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Quality assessment of fifteen brands of artemether-lumefantrine tablets in Lagos metropolis, Nigeria

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ABSTRACT

Background: Nigeria has been shown to have the highest number of malaria casualties worldwide. Due to the increased demand for anti-malarial drugs, the Nigerian pharmaceutical market is flooded with a wide range of generic drugs whose quality must be regularly checked.

Objectives: The objective of this research was to carry out quality assessment of artemether-lumefantrine tablets marketed in Lagos metropolis, Nigeria.

Methods: Fifteen different brands of artemether-lumefantrine tablets gotten from five local government areas (Mushin, Oshodi-Isolo, Surulere, Ikorodu and Lagos Island) in Lagos were evaluated for weight variation, diameter, thickness, disintegration, hardness, friability according to the methods specified in the British Pharmacopoeia (2014) and the United States Pharmacopoeia (2014). The quantitative assay was carried out according to a previous research by Vinodh *et al*., (2013) with some modifications.

Results: The results showed that 100 % of the tested brands of artemether-lumefantrine tablets passed the weight variation test, disintegration test (30 minutes) and diameter test (±5% and ±3%, $\leq$12.5mm and >12.5 mm respectively). It was observed that 87 % of the brands tested passed the friability test ($\leq$1%) and thickness test (±5% deviation) while 80 % conformed to the standard limit (4– 10kp) for hardness. Only, 67% of the brands tested conformed to the quantitative assay standard limit (90- 110%). Summarily, the results indicated that only 47 % of all the brands which included the innovator brand, passed all the tests carried out on them.

Conclusion: This study has been able to show that of all the brands of artemether-lumefantrine tablets assessed, 53% of the brands did not pass all the quality tests that they were subjected to. Hence, the importance of continuous monitoring of the safety and efficacy of drugs.

Key words: Artemether, Lumefantrine, Malaria, Pharmaceutical, quality

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Évaluation de la qualité de quinze marques de comprimés d'artéméther-luméfantrine dans la métropole de Lagos, au Nigéria

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RESUME

Contexte: Selon des études, le Nigéria compte le plus grand nombre de victimes du paludisme dans le monde. En raison de la demande accrue de médicaments antipaludiques, le marché pharmaceutique nigérian est inondé d'une large gamme de médicaments génériques dont la qualité doit être régulièrement vérifiée.

Objectifs: L'objectif de cette recherche est de procéder à une évaluation de la qualité des comprimés d'd'artéméther-luméfantrinecommercialisés dans la métropole de Lagos, au Nigeria.

Méthodes: Quinze marques différentes de comprimés d'artéméther-luméfantrine obtenues auprès de cinq collectivités locales (Mushin, Oshodi-Isolo, Surulere, Ikorodu et Lagos Island) à Lagos ont été évaluées pour la variation de poids, le diamètre, l'épaisseur, la désintégration, la dureté, la friabilité selon la méthode spécifiée dans la pharmacopée britannique (2014) et la pharmacopée américaine (2014). Le dosage quantitatif a été réalisé selon une recherche antérieure de Vinodh et al., (2013) avec quelques modifications.

Résultats: Les résultats montrent que 100% des marques testées de comprimés d'artéméther-luméfantrine ont réussi le test de variation de poids, le test de désintégration (30 minutes) et le test de diamètre (±5% et ±3%, $\leq$12,5 mm et>12,5 mm respectivement). Il a été observé que 87% des marques testées ont réussi le test de friabilité ($\leq$1%) et le test d'épaisseur (écart de ±5%) tandis que 80% étaient conformes à la limite standard (4-10kp) pour la dureté. Seulement, 67% des marques testées étaient conformes à la limite standard de dosage quantitatif (90-110%). En résumé, les résultats indiquent que seulement 47% de toutes les marques qui comprenaient la marque innovatrice, ont réussi tous les tests effectués sur elles.

Conclusion: Cette étude a pu montrer que de toutes les marques de comprimés d'artéméther-luméfantrine évaluées, 53% des marques n'ont pas réussi les tests de qualité auxquels elles ont été soumises. D'où l'importance d'une surveillance continue de l'innocuité et de l'efficacité des médicaments.

Mots-clés: artéméther, luméfantrine, paludisme, qualité pharmaceutique

INTRODUCTION

According to the Nigerian National Malaria Strategic Plan 2014-2020, malaria is accountable for 60 percent of out-patient visits to healthcare facilities, 11 percent of maternal deaths, 30 percent of childhood deaths and 25 percent of deaths in neonates and infants.[1] Nigeria is known as the country that has the highest number of malaria casualties all over the world with an estimated number of 100 million malaria cases and about 300,000 malaria deaths each year.[2]

The name malaria took its origin from Latin's *malaira* which means bad air. Malaria is characterized by different symptoms such as fever, nausea, vomiting, headache, muscle ache, back pain, joint pains, chest pain, sometimes cough, in severe cases it leads to coma and finally it causes death of the persons, approximately one million people per year. About 90% of the people who are living in Sub-Saharan Africa, mainly children under five years of age and pregnant women are more prone to malaria.[3]

There are four main species of the parasite (*P. falciparum, P. vivax, P. ovale*, and *P. malariae*) that are known to affect man. However, malaria caused by *P. falciparum* is the deadliest and most prevalent (90% - 98%). It is the most common disease in Africa, south of the Sahara, which accounts for the extreme mortality in this region.[4]

Management of the disease in Africa has moved from single drug therapies like chloroquine to the new Artemisinin-based Combination Therapies (ACT) because of resistance associated with mono- therapies.[4,5] Fixed-combination and multiple-drug therapies are used to exploit the synergistic and additive potential of individual drugs. The aim is to improve efficacy and to retard the development of resistance to the individual components of the combination.[4] However, some of these anti-malarial therapies are prone to different adverse effects.

According to National Guidelines for Diagnosis and Treatment of Malaria in 2015, artemether-lumefantrine is the medicine of choice for the treatment of uncomplicated malaria in Nigeria.[6] Artemether and lumefantrine are used to treat uncomplicated malaria caused by *P. falciparum* in a fixed ratio dosage of (1:6) and they produce minimal side effects.[3]

Hence, in a bid to search for anti-malarial drugs with minimal side effects, some people have resolved to continuously prescribe, dispense, administer and use artemether-lumefantrine combination tablets.[7] Thus as a result of the increased demand for artemether-lumefantrine tablets, the Nigerian pharmaceutical market is continuously flooded with a wide range of generic drugs of such with improbable quality. This statement is substantiated by the research on the quality of artemether-lumefantrine tablets in south west, Nigeria by Izeibekhai *et al*.,[8] where some of the brands tested failed, for example 60% of the brands failed dissolution test while 20 % of the brands tested failed quantitative assay.

Another study carried out on the quality assessment of artemether-lumefantrine tablets in Rivers state, Nigeria has revealed that 50% of the brands tested failed hardness test and 30 % of the tested brands failed quantitative assay.[9] With previous and recent evidences of the presence of substandard artemisinin-lumefantrine tablets in the Nigerian market,[8,9,10,11] there is the need for constant post-marketing surveillance studies on these medications as ways of interventions in their safety and efficacy.

Therefore, the aim of this research work was to carry out the quality assessment of fifteen brands of artemether-lumefantrine tablets in Lagos Metropolis, Nigeria.

METHODS

Materials

Working standards of artemether and lumefantrine (manufactured by Calyx Chemicals and Pharmaceuticals Limited, India) were provided by Emzor Pharmaceutical Industries Limited, Lagos, Nigeria. Fifteen different brands of artemether-lumefantrine tablets were analyzed. Chemicals and reagents used include Tetra-n-butyl ammonium hydrogen sulphate-Laboratory reagent grade, Acetonitrile-HPLC grade, Methanol-analytical reagent grade, Hydrochloric acid- (All chemicals werefrom Fisher Scientific, UK).

Equipment

Uni Bloc electronic balance (Shimadzu Corporation, Japan); Disintegration time test machine (Copley/DGT/4000, Nottingham, United Kingdom); Friability Test Machine (Copley FRV/2JY, Nottingham, United Kingdom); Tablet Hardness Tester (TBF 1000 Copley, NG4 2JY Nottingham, United Kingdom); Mitutoyo Absolute Micrometer Gauge (ID-C1012EXBS, Mitutoyo Corp., Kawasaki, Japan); Millipore Filter (WP 6122050, Millipore Corporation Billerica MA , India); Vial Cronus amber (12×32 mm, 8mm screw pk/100, SMI-Lab Hut Ltd, Gloucester, GL2 8AX, United Kingdom); Branson Ultrasonic Bath (Branson Ultrasonics Corporation,

1510E-DTH , USA); Hot plate and Magnetic stirrer (Jenway 1000, United Kingdom); Cecil UV Spectrophotometer (CE 7500, Cambridge, England); High Performance Liquid Chromatography apparatus (Agilent Eclipse Plus, Column- C18 (100mm x 4.6mm) 3.5µm (S/N USUXR15200 USA).

Sample collection

Fifteen brands of unexpired NAFDAC (National Agency for Food and Drug Administration and Control) registered artemether-lumefantrinetablets were obtained from some drug stores from five local government areas (Mushin, Oshodi-Isolo, Surulere, Ikorodu and Lagos Island) in Lagos metropolis, Nigeria. The fifteen samples were designated as AL1 to AL15.

Physical evaluation

The following identification parameters were noted- the country of manufacture, batch number, NAFDAC number, tablet's surface orientation and legibility of any identifying markings. Confirmation of the originality of each brand by utilizing the Mobile Authentication Service (M.A.S) specified by NAFDAC was done. All the tablet samples obtained were within their shelf lives during the period of the experiment.

Weight variation

Weight variation test was carried out according to the United States Pharmacopoeia's specification.[12] Twenty (20) tablets were randomly selected and weighed individually, also the average weight of the 20 tablets were calculated and the percentage deviations of the tablets from the average weight were determined. The tablet batches pass the test if not more than two of the individual weights deviate from the average weight by more than ± 7.5% and none deviated by twice ± 7.5%, for tablets weighing between 130-324 mg; for tablets weighing above 324 mg, the tablet batches pass the test if not more than two of the individual weights deviate from the average weight by more than ± 5% and none deviated by twice± 5%.[12,13]

Measurement of diameter and thickness

Twenty (20) tablets were randomly selected and their diameter and thickness were measured individually using Mitutoyo® Absolute Micrometer Gauge (ID-C1012EXBS, Mitutoyo Corp., Kawasaki, Japan), the average diameter and thickness of the tablets were also calculated. The deviations of each individual tablet from the average diameter should not exceed ±5 % for tablets with diameter of less than 12.5mm and ±3 % for tablets with diameter of 12.5 mm or more.[13] Thickness of each tablet should not exceed ±5 % from the average thickness.[14]

Friability test

Twenty tablet samples were weighed accurately and tested in a friabilator (Copley FRV/2JY, Copley scientific limited, Nottingham, United Kingdom). The friabilator was set to revolve at 25 revolutions per minute for four minutes. Loose dust was removed from the tablets and the tablets were re-weighed. The loss in weight was noted and the percentage loss calculated.[15]

Hardness test

The hardness of the tablets was measured using a tablet hardness tester (TBF 1000 Copley, NG4 2JY Nottingham, United Kingdom). The tablet to be tested was held between a fixed and moving jaw. The force applied to the edge of the tablet was gradually increased as the tester was set to automatically measure the hardness by the movement of the indenter forward until the tablet breaks. Ten tablets were used for each brand.[13]

Disintegration test

Disintegration time was measured for 6 tablets without inserting disks using 600 mL of purified water at 37±2°C in a disintegration apparatus(Copley/DGT/4000, Nottingham, United Kingdom). The tube was allowed to move up and down at a constant rate of 30 times per minute through a distance of 75 mm.[13]

Quantitative assay test

The quantitative assay test was carried out using the High Performance Liquid Chromatography as reported by Vinodh[16] with some modifications.

Preparation of buffer

The buffer was prepared by weighing 6.78 g of tetra-n-butyl ammonium hydrogen sulphate salt into a 2000 mL volumetric flask and it was made up to 2000 mL with distilled water.[16]

Preparation of mobile phase

The mobile phase was prepared by mixing the above tetra-n-butyl ammonium hydrogen sulfate (TBAHS) buffer solution and acetonitrile in the ratio 1:4; 500 ml of TBAHS was mixed with 2000 ml of acetonitrile. The mixture was filtered through 0.45 µm membrane filter using a Millipore filter and degassed by means of a Millipore vacuum pump Filter (WP 6122050, Millipore Corporation Billerica MA, India).[16]

Chromatographic conditions

The mobile phase was delivered into the HPLC apparatus (Agilent Eclipse Plus, Column- C18 (100mmx4.6mm) 3.5µm (S/N USUXR15200 USA) at a column oven temperature of 30°C, at a flow rate of 1mL/min.[16] The injection volume was 10 µl and the run time was 5 minutes. The detection for both artemether and lumefantrine was done at 210 nm, using a UV detector.

Preparation of the diluent

The diluent was prepared by mixing Tetra-n-butyl ammonium hydrogen sulfate (TBAHS) solution above and acetonitrile in the ratio 1:1.5 (1000 ml of TBAHS and 1500 ml of acetonitrile).[16]

Reference sample preparation

The method used by Vinodh et al., in 2013 was adopted with some modifications.[16]Artemether (20 mg) and lumefantrine (120 mg) were weighed into a 100 mL volumetric flask and an aliquot portion of the diluent was added. The content of the volumetric flask was placed in a sonicator for about 10 minutes to aid complete dissolution. The volume was made up to the 100 ml mark with the same diluent. Subsequently, 2 mL of the above solution was transferred into a 20 mL volumetric flask and made up to the 20 mL mark, using the diluents to obtain a solution of 20 µg/mL of artemether and 120 µg/mL of lumefantrine.[17] Six replicate injections of 10µL of each final concentration were injected into the amber Cronus vial for analysis.

Test sample preparation

Twenty tablets of each brand of tablet formulation-artemether/ lumefantrine: 20 mg/120 mg (Ten tablets were used for artemether/ lumefantrine: 80mg/480mg) were weighed and triturated into powder form. The average weight of the powder (a quantity equivalent to 20 mg of artemether and 120 mg of lumefantrine) was transferred into a 100 mL volumetric flask which was made up to 100 mL mark. The content of the volumetric flask was sonicated for 10 minutes. Subsequently, 2 mL of the above solution was transferred into a 20 ml volumetric flask and made up to the 20 mL mark using the diluent above.[17] Three replicate injections of 10 µL of each final concentration were injected into the amber Cronus vial for analysis.

RESULTS

Physical evaluation

The analysis of the physical appearance showed that the tablets of the different brands had similar characteristics (Table 1). Confirmation of originality of the drugs using the Mobile Authentication Service showed that all the brands for which the service was available passed. The service was not available on some of the packaging of the tablets.

Weight variation analysis

The weight variation analysis showed that all the brands tested passed the test. The weight variation analysis of all the brands tested were within the United States Pharmacopoeia (USP) specification as seen in Table 2.

Diameter test analysis

The diameter test analysis of the tablets showed that all the brands tested passed the diameter test (table 3).

Thickness test analysis

The thickness test analysis of the tablets showed that only brands AL12 and AL13 failed the thickness test (Table 4).

Disintegration test analysis

Table 5 showed that all the brands of tablets passed the disintegration test.

Hardness test analysis

Three brands (AL5, AL12 and AL15) failed the hardness test (table 5).

Friability test analysis

Only two brands (AL8 and AL13) out of the fifteen brands tested failed the friability test (table 5).

Quantitative assay

Five brands (AL4, AL8, AL10, AL11, AL12) failed the quantitative assay (table 5).

Figures 1 and 2 showed typical chromatograms of artemether and lumefantrine respectively used in the quantitative assay.

Table 1: Description of artemether-lumefantrine tablets evaluated

Brand Code	Country	Batch No.	Registration status	Surface Orientation	Identifying Markings	Confirmation of Originality by M.A.S
AL1	India	FD4F67;ID45635	R	Biconvex	Scored / No embossment	Confirmed
AL2	India	PO6614H	R	Plain	None	Confirmed
AL3	U.S.A.	F3265	R	Concave and Convex	Non- scored /Embossed on both sides	N/A
AL4	India	VT425	R	Biconvex	Non- scored/ Embossed on both sides	Confirmed
AL5	India	LN-606	R	Biconvex	Scored /Embossed on both sides	Confirmed
AL6	India	AMMH0043	R	Biconvex	None	Confirmed
AL7	India	CWY063016	R	Biconvex	Non- scored/ Embossed on one side	N/A
AL8	India	7222853	R	Biconvex	Scored / No embossment	Confirmed
AL9	India	DY1444524	R	Biconvex	Scored / No embossment	Confirmed
AL10	India	AR4034	R	Biconvex	Scored / No embossment	N/A
AL11	India	123	R	Biconvex	None	N/A
AL12	China	130555	R	Biconvex	Scored / No embossment	Confirmed
AL13	Nigeria	4 V02	R	Biconvex	Scored /Embossed on both sides	Confirmed
AL14	Nigeria	AF2501	R	Biconvex	Scored / No embossment	Confirmed
AL15	India	J061	R	Biconvex	Non -scored/ embossed on one side	Confirmed

M.A.S- Mobile authentication service, N/A – Not available
R- Registered by National Agency for Food and Drug Administration and Control (NAFDAC)

Table 2: Weight variation test for the artemether-lumefantrine tablets

Brand Code	Weight of 20 tablets (mg)	Average weight per tablet ±SD(mg)	Maximum weight of tablet (mg)	Minimum weight of tablet (mg)	Positive Deviation (%)	Negative Deviation (%)	Total number of tablets outside the USP specification	Status
AL1	7006	350.30±1.95	354	347	1.06	-0.94	0	Pass
AL2	4847	242.40±3.82	249	237	2.72	-2.23	0	Pass
AL3	4810	240.50±2.54	246	237	2.29	-1.46	0	Pass
AL4	6379	318.95±3.72	324	311	1.58	-2.49	0	Pass
AL5	6857	342.85±5.18	350	327	2.09	-4.62	0	Pass
AL6	6658	332.90±2.88	339	328	1.83	-1.47	0	Pass
AL7	4962	248.10±2.13	252	245	1.57	-1.25	0	Pass
AL8	8110	405.50±2.16	409	402	0.86	-0.86	0	Pass
AL9	4987	249.35±3.25	254	241	1.86	-3.35	0	Pass
AL10	5142	257.10±4.41	269	251	4.63	-2.37	0	Pass
AL11	5874	293.70±5.39	302	282	2.83	-3.98	0	Pass
AL12	4628	231.40±9.39	250	215	8.04	-7.08	2	Pass
AL13	7114	355.70±1.46	375	327	5.43	-8.07	2	Pass
AL14	16660	833.00±6.45	845	819	1.44	-1.68	0	Pass
AL15	13750	687.45±13.45	712	655	3.57	-4.72	0	Pass

SD- Standard deviation, USP – United StatesPharmacopoeia

Table 3: Diameter test for the artemether-lumefantrine tablets

Brand Code	Sum of diameter of tablets (mm)	Average diameter per tablet±SD (mm)	Maximum diameter of tablet (mm)	Minimum diameter of tablet (mm)	Positive Deviation (%)	Negative Deviation (%)	Total number of tablets outside specification	Status
AL1	201.60	10.08±0.01	10.09	10.07	0.10	-0.10	0	Pass
AL2	183.90	9.20±0.03	9.24	9.16	0.43	-0.43	0	Pass
AL3	181.60	9.08±0.01	9.09	9.07	0.11	-0.11	0	Pass
AL4	194.90	9.74±0.02	9.78	9.71	0.41	-0.31	0	Pass
AL5	209.20	10.46±0.01	10.47	10.44	0.10	-0.19	0	Pass
AL6	191.10	9.56±0.01	9.56	9.55	0.00	-0.10	0	Pass
AL7	182.90	9.15±0.01	9.16	9.13	0.11	-0.22	0	Pass
AL8	202.60	10.13±0.01	10.14	10.12	0.10	-0.10	0	Pass
AL9	182.20	9.11±0.01	9.12	9.10	0.11	-0.11	0	Pass
AL10	189.60	9.48±0.03	9.53	9.43	0.53	-0.53	0	Pass
AL11	195.70	9.79±0.02	9.83	9.76	0.41	-0.31	0	Pass
AL12	182.40	9.12±0.02	9.15	9.09	0.33	-0.33	0	Pass
AL13	204.00	10.20±0.04	10.28	10.14	0.78	-0.59	0	Pass
AL14	263.80	13.19±0.02	13.22	13.17	0.23	-0.15	0	Pass
AL15	254.20	12.71±0.02	12.79	12.68	0.63	-0.24	0	Pass

SD- Standard deviation

Table 4: Thickness test for the artemether-lumefantrine tablets

Brand Code	Sum of thickness of tablets (mm)	Average thickness per tablet ±SD (mm)	Maximum thickness of tablet (mm)	Minimum thickness of tablet (mm)	Positive Deviation (%)	Negative Deviation (%)	Total number of tablets outside specification	Status
AL1	71.40	3.57±0.01	3.60	3.55	0.84	-0.56	0	Pass
AL2	62.20	3.11±0.05	3.18	3.03	2.25	-2.57	0	Pass
AL3	63.30	3.16±0.03	3.24	3.12	2.53	-1.27	0	Pass
AL4	91.30	4.57±0.04	4.63	4.48	1.31	-1.97	0	Pass
AL5	89.40	4.47±0.06	4.63	4.32	3.58	-3.36	0	Pass
AL6	76.30	3.82±0.02	3.87	3.77	1.31	-1.31	0	Pass
AL7	62.50	3.13±0.03	3.18	3.09	1.60	-1.28	0	Pass
AL8	82.20	4.11±0.01	4.13	4.09	0.49	-0.49	0	Pass
AL9	62.70	3.14±0.03	3.18	3.05	1.27	-2.87	0	Pass
AL10	64.80	3.24±0.08	3.35	3.12	3.40	-3.70	0	Pass
AL11	85.60	4.28±0.05	4.37	4.19	2.10	-2.10	0	Pass
AL12	72.60	3.63±0.10	3.87	3.49	6.61	-3.86	1	Fail
AL13	73.90	3.70±0.12	3.87	3.46	4.59	-6.49	3	Fail
AL14	138.00	6.90±0.05	6.99	6.84	1.30	-0.87	0	Pass
AL15	112.60	5.63±0.07	5.72	5.44	1.60	-3.37	0	Pass

SD- Standard deviation

Table 5: Disintegration, hardness, friability and quantitative assayof the different brands of artemether-lumefantrine tablets

Brand Code	Average Disintegration time ± SD (Minutes)	Average Hardness Test (kp)	Friability Test (%)	Assay (%)± SD	
				Artemether	Lumefantrine
AL1	2.47±0.04	7.29±0.35	0.01	106.4±0.18	95.45±0.60
AL2	4.43±0.09	7.89±0.34	0.14	100.5±0.08	94.35±0.24
AL3	1.59±0.28	9.03±0.25	0.15	108.5±0.12	90.01±0.19
AL4	3.18±0.92	5.96±0.22	0.00	107.1±0.10	88.14±0.76
AL5	0.43±0.08	3.33±0.08	0.16	109.7±0.07	94.62±0.23
AL6	0.84±0.36	7.53±0.16	0.08	109.3±0.05	95.20±0.80
AL7	6.48±0.33	7.57±0.22	0.14	98.14±0.11	90.07±0.48
AL8	0.15±0.05	4.09±0.13	3.19	95.85±0.24	86.63±0.36
AL9	4.05±0.29	5.43±0.13	0.10	93.67±0.17	94.21±0.39
AL10	0.30±0.04	5.89±0.19	0.16	91.63±0.15	79.78±0.26
AL11	0.96±0.28	5.77±0.16	0.00	97.47±0.08	84.85±1.66
AL12	8.22±2.04	2.40±0.20	0.15	89.37±0.08	77.79±1.50
AL13	0.57±0.62	8.59±0.61	10.04	104.6±0.10	93.07±0.30
AL14	0.78±0.05	4.76±0.22	0.00	100.4±0.06	101.5±0.41
AL15	2.68±1.26	14.8±0.29	0.22	99.96±0.14	98.05±0.66

SD- Standard deviation

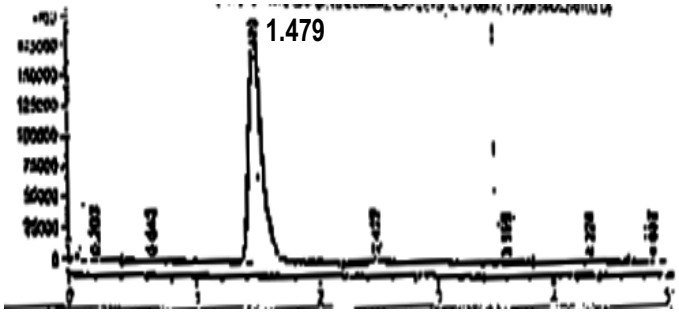

Figure 1: Typical Chromatogram of artemether showing retention time at 1.479 min.

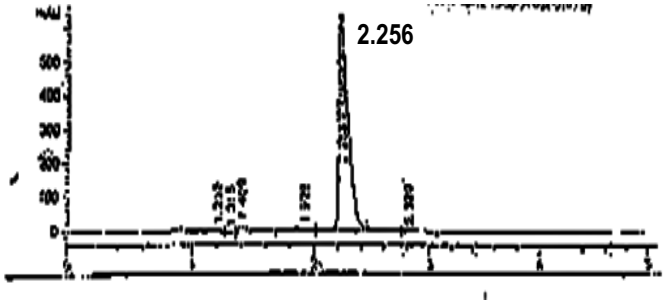

Figure 2: Typical Chromatogram of lumefantrine showing retention time at 2.256 min.

DISCUSSION

All the brands of artemether-lumefantrine tablets evaluated purchased were within their shelf lives throughout the period of the research work. They all had NAFDAC registration numbers, which supposedly means that they all met NAFDAC requirements for pharmaceutical products in Nigeria. Only 13% of the brands were manufactured in Nigeria, 73% were manufactured in India, 7% each were manufactured in China and the United states of America thus, suggesting that a great percentage of artemether-lumefantrine tablets used in Nigeria are imported (Table 1).

All the samples had impressive appearance even though there were variations in their organoleptic properties. They were yellow in colour, they all had agreeable to slightly pungent odour, their surface orientations being plain, concave and convex. Some were scored and others were not. Scoring allows accurate subdivision of a tablet in order to provide a dose of less than one tablet.[18] All the tablet samples had embossment on either one or both sides. Embossment can serve as a means of identifying the tablet when the name of the drug is not known or when the package is missing.[19]

Confirmation of originality of the drugs using the mobile authentication service showed that all the brands for which the service was available passed the test of originality as confirmed by the service. Subsequent

results will actually show if these claims of originality are true or not. However, for some of the drugs like AL3, AL7, AL10 and AL11, this service was not available.

All the sample brands complied with the United States Pharmacopoeia specification for uniformity of weight which states that for tablets whose average weight is between 130 - 324 mg, the percentage deviation of not more than two tablets can be more than ±7.5% and none of the tablets must deviate by ±15%, also for tablets whose average weight is more than 324 mg, the percentage deviation of not more than two tablets can be more than ±5% and none of the tablets must deviate by ±10%.[12]

The weight variation test analysis has shown that all the brands of artemether-lumefantrine tablets tested passed the test. Table 2 revealed that the weight variation test analysis of brands AL12 and AL13 showed that only two tablets each for both brands were out of specification. Thus 100% of the brands tested passed the weight variation test.

The essence of the weight variation is to ascertain uniformity of weight, this is because when the weight is not uniform, it can lead to lack of uniformity in the active ingredient and thus can lead to substandard drugs. This result is similar to a research work [20] on the quality assessment of artemether-lumefantrine tablets carried out in Ethiopia in 2019, where all the artemether–lumefantrine tablets tested for weight variation also passed the test.

The diameter test has shown that all the brands of artemether-lumefantrine tablets tested passed (tablets less than or equal to average diameter of 12.5 mm should not deviate by more than ±5% and tablets more than average diameter of 12.5 mm should not deviate by more than ±3%). The diameter values were within a range of 9.11 mm to 13.19 mm (Table 3). Table 3 revealed that the percentage deviations of all brands were within specification as both deviations for the maximum and minimum diameter values were all within specification. Most times in the analysis of the diameter of tablets, deviations outside the standard specification are hardly encountered since the diameter size usually depends on the dimension of the die and punches selected for the making the tablets.[14]

The thickness test has shown that not all the brands of artemether-lumefantrine tablets tested passed. Table 4 revealed that the percentage deviations of thirteen of the brands were within specification (±5 % deviation).[14] However, it was shown that the thickness test analysis of brand AL12 showed that one tablet was out of specification (+6.61 % deviation) while the thickness test analysis of brand AL13 showed that three tablets were out of specification (-6.22 %, -6.22 %, -6.49 %). Thus, brands AL12 and AL13 have failed the thickness test. The variation in the thickness of the tablets can be attributed to three key factors which are the difference of density of granules, pressure and speed of compression.[14]

All the brands of artemether-lumefantrine tablets tested fell within the acceptable limits of the British Pharmacopoeia requirements for disintegration test which states that film coated tablets should disintegrate within 30 minutes.[13] The average disintegration time ranged from 0.30 minute to 6.48 minute (Table 5). Disintegration test is a very important evaluation parameter because it shows that a tablet with good disintegration profile would likely give a good dissolution profile and thus will lead to enhanced bioavailability of the active ingredient.[21] The relationship between disintegration time and dissolution rate was seen in a research work,[13] whereby out of eight brands of methyl dopa tablets subjected to disintegration test, it was only one brand that failed and it was just that brand that also failed dissolution test. Disintegration time can also influence onset of drug action.[22]

The hardness test results showed that three of the brands- AL5, AL12 and AL15 were out of specification. The hardness values were 3.33kp, 2.40kp and 14.8kp respectively (Table 5), these hardness values were outside the permissible limit of 4 – 10kp.[23] Hardness is defined as a force required to break a tablet across the diameter and it is also known as tablet crushing strength.[23] Thus for a tablet whose hardness value is lower 4kp, the tablet may easily break and possess less friability. However, for a tablet that is too hard with hardness values above 10kp, the tablet may fail in disintegration and dissolution studies.[13]Using excess of fatty lubricants like Magnesium stearate during tableting can bring about very hard tablets.[13]

The friability test analysis showed that two of the brands (AL8 and AL13) tested were out of specification. The permissible limit is 1.0 %.[15] Brand AL8 gave a friability value of 3.19 % while AL13 gave a friability value of 10.04% (Table 5). This means that brands AL8 and AL13 will not be able to withstand mechanical attrition by virtue of shipping and subsequent transportation and thus could easily become capped, laminated and could out rightly break which could cause reduction in the amount of active ingredient to be delivered per tablet.[13]

Figures 1 and 2 are typical chromatograms of artemether and lumefantrine respectively used in the quantitative assay study and they showed that the retention time of artemether was 1.479 min and the retention time of lumefantrine was 2.256 min. These figures showed that the method adopted was sufficient to separate artemether and lumefantrine for their quantitative assay determination from their fixed- dose combination tablet formulations. This method is more rapid and may be consequentially more cost - effective when compared with that of Vinodh *et al.,* where the retention time was 4.19 and 5.22 respectively for artemether and lumefantrine.[16]

The result of the quantitative assay for artemether in the tablets showed that the values ranged from 89.37 % to 109.7% (table 5). Only brand AL12 (89.37%) fell out of specification. The result of the quantitative assay test for lumefantrine ranged from 77.79% to 101.5% (table 5) and brands AL4, AL8, AL10 and AL11 and AL12 failed. The specification required is 90% - 110%.[14] Thus, only 67% of the brands tested passed the quantitative assay for both artemether and lumefantrine. The importance of quantitative assay is to show the amount of active ingredient in each tablet. All the brands that failed had insufficient active ingredient which indicates reduced dosing and this can in turn lead to development of resistance and thus therapeutic failure. However, when the amount of active ingredient is more than required it can lead to toxic effects and different adverse events for example QT interval prolongation due to excess lumefantrine which can lead to arrhythmia.[9]Generally, drugs with too low or high level of active ingredient are usually caused by poor manufacturing practice and inappropriate storage conditions .[24]Similarly, another study carried out in Ghana in 2016 *on the quality of artemether-lumefantrine tablets and suspensions showed* that 88% of the artemether-lumefantrine samples tested passed the quantitative assay. This value is higher than this present study where 67% of the brands tested passed the assay test.[17]

This present research has shown that 100 % of the fifteen brands of artemether-lumefantrine tablets tested fell within standard limit for the weight variation test, disintegration test and diameter test. Eighty- seven percent passed the friability test and thickness test while 80% conformed to the standard limit for hardness. The quantitative assay test showed that only 67% of the brands tested conformed to the standard limits.

Summarily, only 47 % of all brands tested which included the innovator brand, passed all the tests carried out on them. Another study reported in Rivers state, Nigeria in 2017 *has also* shown that on analyzing the number of artemether-lumefantrine tablet brands that passed all tests, only 10% of the artemether-lumefantrine tablet brands passed all the tests that they were subjected to.[9] These findings are calls for concern.

Furthermore, this research has also shown that the confirmation of originality using the mobile authentication service may not suffice, as only 46% of the brands for which the service was available passed all the quality assessment tests carried out on them.

This study lacks data for dissolution studies and therefore does not show the tablets' release profiles which can give some insight to their bioavailability. For further studies, an appropriate method for possible simultaneous dissolution of artemether and lumefantrine will need to be adopted.

CONCLUSION

An inference from this study is that many of the brands of artemether-lumefantrine tablets in the Nigerian market do not meet up to standard specifications and they have been found to be substandard thereby prone to causing resistance, treatment failure and unwarranted toxicity effects. Therefore, there is need for continuous post – marketing surveillance of drugs in Nigeria.

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