

SPECTROPHOTOMETRIC ESTIMATION OF ARTEMETHER & LUMEFANTRINE IN PHARMACEUTICAL FORMULATION BY USING MEAN CENTERING OF RATIO SPECTRA & H- POINT STANDARD ADDITION METHOD

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ABSTRACT

Background: Artemether–lumefantrine is a World Health Organization-recommended artemisinin-based combination therapy for uncomplicated falciparum malaria, marketed as a fixed-dose combination in a 1:6 ratio. Quality-control estimation of both components in combined dosage forms conventionally relies on chromatographic methods that are costly, time-consuming, and solvent-intensive. **Objective:** To develop and validate two simple, rapid, and economical UV-spectrophotometric methods — mean centering of ratio spectra and the H-point standard addition method — for the simultaneous estimation of artemether and lumefantrine in combined tablet dosage form without prior separation, and to validate them in accordance with ICH Q2 guidelines. **Methods:** Absorbance measurements were performed in the wavelength range 200–400 nm, with analytical wavelengths of 271 nm (artemether, methanol) and 340 nm (lumefantrine, chloroform); HPSAM was executed at the wavelength pair 280/260 nm. Validation covered specificity, linearity, range, precision (repeatability, intra-day and inter-day), accuracy, limit of detection, limit of quantitation, and robustness. **Results:** Calibration curves were linear over 5–25 µg/mL for both drugs (regression equations $y = 0.1014x - 0.0639$, $R^2 = 0.9998$ and $y = 0.0954x + 0.0886$, $R^2 = 0.9961$ for artemether and lumefantrine, respectively). All %RSD values for repeatability, intra-day, and inter-day precision were below 2%, as prescribed by ICH. Mean recoveries ranged from 99.06% to 100.80%. Assay results were 99.37% for artemether and 98.40% for lumefantrine, within ICH limits. **Conclusion:** Both proposed methods are accurate, precise, specific, robust, and economically attractive, and they are suitable for the routine simultaneous determination of artemether and lumefantrine in pharmaceutical dosage forms.

KEYWORDS: Artemether; lumefantrine; mean centering of ratio spectra; H-point standard addition method; simultaneous UV-spectrophotometric estimation; ICH Q2 validation; antimalarial combination therapy.

1. INTRODUCTION

Analytical method development and validation occupy a central role in the discovery, development, and manufacture of pharmaceuticals. Official test methods derived from these processes are used by quality-control laboratories to ensure the identity, purity, potency, and performance of drug products. Among the available instrumental techniques, UV-visible molecular absorption spectrophotometry remains one of the most widely used tools for quantitative analysis because of its wide applicability to organic and inorganic analytes, typical detection limits of 10^{-4} – 10^{-5} M, moderate to high selectivity, good accuracy (relative uncertainties of 1–3%), and ease of data acquisition. The technique is based on the measurement of transmittance (T) or absorbance (A) and the linear relationship between absorbance and concentration expressed by the Beer–Lambert law, $A = -\log T = \epsilon bc$, where ϵ is the molar absorptivity, b the path length, and c the analyte concentration. This linearity is, however, limited by chemical and instrumental factors, including deviations in absorptivity at high concentrations (>0.01 M), scattering by particulates, sample fluorescence or phosphorescence, refractive-index changes, shifts in chemical equilibria, non-monochromatic radiation, and stray light.

Malaria remains a major global health challenge, and artemisinin-based combination therapy is the treatment of choice recommended by the World Health Organization for uncomplicated falciparum malaria. The fixed-dose combination of artemether and lumefantrine (1:6) is one of the most widely deployed ACTs. Artemether, a methyl ether derivative of artemisinin isolated from *Artemisia annua*, acts rapidly against the blood schizonts of *Plasmodium falciparum* and *P. vivax*, reducing parasite biomass by approximately 10,000-fold per reproductive cycle, and is metabolized to the active metabolite dihydroartemisinin. Lumefantrine, a synthetic fluorene derivative structurally related to quinine, mefloquine, and halofantrine, acts more slowly, inhibiting the conversion of heme to hemozoin, and possesses a considerably longer elimination half-life (approximately 3–6 days), thereby clearing residual parasites. Because the two drugs differ markedly in their physicochemical and spectral properties, their simultaneous quantitation in a single dosage form requires either a separation step or a chemometric resolution strategy.

Reported simultaneous estimation methods for this combination are predominantly chromatographic, including HPLC-UV procedures that are linear, precise, and accurate but demand expensive columns, organic mobile phases, and lengthy run times. By contrast, chemometric UV-spectrophotometric approaches permit the resolution of binary and ternary mixtures without any prior chemical separation. The mean centering of ratio spectra, developed by Afkhami and co-workers, is a simple, rapid, accurate, and precise procedure for binary and ternary mixtures, while the H-point standard addition method, introduced by Bosch-Reig and Campins-Falco in 1988, combines the principles of dual-wavelength spectrophotometry and the standard addition method and is particularly advantageous because it eliminates errors arising from interfering and blank reagents. Both techniques have been successfully applied to diverse pharmaceutical and environmental mixtures, including levodopa/carbidopa, valsartan/hydrochlorothiazide, rabeprazole/domperidone, Fe/Fe speciation, and binary metal-ion systems.

A survey of the literature indicated that no reported method had applied mean centering of ratio spectra and the H-point standard addition method to the simultaneous estimation of artemether and lumefantrine in combined dosage form. The aim of the present study was therefore to develop and validate UV-spectrophotometric methods based on these two approaches for the routine analysis of artemether and lumefantrine in their fixed-dose combination, and to compare the results with published simultaneous HPLC and UV methods.

2. MATERIALS AND METHODS

2.1 Chemicals, reagents, and samples

Artemether and lumefantrine were received as gift samples from Ipca Laboratories Ltd, Ratlam, India. Methanol and chloroform of analytical grade were used as solvents. The commercial fixed-dose combination tablets (label claim: artemether 10 mg, lumefantrine 120 mg) were procured for the assay.

2.2 Instrumentation

All spectral measurements were recorded on a double-beam UV–visible spectrophotometer over the wavelength range 200–400 nm with 1 nm intervals. Infrared spectra for drug identification were recorded on an FT-IR spectrophotometer using the KBr pellet technique, and melting points were determined by differential scanning calorimetry on 2 mg samples of each drug.

2.3 Identification of drugs

The procured drugs were identified and authenticated by comparing their FT-IR spectra with the Indian Pharmacopoeia reference frequencies. Thermal identification was performed by determining the melting points of artemether and lumefantrine by DSC.

2.4 Solubility studies and selection of analytical wavelengths

The solubility of each drug was assessed in water, methanol, and chloroform. A stock solution of artemether (100 µg/mL) was prepared by dissolving 10 mg in 100 mL of methanol; 1 mL of this solution was diluted to 10 mL to obtain a 10 µg/mL working solution, which was scanned over 200–400 nm. A corresponding 10 µg/mL solution of lumefantrine in chloroform was scanned similarly. The overlain spectra indicated wavelengths of maximum absorbance (λ_{max}) of 271 nm for artemether and 340 nm for lumefantrine, which were selected as the working wavelengths for analysis.

2.5 Preparation of standard solutions

Standard stock solutions (1000 µg/mL) of artemether and lumefantrine were prepared by dissolving 100 mg of each reference standard in 100 mL of the respective solvent and were diluted appropriately to obtain working standards of 100 µg/mL and 10 µg/mL for spectral scanning. Calibration standards spanning 5–25 µg/mL were prepared from the stock solutions for construction of the calibration graphs.

2.6 Method A: Mean centering of ratio spectra

For a binary mixture of artemether (X) and lumefantrine (Y), and assuming no interaction between the compounds and obedience to Beer's law, the absorbance vector of the mixture is given by:

$$A = a_x c_x + a_y c_y \quad (1)$$

where a_x and a_y are the molar absorptivity vectors and c_x and c_y are the concentrations of artemether and lumefantrine, respectively. Dividing equation (1) by the spectrum of a standard solution of lumefantrine, c_y , yields the first ratio spectrum:

$$B = \frac{A}{c_y} = \frac{a_x c_x}{c_y} + a_y \quad (2)$$

Because mean centering of the constant term is zero, mean centering of equation (2) gives:

$$MC(B) = MC\left(\frac{a_x c_x}{a_y}\right) \quad (3)$$

Equation (3) shows a linear relationship between and the concentration of artemether, permitting its determination without interference from lumefantrine; the calibration graph was constructed by plotting against the concentration of artemether, measuring the amplitude at the maximum wavelength (270 nm) for maximum sensitivity. The analogous procedure, dividing by the normalized artemether spectrum and measuring at 340 nm within 320–350 nm, was applied for the determination of lumefantrine.

2.7 Method B: H-point standard addition method

HPSAM requires the selection of two wavelengths, λ_1 and λ_2 , at which the interferent species possesses equal absorbance. Known amounts of the analyte are then successively added to the mixture and absorbances are measured at both wavelengths, giving:

$$A(\lambda_1) = b_0 + b + M_{\lambda_1} c_i \quad (4)$$

$$A(\lambda_2) = A_0 + A' + M_{\lambda_2} c_i \quad (5)$$

where and are the original analytical signals of the analyte, and the signals of the interferent, and the slopes of the standard-addition lines at the two wavelengths, and the added analyte concentration. The two straight lines intersect at the H-point (,), at which the analyte contribution is eliminated. For the selection of the wavelength pair, the analyte signal must be linear with concentration, the interferent signal must remain constant upon analyte addition, the analytical signals must be additive, and the difference between the slopes of the two lines must be as large as possible to ensure good accuracy and sensitivity; the pair 280/260 nm satisfied these criteria and was selected. Absorbances of standard additions were measured at 280 and 260 nm, with calibration graphs constructed over 4.00–32.00 $\mu\text{g/mL}$ for artemether and 5.00–45.00 $\mu\text{g/mL}$ for lumefantrine.

2.8 Validation of analytical procedures

Both methods were validated in accordance with the ICH Q2 guideline for the characteristics applicable to assay procedures: accuracy, precision (repeatability, intermediate precision, reproducibility), specificity, detection limit, quantitation limit, linearity, range, and robustness . Precision was assessed by five-replicate measurements (repeatability) and by intra-day (three times on the same day) and inter-day (three days) studies at low, medium, and high concentration levels . Accuracy was evaluated by recovery studies using the standard-addition technique at three concentration levels. The detection and quantitation limits were calculated from the standard deviation of the response (σ) and the slope of the calibration curve (S):

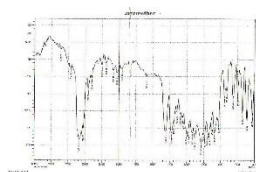
$$\{LOD\} = \frac{3.3\sigma}{S} \quad \{LOQ\} = \frac{10\sigma}{S} \quad (6)$$

Robustness was evaluated during the development phase through deliberate variations in method parameters, in line with the ICH requirement that the reliability of the analysis be demonstrated with respect to such variations.

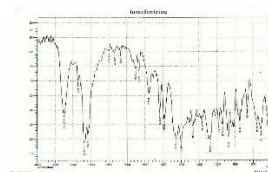
3. RESULTS AND DISCUSSION

3.1 Identification of drugs

The FT-IR spectra of the procured artemether and lumefantrine samples were found to be consistent with the reference spectra of the Indian Pharmacopoeia, confirming the identity and authenticity of the drugs. DSC analysis yielded melting endotherms at 101.56 °C for artemether and 130.72 °C for lumefantrine, the latter being in close agreement with the reported range of 128–132 °C.



FT-IR spectrum of Artemether



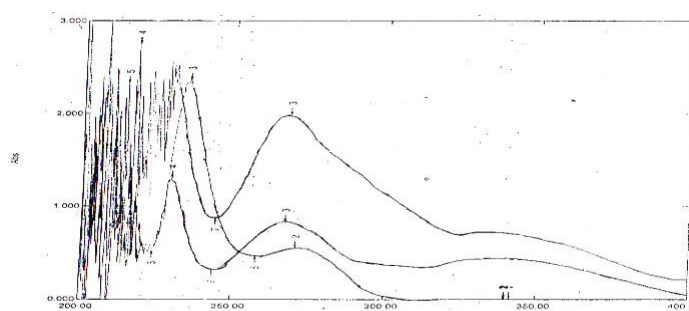
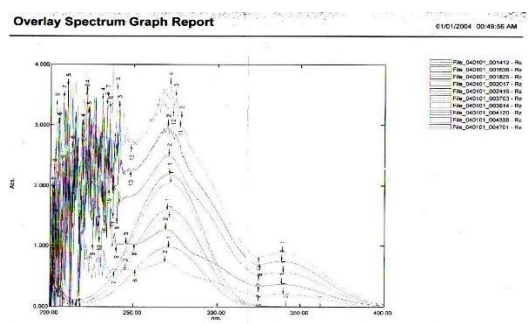
FT-IR spectrum of Lumefantrine

3.2 Solubility and solvent selection

Both drugs were found to be insoluble in water and soluble in methanol and chloroform. Accordingly, methanol was selected as the solvent for artemether and chloroform for lumefantrine throughout the study.

3.3 Spectral characteristics and wavelength selection

The overlain UV spectra showed distinct maxima at 271 nm (artemether, methanol) and 340 nm (lumefantrine, chloroform), which were adopted as the analytical wavelengths for the MCRS procedure. The optimized conditions are summarized in Table 1. For HPSAM, the wavelength pair 280/260 nm was selected on the basis of the criteria described in Section 2.7.



Artemether (5µg/ml), Lumefantrine (5µg/ml) and Sample Mixture(5:5µg/ml) for H-point Standard Addition Method-

Table 1: Optimized spectrophotometric conditions for Method A and Method B.

Parameter	Mean centering ratio method	H-point standard addition method
Wavelength (artemether)	270/271 nm (methanol)	280 nm / 260 nm
Wavelength (lumefantrine)	340 nm (chloroform)	280 nm / 260 nm
Working range (artemether)	5–25 µg/mL	4.0–32.0 µg/mL
Working range (lumefantrine)	5–25 µg/mL	5.0–45.0 µg/mL

3.4 Linearity and calibration

In the MCRS method, calibration graphs constructed over 5–25 µg/mL were found to be linear for both drugs. The regression equations were $y = 0.1014x - 0.0639$ ($R^2 = 0.9998$) for artemether and $y = 0.0954x + 0.0886$ ($R^2 = 0.9961$)

for lumefantrine. The mean absorbance values and within-level precision of the calibration standards are shown in Table 2. The high correlation coefficients, together with %RSD values below 2% at each level, confirm excellent linearity within the stated range .

Table 2: Calibration data for the mean centering of ratio spectra method (n = 3).

Concentration (µg/mL)	Mean absorbance (artemether)	%RSD (artemether)	Mean absorbance (lumefantrine)	%RSD (lumefantrine)
5	0.4503	0.795	0.6027	0.558
10	0.9453	1.834	1.0359	0.141
15	1.4582	0.810	1.4783	0.612
20	1.9505	0.643	1.9475	0.908
25	2.4834	0.722	—	—
Regression equation	$y = 0.1014x - 0.0639$	—	$y = 0.0954x + 0.0886$	—
R ²	0.9998	—	0.9961	—

For HPSAM, the method showed linearity over 5–45 µg/mL for lumefantrine and 4–20 µg/mL for artemether, with the same ranges confirmed for the range parameter.

3.5 Precision

The precision of both methods, expressed as %RSD, is summarized in Table 3. Repeatability %RSD values were 0.164841 for artemether and 0.720631 for lumefantrine in the MCRS method, and 1.89 and 1.90, respectively, in HPSAM. Intra-day and inter-day %RSD values at low, medium, and high concentration levels were uniformly below 2% in all cases, satisfying the ICH acceptance criterion for precision.

Table 3: Precision data (%RSD) for the two methods.

Precision level	MCRS — Artemether	MCRS — Lumefantrine	HPSAM — Artemether	HPSAM — Lumefantrine
Repeatability	0.164841	0.720631	1.89	1.90
Intra-day	0.6728	0.218	0.86666	0.7888
Inter-day	0.4937	0.5271	1.4666	1.8733

3.6 Accuracy (recovery studies)

Recovery studies were performed by the standard-addition technique at low, medium, and high levels relative to the test concentration. In the MCRS method, mean recoveries for artemether were 99.733%, 99.056%, and 99.246% at the three levels (range 99.06–99.73%), with %RSD values of 0.5573, 0.0210, and 0.02535 ; corresponding mean recoveries for lumefantrine were 100.80%, 99.266%, and 99.92% (range 99.27–100.80%), with %RSD values of 0.10452, 0.088014, and 0.829941 . In HPSAM, mean recoveries for artemether were 99.85%, 100.64%, and 99.71% (%RSD 1.054724, 0.827284, 0.880962) , and those for lumefantrine were 99.84%, 100.64%, and 99.71% . All recovery values lay within the limits prescribed by ICH, demonstrating that both methods are accurate and free from interference by excipients and matrix components.

3.7 Limit of detection and limit of quantitation

LOD and LOQ were calculated from the standard deviation of the response and the slope of the calibration curve (equation 6). For the MCRS method, LOD and LOQ were 3.41546746 and 10.3499014 µg/mL, respectively, for artemether and 0.504374214 and 1.52840671 µg/mL for lumefantrine . For HPSAM, LOD values were 0.58353 (280 nm) and 0.804463 (260 nm) µg/mL for artemether and 2.2687 (280 nm) and 2.28375 (260 nm) µg/mL for lumefantrine;

corresponding LOQ values were 1.76875 and 2.438454 µg/mL (artemether) and 6.75305 and 6.92048 µg/mL (lumefantrine). These low values confirm the adequate sensitivity of both methods for the intended assay application.

3.8 Specificity and robustness

The overlain spectra of the pure drugs showed no interfering peaks attributable to excipients or foreign particles, confirming the specificity of both methods. Robustness was evaluated during the development phase through deliberate, small variations in method parameters; the results indicated that measurements were not susceptible to uncontrolled variations, and the appropriate analytical conditions could be maintained with the established system suitability checks.

3.9 Assay of the commercial formulation

The validated MCRS method was applied to the simultaneous determination of both drugs in the commercial fixed-dose combination tablets; the results are presented in Table 4. The assay values — 99.37% for artemether and 98.40% for lumefantrine — were within the limits prescribed by ICH, confirming the suitability of the method for routine quality control of the combined dosage form.

Table 4: Assay results for the combined tablet formulation (label claim: artemether 10 mg, lumefantrine 120 mg).

Parameter	Artemether	Lumefantrine
Claim amount (mg)	10	120
Found amount (mg)	9.37	18.834
% Purity	99.37	98.40
SD	0.14363	0.0805536
%RSD	0.148778	0.0818579

3.10 Comparison with reported methods

The performance of the proposed methods compares favorably with published simultaneous HPLC-UV procedures for this combination. Reported HPLC methods have demonstrated linearity over 20–120 µg/mL (artemether) and 120–720 µg/mL (lumefantrine), correlation coefficients ≥ 0.999 , recoveries of 98.87–101.16%, and %RSD below 0.43%, with retention times of approximately 6–14 min per run. The proposed UV-spectrophotometric methods achieve comparable accuracy (99.06–100.80%) and precision (%RSD < 2%) while eliminating the need for chromatographic columns, organic mobile-phase consumption, and lengthy run times, and without requiring any prior separation step. These attributes make the methods particularly attractive for routine quality-control laboratories, especially in resource-limited settings.

4. CONCLUSION

Two UV-spectrophotometric methods — mean centering of ratio spectra and the H-point standard addition method — were successfully developed and validated for the simultaneous estimation of artemether and lumefantrine in combined tablet dosage form. Validation according to ICH Q2 guidelines confirmed that all parameters, including specificity, linearity, range, precision, accuracy, LOD, and LOQ, lie within the prescribed limits: calibration was linear with $R^2 \geq 0.9961$, all precision %RSD values were below 2%, and mean recoveries ranged from 99.06% to 100.80%. The recovery studies demonstrated the capability of both methods to recover the analytes quantitatively from their formulation, and the inter-day and intra-day precision results confirm that the methods are precise. Both methods are simple, rapid, accurate, precise, robust, and economical, require no separation or derivatization steps, and are therefore

recommended for the routine simultaneous determination of artemether and lumefantrine in pharmaceutical quality control.

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