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Simultaneous Estimation of Artemether and Lumefantrine in Tablet Formulation by UV-Visible Spectroscopy using Simultaneous Equation Method

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Abstract: *In the present work, a simple, accurate and precise method has been developed and validated for the simultaneous estimation of antimalarial agents, Artemether & Lumefantrine and in their combined dosage form i.e. tablets by UV Spectrophotometric Method. It employs estimation of drugs by Simultaneous Equation Method (SEM) using 250 nm and 305 nm in Chloroform as λ_{max} values of Artemether and Lumefantrine respectively. Both drugs obey Beer-Lamberts law in the concentration range of 4.5 µg/ml to 82.5 µg/ml. Validation of the proposed methods was carried out for its precision, linearity and limit of detection according to specifications. The recovery studies ascertained accuracy and reproducibility. The method was applied successfully for the estimation of Artemether and Lumefantrine in tablet dosage form without the interference of common excipients*

Keywords:. Artemether, Lumefantrine, Simultaneous Estimation, UV-spectroscopy

I. INTRODUCTION

India is amongst top three generic manufacturers of drugs in the world which holds 23 % share of generic market. According to FDA only those drugs, which will be proved to be pharmaceutical and biological equivalent to the branded formulations may be sold into the market. Various methods are available for the analysis of the pharmaceuticals, such as titrimetric, gravimetric, non-aquous volumetric, polarography, chromatography, spectrophotometry etc.

In some cases, extraction of mixture may be required to estimate them quantitatively.In some cases, analytical methods for some drugs, their combination or their specific dosage form may not be available. The existing analytical procedures may require expensive instruments, reagents and solvents or may be time consuming. It may also involve cumbersome extraction and separation procedures and these may not be reliable. Under these circumstances, rhobust, efficient, rapid, accurate, precise and cost effective method is required to verify identity, purity and potency of active pharmaceutical ingredient. UV spectroscopy is a comprehensive and proven option that has been successfully used in the analysis of pharmaceuticals, plant constituents, food products, biomolecules, environmental and metallurgic sciences etc.

Since past 35 years, it is one of most widely used methods for quick and easy determination of quality, authenticity and purity of the raw materials, crude drugs and market formulations. In many applications, other technique could be employed but none rival UV-Visible spectrometry for its simplicity, versatility, speed, accuracy and cost effectiveness. Ultraviolet–visible spectroscopy or ultraviolet-visible spectrophotometry (UV-Vis or UV/Vis) refers to absorption spectroscopy or reflectance spectroscopy in the ultraviolet-visible spectral region. This means it uses light in the visible and adjacent (near-UV and near-infrared (NIR)) ranges. The absorption or reflectance in the visible range directly affects the perceived color of the chemicals involved. In this region of the electromagnetic spectrum, molecules undergo electronic transitions. This technique is complementary to fluorescence spectroscopy, in that fluorescence deals with transitions from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state.

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The basis of all the spectrophotometric techniques for multi component samples is the property that at all wavelengths, the absorbance of a solution is the sum of absorbance of individual component(s). The measured absorbance is a difference between the total absorbance of the solution in the sample cell and that of the solution in the reference cell.

UV-VIS spectroscopy is one of the oldest methods in molecular spectroscopy. The definitive formulation of the Bouguer-Lambert &Beer law in 1852 created the basis for the quantitative evaluation of absorption measurements at an early date. This led firstly to colorimetry, then to photometry and finally to spectrophotometry.

With the development of quantum chemistry, increasing attention was paid to the correlation between light absorption and the structure of matter with the result that in recent decades a number of excellent discussions of the theory of electronic spectroscopy (UV-VIS and luminescence spectroscopy) have been published.

The Beer-Lambert law states that there is a linear relationship between the concentration and the absorbance of the solution, which enables the concentration of a solution to be calculated by measuring its absorbance.

In double beam UV spectrophotometer, two beams are formed in the space by a U-Shaped mirror known as the beam splitter, a circular disc is opaque and third is transparent and remaining one third is mirrored.The monochromatic beam of light splits into two beams of equal intensities using a beam splitter.It provides a ratio of intensities of sample and reference beams simultaneously.

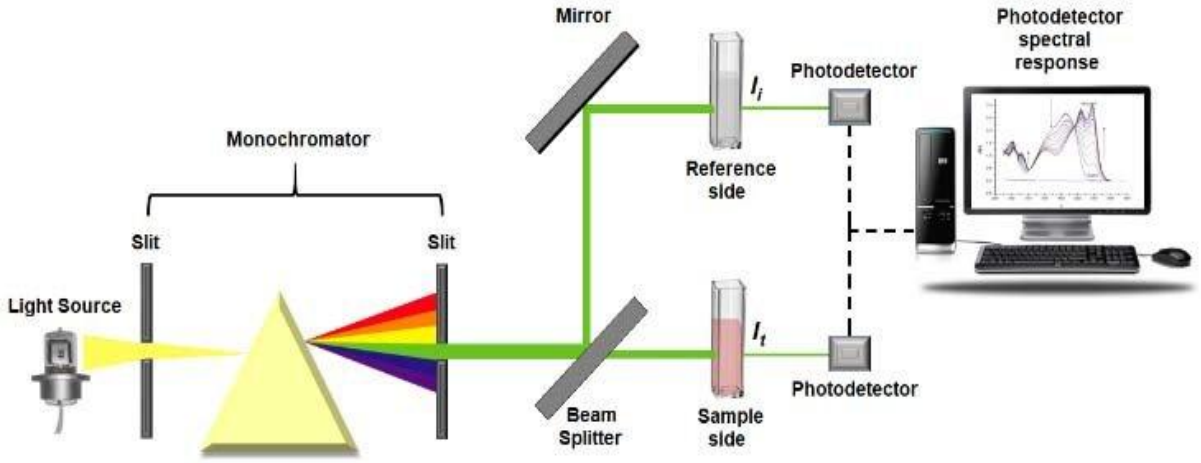

Fig. 1.1 Instrumentation of Double beam UV-Visible spectrophotometer

1.1 Applications of UV-Visible Spectroscopy

- Detection of Impurities
- Quantitative &Qualitative analysis
- Chemical kinetics & monitoring studies
- Detection of functional groups
- Characterization of smaller nanoparticulate matter
- Quantitative analysis of pharmaceutical substances
- Examination of structural protein by tracking changes in peak wavelength absorbance
- Measures of concentration in a standard & unknown solution (purity testing)

1.2 Multicomponent analysisin UV-Visible Spectroscopy

- Simultaneous equation method (Vierdotts method)
- Derivative spectroscopic methods
- First derivative curve (dy/dx)
- Second derivative curve (d^2y/dx^2)
- Third derivative curve (d^3y/dx^3)
- Absorbance ratio method (Q-absorbance method)

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- Solvent extraction or infusion method
- Dual wavelength sigma method
- Difference spectroscopic method
- Geometric correction method
- Orthogonal polynomial method
- H-point standard addition method
- Least square approximation method
- Area under the curve method

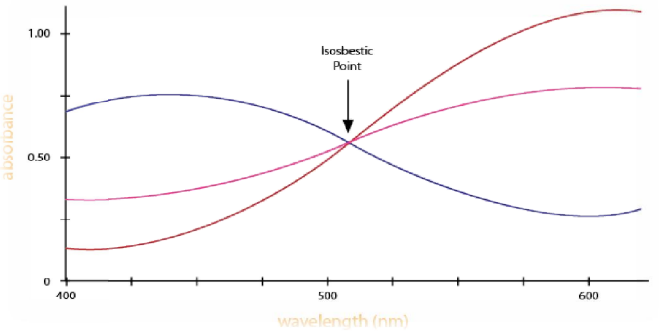

Fig. 1.2 Isosbestic point in UV-Visible spectroscopy

Malaria is a life-threatening disease primarily found in tropical countries. It is both preventable and curable. However, without prompt diagnosis and effective treatment, a case of uncomplicated malaria can progress to a severe form of the disease, which is often fatal without treatment.

Malaria is not contagious and cannot spread from one person to another; the disease is transmitted through the bites of female *Anopheles* mosquitoes. Five species of parasites can cause malaria in humans and 2 of these species – *Plasmodium falciparum* and *Plasmodium vivax* – pose the greatest threat. There are over 400 different species of *Anopheles* mosquitoes and around 40, known as vector species, can transmit the disease.

This risk of infection is higher in some areas than others depending on multiple factors, including the type of local mosquitoes. It may also vary according to the season, the risk being highest during the rainy season in tropical countries.

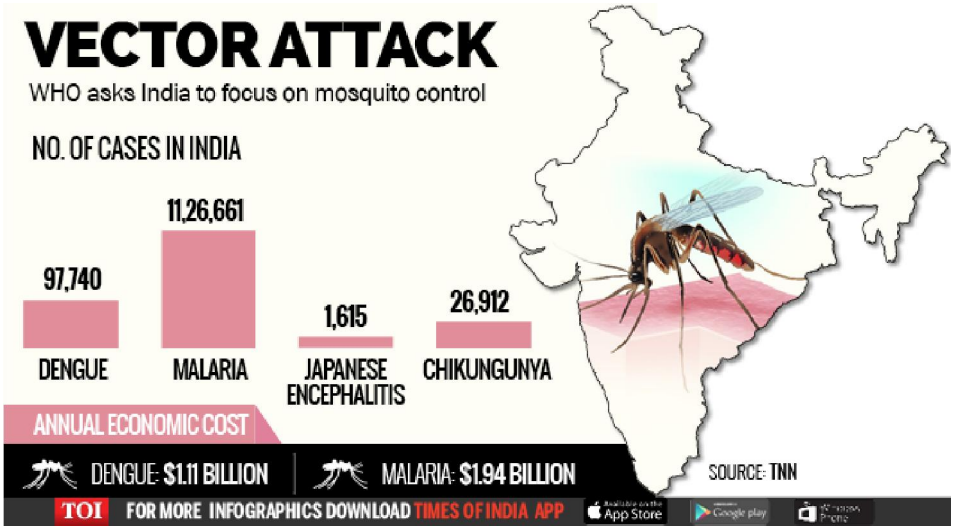

Fig. 1.3 Survey on Malarial mosquito attack

Malaria is treated with prescription drugs to kill the parasite. The types of drugs and the length of treatment will vary, depending on:

- which type of malaria parasite you have

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- the severity of your symptoms
- your age
- whether you're pregnant

The most common antimalarial drugs include: -

Chloroquine phosphate - Chloroquine is the preferred treatment for any parasite that is sensitive to the drug. But in many parts of the world, parasites are resistant to chloroquine, and the drug is no longer an effective treatment.

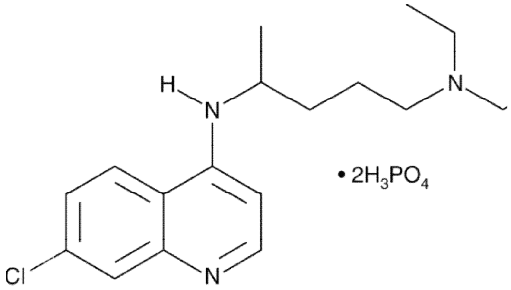

Fig. 1.4 Chloroquinephosphate

Artemisinin-based combination therapies (ACTs) -Artemisinin-based combination therapy (ACT) is a combination of two or more drugs that work against the malaria parasite in different ways. This is usually the preferred treatment for chloroquine-resistant malaria. Examples include Artemether-Lumefantrine (Coartem) and Artesunate-Mefloquine.

Other common antimalarial drugs include: -

- Atovaquone-Proguanil (Malarone)
- Quinine sulfate (Qualaquin) with Doxycycline (Oracea, Vibramycin)
- Primaquine phosphate

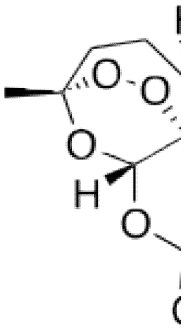

Fig. 1.5 Artemether

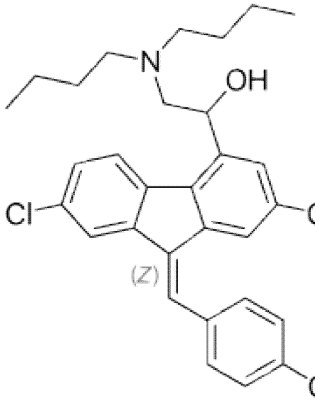

Fig. 1.6 Lumefantrine

II. REVIEW OF LITERATURE

Mishra Megha & Mundada Anand (2021) [1] developed UV spectroscopic method for quantitative determination of Artemether and Lumefantrine which is reported to be rapid, economic, linear, reproducible, specific and cost effective. The method was validated showing satisfactory data for all the method validation parameters tested. The developed method can be used for routine analysis of in process quality control and marketed samples of Artemether and Lumefantrine.

Lefevre Gilbert & Thomsen Mikael S. (1999) [2] studied that Riamet, the fixed dose combination of the two active antimalarial principles Artemether and Lumefantrine, is well tolerated and highly efficacious with a wide therapeutic index. The two compounds have very different and synergistic pharmacokinetic properties. Artemether is rapidly absorbed and rapidly eliminated, whereas Lumefantrine is slowly absorbed and slowly eliminated. Both compounds are metabolised predominantly through CYP3A4, artemether being transformed to the active metabolite DHA. The wide

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therapeutic index and the short duration of administration of Co-Artemether suggest that the risk for any tolerability concerns because drug accumulation is minimal.

B. Sridhar, K. Hanumantha Rao *et. al.*(2010)[3]developed a simple RP-HPLC which was found to besensitive, precise and accurate using UV-Visible spectrophotometric detector. Hence,itcan be used in routine for the simultaneous determination of Artemether and Lumefantrien in bulk as well as in pharmaceutical preparations.

Karajgi S. R., Tanveer A. R. and Kalyane N.V. (2016)[4] detected both Artemether and Lumefantrine simultaneously by UV Spectrophotometric Area UndertheCurve Method. They choose ethanol as solvent.

M. Haripriya, Neethu Antony & P. Jayasekhar(2013) [5]studied estimation of combination of Clinidipine & Telmisartan (CIL & TEL) by UV spectroscopic simultaneous equation method and verified by absorbance ratio method

III. RATIONALE BEHIND SELECTION OF TOPIC

The project rationale focuses on selection of UV-Visible spectroscopic method of determination of multicomponent in single marketed formulation using analytical and algebraic method called as Simultaneous Equation method.

Artemether is a methyl ether derivative of artemisinin, which is a peroxide lactone withdrawn from the antimalarial plant *Artemisia annua*. It is an antimalarial for the treatment of multiple drug strains of *Plasmodium falciparum* malaria. Artemether is effective against the blood schizonts of both the malarial parasites *P. falciparum* and the *P. vivax*. It, however, may not be as good as artesunate for severe malaria.

Lumefantrine (or benflumetol) is also an antimalarial drug. It is only used in combination along with Artemether. The term **"co-artemether"** formerly describes this combination.

Review of literature revealed that there are very few methods reported for the estimation of Artemether and Lumefantrine in combined dosage forms. Eight HPLC methods, one UV spectrophotometric absorption factor correction method and one UV simultaneous equation method were reported and no area under curve method has been so far reported for simultaneous estimation of these drugs in combined dosage form. There were solubility issues reported for bulk as well as marketed formulation samples.

So, the aim and objective of the present study were to develop an area under the curve UV-Visible spectrophotometric analytical method for the estimation of Artemether and Lumefantrine in bulk and formulated dosage form in combination without prior separation and to establish a simple, sensitive, standard, reproducible method for the quality control of these drugs in combined dosage forms

IV. AIM AND OBJECTIVES

AIM: Simultaneous Estimation of Artemether & Lumefantrine in tablet formulation by UV-Visible Spectroscopy using Simultaneous Equation method.

PRINCIPLE :Simultaneous determination of multi-components in single formulation by UV-Visible spectroscopic analytical methods.

4.1 Objectives

- To estimate % strength & concentration of Artemether & Lumefenthrine in marketed tablet formulation (Lumerax) by UV-Visible Spectroscopy using Simultaneous Equation method

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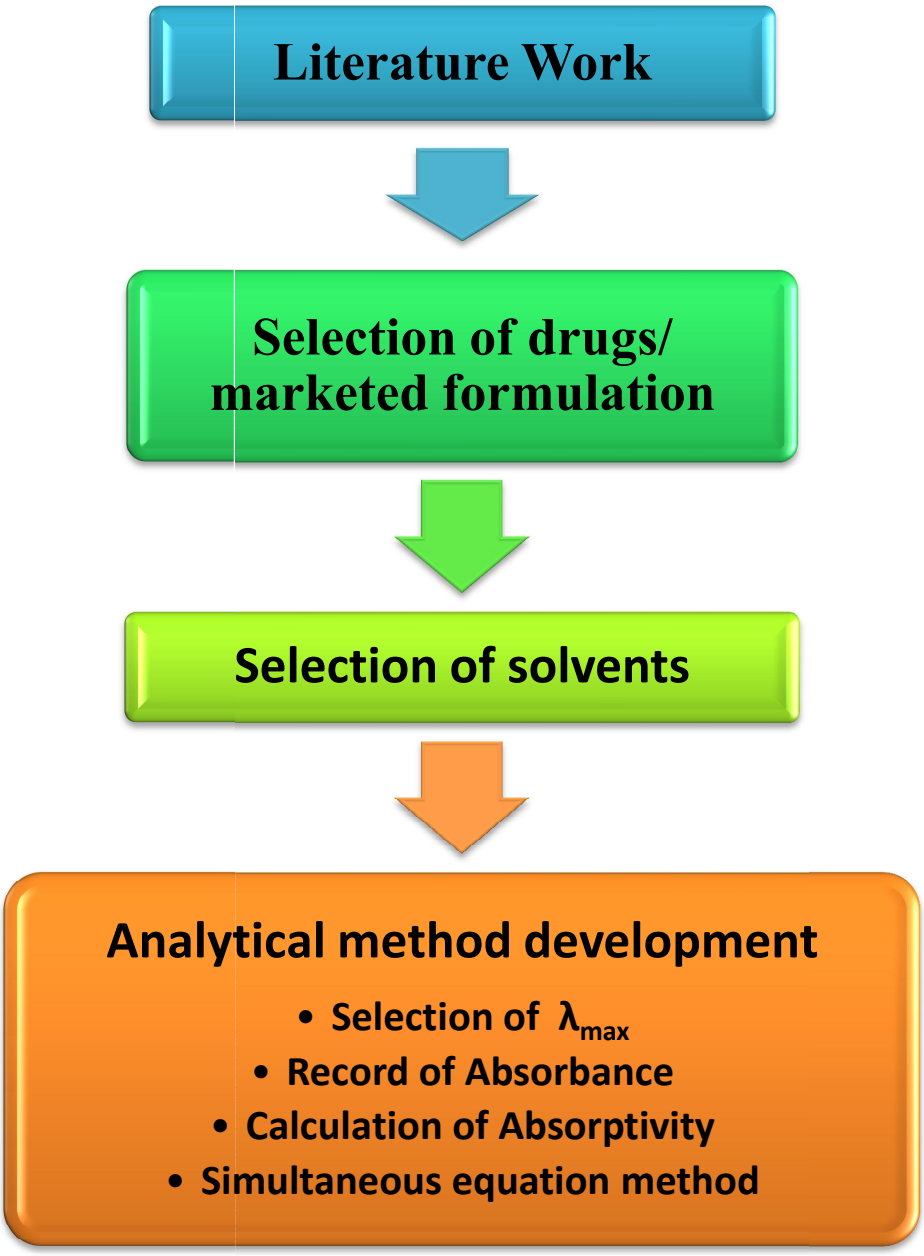
V. PLAN OF WORK



VI. MATERIALS & EQUIPMENTS

Chemicals

Table 6.1 List of Chemicals

Sr. No.	Material	Particulars
01.	Artemether	Ripcord Pvt. Ltd.
02.	Lumefantrine	Ripcord Pvt. Ltd.
03.	Ethanol	LobaChem, India
04.	Chloroform	UV/ AR grade

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Equipments

Table 6.2 List of Equipments

Sr. No.	Equipment	Particulars
01.	Double beam UV-Visible Spectrophotometer	Shimadzu (UV-1780)
02.	Digital Weighing Balance	Wensar (91484)

Marketed formulation selected:

Fig. 6.1 (a) Front view of tablets

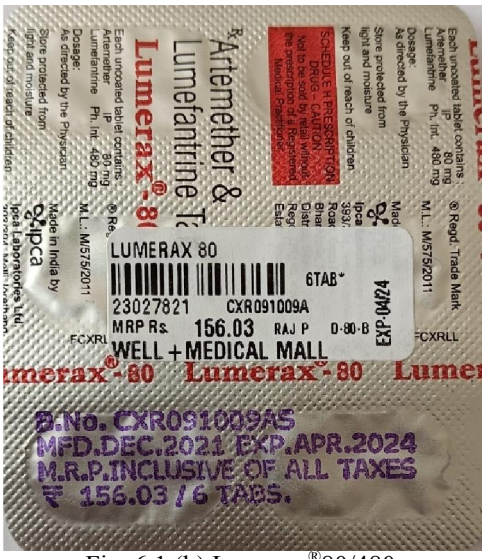

Fig. 6.1 (b) Lumerax®80/480

VII. EXPERIMENTAL WORK

Materials & Methods

Artemether and Lumefantrine were obtained as a gift sample from Ripcord Pharma. Pvt. Ltd.in Halsavade,Kagal - Kolhapur, Maharashtra.

Selection of Solvent System

An ideal solvent should not absorb in the region where analyte gives absorption. It should also be cheap/in-expensive, stable and should not interfere with the analyte.

The solubility of the Artemether and Lumefantrine was testedwith Benzene, Chloroform, Acetone & Ethanol. Out of all combinations, tested was found that both drugs were easily soluble in prepared Chloroform, which is cheap. Since UV cutoff of Chloroform and Ethanol was near 169 nm and 250 to 260 nm respectively, this solvent will not interfere with the analyte in UV region, thus Chloroform was selected as a solvent .

Preparation of stock solution

Standard stock solution (50 µg/ml) of Artemether was prepared by transferring accurately weighed 0.50 mg of Artemether in 10ml calibrated volumetric flask and added 10 ml Chloroform. Flask were shaken for few seconds and heated on the water bath for 10 minutes at temperature 60±5ºC.

The solutions were allowed to cool at room temperature and volume was made up to mark with 20 ml Chloroform from this stock solution different dilutions were prepared ranging from 4.2 µg/ml to 50 µg/ml. Standard stock solution (0.50 µg/ml) of Artemether was prepared by transferring approximately but accurately weighed 20 mg of Artemether in 10 ml calibrated volumetric flask and added 10ml Chloroform.

Flasks were shaken for few seconds and heated on the water bath for 10 minutes at temperature 60±5ºC.The solutions were allowed to cool at room temperature and volume was made up to mark with 20 ml Chloroform from this stock

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solution different dilutions were prepared ranging from 4.5 µg/ml to 40 µg/ml. Blank was prepared by heating 5 ml of Chloroform in the same condition and diluting up to the 10ml with Chloroform

Determination of absorption maxima of Artemether

1 ml of stock solution of Artemether was pipetted out into 10 ml calibrated volumetric flask and volume was made upto mark with Chloroform. The final concentration of drug was 67.20 µg/ml. The solution was than scanned in the UV region 200 – 400 nm to get absorbance maxima using blank. The absorbance maximum was found to be 250nm.

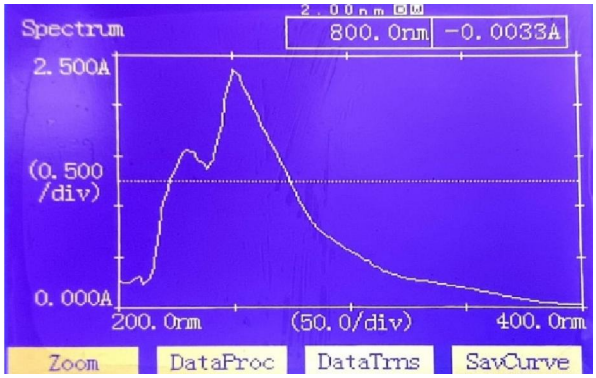

Fig. 7.1$\lambda_{max}$of Artemether

Determination of absorption maxima of Lumefantrine

1 ml of stock solution (115 µg/ml) of Lumefantrine was pipetted out into 10 ml volumetric flask and volume was made upto mark with Chloroform. The final concentration of drug was 32.20 µg/ml. The solution was scanned in UV region 200 – 400 nm to get absorption maxima using Chloroform as Blank. The absorbance maxima was found to be 305 nm.

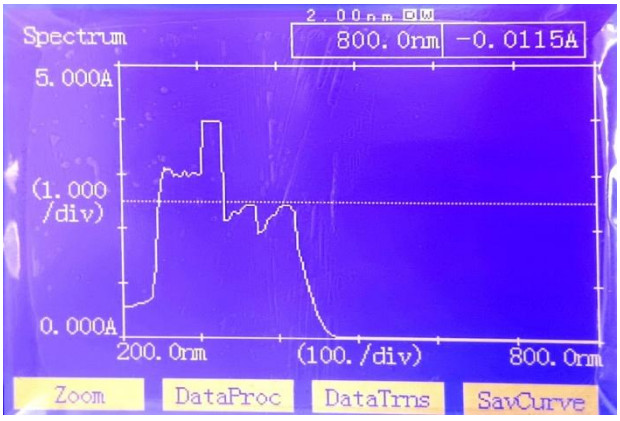

Fig. 7.2 λ_{max} of Lumefantrine

Determination of Artemether and Lumefantrine in tablet formulation

Six tablets were powdered and weight equivalent to approx. 10 mg of Artemether was weighed accurately and dissolved in 10 ml Chloroform.

Flask was shaken for few seconds and heated on the water bath for 10 minutes at temperature 60±5 ºC. The solution was allowed to cool at room temperature. The solution was filtered through whattman filter paper no. 41 and quantitatively transferred to 10ml calibrated volumetric flask; the volume was made upto 20 ml with Chloroform by continuously washing filter paper to quantitatively transfer the total amount of drug.

In a 10 ml calibrated volumetric flask, 1ml of the sample solution was placed and volume was made upto 10 ml with Chloroform and absorbance was measured at 250 nm and 305 nm against blank (Blank was prepared by gentle heating small amount of Chloroform in the same condition and diluting upto the mark with cold solvent).

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Analysis of tablet Formulation

Table 7.1 Label claim of marketed formulation

Sr. No.	Drug component in marketed formulation	Analyte Label claim	Quantity Taken
01	Artemether	80 mg	50mg
02	Lumefantrine	480 mg	300mg

Table 7.2 Absorbance readings & molar absorptivity

Sr. No.	Name of the drug	Concentration of the drug	λ_{max}	absorbance		absorptivity	
				λ_1	λ_2	λ_1	λ_2
01	Artemether	0.002 µg/ml	250 nm (λ_1)	2.1679	1.5674	118.625	78.37
02	Lumefantrine	0.002 µg/ml	305 nm (λ_2)	4.000	2.1991	200	109.955

VIII. RESULTS AND DISCUSSION

From the absorptivity values determined for Artemether and Lumefantrine, simultaneous equations are derived for determination of these two drugs in combination in their pharmaceutical formulations.

A_1= 2.167 abs. @ λ_1 = 250nm (1)

A_2= 4.000 abs. @ λ_2 = 305 nm (2)

The absorbance and the absorptivity values at the particular wavelength were calculated and substituted in the following equation, to obtain the concentration.

$C_x = (A_1 * ax_2 - A_2 * ax_1) / (ax_2 * ay_1 - ax_1 * ay_2)$ &

$C_y = (A_2 * ay_1 - A_1 * ay_2) / (ax_2 * ay_1 - ax_1 * ay_2)$

where, C_x = Concentration of Artemether

C_y = Concentration of Lumefantrine

A_1 &A_2= absorbance of sample @λ_1=250 nm and λ_2 =305nmrespectively

ax_1& ax_2= absorptivity of Artemether @λ_1=250 nm and λ_2 =305 nm respectively

ay_1& ay_2= absorptivity of Lumefantrine @λ_1=250 nm and λ_2 =305 nm respectively

Sr. No.	Name of the drug	Cx	Cy	% purity / strength	Limit as per IP specifications	Status
01	Artemether	0.0489 g	-	97.80 % $^{w}/_{w}$	NLT 95.0 % & NMT 105.0 % $^{w}/_{w}$	Complies
02	Lumefantrine	-	0.3027 g	100.90 % $^{w}/_{w}$	NLT 98.5 % & NMT 102.5 % $^{w}/_{w}$	Complies

IX. ACKNOWLEDGEMENTS

Words are not enough to express my gratitude to the almighty that directed and helped me up to the final touch of my endevour.

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There are many others whose names flashed across my mind when I enlist those who have been grateful to me. It would rather be impracticable to mention each of them separately, but I am conscious my obligation and thank them collectively. Thank you one & all…

X. SUMMARY & CONCLUSION

The UV spectroscopic method developed for quantitative determination of Artemether and Lumefantrine is rapid, economic, linear, reproducible, specific and cost effective.Hence, can be used in routine for simultaneous estimation of Artemether & Lumefantrinein pharmaceutical preparations.
The concentration of Artemether was found to be 48.90 mg against 50 mg label claim (97.80 % $^{w}/_{w}$)and that of Lumefantrine was found to be 302.70 mg against 300 mg label claim (100.90 % $^{w}/_{w}$).
Limit of detection given in Indian Pharmacopoeia 2014 for Artemether is NLT 95.0 % & NMT 105.0 % $^{w}/_{w}$& that for Lumefantrine is specified as NLT 98.50 % & NMT 102.50 % $^{w}/_{w}$. Therefore, the selected marketed formulation – **Lumerax®80/480** complies with the standard specifications given in the Indian Pharmacopoeia 2014.

Future investigations

- Simultaneous estimation of Artemether & Lumefantrine by derivative spectroscopy- First derivative curve (dy/dx), Second derivative curve (d^2y/dx^2), Third derivative curve (d^3y/dx^3). Derivative spectroscopy enables linearity in the analytical range of detection of pure APIs & marketed formulations which are available in combinations.
- Vierdotts method can be verified by Q-absorbance method for specificity & sensitivity (absorbance ratio mathod).
- Many a times, tablet formulations are prone to stability and solubility issues which do not guarantee accuracy and concentration strength of solutions prepared. Hence, a detailed study of appropriate solvent will help better accuracy and precision of the analytical method

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