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Comparative Assessment of Different Commercially Available Artemether-Lumefantrine 20/120mg Tablets in Kaduna State, Nigeria.

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ABSTRACT

Background: The problems of fake drug proliferation in Nigeria have affected the credibility of the healthcare system and can exert very harmful effects on the consumer resulting to illness, disability and even death which anyone can be a victim. Malaria is a major public health problem in Nigeria and accounts for an estimated 225,000 deaths annually. Artemether-lumefantrine combination remains the first line artemisinin combination therapy (ACT) for treatment of malaria as recommended by World Health Organization (WHO). This study assessed the quality of the various brands of Artemether-Lumefantrine tablets to determine if these products contain the level of active ingredient claimed on the label as well as determine their conformity with specified requirements in the pharmacopoeia. It also determined the percentage content of the various brands using developed HPLC method.

Method: Physical assessment studies, pharmacopoeia test (weight uniformity USP and Dissolution BP) and non-pharmacopeial tests; (hardness, disintegration and friability) were carried, and the percentage content of the active ingredients obtained using developed and validated HPLC method.

Result: The physical assessment tests showed that all artemether-lumefantrine brands conformed to NAFDAC stipulations for packaging and labelling. All the brands passed weight uniformity test, disintegration and friability tests, while 33.4% of the sampled brands failed the hardness test. The result of the dissolution profile for Artemether-Lumefantrine indicated that all samples complied with official standard. Assay of active ingredients using HPLC showed that only 50% of Artemether sample and 55.6% of Lumefantrine sample met the International Pharmacopoeial[7] percentage content requirement of 90% - 110% for both Artemether and Lumefantrine.

Conclusion: The need to continuously assess the quality of commercially available medicines for use by the populace cannot be overemphasized due to safety reasons.

1. Introduction

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. 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.

Drug quality assurance is very important in the effective fight against malaria. However, quality assurance of antimalarial drugs in the third world countries where malaria is endemic is often a neglected issue. Lack of quality drugs for malaria treatment can result in many dire consequences which can range from failure of therapy to death of patients. Another serious consequence is the development of resistance to antimalarial medication by Plasmodium species which has led to the ineffectiveness of some important antimalarial medications, an example of which is chloroquine. To counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcomes, combinations of antimalarials are now recommended by the WHO for the treatment of falciparum

malaria[1].

The Artemisnin-based Combination Therapies (ACTs), which are recommended by the WHO, have become the main-stay of malaria treatment. Artemether-Lumefantrine is the first fixed-dose ACT regimen to be manufactured under Good Manufacturing Practice conditions, and is the most widely adopted ACT regimen used in malaria control programs[2]. It is necessary to prevent the development of resistance by plasmodium to the ACTs including Artemether and Lumefantrine. Numerous brands of these medicines manufactured in various countries are commercially available in Nigeria. The National Agency for Food, Drug Administration and Control (NAFDAC) has fought for several years in the war against fake and counterfeit medicines. The increasing use of Artemether–Lumefantrine combination as an effective treatment for resistant malaria demands the need of analytical methods to quantify these formulations in order to evaluate their quality.

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. The effect of fake and substandard drugs in both economic terms and 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[3]. 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[4].

In 2017, a study conducted to assess the quality of 10 brands of artemether-lumefantrine tablets available in Port Harcourt showed that 50% of the samples fell short of specification in their percentage content of active ingredients[5]. Another study Onalo et al[6] on quality of generic medicines, showed how generic brands of antibiotics meet standard criteria for chemical and pharmaceutical equivalences in compliance with official requirements for quality parameters. Thus, the need for assessment of quality of antimalarial products available for use by the populace cannot be over emphasized due to safety reasons. Therefore, the increasing use of Artemether–Lumefantrine combination as an effective treatment for resistant malaria demands the need of analytical methods to quantify these formulations to evaluate their quality.

The study assessed the quality of various brands of artemether-lumefantrine antimalarial tablets commercially available in Kaduna State, North-west Nigeria.

2. MATERIALS AND METHO

2.1 Materials

A total of six different brands of Artemether-Lumefantrine antimalarial combination tablets (20/120mg) purchased across pharmacies within Kaduna State (10°31′35″; 7°26′19″ E1), were analyzed at NAFDAC Laboratory at Barnawa, Kaduna State., Nigeria. Ethanol (VWR Chemicals, UK), Vanilla/Sulphuric Acid (VWR Chemicals, UK), Simulated Gastric Fluid (USP, Rockville, USA), Sodium Hexanesulfonate (Sigma Aldrich, Germany) Sodium Dihydrogen Phosphate (MG Chemical, South Africa) Distilled Water (In-House Laboratory made) Phosphoric Acid (ICL, Israel).

2.1 Pharmacopoeia Tests

2.1.1 Physical Assessment

The packaging and labelling 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 2.

2.1.2 Uniformity of Weight

Six (6) 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 together 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).

2.2.3 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 Ultrasonic Cleaner (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 in triplicate.

2.2.4 Friability Test

Six tablets of artemether-lumefantrine were randomly selected from each brand of the samples using FAB-2S friability tester to carry out the friability test. The six tablets were first weighed together before placing them in the friabilator. The tablets were rotated in the friabilator for 4 mins 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, (Equation 1)

$$F = \frac{Wo - Wf}{Wo} X\ 100 \text{ .....Equation 1}$$

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

2.1.5 Hardness Test

Six (6) tablets were randomly selected from each brand of the samples. The HDT–300 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.

2.1.6 Identification and Authentication of Artemether and Lumefantrine

The presence of artemether in artemether –lumefantrine tablet samples was determined using basic official tests[7] 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.

2.1.7 Dissolution Rate Test of Artemether and Lumefantrine Tablet

Simulated gastric fluid (SGF) without enzyme was prepared based on BP official standard[8].

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. $y = 0.0336x + 0.0839$, $r2 = 0.998$

Determination of percentage content of Artemether and Lumefantrine using High Performance Liquid Chromatography.

Preparation of Ion Pair: 5.65g of sodium hexanesulfonate and 2.75g of sodium dihydrogen phosphate were dissolved in 900 mL of water. The pH was adjusted to 2.3 using phosphoric acid, the volume diluted to 1000 mL and filtered through a 0.45um filter. The following conditions for gradient elution were used:

a. Mobile phase A: 700 volumes of ion pair reagent and 300 volumes of acetonitrile.

b. Mobile phase B: 300 volumes of ion pair reagent and 700 volumes of acetonitrile.

Table 1: Gradient Elution Table for Artemether-Lumefantrine Assay

Time (min)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comments
0-28	60	40	Isocratic
28-29	60 to 0	40 to 100	Linear gradients
29-45	0	100	Isocratic
45-46	0 to 60	100 to 40	Return to initial composition
46-55	60	40	Isocratic re-equilibrations

The following solutions were prepared in the solvent which was obtained by mixing 200mLmL of ion pair reagent, 60mL of water and 200mL of 1-propanol and diluted to 1000mL with acetonitrile. Both solutions were prepared and kept at a temperature of not below 20°C. For solution (1), 20 tablets were weighed and powdered.
About 5mg of the powdered tablet containing 20mg of Artemether and 120mg of Lumefantrine was accurately weighed into a 100mL volumetric flask.
85mL of the solvent was added, allowed to cool to room temperature and filtered through a 0.45um. For solution (2), 20mg of artemether reference standard and 120mg of lumefantrine reference standard were accurately weighed in a 100mL volumetric flask, 85mL of the solvent was added, sonicated until dissolved and allowed to cool to room temperature. The HPLC machine was operated at a flow rate of 1.3mL per minute and at a wavelength of about 210nm for the first 28 minutes and the switched to about 380nm. 20uL each of solutions (1) and (2) were injected alternately, and the peak of artemether was eluted at a retention time of approximately 19 minutes and that of lumefantrine at approximately 34 minutes. The areas of the peak responses obtained in the chromatograms from the solutions were measured and used to calculate the content and percentage content of artemether ($C_{16}H_{26}O_5$) and lumefantrine ($C_{30}H_{32}Cl_3NO$) in the tablets.

3. RESULTS

The result of physical assessment of the packaging of all the sample brands of Artemether– Lumefantrine (A – F) shown in Table 3 below shows that all the brands complied with NAFDAC
labeling requirements. Of all the brands studied, 90% originated from India and only 10% were from Nigeria.

Table 2: Physical Assessment of the commercial Brands of Artemether-Lumefantrine Tablets.

Brand	NAFDAC Reg. no	Manf. & Exp. Date	Qty of active drug	Batch no	Colour	Packaging	Country
A	04 – 8969	Oct 2019 Sep 2022	Yes	GRT055	Yellow	Blisters	India
B	B4 – 0953	Nov 2020 Apr 2023	Yes	S20K043	Yellow	Blisters	India
C	A4 – 6700	Jun 2020 Jul 2023	Yes	7225119	Yellow	Blisters	India
D	A4 – 9435	Feb 2021 Jan 2024	Yes	ORMO 0721	Yellow	Blisters	Nigeria
E	B4 – 6461	Jan 2091 Dec 2021	Yes	T19010	Yellow	Blisters	India
F	B4 – 2289	Aug 2018 Jul 2021	Yes	NAA8610A	Yellow	Blisters	Ind ia

All the artemether-lumefantrine brands passed the British Pharmacopoeia stipulation for weight uniformity with brand B having the highest % weight deviation of 3.75% and brand A with the least percentage weight deviation of 0.38%. Official compendia[7] 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 15mins. All the studied brands passed the specification with brand C having the highest disintegration time of 12.78mins and brand E having the least disintegration time of 0.30 minutes. About 66.6% of the commercial samples of the brands of Artemether-Lumefantrine tablets studied passed the hardness test. Brands C and D failed the crushing strength test. They had suboptimal crushing strength that ranged between 2.43 ± 0.01kgf to 3.98 ±0.02. The brands that passed (A, B, E and F) 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 0.05 – 0.24%, with brands E having the least % friability of 0.05, and brand B having the highest % friability of 0.24% as shown in Table 3.

Table 3: Pharmacopoieal Test Results of Artemether-Lumefantrine Brands

Brand	Mean tablet weight±SEM (gm)	%weight deviation	Mean disintegration time (min) ± SEM	Mean hardness ± SEM (kgf)	% friability
A	0.32 ± 0.001	0.38	1.170 ± 0.030	7.82 ± 0.05	0.078
B	0.31 ± 0.011	3.75	11.33 ± 0.290	5.45 ± 0.14	0.248
C	0.22 ± 0.004	1.40	12.78 ± 0.150	2.43 ± 0.01	0.068
D	0.32 ± 0.003	0.98	9.650 ± 0.210	3.98 ± 0.02	0.1 96
E	0.27 ± 0.001	0.42	0.300 ± 0.005	7.75 ± 0.09	0.054
F	0.25 ± 0.0024	0.78	3.070 ± 0.080	4.31 ± 0.01	0.229

Qualitative Test to authenticate the presence of Artemether and 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 Lumefantrine.

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 D having the highest release at 100 minutes and sample B the least release for Artemether.

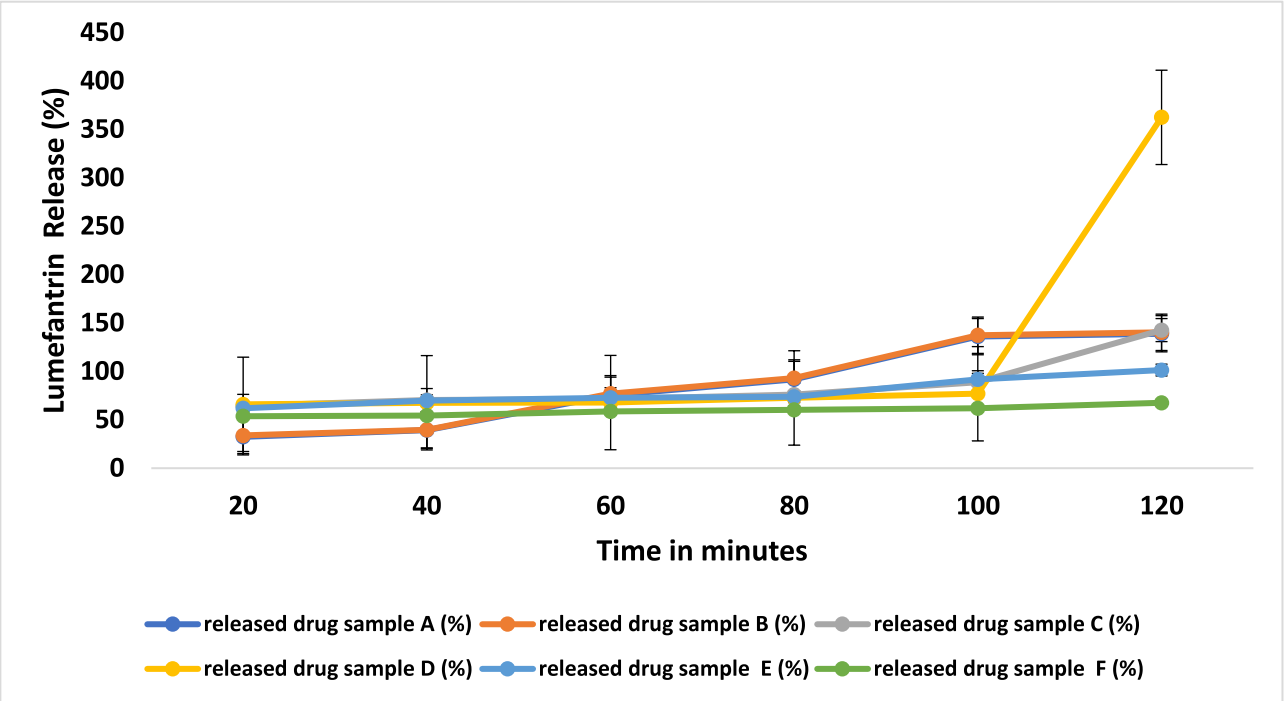

Figure 1: Dissolution profile of Artemether in Artemether-Lumefantrine tablet samples

Sample E and D showed highest released at 100 minutes for lumefantrine and sample A showed the least released at 60 minutes.

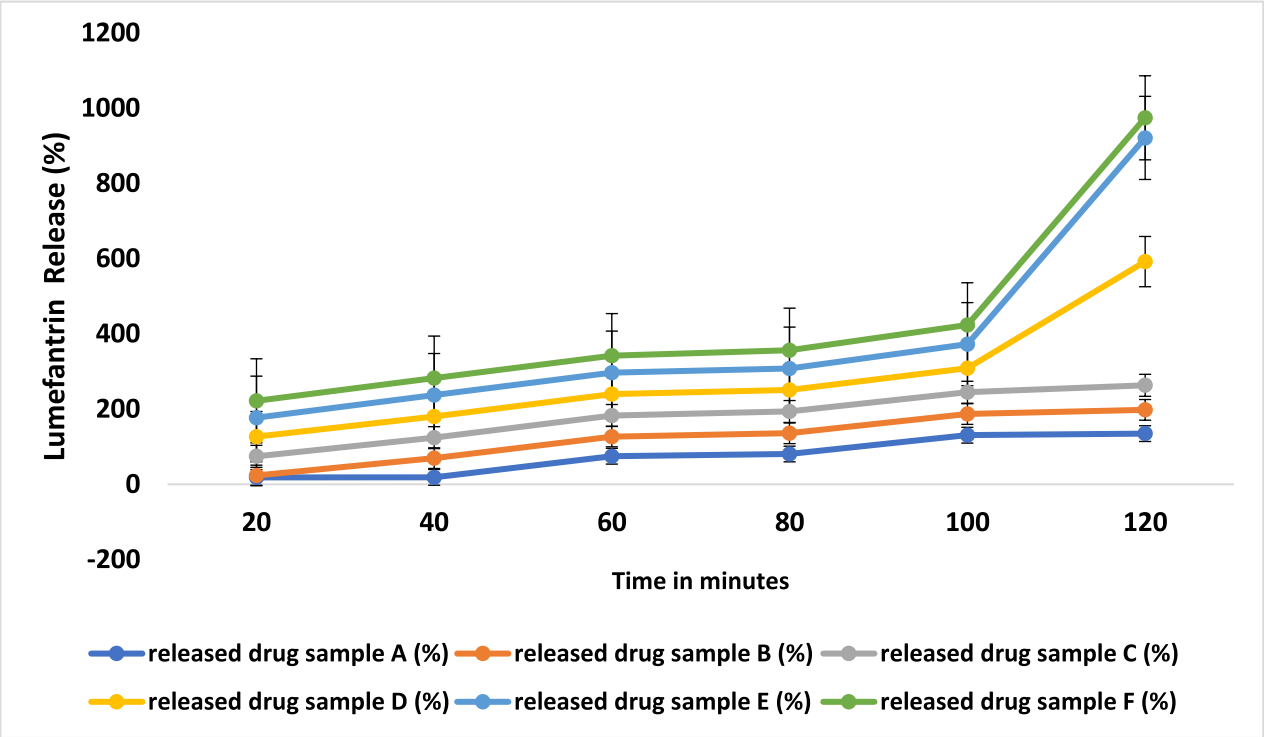

Figure 2: Dissolution Profile of Lumefantrine in sample of Artemether-Lumefantrine tablets

Table 6: Percentage content of Artemether and Lumefantrine in Tablets of brands of samples of Artemether-Lumefantrine.

Brand	Concentration of Artemether	%w/w content Artemether	Remark	Concentration of Lumefantrine	%w/w content of Lumefantrine	Remark of AL
A	16.50	82.51	**Fail**	117.36	97.80	Pass
B	19.20	96.00	Pass	129.60	108.30	Pass
C	13.04	65.20	**Fail**	11.10	9.25	**Fail**
D	18.08	90.40	Pass	116.10	97.00	Pass
E	19.20	96.00	Pass	122.60	102.17	Pass
F	12.60	63.00	**Fail**	145.20	121.00	**Fail**

4. 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 labelling requirements. Also, a study by Danraka, et al[9] showed overall availability of antimalarials tablets and other essential medicines in all hospital and community pharmacies in Abuja, which indicated the readily availability of antimalarials at grassroots, hence the need for their periodic quality assessments. This may be attributed to the recent re-invigorated NAFDAC efforts 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 (BCS). Artemether is a BCS Class II drug which exhibits low aqueous solubility with higher permeability and quickly metabolized in GIT, while Lumefantrine is a BCS Class IV drug which has low solubility and low permeability. 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[7] stipulation of less than 15 minutes for uncoated tablets with sample C having the highest disintegration time of 12.78 minutes and sample E having the least disintegration time of 0.30minutes. 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. In this study, sample brands C and D failed the BP[8] hardness test specification for uncoated tablets. 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 and thus affect bioavailability of the active ingredient. Worse still the tablet may be passed out in the phases undissolved. Hence, there is a strong correlation between disintegration time and the rate of dissolution. 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[8].

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. Dissolution test is a measure of amount of the active ingredient 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. The International Pharmacopoeia[7], specified minimum required percentage release for artemether and lumefantrine as 45% in 1 hr., and 60% in 45minutes of the labelled amount of claim respectively. In this study, the dissolution profile for artemether (Figure 1 above) and that of lumefantrine (Figure 2 above) 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.

The International Pharmacopoeia[7] specifies that Artemether-Lumefantrine tablets containing Artemether and Lumefantrine, must contain 90% - 110% of the amount of the two active ingredients stated on the label. This study showed that 50% and 44.4% of the samples of Artemether and Lumefantrine respectively failed the official

specification for both Artemether and Lumefantrine respectively as shown in Table 3. In a similar study reported in Ghana[10] all the brands of Artemether-Lumefantrine tablets analyzed contained more than 110% of lumefantrine. 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 in therapeutic failure with undesirable consequences as well. The manufacturing of substandard antimalarials is mostly 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. The findings of this study are consistent with previous findings; such as a study by Bate and Hess[10] which reported that over 30% of samples of anti-malarial drugs collected from pharmacies in Lagos area failed percentage content using thin layer chromatography, also in another study by Mbahurike et al[5], on brands of Artemether-Lumefantrine tablets available in Port Harcourt, it reported that 50% of the samples fell short of specification in their percentage content of active ingredients. The major limitation of this study was the absence of a similarity factor calculation, which is crucial in providing information about drug release in comparison with a marketed innovator product[11,12], which could have shed more light on the quality of the six brands of ACT assessed.

5. Conclusion

This study assessed the quality of 6 brands of artemether-lumefantrine tablets available in the market in Kaduna state. The brands of artemether-lumefantrine sampled for this study satisfied the specification for identification, disintegration test, uniformity of weight test and friability test.

The study established a good conformation to some of the official specifications and requirements. However, the HPLC analysis showed that 50% of the samples of artemether and 44.4% of samples of lumefantrine 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. A similarity factor calculation that compares the findings on the assessed ACTs with innovator brands was not done in this study, which could shed more light on the bioequivalence parameters of the ACT assessed.

CONFLICT OF INTEREST: The authors declared that there was none.

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