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Dissolution Profile of Dosage forms of ACT Anti-Malarial Drugs from North-Central Part of Nigeria

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Authors' contributions

This work was carried out with contribution from all the authors. Author AS designed the study, wrote the protocol, and the first draft of the manuscript and managed the experimental process. Authors MIM and MBI co-supervised the work proof-read the protocol, the draft and add inputs. Author CCM performed the spectroscopic analysis. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims/Objective: To examine the rate and percentage release of the active constituents of brands of ACT anti-malarial drugs using UV-Visible Spectrophotometric method to ascertain its applicability in quality control of ACTs for effective treatment.
Place and Duration of Study: The study was carried-out on the North-central part of Nigeria between the March, 2013 and July 2013.
Methodology: *In vitro* release of artemether and lumefantrine from tablets dosage form was evaluated one after the other. The methods comprised of dissolution medium of 900 ml distilled water (for artemether) and 1000 ml of 0.1 M HCl (for lumefantrine) per vessel with the paddle rotating at 100 rpm for 60 minutes (artemether) and 45 minutes (lumefantrine) at the temperature of 36°C to 37°C.The dissolved samples were analyzed using UV-Visible spectrophotometer at 216

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nm (artemether) and 302 nm (lumefantrine) after method validation for accuracy, precision, linearity and specificity.

Results: The outcome of the study indicated the best release time for artemether from 2-10 minutes and 10 - 30 minutes for lumefantrine with 88% of the samples complied with USP specified requirement for dissolution test. The statistical P-value ($P < 0.05$) of mean (0.1007) and variance (0.7533) for artemether released were non-significant, while for lumefantrine, mean (0.0130) and variance (0.0446) were significant among the samples.

Conclusion: This method indicated that, UV-Visible spectrophotometric method could be used as non-simultaneous *in vitro* dissolution test for artemether and lumefantrine in tablet dosage combination forms. The method is simple, fast and cost-effective therefore it can be adopted for continual periodic monitoring of drug quality in order to sustain survival of quality drugs for malaria treatment among the populace.

Keywords: Artemether; lumefantrine; tablet dissolution test; uv-visible spectrophotometer; northern-central Nigeria.

1. INTRODUCTION

The endemic malaria treatment failure has been observed over the recent years due to drug quality problems associated to poor manufacturing practice, adaptation by the parasite due to sub-optimal treatment and poor handling process by both the marketers and the end users. The well known persistent parasite which resurfaces after treatment with monotheraphy drugs such as chloroquine or artemether alone is *Plasmodium falciparum,* species which *A*CT combination therapy has proven effectiveness in clearing the parasite. The effectiveness of the combination has therefore led to its recommendation and adoption by WHO and also Nigerian Federal ministry of health as first-line treatment for the malaria disease [1,2,3,4]. According to the Federal Ministry of Health recommendation, the uncomplicated malaria is to be treated with ACTs such as Artemether-Lumefantrine and Artesunate-amodiaquine (as first-line treatment) while severe malaria to be treated with quinine alone. Chemical structure of artemether and lumefantrine are shown as Figs. 1 and 2 below.

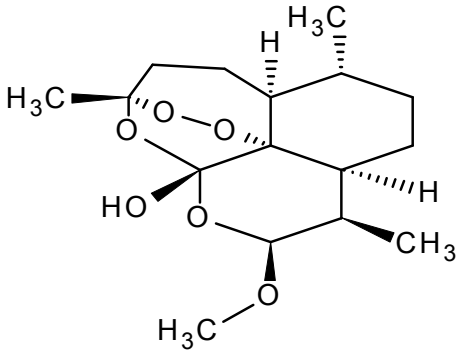

Fig. 1. Chemical structure of artemether

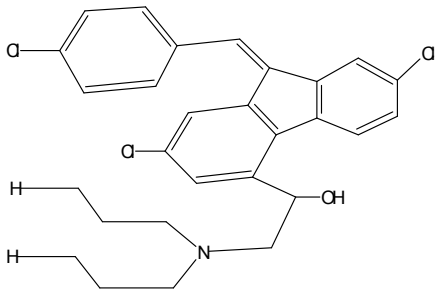

Fig. 2. Chemical structure of lumefantrine

Literature indicated that, more than 10% of the traded medicines worldwide are counterfeits which could be due to wrong ingredients, without active ingredients, insufficient active ingredient or fake packaging [5,6,7,8]. Onwujekwe et al. (2009) [9] specifically stated that 37% of the anti-malarials obtained from public and private healthcare providers in the south-eastern part of Nigeria when tested for quality did not meet the USP pharmacopoeia specification.

This study was carried out in order to ascertain applicability of UV Spectroscopic method in quality assessment of artemether-lumefantrine combination form of anti-malarial drugs collected from different sites in the north-central region of Nigeria in order to generate primary database which could be use for health policy making toward fighting the menace of malaria through sustenance of quality drugs for effective treatment of the disease in the region and the country as whole.

2. MATERIALS AND METHODS

UV-Visible spectrophotometer of variable wavelength [Shimadzu Japan (Model 160A)],

Pharmaceutical grade of artemether and lumefantrine reference standards were obtained as a gift sample from Pharmaceutical Company in Lagos, Nigeria. All other associated reagents used were of analar grade from Sigma Aldrich Company. Distilled water obtained from a Millipore system (Bedford, MA, USA) was used, Whatman filter-paper, appropriate sizes of glass-wares, Ependorf precision pipette of appropriate sizes, Erweka dissolution apparatus of Paddle assembly and Glass wares of appropriate sizes were used. Seven numbers of four brands of artemether-lumefantrine combination anti-malaria were purchased from both pharmacies and patent medicine stores and used. The statistical method used for analyzing the data obtained was One-way ANOVA.

2.1 Experimental Condition

UV-Visible double beam Spectrophotometer with 1 cm quartz cell programmed at 216 nm and 302 nm for artemether and lumefantrine respectively was used. The dissolution medium used for artemether (distilled water; 900 ml) and for lumefantrine (0.1 M HCl, 1000 ml), revolution (100 rpm), temperature (36°C to 37°C), dissolution period (artemether: 1 hour and lumefantrine: 45 minutes) [10,11].

2.2 Calibration Standards

Artemether stock standard equivalent to 0.2 mg/ml artemether was prepared using acetonitrile/water (1:1) as diluents. Working standards of concentration of 0.0125, 0.0250, 0.0500, 0.1000 and 0.2000 mg/ml were prepared by serial dilution of the aliquot of the stock standard solution quantitatively. While lumefantrine stock of concentration of 2.4 mg/ml was prepared in 0.1 M methanolic HCl from which working standard of concentrations 0.250, 0.500, 1.000, 1.500 and 2.000 mg/ml were prepared by serial dilution of the stock using the same diluents. After scanning the standards, artemether was analyzed at 216 nm and lumefantrine at 302 nm respectively using the UV-Visible spectrophotometer where the calibration curve for artemether and lumefantrine were obtained respectively.

2.3 The Assay Procedure

A milliliter of the dissolved tablet sample from the paddle apparatus dissolution assembly was withdrawn from the medium of the dissolution apparatus at time interval of 2, 10, 20, 30, 40 and 60 minutes for both artemether and lumefantrine. The solutions were diluted with appropriate diluents and measured at the specified wavelength respectively with the diluents as blank using calibrated UV-Visible spectrophotometer.

3. RESULTS

Absorption of artemether and lumefantrine were obtained by scanning the standard solutions between 200 to 400 nm against each diluents used as blank where the maximum absorption was obtained. The method was validated by following the validation guidelines by ICH [12,13].

The results of the study were presented in Tabular and Figure forms (sample identities Table 1 and calibration curve parameter Table 2) and calibration curves Figs. 1a & 1b, release pattern Figs. 2a, 2c and percentage Figs. 2b, 2d release.

Table 1. Sample identities

Samples' assigned code	Doses of Art/Lm	Obtained from	Manufacture date -expiry date	Indication of NAFDAC no.	Indication of manufacturer's address
LM1	20/120 mg	Pat.med.	01/2012 - 12/2013	Indicated	Indicated
LM2	20/120 mg	Pharm.	11/2012 - 10/2014	Indicated	Indicated
LM3	20/120 mg	Pat.med.	08/2012 - 07/2014	Indicated	Indicated
LM4	20/120 mg	Pharm.	09/2012 - 08/2014	Indicated	Indicated
AF	20/120 mg	Pat.med.	08/2011 - 07/2013	Indicated	Indicated
CL	20/120 mg	Pharm.	10/2012 - 09/2014	Indicated	Indicated
FY	80/480 mg	Pharm.	07/2011 - 06/2014	Indicated	Indicated

Note: Art/Lm represents artemether/ lumefantrine; Pat. Med. represent patent medicine store; Pharm. represent pharmaceutical shops. LM1, 2, 3, 4 are brands of different batches, while AF, CL and FY are other different brands. NAFDAC No is a registration number usually obtained from Nigerian Food & Drug Regulatory Commission

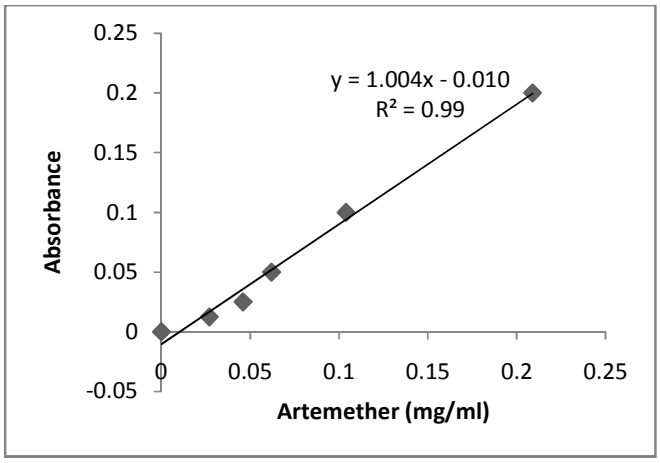

Fig. 1a. Artememther calibration curve

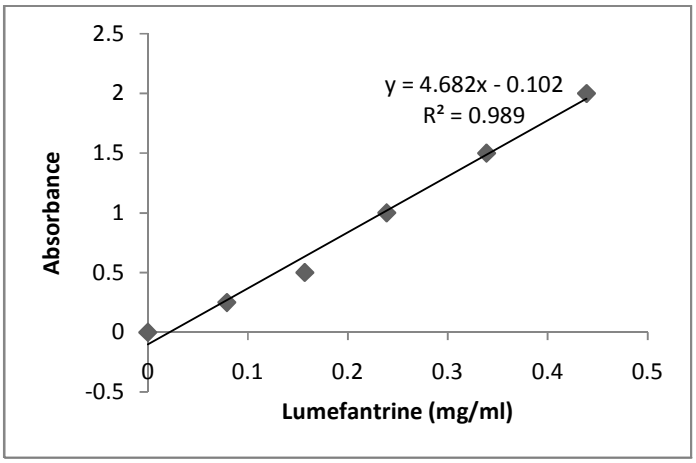

Fig. 1b. Lumefanrine calibration curve

Table 2. Calibration curve parameters

Regression parameters	Artemether	Lumefantrine
Wavelength of absorption (λ_{max})	216 nm	302 nm
Range	0.0125 mg/ml -0.2 mg/ml	0.250 mg/ml to 2.0 mg/ml
Regression equation	Y=1.0043x – 0.0104	Y=4.6824x – 0.1028
Slope (b)	1.0043x	4.6824x
Intercept (a)	0.0104	0.1028
Correlation coefficient (r^2)	0.99	0.9895

Calculations:

$$Percentatege\ (\%)\ release\ = \frac{Amount\ released}{Concentration\ in\ the\ dissolution\ medium} \times 100$$

Where; Amount released = $Concentration\ \left(\frac{mg}{ml}\right) \times dilution\ factor$

$$\text{Concentration in the medium } \left(\frac{\text{mg}}{\text{ml}}\right) = \frac{\text{Label claim}}{\text{Volume of the dissolution medium used}}$$

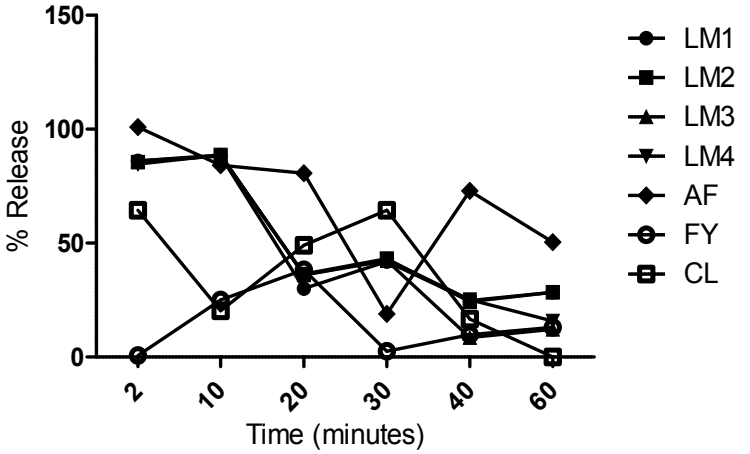

Fig. 2a. Release pattern of artemether from tablet samples

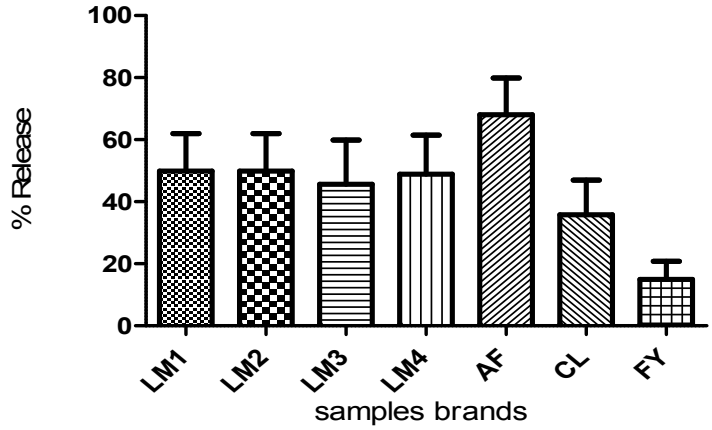

Fig. 2b. % release of artemether from sample tablets

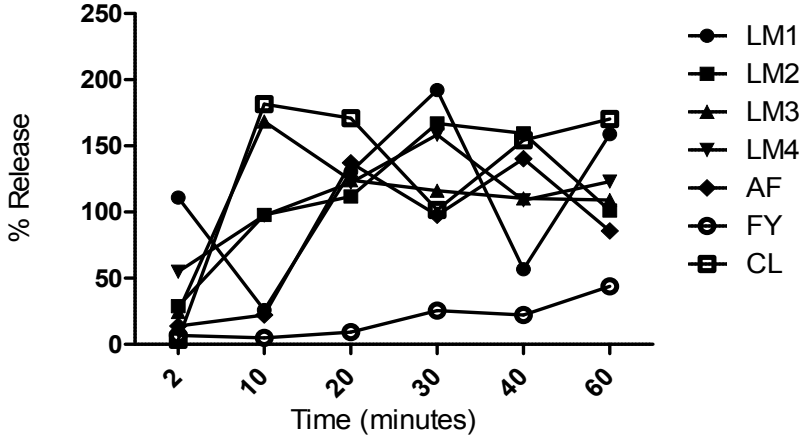

Fig. 2c. Release pattern of lumefantrine from tablet samples

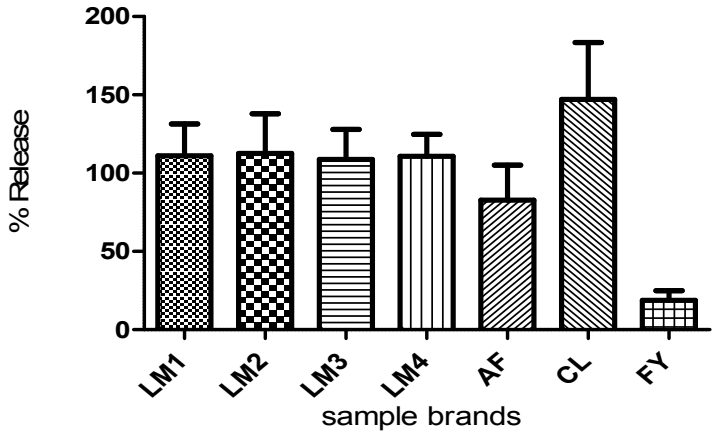

Fig. 2d. % release of lumefantrine from sample tablets

4. DISCUSSION

Dissolution test is a measure of the amount of the active ingredient (s) released from a solid dosage form using a known volume of dissolution medium within a predetermined length of time. The test revealed the profile of the release pattern of the drug samples which could also be directly related to the [rate of absorption and efficacy of the products [8]. [10] specified minimum required percentage released for artemether and lumefantrine as 45% in 1 hr and 60% in 45 minutes of the labelled amount of claim respectively.

Figs. 2a & 2c shows the release pattern of artemether and lumefantrine from the various samples analyzed. The points of intersection or overlaps observed on these figures were points at which those samples' exhibited similar release pattern. The best release time from sample LM1,2,3,4 and AF for artemether was from 2 – 10 minutes and 10 - 30 minutes for lumefantrine (Figs. 2a and 2c) where each sample released more than 45% artemether in an hour and 60% lumefantrine within 45 minutes respectively as shown in Figs. 2b and 2d. Both artemether and lumefantrine released from the various brands indicated 88% of the samples' complied with USP standard requirement for dissolution test [10]. Poor release of artemether-lumefantrine by sample CL and FY as compared to others (Fig. 2b and Fig. 2d) this could be due to factors such as nature and amount of the excipients, lubricant, diluents, binders used as well as compacting pressure during the formulation process. Consumption of these brands can lead to inadequate absorption of the active ingredient by the body system, which could result to treatment failure. For a tablet dosage form of drug to attain to good dissolution it must disintegrate within specified required time in the dissolution medium.

Statistical analysis of the data using one way ANOVA indicated P-value ($P < 0.05$) of both mean (0.1007) and variance (0.7533) for artemether release from the samples as non significant; while for lumefantrine it was significant for both mean (0.0130) and variance (0.0446).

5. CONCLUSION

In this study, UV-visible spectrophotometric method was used to study the dissolution profile which revealed the pattern and the percentage release of artemether and lumefantrine from ACT anti-malarial drugs. The results indicated that 88% of the samples within the studied area complied to standard requirement, while 12% failed. The method is simple, fast and cost-effective therefore it can be adopted for continual periodic monitoring of drug quality in order to sustain survival of quality drugs for malaria treatment.

6. RECOMMENDATION

Conscious effort is required by Government and all relevant stakeholders to work toward complete elimination of the 12% samples which indicated non-compliance in the region which could be achieved by sustainable periodic market surveillance and Good Manufacturing Practice by the Pharmaceutical Companies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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