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Research Article

NEW ANALYTICAL METHODS FOR ESTIMATION OF ARTEETHER BY UV AND FLUORESCENCE SPECTROPHOTOMETRY: DEVELOPMENT AND VALIDATION

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ABSTRACT

The research work is based on the development and validation of two different spectrophotometric methods (UV spectrophotometer and spectrofluorimeter) for estimation of α - β arteether. Two simple, accurate, precise, sensitive and economical methods has been developed, validated for the estimation of α - β arteether in bulk and pharmaceutical dosage form as per ICH guidelines Q2(R1). The solvent used for UV spectroscopy was methanol and HCl (8:2) and methanol was used for fluorimeter. For qualitative and quantitative analysis, 254 nm was used in UV spectroscopy and excitation and emission wavelengths were set at 354 nm and 697 nm, respectively for fluorimetry. Coefficients of correlation were found to be 0.993 and 0.992 for UV spectroscopy and fluorimetry respectively. Both methods show good accuracy and precision and were compared statistically by using two way ANOVA which shows no significant difference between these methods. So, the proposed methods were found to have equal applicability for estimation and routine analysis of arteether in pharmaceutical formulations.

Keywords: Arteether, Analytical method, Fluorimeter, Pharmaceutical formulation, UV spectrophotometer.

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INTRODUCTION

α - β arteether, (3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-10-ethoxy-3,6,9-trimethyl-3,12-epoxy-12 H-pyrano[4,3-j]-1,2-benzodioxepin, is an oil-soluble ethyl ether derivative of dihydroartemisinin, which is an efficient erythrocyteschizontocidal drug for the treatment of multi-drug resistant falciparum malaria. α - β arteether (**Fig. 1**) shows rapid schizontocidal action and brings about quick clinical improvement in falciparum malaria with low recrudescence rate. In multicentric clinical trials in patients with complicated and uncomplicated *P. falciparum* malaria, α - β arteether has been demonstrated for rapid parasite and fever clearance with no adverse effects^{1,2}. The mechanism of action responsible for its pharmacological activity is haem-catalyzed cleavage of the peroxide that generates

unstable free radicals to which malaria parasites are particularly sensitive. α - β arteether has been proven to be 100% effective in treating patients for acute chloroquine resistant, complicated as well as uncomplicated falciparum malaria³.

Extensive literature survey revealed that although there are many methods like HPTLC⁴, HPLC⁵ for determination of arteether and simultaneous estimation method using HPLC/MS⁶ were reported previously. A simple method for routine estimation of arteether is the need of the hour. As the analysis is important component in the formulation development of any drug molecule.

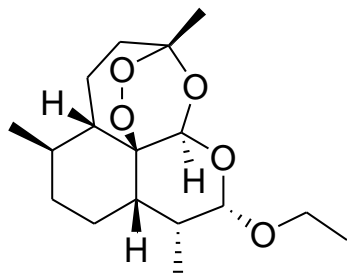


Figure 1: Chemical structure of Arteether

So, the object of this work was to develop new, simple, sensitive, precise, and accurate methods for the estimation of α - β arteether in pure form and in pharmaceutical formulation and to validate the developed methods as per the ICH guidelines⁷ for reliability and industrial acceptance.

MATERIAL AND METHODS

Apparatus

SHIMADZU UV-1700 double beam UV-Vis spectrophotometer equipped with 1cm matched pair of rectangular quartz cells was used in present study. Fluorescence measurements were carried out on LS-50 spectrofluorimeter (Perkin Elmer) equipped with xenon lamp and 1 cm quartz cells. The slit width of both the excitation and emission monochromators were set at 10 nm. All the apparatus and instruments were calibrated and validated before starting the experimental work.

Materials

Arteether pure drug was obtained as a gift sample from Cipla Pvt. Ltd., Baddi. All the chemicals and reagents used were of analytical grade. Two injection formulations procured from local market, were MATCH (MANKIND) and KAPITHER-150 (GODRAMS LIFELINE) each containing α - β arteether 150 mg/2 ml.

Methods

Preparation of standard stock solution

Standard stock solution of α - β arteether was prepared by dissolving 10 mg of α - β arteether in 10 ml of methanol which gives 1000 μ g/ml concentration.

Preparation of calibration curve

As no direct spectrophotometric method was reported so far in literature for the drug estimation. So, the problem of UV detection of α - β arteether has been tackled by acid decomposition using 5 M HCl inducing the formation of UV detectable degradation product. The optimum conditions for the estimation of α - β arteether were established by varying concentration of HCl and heating conditions and the maximum absorption was obtained by heating at 50°C for 30 min. with 2 ml of 5M HCl. The peak at 254 nm was the most intense and prominent one and was produced in every condition of heating⁸.

For UV spectrophotometry 100 μ g/ml solution was prepared from stock solution, pipetted out 0.8ml, 1.2 ml, 1.6 ml, 2.0 ml, 2.4 ml, 2.8 ml, 3.2 ml and 3.6 ml into 10 ml volumetric flasks and 2 ml of 5 M HCl was added to

each and finally volume was made up to 10 ml with methanol to produce concentrations of 8 μ g/ml, 12 μ g/ml, 16 μ g/ml, 20 μ g/ml, 24 μ g/ml, 28 μ g/ml, 32 μ g/ml, 36 μ g/ml respectively. The solution were kept in water bath at 50°C for 30 minutes for its acid decomposition to produce α , β -unsaturated decalone [8-methyl-5-(2-propanyl) decalin-4-ene 3-one]. The absorbance was measured at λ_{max} 254 nm using methanol and HCl (8:2) as blank. At this absorbance maximum, calibration curve of concentration against the absorbance was prepared (Fig.2). The overlay spectra of arteether are shown in Fig.3.

For fluorimetry 100 μ g/ml solution was prepared from stock solution and pipetted out 0.1 ml and was diluted upto 10 ml using methanol as solvent. The solution such obtained was further diluted to 6.25 ng/ml, 12.5 ng/ml, 25 ng/ml, 50 ng/ml and 100 ng/ml by using same solvent. The fluorescence intensity was measured at the excitation wavelength of 354 nm and emission wavelength of 697 nm. The calibration curve was drawn by plotting graph between fluorescence intensity at emission wavelength and concentration (Fig.4). The overlay spectra of arteether by using fluorimeter are shown in Fig. 5.

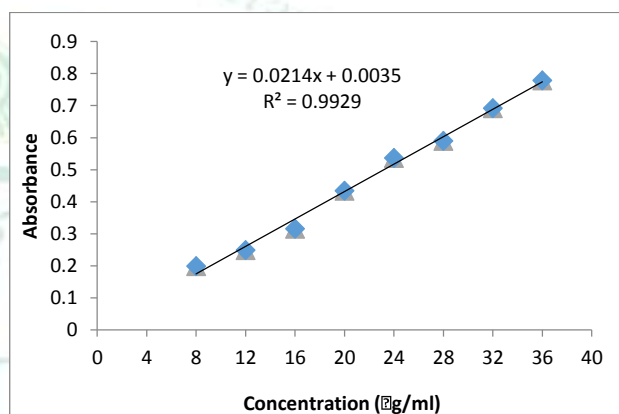


Figure 2: Calibration curve of arteether using UV Spectrophotometer

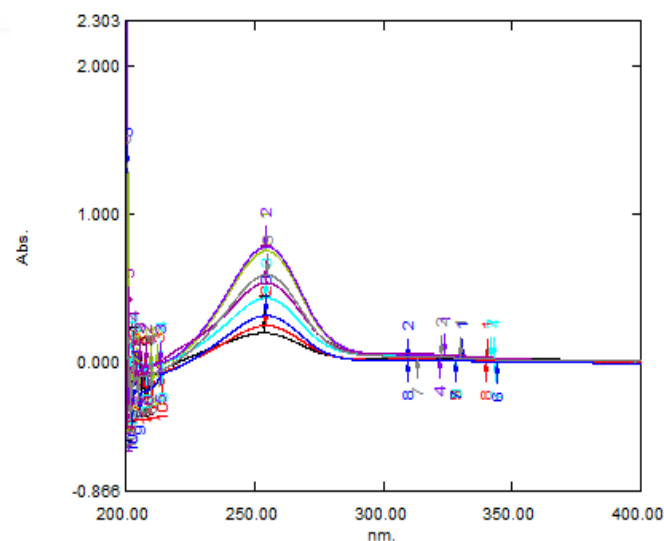


Figure 3: Overlay Spectra of arteether using UV Spectrophotometer

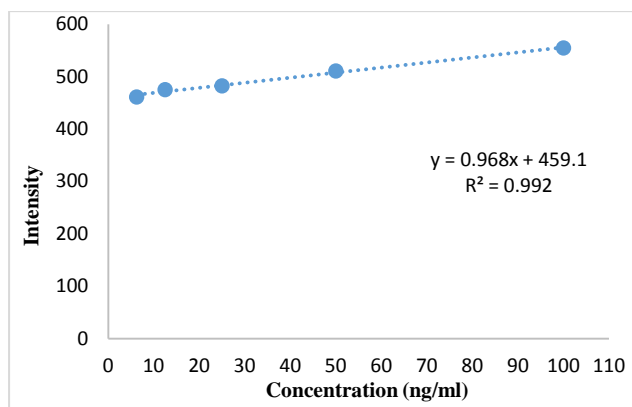


Figure 4 Calibration curve of arteether using fluorimeter

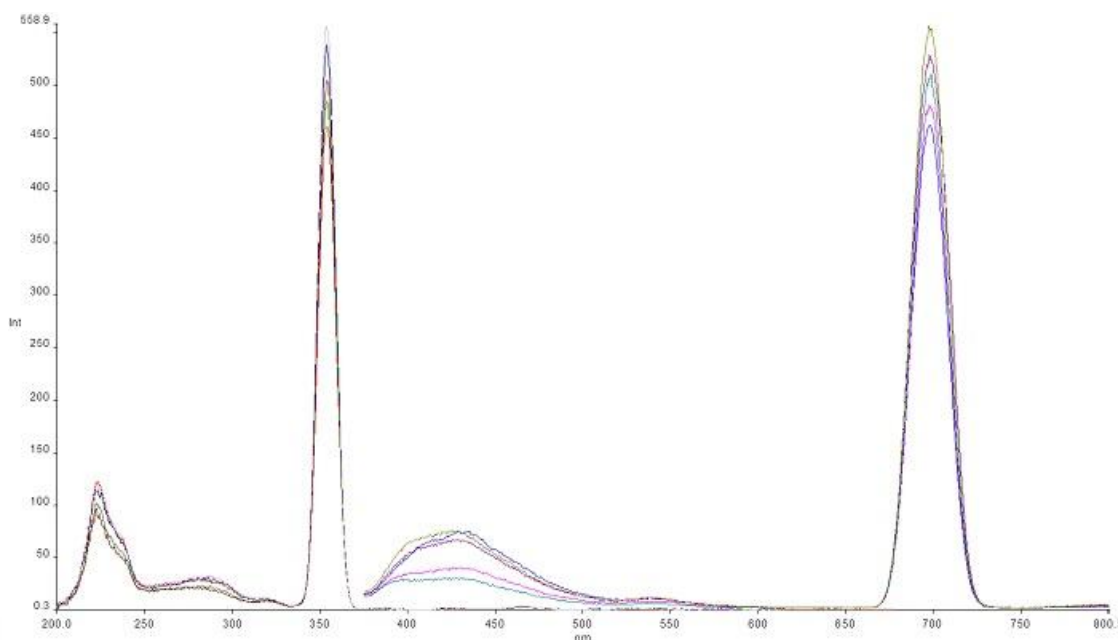


Figure 5 Overlay spectra of Arteether using fluorimeter

Analytical method validation of the proposed method

Validation is the process of demonstrating that analytical procedures are suitable for their intended use and that they support the identity, strength, quality, purity and potency of the drug substances and drug products.

The analytical method validation includes linearity, precision, accuracy, robustness, limit of detection (LOD) and limit of quantification (LOQ) as per ICH guidelines⁷.

Linearity and range

The linearity of the analytical method is its ability to elicit test results which are directly proportional to analyte concentration in samples within a given range⁹. The various aliquots were prepared by suitable dilution of the standard stock solution (100 µg/ml) ranging from 8-36 µg/ml and the samples were scanned in UV-Vis Spectrophotometer against methanol and HCl (8:2) as blank. The absorbances of respective concentrations were then calculated for coefficient of correlation using Microsoft excel.

For fluorimeter, linearity was established by preparing five different dilutions (6.25 ng/ml, 12.5 ng/ml, 25 ng/ml, 50 ng/ml and 100 ng/ml) of drug. Intensities of respective concentrations were then calculated for coefficient of correlation using Microsoft excel.

Precision

The precision of an analytical procedure is usually expressed as the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions¹⁰. Intraday precision study was carried out by preparing drug solution of three different concentrations and analyzing them at three different times in a same day. Likewise for interday drug solutions were analyzed for three different days. The same procedure was followed to calculate precision by using fluorimeter. The results were reported in terms of %RSD.

Accuracy

The accuracy of the method is the closeness of the measured value of the true value for the sample¹¹. To determine the accuracy of proposed method, recovery

studies were performed by standard addition method. The recovery studies were performed at three levels, 80, 100 and 120 % of working standard solution (100 µg/ml). The recovery samples were prepared in aforementioned procedure. The solutions were then analyzed at respective wavelength (254 nm) for UV spectroscopy and at 697 nm for fluorimetric analysis. The percentage recoveries were calculated for the formulation from the calibration curve.

Robustness

Robustness of the proposed method was determined by carrying out analysis under different wavelengths (252 nm, 254 nm, 256 nm) and by making deliberate small changes in ratio of HCl and methanol (1:9 and 3:7) used for UV spectrometer. In case of fluorimeter, robustness was determined at different wavelengths (695 nm, 697 nm, 699 nm). The respective absorbances were noted and the results were indicated as % RSD.

LOD and LOQ

Limit of detection (LOD) is the lowest amount of analyte in the sample that can be detected. Limit of quantification (LOQ) is the lowest amount of analyte in the sample that can be quantitatively determined. The LOD and LOQ for arteether by the proposed method were determined using calibration standards. LOD and LOQ were calculated using following equations:

$$\text{LOD} = 3.3 \sigma/S,$$

$$\text{LOQ} = 10 \sigma/S;$$

Where σ standard deviation of the response and S is the slope of the related calibration curve.

RESULTS

Linearity and Range

The calibration curve was obtained by its correlation coefficient. The curve of Arteether was linear in the

concentration range of 8-36 µg/ml with correlation coefficient of 0.993 for UV spectroscopy. For fluorimetric analysis curve was linear in range of 6.25-100 ng/ml with correlation coefficient of 0.992. The linearity data of arteether for UV and fluorimetric analysis are shown in **Table 1** and **Table 2** respectively.

Table 1: Linearity of arteether estimation by UV spectroscopy

Concentration (µg/ml)	Absorbance
8	0.19934
12	0.24927
16	0.31604
20	0.43457
24	0.53687
28	0.59021
32	0.6922
36	0.77893

Table 2: Linearity of arteether estimation by fluorimetry

Concentration (ng/ml)	Intensity
6.25	461.02
12.5	475.03
25	482.22
50	510.61
100	554.57

Precision

Precision was calculated as intraday and interday variation (%RSD) for the drug. The results confirmed adequate sample stability and method reliability where % RSD was < 2%. The results of interday and intraday precision for UV analysis are mentioned in **Table 3** and **Table 4**. Same results are summarized in **Table 5** and **Table 6** for fluorimetric analysis.

Table 3: Intraday Precision at 254 nm in UV spectroscopy

S. No.	Concentration (µg/ml)	Absorbance			Mean	S.D.	%R.S.D.
1 st time	20	0.4375	0.4396	0.4435	0.44028	0.00303	0.68966
	24	0.6113	0.6114	0.6130	0.61194	0.00095	0.15598
	28	0.7825	0.7801	0.7833	0.78198	0.00164	0.21035
2 nd time	20	0.4485	0.4525	0.4557	0.45235	0.00342	0.75667
	24	0.6156	0.6174	0.6205	0.61784	0.00246	0.39902
	28	0.7850	0.7869	0.7889	0.78695	0.00196	0.24857
3 rd time	20	0.4565	0.4592	0.4613	0.45902	0.00238	0.51996
	24	0.6216	0.6230	0.6252	0.62329	0.00184	0.29549
	28	0.7907	0.7930	0.7936	0.79244	0.00148	0.18652

Table 4: Interday Precision at 254 nm in UV spectroscopy

S. No.	Concentration (µg/ml)	Absorbance			Mean	S.D.	%R.S.D.
1 st day	20	0.4375	0.4396	0.4435	0.44028	0.00303	0.68966
	24	0.6113	0.6114	0.6130	0.61194	0.00095	0.15598
	28	0.7825	0.7801	0.7833	0.78198	0.00164	0.21035
2 nd day	20	0.4520	0.4539	0.4554	0.45377	0.00170	0.37607
	24	0.6194	0.6221	0.6252	0.62223	0.00293	0.47141
	28	0.7969	0.7978	0.8004	0.79838	0.00183	0.22912
3 rd day	20	0.4661	0.4664	0.4696	0.46736	0.00194	0.41634
	24	0.6229	0.6278	0.6269	0.62589	0.00261	0.41710
	28	0.7927	0.7958	0.7991	0.79586	0.00318	0.39903

Table 5: Intraday Precision at 697 nm in fluorescence spectroscopy

S. No.	Concentration (ng/ml)	Absorbance			Mean	S.D.	%R.S.D.
1 st time	12.5	471.89	472.59	472.2	472.23	0.35076	0.07428
	25	494.91	493.21	494.17	494.09	0.85237	0.17251
	50	517.99	517.99	516.72	517.34	0.63553	0.12285
2 nd time	12.5	477.91	476.18	476.87	476.99	0.87089	0.18258
	25	498.19	499.72	499.11	499.01	0.77021	0.15435
	50	523.29	524.49	525.66	524.48	1.18502	0.22594
3 rd time	12.5	481.99	478.21	480.23	480.14	1.8915	0.39394
	25	502.81	502.52	503.99	503.11	0.7786	0.15476
	50	526.31	523.99	525.83	525.83	1.2246	0.23309

Table 6: Interday Precision at 697 nm in fluorescence spectroscopy

S. No.	Concentration (ng/ml)	Absorbance			Mean	S.D.	%R.S.D.
Day 1	12.5	471.89	472.59	472.2	472.23	0.35076	0.07428
	25	494.91	493.21	494.17	494.09	0.85237	0.17251
	50	517.99	517.99	516.72	517.34	0.63553	0.12285
Day 2	12.5	480.97	478.19	481.27	480.14	1.69827	0.35370
	25	503.45	501.77	505.29	503.50	1.76060	0.34967
	50	522.9	523.78	525.51	524.06	1.32787	0.25338
Day 3	12.5	487.89	485.91	488.18	487.33	1.2354	0.25350
	25	507.19	504.85	506.87	506.30	1.2687	0.25059
	50	529.09	531.14	532.86	531.03	1.8874	0.35542

Accuracy

Accuracy was determined by calculating the recovery and the mean was determined. The assay values with respect to the label claim of marketed formulation of

arteether in both methods ensure the accuracy of proposed methods. The results of accuracy for UV and fluorimetric analysis are mentioned in **Table 7** and **Table 8** respectively.

Table 7: Accuracy data of UV method

Drug	Injection amount (µg/ml)	Level of addition (%)	Amount spiked (µg/ml)	Amount recovered (µg/ml)	Recovery (%)	Average recovery (%)
Arteether	10	80	8	17.97	98.75	99.71
	10	100	10	20.06	100.8	
	10	120	12	21.93	99.58	

Table 8: Accuracy data of fluorimetric analysis

Drug	Injection amount (µg/ml)	Level of addition (%)	Amount spiked (µg/ml)	Amount recovered (µg/ml)	Recovery (%)	Average Recovery (%)
Arteether	100	80	80	179.55	99.53	99.95
	100	100	100	199.96	100.04	
	100	120	120	220.25	100.28	

Robustness

Robustness was calculated by varying the ratio of solvents and wavelengths and results are shown in **Table**

9 and **Table 10** for UV analysis and in **Table 11** for fluorimetric analysis.

Table 9: Robustness studies (1:9 ratio of HCl:Methanol) in UV estimation

Wavelength	Concentration (µg/ml)	Absorbance			Mean	S.D.	%R.S.D.
252 nm	20	0.1216	0.1219	0.1209	0.12149	0.000476	0.39175
	24	0.1742	0.1760	0.1739	0.17469	0.001162	0.66518
	28	0.2259	0.2248	0.2267	0.22581	0.000977	0.43258
254 nm	20	0.1209	0.1217	0.1202	0.12096	0.00072	0.59533
	24	0.1737	0.1729	0.1730	0.17319	0.00042	0.24009
	28	0.2235	0.2228	0.2240	0.22399	0.00062	0.27746
256 nm	20	0.1187	0.1195	0.1183	0.11885	0.00057	0.47867
	24	0.1708	0.1716	0.1702	0.1709	0.00069	0.40746
	28	0.2173	0.2186	0.2186	0.21766	0.00080	0.36838

Table 10: Robustness studies (3:7 ratio of HCl:Methanol) in UV estimation

Wavelength	Concentration (µg/ml)	Absorbance			Mean	S.D.	%R.S.D.
252 nm	20	0.4957	0.4948	0.4966	0.49573	0.00089	0.18054
	24	0.7872	0.7869	0.7879	0.78734	0.00055	0.06971
	28	0.9517	0.9528	0.9521	0.9522	0.00059	0.06197
254 nm	20	0.5030	0.5049	0.5024	0.50347	0.00129	0.25555
	24	0.8007	0.8012	0.8028	0.80156	0.00110	0.13775
	28	0.9635	0.9629	0.9646	0.96368	0.00089	0.09264
256 nm	20	0.5009	0.5023	0.5039	0.50241	0.00149	0.29713
	24	0.7989	0.7972	0.8004	0.79886	0.00159	0.19925
	28	0.9591	0.9581	0.9615	0.95958	0.00174	0.18166

Table 11: Robustness data at different wavelengths in fluorimetric analysis

Wavelength	Concentration (ng/ml)	Absorbance			Mean	S.D.	%R.S.D.
695 nm	12.5	472.12	473.71	474.10	473.31	1.0489	0.2216
	25	479.91	481.29	481.89	481.03	1.0153	0.2111
	50	506.78	507.99	506.12	506.96	0.9484	0.1871
697 nm	12.5	475.91	473.72	476.19	475.27	1.3525	0.2846
	25	481.81	482.88	483.11	482.60	0.6938	0.1438
	50	511.32	509.29	510.81	510.47	1.0561	0.2069
699 nm	12.5	482.33	483.12	482.91	482.79	0.4092	0.0848
	25	491.91	492.19	493.01	492.37	0.5717	0.1161
	50	517.81	515.19	518.12	517.04	1.6096	0.3113

LOD and LOQ

The LOD and LOQ for UV method were found to be 0.524 µg/ml, 1.588 µg/ml respectively. The fluorimetry based method was found to be more sensitive, LOD and LOQ, as determined for this method, were 18.77 ng/ml and 61.94 ng/ml respectively.

Statistical comparison of the results obtained by both the developed methods by two way ANOVA and t-test.

To compare the significant difference between the developed methods, two way ANOVA test and t-test were applied to both the methods: UV spectroscopy, Spectrofluorimetry (**Table 12**). Assay results in two marketed formulations were taken in account for performing the ANOVA test. The results of statistical comparisons are shown in **Table 13**. Various validation parameters of both methods developed for estimation of α - β arteether are mentioned in **Table 14**.

Table 12: Results of statistical t-test analysis

Method	Drug	Label claim	Concentration found	% Purity	S.D.	% R.S.D.	t-test
UV method	F1	10	9.91	99.10	0.06	0.64	2.42
	F2	10	9.98	99.80	0.01	0.14	2.44
Fluorimetric method	F1	100	100.12	100.12	0.08	0.08	2.45
	F2	100	99.92	99.92	0.06	0.06	2.44

$t_{cal} = |100 - R| \sqrt{n/R.S.D.}$, where t_{cal} is the calculated t value, n is the number of replicates, and R is mean accuracy. Tabulated t-value for 95% two sided confidence interval for 5 degree of freedom was ($t_{tab=}$) 2.92.

Table 13: Statistical results of one way ANOVA

Statistical parameters (n=3)	F-value(Calculated)	F-value (Theoretical)
Accuracy	4.41	19.37

Table 14: Validation parameters of developed analytical methods for estimation of α - β Arteether

Validation parameters	UV method	Fluorimetric method
Absorption maxima (nm)	254	697
Linearity range	8-36 μ g/ml	6.25-100 ng/ml
Standard Regression equation	Y= 0.0214x + 0.0035	Y=0.9684x + 459.17
Correlation coefficient (r^2)	0.993	0.992
Accuracy	99.71%	99.95%
Precision	Intraday(0.385)	Intraday (0.190)
	Interday(0.374)	Interday (0.243)
Robustness	1:9 ratio (0.42855) 3:7ratio (0.16403)	0.19635
LOD	0.52408 μ g/ml	18.77 ng/ml
LOQ	1.58814 μ g/ml	61.94 ng/ml

DISCUSSION

The proposed methods provide sensitive, precise, economical and accurate UV spectrophotometric as well as fluorimetric method for the estimation of arteether in injection dosage forms. In the UV spectrometric method, methanol was used as solvent and HCl was used for acid decomposition, which induce the formation of UV detectable degradation product. The maximum absorption was found to be 254 nm for UV and 697 nm(emission wavelength) for fluorimetric analysis. The linearity range was found to be 8-36 μ g/ml with correlation coefficient of 0.993 for UV method. The linearity for fluorimetric method is in range of 6.25-100 ng/ml with correlation coefficient of 0.992. The method was found to be precise as % RSD values for intraday and interday were within the limits less than 2. Accuracy of the proposed methods was determined by the recovery studies and the mean recoveries (% RSD) for the three concentrations were found to be 98.75% (80% spiking), 100.8% (100% spiking), 99.58% (120% spiking) for UV analysis and 99.53% (80% spiking), 100.04% (100% spiking), 100.28% (120% spiking) respectively for fluorimetric analysis. The good % recovery of the drug obtained indicates that the methods are accurate. The proposed method was found to be robust as the % RSD values were found to be less than 2. The limit of detection and limit of quantification for UV and fluorimetric method was found to be 0.524 μ g/ml, 1.588 μ g/ml and 18.77 ng/ml, 61.94 ng/ml indicating the methods developed are sensitive. The

calculated F value did not exceed the theoretical value, at 0.05 level of significance, indicating no significant difference with respect to accuracy among the results of developed methods.

CONCLUSION

The developed spectroscopic methods are not only rapid but also simple, sensitive, accurate, and precise and hence used for the routine analysis of arteether in bulk and in pharmaceutical formulation. This method helps us in estimating that in contrast to UV spectrophotometric method, results of fluorimetric analysis were more sensitive and accurate as the accuracy from fluorimetric was 99.95% which is better than UV method *i.e.* 99.71%. The LOD and LOQ of fluorimetric method were 18.77 ng/ml and 61.94 ng/ml whereas that of UV method are 0.524 μ g/ml and 1.588 μ g/ml indicating that reported fluorimetric method is more sensitive. As the samples with low concentration can be detected by these methods, hence both methods may be applied in pharmaceutical industries for routine estimation as evident by studies on novel drug delivery system of arteether by author's group¹².

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Conflicts of Interests: None

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