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Performance Demonstration of a Frugal and Green UV–Visible Spectrophotometric Method for the Direct Determination of Artemether in Artemether–Lumefantrine Tablets

Bugugu, J. B.[1], Mwanga, J. M.[2], Ciza, P. H.[3], Shabani, M. L.[1], Marini, D. R.[4], & Mbinze, J. K.[3]

[1]*Drug Analysis Laboratory, Pharmaceutical Techniques Section, Higher Institute of Medical Techniques, Bukavu, Democratic Republic of the Congo*
[2]*Chemistry Laboratory, Faculty of Sciences, University of Kinshasa, Kinshasa, Democratic Republic of the Congo*
[3]*Laboratory of Drug Analysis, Faculty of Pharmaceutical Sciences, University of Kinshasa, Kinshasa, Democratic Republic of the Congo*
[4]*Laboratory of Pharmaceutical Analytical Chemistry, Faculty of Medicine, University of Liège, Liège, Belgium.*

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Correspondence to:
J. B. Bugugu
bugugubis@gmail.com

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ABSTRACT

Introduction
The proliferation of poor-quality antimalarials poses a severe threat to public health in sub-Saharan Africa. Systematic quality control requires accessible and eco-friendly analytical methods.

Purpose
This study documents the performance demonstration and validation of a direct, green, and frugal UV–Visible spectrophotometric method for the quantification of artemether in fixed-dose combination tablets without chemical derivatization.

Methods
Selective separation was achieved at 255.0 nm using a 0.5% (w/v) aqueous sodium lauryl sulfate (SLS) micellar matrix, which encapsulates hydrophobic artemether while selectively precipitating the masking co-formulated lumefantrine.

Results
Validated through the total error strategy via a 95% β-expectation accuracy profile over a working range of 28.0–36.0 µg/mL (n = 45), the global Ordinary Least Squares (OLS) calibration model demonstrated excellent predictability ($y = 0.0208x + 0.0627$, $R^2 = 1.000$). Metrological sensitivity boundaries yielded a limit of detection (LOD) of 0.5187 µg/mL and a limit of quantification (LOQ) of 1.5718 µg/mL. Method trueness was confirmed with mean recoveries ranging from 98.71% to 100.34% and relative systematic bias between −1.29% and +0.34%. Random error components evaluated via ANOVA showed high precision, with repeatability and intermediate precision coefficients of variation strictly below 0.181% and 0.205%, respectively.

Conclusion
Field application to commercial tablet samples collected in Kisangani established compendial compliance within the 90.0%–110.0% pharmacopeial limits (98.75%–106.76%). Although its resolution is lower than compendial HPLC-UV methods, this low-cost, solvent-free protocol serves as an effective frontline screening tool for decentralized surveillance laboratories in low- and middle-income countries.

INTRODUCTION

Despite significant therapeutic advancements, malaria remains a critical global health emergency, causing hundreds of thousands of deaths annually, predominantly in sub-Saharan Africa (World Health Organization [WHO], 2025). To counter this ongoing crisis and mitigate the emergence of drug-resistant strains of *Plasmodium falciparum*, the deployment of artemisinin-based combination therapies (ACTs) is imperative (White et al., 2014). Among these protocols, the fixed-dose artemether–lumefantrine association serves as the foundation of national malaria control programs, with millions of treatment courses distributed globally (WHO, 2025).

However, the therapeutic efficacy of these programs is severely threatened by the widespread proliferation of substandard and falsified antimalarial medications. Recent epidemiological and modeling data reveal that counterfeit and poor-quality antimalarials represent a major public health and economic burden across sub-Saharan Africa (Salami et al., 2023; United Nations Office on Drugs and Crime [UNODC], 2013). Field monitoring studies and post-marketing surveillance programs indicate that a significant proportion of artemether–lumefantrine samples circulating in private retail or informal channels exhibit critical dosage deviations or dissolution defects, heavily compounding the public health burden and accelerating parasitic resistance (Lawal et al., 2022; Salami et al., 2023).

Faced with this threat, systematic laboratory quality control is a strategic priority. Although High-Performance Liquid Chromatography (HPLC) coupled with ultraviolet detection remains the compendial gold standard mandated by modern pharmacopoeias (United States Pharmacopeia [USP], 2024), its steep operational costs, high technical complexity, and reliance on hazardous organic solvents hinder its deployment in decentralized laboratories within resource-limited countries (Mbinze et al., 2015a). UV–Visible spectrophotometry emerges as a practical screening alternative, provided that the major analytical hurdle—the severe spectral masking of artemether by lumefantrine—is overcome (Chan et al., 2014). Analyzing this specific pair presents a major challenge: lumefantrine possesses an extensive conjugated system generating a highly potent chromophore that completely dominates the ultraviolet range, completely masking the nearly negligible UV absorption of artemether (Belew et al., 2020).

Currently, there is a distinct lack of a validated, direct, and cost-effective UV-only method for selective artemether quantification without chemical derivatization or phase separation. This study addresses this scientific gap by executing a formal performance demonstration and validation of a direct spectrophotometric method utilizing micellar surfactant chemistry, in alignment with international guidelines for instrument qualification (USP, 2025). By avoiding toxic organic solvents and utilizing selective micellar isolation (Belew et al., 2020), this approach aims to strengthen local analytical capacities in resource-limited settings, helping ensure the quality assurance of essential medicines and protect patient safety (Mbinze et al., 2015a; Sacré et al., 2024).

METHODS

Instrumentation and Equipment

Spectrophotometric measurements were performed using an Agilent 8453 UV–Vis spectrophotometer equipped with Cary WinUV software, qualified in compliance with official spectroscopic standards (USP, 2025). Sample and standard massing were conducted on a Scaltec SPB31 analytical balance (maximum capacity: 210 g, sensitivity: d = 0.1 mg) following standard calibration verification principles (Chan et al., 2014). Solution dissolution was accelerated using a Branson 5510 ultrasonic bath.

Reagents and Samples

Artemether (99.5% purity) and lumefantrine (99.99% purity) chemical reference standards were supplied by Fourrts Laboratories (Chennai, India) and Meridian Pharmacare Pvt. Ltd. (Bangalore, India), respectively, and verified against compendial specifications (USP, 2024). Reagent-grade sodium lauryl sulfate (SLS) was supplied by Merck (Darmstadt, Germany). Ultrapure water was obtained from a Milli-Q Plus 185 water purification system (Millipore, Billerica, MA, USA). Three distinct commercial brands of combination tablets (labeled 20 mg of artemether and 120 mg of lumefantrine per tablet) were purchased randomly from licensed retail pharmacies in Kisangani, Democratic Republic of the Congo.

Preparation of Solutions

A standard stock solution containing 400 µg/mL of artemether and 2400 µg/mL of lumefantrine was prepared by accurately weighing approximately 10.07 mg of artemether and 60.02 mg of lumefantrine into a calibrated 25 mL volumetric flask. The reference compounds were dissolved in 20 mL of 0.5% (w/v) aqueous sodium lauryl sulfate (SLS) solution. The flask was shaken manually and exposed to ultrasonic dissolution for 1.5 hours at a controlled temperature of 50 ± 5°C} to achieve optimal micellar encapsulation of the hydrophobic cores (Mudyahoto et al., 2025).

After cooling to room temperature (25 °C), the volume was brought to the mark with 0.5% SLS solution. Reflecting established screening guidelines for multi-component separations (Lieberman et al., 2020), the mixture was centrifuged at 4000 rpm for 15 minutes and filtered through a 0.45 µm Chromafil syringe filter to eliminate the precipitated lumefantrine fraction. Working calibration standards were prepared daily by serial dilution with 0.5% SLS solution to generate five independent concentration levels: 28.0, 30.0, 32.0, 34.0, and 36.0 µg/mL.

Ethical Considerations

The study protocol was formally reviewed and approved by the Ethics Committee and Institutional Review Board of the University of Kisangani under official clearance certificate number UNIKIS/CER/013/2024.

RESULTS

Micellar Solvent Optimization and Optical Behavior

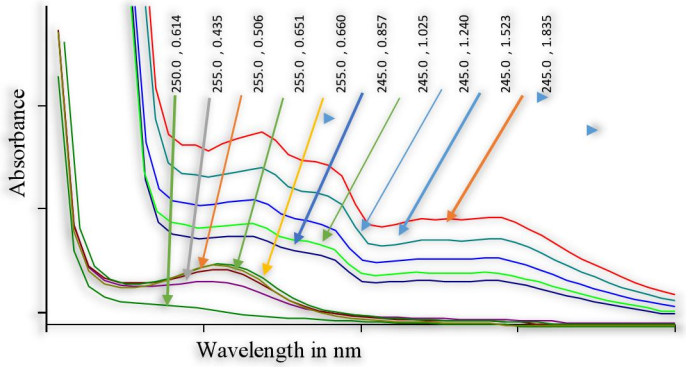
Aqueous solutions of sodium lauryl sulfate (SLS) at concentrations of 0.5% and 1.0% (w/v) were evaluated as dissolution matrices to optimize solubility and ensure photometric signal clarity **(Table 1)**. An artemether standard solution (401.7 µg/mL) was scanned in the UV region from 200 to 400 nm against respective surfactant blanks.

Table 1:
Surfactant matrix optimization and photometric range compliance (n = 3)

SSS	Identified λ_{max} (nm)	RAR	PSTD
1.0% Aqueous SLS	245.0	0.857–1.835	**Rejected**
0.5% Aqueous SLS	255.0	0.435–0.660	**Selected**

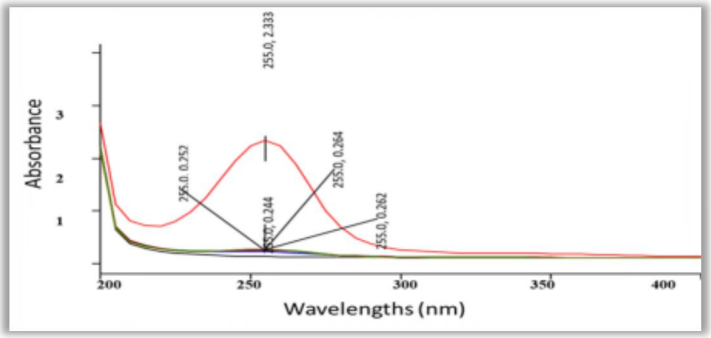
Note: SSS = Surfactant Solvent System, RAR = Recorded Absorbance Range, PSTD = Photometric Status & Technical Decision, ***Rejected:*** Exceeds strict spectrophotometric tolerances; high susceptibility to Beer–Lambert law deviations, ***Selected:*** Confined within the optimal instrumental precision window (0.2–0.8).

Figure 1:
Comparative UV absorption spectra of artemether demonstrating the micellar solvent effect between 0.5% and 1.0% aqueous SLS



Spectral profiles recorded in the 1.0% aqueous SLS matrix reached an upper absorbance threshold of 1.835 at λ_{max} = 245.0 nm. Conversely, reducing the surfactant concentration to 0.5% aqueous SLS generated a distinct bathochromic shift (λ_{max} = 255.0 nm) while dampening the absolute photometric response into a highly stable 0.435–0.660 range **(Figure 2)**.

Figure 2:
Optimized UV spectrum of artemether in 0.5% aqueous sodium lauryl sulfate showing chemical baseline resolution at λmax = 255.0 nm

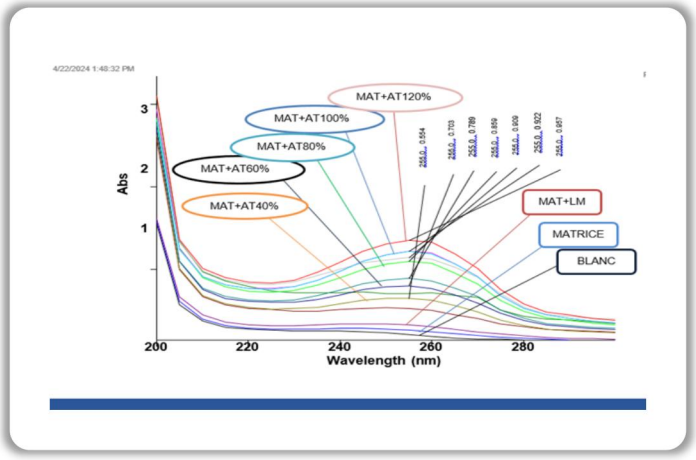


Method Validation

Specificity and Selectivity

The specificity of the proposed UV–Vis spectrophotometric method was verified at 255.0 nm via multi-component matrix monitoring to ensure the absence of analytical interference (USP, 2025) **(Figure 3)**.

Figure 3:
Three-dimensional spectral overlay evaluating analytical specificity and baseline resolution



The solvent vehicle baseline (0.5% w/v aqueous SLS) and the placebo formulation matrix (containing starch, lactose, and magnesium stearate) exhibited absolute optical transparency at 255.0 nm. Crucially, the lumefantrine chemical standard prepared within the excipient vehicle displayed a flat profile at the operational wavelength, confirming its micellar exclusion and selective precipitation from the system. Concurrently, five sequential standard concentration levels of artemether embedded within the matrix (40% to 120% nominal concentration) generated well-resolved, concentration-dependent absorbance responses.

Linearity and Calibration Architecture

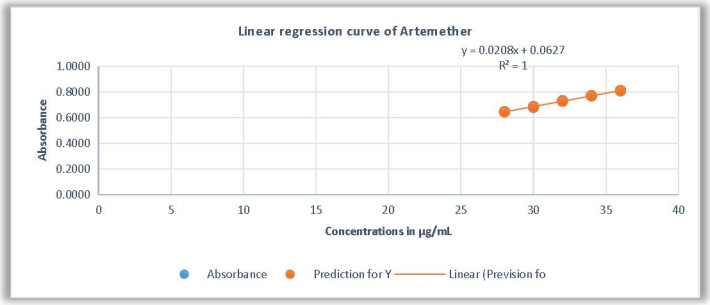
The relationship between analyte concentration and optical response was assessed across a dynamic range of 28.0 to 36.0 µg/mL. The experimental design incorporated 5 concentration levels across two independent multi-day replication series (n = 45 total data points), evaluated via Ordinary Least Squares (OLS) regression analysis **(Table 2)**.

Table 2:
Statistical calibration parameters for artemether linear regression (n = 45)

CP	Statistical Value	Operational Analytical Meaning
CE	y = 0.0208x + 0.0627	Quantitative model equation
Slope (a)	0.0208	High method analytical sensitivity
Y-Intercept (b)	0.0627	Non-zero residual background signal
CoD (R^2)	1.000	100% of variance explained by concentration

CP = Calibration Parameter, CE = Calibration Equation, CoD = Coefficient of Determination

Figure 4:
Linear regression curve for artemether



An R^2 value of 1.000 indicates that response variability is directly explained by concentration variations, fully complying with standard regulatory criteria (R^2 > 0.9900) (ICH, 2005). The regression model includes the non-zero Y-intercept (b = 0.0627) rather than forcing the line through the origin, preventing systematic calculation biases during routine quantification.

Metrological Sensitivity (LOD and LOQ Thresholds)

Detection and quantification limits were derived statistically from the residual standard deviation of the regression response (σ = 0.0033) and the analytical sensitivity slope (s = 0.0208) in compliance with ICH Q2(R1) guidelines **(Table 3)**.

Table 3:
Metrological sensitivity thresholds and signal parameters (n = 45)

Metrological Parameter	Statistical Derivation Formula	Calculated Value (µg/mL)
Limit of Detection (LOD)	3.3*σ / s	0.5187
Limit of Quantification (LOQ)	10*σ / s	1.5718

Trueness and Tolerance Intervals Assessment

Trueness was evaluated by assessing systematic bias alongside Lower Tolerance Interval (LTI) and Upper Tolerance Interval (UTI) boundaries, extracted from the 95% β-expectation accuracy profile **(Table 4)**.

Table 4:
Trueness evaluation matrix and back-calculated statistical tolerance intervals (n = 9 per level)

NC (µg/mL)	MC (µg/mL)	MR (%)	RB (%)	LTL (LTI, %)	UTL (UTI, %)	RS (AL: ±5%)
28.0	27.94	99.77	−0.23	99.42	100.12	Compliant
30.0	29.61	98.71	−1.29	98.15	99.27	Compliant
32.0	32.11	100.34	+0.34	99.75	100.93	Compliant
34.0	34.05	100.16	+0.16	99.65	100.67	Compliant
36.0	35.96	99.90	−0.10	99.60	100.20	Compliant

Note: MNC = Nominal Conc., MC = Mean Conc., RS = Relative Bias, LTI = Lower Tolerance Limit, UTL = Upper Tolerance Limit, RS (AL) = Regulatory Status (Acceptance Limits)

Relative systematic bias ranged from −1.29% (at 30.0 µg/mL) to +0.34% (at 32.0 µg/mL). Both LTI and UTI boundaries across all five concentration levels remain strictly within pre-defined ± 5% acceptance limits.

Precision and Variance Component Analysis

Random error components were evaluated to establish intra-series and inter-series variability across the dynamic calibration range **(Table 5)**.

Table 5:
Precision component matrix and total error profile

NC (µg/mL)	RCV (%)	ICV (%)	TEA (%)	MCS
28.0	0.125	0.125*	0.35	High Precision
30.0	0.142	0.198	0.40	High Precision
32.0	0.118	0.205	0.35	High Precision
34.0	0.181	0.181*	0.25	High Precision
36.0	0.106	0.106*	0.30	High Precision

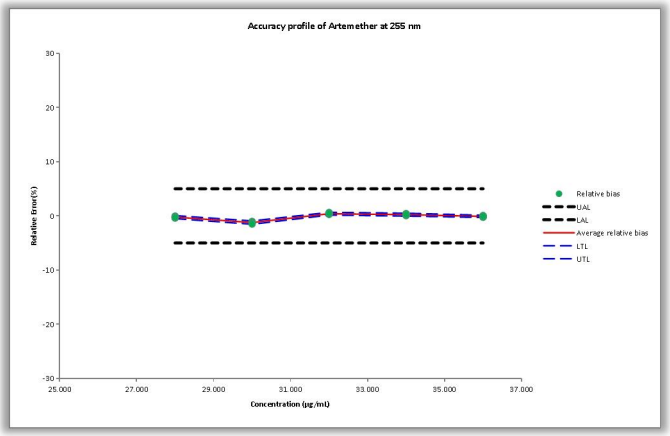
*Note: At 28.0, 34.0, and 36.0 µg/mL, calculated inter-series variance components via ANOVA yielded negative values. In compliance with SFSTP guidelines, these components were set to zero, equating intermediate precision to repeatability. NC = Nominal Conc., RCV = Repeatability CV, IPCV = Intermediate Precision CV, TEA = Total Error Amplitude, MCS = Method Capability Status

Coefficients of variation (CV) for repeatability remained below 0.181%, while intermediate precision CVs peaked at 0.205%. Total error amplitude remained under 0.40%.

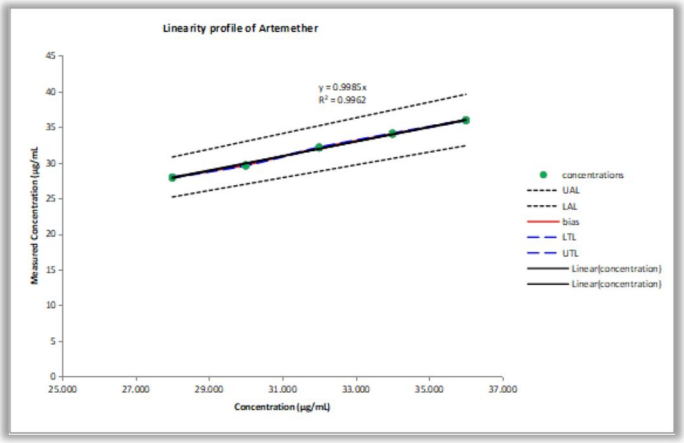
Accuracy Profile and Residual Diagnostic Analysis

The 95% β-expectation accuracy profile confirmed that total error boundaries (LTI and UTI) remained enclosed within specified ± 5% acceptance limits across the entire operational range.

Figures 5:
Accuracy and linearity profile of the validated UV-Vis method for artemether A

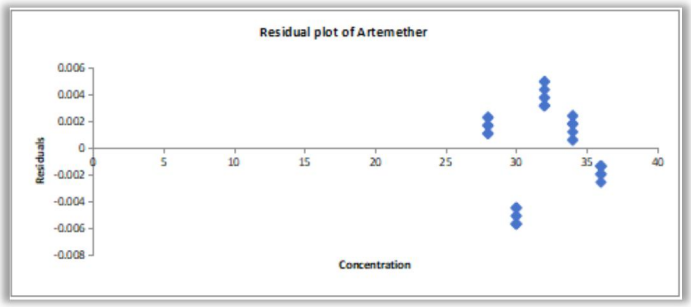


Figures 6:
Accuracy and linearity profile of the validated UV-Vis method for artemether B



Calculated absorbance residuals were uniformly distributed between −0.005 and +0.004 absorbance units. Residuals exhibited a minor sinusoidal wave pattern across concentration levels, suggesting a minor linear lack-of-fit in the unweighted OLS model. However, because the maximum absolute magnitude of these residuals remained below 0.005 absorbance units, their effect on analytical accuracy was negligible **(Figure 7)**.

Figure 7:
Residual plot of Artemether



Application to Commercial Tablet Formulations

The optimized method was applied to the quantitative assay of three commercial brands of fixed-dose artemether–lumefantrine tablets collected from retail pharmacies in Kisangani (n = 3 independent replicates per sample). Pure reference standard and matrix placebo controls were analyzed under identical conditions **(Table 6)**.

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Table 6:
Quantitative field assay results and compendial compliance testing (n = 3)

SC	SDBN	LC (mg)	MAC (mg)	MA (A)	CL	RC
AL–LM STD	Artemether Reference Powder	20.00	–	0.633	–	CR
AL–LM MAT	Excipient Matrix Control	–	–	0.002	–	MBB
AL–LM ECH1	Commercial Sample 1	20.00	19.75	0.678	98.75	Compliant
AL–LM ECH2	Commercial Sample 2	20.00	20.06	0.689	100.28	Compliant
AL–LM ECH3	Cether-L (Commercial Sample 3)	80.00	85.40	0.733	106.76	Compliant

Note: SC = Sample Code, SDBN: Sample Description / Brand Name, LC = Labeled Claim, MAP = Measured API Content, MA = Mean Absorbance, RC = Regulatory Conclusion, Compliant: Compliant (USP Range), CP = Control Reference, MB = Matrix Baseline Blank

Mean absorbance values for controls and commercial samples ranged from 0.633 to 0.733. Active pharmaceutical ingredient (API) content across commercial samples ranged from 98.75% to 106.76%, within official pharmacopeial specifications of 90.0%–110.0% (USP, 2024).

DISCUSSION

Micellar Solvent Optimization and Optical Behavior

Selection of 0.5% (w/v) aqueous sodium lauryl sulfate (SLS) as the analytical solvent matrix balances thermodynamic solubility with photometric precision. Artemether is hydrophobic and lacks strong chromophores, requiring solubilization to produce measurable UV absorbance without organic solvents (Mudyahoto et al., 2025). Using SLS as an anionic surfactant facilitates micellar encapsulation, altering the microenvironment of the analyte and increasing its apparent solubility in aqueous media (Pokhrel et al., 2023). Surfactant concentration directly impacts optical performance (USP, 2025). As shown in **Table 1**, 1.0% aqueous SLS produced high absorbance levels (0.857–1.835) at λ_{max} = 245.0 nm. Absorbance values above 0.800 increase relative photometric error according to the Twyman–Lothian principle and risk deviations from the Beer–Lambert law due to molecular crowding (Chan et al., 2014). Transitioning to 0.5% aqueous SLS shifted the wavelength to λ_{max} = 255.0 nm and maintained absorbances within an optimal range (0.435–0.660), securing an ideal photometric range (0.2–0.8) for precise quantification in resource-limited environments (Chan et al., 2014; Lieberman et al., 2020).

Method Validation

Specifcity and Selectivity: Micellar Isolation Mechanism

The 0.5% aqueous SLS matrix provides selective solubilization through micellar encapsulation and ion-pairing interactions (Mudyahoto et al., 2025). Artemether, a non-ionizable neutral lipophilic endoperoxide, partitions into the hydrocarbon core of SLS micelles above the critical micelle concentration (CMC) (Pokhrel et al., 2023).

Conversely, lumefantrine is a lipophilic weak base containing a dibutylaminoethanol group that exhibits low solubility in neutral aqueous solutions (Belew et al., 2020). Electrostatic interactions between anionic sulfate headgroups of SLS and protonated amino groups of lumefantrine form an insoluble ion-pair complex (Rivelli et al., 2018), which precipitates during centrifugation (4000 rpm) and micro-filtration (0.45 µm). Physical removal of lumefantrine eliminates spectral masking at 255.0 nm (Belew et al., 2020). Complete optical transparency of common tablet excipients confirms overall method specificity (USP, 2025).

Linearity and Calibration Architecture

Linearity established over 28.0–36.0 µg/mL confirmed a strong linear relationship (R^2 = 1.000), meeting international validation criteria (R^2 > 0.9900) (ICH, 2005; USP, 2024). Retaining the calculated non-zero intercept (y = 0.0208x + 0.0627) prevents proportional calculation bias during routine analysis (Mbinze et al., 2015a).

Sensitivity (LOD and LOQ Thresholds)

Calculated limits of detection (LOD = 0.5187 µg/mL) and quantification (LOQ = 1.5718 µg/mL) confirm method sensitivity in accordance with ICH Q2(R1) guidelines (ICH, 2005). Because the LOQ is substantially lower than the minimum operational working concentration (28.0 µg/mL), the protocol reliably detects sub-potent formulations during quality screening (Mbinze et al., 2015a).

Trueness and Tolerance Intervals Assessment

Evaluating trueness via total error metrics offers rigorous validation relative to single-point calibration strategies (Mbinze et al., 2015a). Recoveries between 98.71% and 100.34% with relative bias under 1.29% fall within standard API assay criteria (98.0%–102.0%) (USP, 2024). Statistical tolerance intervals (LTI and UTI) derived from

the 95% β-expectation accuracy profile confirmed that experimental variations remained within ± 5% specification limits across all evaluated levels (Feinberg et al., 2010).

Precision and Variance Component Analysis

Precision parameters demonstrated high repeatability (CV ≤ 0.181%) and intermediate precision (CV ≤ 0.205%), meeting general quality control requirements (CV < 1.0%) (Chan et al., 2014). Negative inter-series variance components observed during ANOVA modeling at certain concentration levels reflect instances where within-day variance slightly exceeded between-day variance (Mbinze et al., 2015a). Setting these components to zero aligns with SFSTP recommendations, equating intermediate precision to repeatability for those levels (Hubert et al., 2006a).

Accuracy Profile and Residual Diagnostic Analysis

Combining trueness and precision into a unified accuracy profile provides a comprehensive prediction of analytical performance (Feinberg et al., 2010). Total error amplitude remained under 0.40%, with tolerance limits fully contained within ± 5% acceptance boundaries. Residual distribution showed satisfactory homoscedasticity across the dynamic range, with minor residual curvature presenting minimal impact on quantitative accuracy (Mbinze et al., 2015a).

Method Comparison: Micellar UV–Vis vs. Compendial HPLC UV

Comparing the micellar UV–Vis protocol with compendial HPLC-UV methods highlights key operational trade-offs (Debrah et al., 2016; Alhassan et al., 2023). Chromatographic methods utilize stationary phase separation (e.g., C18) and organic mobile phases (acetonitrile/methanol) to provide stability-indicating capability and separation of degradation products (Habib et al., 2020; Mbinze et al., 2015b). However, reliance on specialized infrastructure, high solvent consumption, and maintenance costs can restrict routine testing in resource-limited surveillance settings (Mbinze et al., 2015b; Sacré et al., 2024).

The 0.5% aqueous SLS spectrophotometric method uses micellar precipitation to isolate the analyte without liquid chromatography (Belew et al., 2020). Using water as the primary solvent aligns with green analytical chemistry principles (Sacré et al., 2024). Sample preparation and analysis are completed in under 20 minutes without instrument column re-equilibration. Although resolution is lower than HPLC, high trueness (98.71%–100.34%) and precision (CV < 0.205%) support its utility as a rapid screening tool to identify substandard or falsified batches prior to confirmatory chromatographic analysis (Mbinze et al., 2015a; Mekasha et al., 2025).

CONCLUSION

This study validated a direct, frugal UV–Visible spectrophotometric method for quantifying artemether in fixed-dose combination tablets without chemical derivatization. Selective micellar isolation using 0.5% (w/v) aqueous sodium lauryl sulfate effectively removed lumefantrine interference, permitting direct determination at 255.0 nm. Method validation using a 95% β-expectation accuracy profile confirmed compliance with regulatory specifications across a 28.0–36.0 µg/mL dynamic range, exhibiting high precision (CV < 0.21%) and sensitivity (LOQ = 1.5718 µg/mL). Application to commercial field samples in Kisangani demonstrated compendial compliance (98.75%–106.76%), establishing the protocol as a practical screening alternative for quality surveillance in resource-limited settings.

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Authors' Contributions: J.B.B.: Writing – original draft (lead). J.M.M.: Conceptualization (supporting); Writing – original draft (supporting). P.H.C.: Conceptualization (supporting); Writing – original draft (supporting). M.L.S.: Writing – review & editing (lead). J.K.M.: Conceptualization (lead); Supervision (supporting). R.M.: Supervision (lead); Writing – review & editing (supporting).

Data Availability Statement: All data generated or analyzed during this study are included in this published article. Raw spectrophotometric data are available from corresponding author upon reasonable request.

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Ethical Approval: This study was conducted in accordance with the ethical standards for research. The research protocol was reviewed and formally approved by the Research Ethics Committee of the University of Kisangani under the authorization number UNIKIS/CER/013/2024. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee.

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ORCID iDs:

Bugugu, J. B.[1]: Nil identified.
Mwanga, J. M.[2]: Nil identified.
Ciza, P. H.[3]: Nil identified.
Shabani, M. L.[1]: https://orcid.org/0009-0001-8928-1711
Marini, D. R.[4]: Nil identified.
Mbinze, J. K.[3]: Nil identified.

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