL)) | % Content |
|--------|--------------------------|----------------------------|--------------------|-----------------------------------|-----------|
| ACF    | 895312                   | 972745                     | 0.92               | 73.6                              | 92.00     |
| OCV    | 966643                   | 972745                     | 0.99               | 79.2                              | 99.00     |
| FCV    | 935680                   | 972745                     | 0.96               | 76.8                              | 96.00     |
| FNV    | 981169                   | 972745                     | 1.01               | 80.6                              | 100.75    |

Table 5 shows the result of the concentration of Artemether in XYZ drug stored using different ventilation condition. From the Table above FCV and OCV has the closest value of 80.6 mg and 79.2 mg with similarly elevated peak area as shown in Figures 2-4 to the claimed manufacturer concentration of 80.00 mg. The percentage content still falls within the recommended NAFDAC range of 90-120%.

Figures 2-5 are chromatograms typical of some samples analyzed and Figure 5 is for the reference standard used for this work.
Figure 2. HPLC Chromatogram for Artemether Analysis in OCV 1 ACT-based Anti-Malarial Drug.

Figure 3. HPLC Chromatogram for Artemether Analysis in OCV 2 ACT-based Anti-Malarial Drug.

Figure 4. HPLC Chromatogram for Artemether Analysis in FCV 1 ACT-based Anti-Malarial Drug.

Figure 5. HPLC Chromatogram for Artemether Analysis of Standard Drug.
Drug quality and stability in the developing countries is a serious concern due to poverty and literacy levels as well as prevailing weather conditions [19]. This study evaluated the effects of different storage temperatures and ventilation conditions on the active pharmaceutical ingredient of a branded antimalarial drug (Artemether; 80 mg and Lumefantrine; 480 mg).

The amounts of these ingredients in the samples were compared to the amount claimed on the product label by the manufacturer of the drug, in a fixed-dose pack. As such, this study answers questions along drug supply, distribution, storage and retail chains, arising from inadequate electricity supply to power cooling systems in shops and retail outlets, and poor storage practices at community and private drug warehouses.

The result for the analysis of the drug shows that there is a significant difference (P<0.05) in the concentration (calculated amount) of lumefantrine. The amount of Lumefantrine in the samples varies according to the ventilation conditions and temperature. The highest amount was found in FNV (494.30±0.91) followed by ACF, FCV and OCV with a mean value of 488.68±0.56, 472.48±0.67 and 438.62±1.06 respectively. This implies that different ventilation conditions and temperature have effects on the concentration of lumefantrine, though the difference is not high enough to affect the potency of the drug [20]. The percentage content of the analyzed lumefantrine sample is from 91.38-102.98 % and this falls within the recommended acceptable range of 90-120 by NAFDAC Standard procedure for Lumefantrine [17] (Figure 6).

Similarly, the concentration of Artemether differs slightly from the manufacturer claim (80 mg), this variation could be attributed to the storage temperature and the difference is above the recommended standard. The results of these analysis is similar to the study carried out by Mehta et al. [21] which shows that amoxicillin and potassium clavulanate (250/62 Co-amoxiclav) oral suspension stored at room temperature 20°C and 8°C over a period of 11 days showed that amoxicillin is stable for 7 days at both temperatures. Also in agreement is the work by Naidoo [22] which showed that amoxicillin suspension stored between 2°C and 8°C for 7 days showed the lowest level of degradation. The percentage content of the analyzed Artemether sample is from 91.25-100.76 and this also falls within the recommended acceptable range of 90-120 by NAFDAC Standard procedure for Artemether [17].

This could however be ascertained that Artemether and lumefantrine exhibits considerable degree of stability in ventilation and temperature considered within the limit of this work.

John et al. [23] reported that a fixed dose ACT- based drug analyzed, contained the same active ingredient in the same amount as on their package label and were identical to the reference product. Spectroscopic results demonstrated that samples stored in Mali were stable for one year without concern for significant degradation of the active ingredients. Similarly, this work observed that lumefantrine remained relatively stable within the conditions considered. The work of Shrivastava et al. [24] on stability reported that High-Performance Liquid chromatography method for the estimation ofartemether in capsule dosage forms is precise, accurate, specific, and stability indicating. Statistical analysis proved that the method is repeatable and selective for the analysis of artemether as bulk drug and in pharmaceutical formulations. Our findings is consistent with the results of Bate et al.[25] who found that though artemether-lumefantrine has passed its labelled expiry date with about 3months, their concentration was stable and not degraded and also agrees with Arun and Smith [26] who developed and validated a HPLC-UV method for the simultaneous estimation of artemether and lumefantrine in fixed-dose combination tablets. In their study, HPLC analyses were carried out with a coupled UV detector. A linear correlation was found between the concentration range of 32-192 µg/mL at 254 nm for artemether.

This present study on the effect of storage and ventilation condition on stability of drug API’s concentration will support other studies on knowledge, attitudes and practices.
(KAP) on malaria prevention and control [27], affirming that improved community knowledge of malaria and its sources of transmission promotes preventive and personal protection practices amongst affected communities. It should be noteworthy that this research focuses on antimalarial formulations for adults. A research on malaria morbidity among under-five Nigerian children had shown that malaria still constitutes a significant health problem in the study area with over 65% having home antimalaria treatment [28]. This calls for investigative analysis on Children’s drug stability.

4. Conclusion

The recent increasing prescription and use of artemether-lumefantrine combined formulation as an effective treatment for resistant malaria calls for appropriate analytical methods that ascertain the quality control of these drugs in tablets dosage form and in suspensions. Results from this work demonstrated that the artemether-lumefantrine compounds in the studied antimalarial drugs were relatively stable under ambient storage conditions and in a high temperature and high humidity environment. Statistical tests of significance revealed that there is no significant difference in analyte concentration with varying storage conditions at 95% confidence interval. Hence, values fell within the recommended Nigerian (NAFDAC) set legislative standard. The constituents of the drug over the different ventilation types fall within the recommended API range of 90-120%. This supports the drug stability. In overall, co-formulation of artemether with lumefantrine has no effect on the stability of either of the active pharmaceutical ingredient (API) with respect to the investigated storage conditions.

References

[1] Bajaj S, Singla D, Sahuja N. (2012). Stability testing of Pharmaceutical products, J. of Applied Pharmaceutical Science, 2(03), 129-138.

[2] Kiron SS, Shirwaikar A, Saritha M. (2011). Influence of storage conditions on the potency of amoxicillin dispersible tablets stored in hospital and community pharmacies in different regions of kerala, Asian J. Pharm Clin Res, 4 (3), 101-102.

[3] Ajayi IO, Browne EN, Bateganya F, (2008). Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: a report from three study sites in sub-Saharan Africa. Malaria Journal. 7(7): 190.

[4] Roca-Feltzre A, Carneiro I & Armstrong Schellenberg JR (2008) Estimates of the burden of malaria morbidity in Africa in children under the age of 5 years. Tropical Medicine and International Health 13, 771–783.

[5] WHO (2010) WHO Guidelines for the treatment of malaria. Geneva: WorldHealth Organization.

[6] Breman JG, Alilio MS, Mills A (2004). Conquering the intolerable burden of malaria: what’s new, what’s needed: a summary. American Journal for Tropical Medicine and Hygiene. 71(2): 1–15.

[7] Koram KA, Abakolu B, Duah N. (2005). Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana. Acta Tropical.95: 194–203.

[8] Malmberg M., Ngasala B., Ferreira P. E., Larsson E., Jovel I., Hjalmarsson A., Petzold M., Premji Z., Gil J. P., Bjorkman A., Martensson A. (2013). Temporal trends of molecular markers associated with artemether–lumefantrine tolerance/resistance in Bagamoyo district, Tanzania. Malar. J. 12: 103.

[9] Li, Y., Wu, Y. L., (2003). An over four millennium story behind qinghaosu (artemisinin)—a fantastic antimalarial drug from a traditional Chinese herb. Curr. Med. Chem. 10, 2197–2307

[10] AdjuikM, BabikerA, GarnerP, Olliario P, Taylor W. (2004) International Artemisinin Study Group. Artesunate combinations fortreatment of malaria: meta-analysis. Lancet.363: 9–17.

[11] Rosenthal, P. J., McKerrow, J. H., Aikawa, M., Nagasawa, H. and Leech, J. H. (1988). A malarial cysteine proteinase is necessary for hemoglobin degradation by Plasmodium falciparum. J. Clin. Invest. 82: 1560-1566.

[12] Nayar G., Breman J.G., Newton P.N., Herrington J. (2012). Poor-quality antimalarial drugs in Southeast Asia and sub-Saharan Africa. Lancet Infect Dis. 12: 488–496

[13] Lefevre G. (2002). PK and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet®) with concomitant administration of ketoconazole in healthy subjects. British Journal of Clinical Pharmacology. 54: 485–492.

[14] Ballereau F, Prazuck T, Schrive I, Lafleuriel MT, Rozec D. (1997). Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. American Journal for Tropical Medicine and Hygiene. 57: 31–36.

[15] Olliario P, Wells T. (2009). The Global Portfolio of New Antimalarial Medicines Under Development. Clinical Pharmacological Therapy.85: 584–595

[16] Bhattarai A, Ali AS, Kachur SP, Martensson A, Abbas AK (2007). Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. PLoS Med 4: e309.

[17] NAFDAC (2014). Standard Operating Procedure for Lumeofantrine Estimation using UV-Vis Spectrophotometer. An Operation Manual of the National Agency for Food and Drug administration and Control. vol 9: 3-7

[18] Isabel D. C. and Gerson A. P. (2009). Quantitation of artemether in pharmaceutical raw material and injections by high performance liquid chromatography, Brazilian Journal of Pharmaceutical Sciences, 45, (4) : 737-742

[19] Gitua, J., Beck, A., and Rovers, J. (2014). Quality and stability of artemether-lumefantrine stored under ambient conditions in rural Mali. Abstract Malaria Journal, 13: 474

[20] Johnson CA, Steglitz N, Schroeder ME. (2009). Opportunities and responsibilities of pharmacists on short-term medical mission teams. J Am. Pharm. Asso. 49: 801–807.
[21] Mehta AC, Hart-Davies S, Payne J, Lacey RW. (1994). Stability of amoxicillin and potassium clavulanate in co-amoxiclav oral suspension. J Clin Pharm Ter., 19(5): 313-315.

[22] Naidoo, K. K., Nompuku, P., Mkalali, S. N., Shabangu, K., Nkabinde, L., Singh, V. (2006) ‘Post-Marketing Stability Surveillance: Amoxicillin’, SA Fam Pract, 48(6): 14-14d

[23] John G, Aaron B. Rovers J (2014) Quality and stability of artemether-lumefantrine stored under ambient conditions in rural Mali. Malaria Journal, 13: 474.

[24] Shrivastava A, Rissarani, Nagori B. P. (2010). Stability Indicating High-Performance Liquid Chromatography Method for the Estimation of Arteether in Capsule Dosage Forms. J Young Pharma. 2; 2(1): 79–84.

[25] Bate R., Tren R., Hess K., and Attaran A. (2009). Physical and chemical stability of expired fixed dose combination artemether-lumefantrine in uncontrolled tropical conditions.

[26] Arun, R. and Smith, A. (2011). Development of Analytical Method for Lumefantrine by UV Spectrophotometry International Journal Research Pharmaceutical Sciences 1 (3): 321-324.

[27] Amusan, V. O., Yahaya A. U., Philip A. V. (2017). Knowledge, Attitudes and Practices on Malaria Prevention and Control Among Private Security Guards Within Kaduna Metropolis, Kaduna State-Nigeria. Science Journal of Public Health. 5 (3): 240-245

[28] GUP I, Orji U. N., Amadi A. (2013). Malaria Morbidity among Under-Five Nigerian Children: A Study of its Prevalence and Health Practices of Primary Care Givers (Mothers) in a Resource-Poor Setting of a Rural Hospital in Eastern Nigeria. European Journal of Preventive Medicine. 1(3): 50-57.