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Spectrophotometric studies of the charge-transfer complexation between lumefantrine and chloranilic acid in acetonitrile

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Abstract

A simple, rapid and accurate spectrophotometric method has been developed for the determination of lumefantrine in bulk and dosage forms. The method involves the utilization of lumefantrine as n-electron donor and chloranilic acid (CAA) as π-electron acceptor with the consequent formation of a stable charge-transfer (CT) complex which absorbed visible light maximally at 520 nm. Factors controlling the formation of the CT complex were studied and optimized. Optimal detector response was obtained at a mole ratio of 1:1 between lumefantrine and CAA at a temperature of 30°C and 5 minutes reaction time in acetonitrile as solvent. Under the optimal conditions obtained the assays of the CT complex were linear over the range 10 -60 $\mu gmL^{-1}$with a correlation coefficient of 0.9980 and the method was accurate and precise (inter-day recoveries = 97.64 ± 1.18 with RSD of 1.21%). Benesi-Hildebrand equation has been used to calculate the formation constant and the molar absorptivity of the CT band. The CT complex was associated with large formation constant (4.677×10^9) and molar absorptivity (1.403 x 103 $M^{-1}cm^2$). Transition energy, free energy change (ΔG^0), oscillator strength (f), transition dipole moment (μ_{EN}), resonance energy (RN), ionization potential (ID) and dissociation energy (W) of the CT band were also determined and related to the stability of the formed complex. The method was successfully applied to the estimation of lumefantrine in combination products with artemether (artemether-Lumenfantrine: A-L) and there was no significant difference ($p>0.05$) between the results when compared with classical non-aqueous titration method. The developed procedure is simple, accurate and precise and could find application as a rapid spectrophotometric method for the assay of lumefantrine.

Keywords: lumefantrine, chloranilic acid, charge-transfer complexation, spectrophotometric studies, drug analysis

Introduction

Lumefantrine, an antimalarial drug (formerly called benflumetol) was first synthesised in the 1970s and registered in China and is now currently available only in a co-formulated product with artemether as Artemether-Lumefantrine (A-L). This combination has proved very well tolerated and highly efficacious in children and adults, even against multi-drug resistant strains of *Plasmodium falciparum* (von Seidlein et al. 1997, Hatz et al. 1998, van Vugt et al. 1998 and 2000, Falade et al. 2005).

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Lumefantrine is a racemic aromatic fluorene derivative, named 2-butylamino-1-[2, 7-dichloro-9(4-chlorobenzylidene)-9H-fluoren-4-yl]-ethanol. It conforms structurally, physicochemically and in mode of action to the aryl amino alcohol group of antimalarial agents (Ezzet et al. 2000).

Many methods have been reported for the determination of lumefantrine in plasma or blood using liquid chromatography with UV detection at 335 nm (Munsor et al. 1996, Zeng et al. 1996, Lindegardh et al. 2005, Annerberg et al. 2008). However, only one method has been reported to date for the determination of lumefantrine in pharmaceutical products such as raw materials and tablets (Césaret al. 2008). This reported method involves the determination of lumefantrine by UV spectrophotometry at 335 nm in methanol, LC-UV and non-aqueous titration with acetous perchloric acid. Lumefantrine monographs are not yet available in official pharmacopoeias. The increasing utilization of this drug in the co-formulation demands the development of new, accurate, precise, sensitive and readily adaptable alternative and more cost-effective methods for its quality control, especially a colorimetric method that can be utilized in poor resource economies.

Charge transfer (CT) complexes result from a donor-acceptor mechanism of a Lewis acid-base reaction between two or more different constituents. CT complexes are associated with the appearance of new UV-VIS absorption bands (Mulliken and Person 1969). CT complexes are sometimes produced as reaction intermediates (Ross and Kuntz 1954, Coloter 1963, Khan and Ahmad 2009) and most often they exist as stable donor-acceptor adducts (Andrews 1954, Yarwood 1973, Al-Attas et al. 2009).

This paper reports the quantitative estimation and spectrophotometric studies of the CT complex formed between lumefantrine as *n*-electron donor and chloranilic acid (CAA) as π-electron acceptor as a possible way of producing a complex that can be determined by visual colorimetry. CAA as a well-known CT acceptor has been successfully applied for the estimation of a wide range of pharmaceuticals (Mahrous et al. 1986, Zakhari et al. 1986, Okide and Udoh 1998, Adikwu et al. 1999, Basavaiah and Charan 2002).

Materials and Methods

Materials

Lumefantrine CRS (Sigma-Aldrich), lumefantrine secondary reference substance (isolated in our laboratory and authenticated with the primary standard), chloranilic acid (Sigma-Aldrich USA), Glacial acetic acid, acetonitrile, dimethylformamide, ethanol, ethylacetate, *n*-hexane, methanol1,2-dioxan (all analytical reagent grade from BDH, Poole, England), perchloric acid (Courtin and Warner, Sussex). Precoated aluminium TLC plates (G. Merck 0.25mm Silica gel F_{254}).

Lumefantrine dosage forms: Coartem® tablets (Novartis Pharm AG, Basel, Switzerland), Lonart® tablets (Bliss GVS Pharm Ltd, India).

Equipment: Mettler H80 balance, Water bath (Gallemkamp), Stuart melting point apparatus, Jenway 6051 colorimeter, UNICO 2802 UV-VIS spectrophotometer, Vortex mixer (Griffiths and George, England).

Preparation of stock solutions

A 1 mg/mL stock solution of lumefantrine was made in DMF by dissolving 10 mg in 10 mL of solvent at room temperature. Similarly a 1 mg/mL stock of chloranilic acid (CAA) solution was made in acetonitrile.

Evidence for Charge transfer complex formation

Aliquots (500 µL) of the CAA reagent solution were place in several test tubes. To each tube, 500 µL of the lumefantrine stock solution was added. The tubes were shaken on a vortex mixer for 10 sec and kept at room temperature. The colours produced were noted immediately and after 20 min. Some other sets of test tubes were place in the water maintained at 80°C and the colours produced at 5 and 20 min were noted.

Thin layer chromatographic analysis

The sample solutions from the room temperature preparation were spotted on the TLC plate and the plates were developed in two solvent systems; Ethylacetate: Methanol (80:20% v/v) and Ethylacetate: *n*-hexane (50:50% v/v). The plates were visualized in daylight and at 254 nm using the UV lamp.

Selection of Analytical wavelength

Into test-tubes containing 500 µL of CAA, 0.5 mL of lumefantrine solution was added into one and the other contain only CAA. The tubes were allowed to stay on the bench at room temperature for 20 min. At the end of the reaction the volume of each tube was made up to 5 mL with acetonitrile. The spectra of the CAA solution alone, lumefantrine solution alone in DMF and the complex formed in acetonitrile were recorded using the UV-VIS spectrophotometer. The wavelength corresponding to the optimum absorbance was selected by overlaying the three spectra on each other.

Optimization studies

The optimum temperature required for the complex formation was determined by the method of steepest ascent (Miller and Miller 1993). Sample solutions were prepared as before and incubated at 30 and 50°C for 5 and 20 min respectively. At the end of the incubation period, the solutions were cooled and made up to 5mL with acetonitrile. Similar procedure was carried out at 60 and 80°C for 5 and 20 min. The optimum temperature was taken as the temperature that gave maximum absorbance at 520 nm on the colorimeter.

The time required at 30°C to attain the optimum absorbance was determined by preparing sample solution and incubating at 30°C for 0, 2, 5, 10, 15, 20, 25 and 30 min. Each reaction tube was made up to 5 mL with acetonitrile at the end of the reaction time. The absorbance values were recorded at 520 nm on the colorimeter.

The effect of the type and nature of the diluting solvent used was investigated by stopping reaction at 30°C after 5 min and diluting to 5 mL with each of acetonitrile, methanol, ethanol and 1,4-dioxan. The visible spectra of the each reaction solution were recorded and the solvent that gave optimum absorbance was selected and the diluting solvent.

The amount of CAA required as reagent was optimized by using 0.1, 0.2, 0.3, 0.4, 0.5 and 1.0 mL of CAA solution for a fixed volume of 0.5 mL of lumefantrine. The reaction was stopped by making up the solution to 5 mL with acetonitrile and the absorbance readings taken at 520 nm on the colorimeter.

Determination of stoichiometric ratio

Job's method of continuous variation was utilized for the determination of stoichiometric ratio (Rose1964). Equimolar solutions (4.79 $x10^{-4}$ M) of CAA and lumefantrine were used for this determination. In 7 different test-tubes; 0, 0.2, 0.33, 0.50, 0.67, 0.8 and 1.0 mL of CAA reagent solution

were placed. Each tube was then made up to 1.0 mL with the lumefantrine stock solution. The mixture was vortex mixed for 10 sec and then incubated at 30°C for 5 min. At the end of the reaction time, each tube was made to 5 mL with acetonitrile and the absorbance reading were taken at 520 nm on the colorimeter against the blank solvent.

Validation studies

The linear range for the assay of lumefantrine by this new procedure was determined by preparing standard solutions containing 0 – 160 µg/mL of lumefantrine with 0.5 mL of CAA reagent. Simple linear regression analysis was conducted to select the range that gave the highest slope and the best fitting line. Standard calibration curves were then determined on each of three successive days using standard solutions containing 0 – 60 µg/mL of lumefantrine. The slope, intercept and coefficient of determination were determined.

A three-day accuracy and repeatability of the new procedure was done by using standard solutions containing 10, 30 and 50 µg/mL of lumefantrine. The pooled recoveries for the three days were calculated for the intra- and inter-day variations.

Spectrophotometric studies of the charge-transfer complexation

The absorbance values obtained in the calibration curve plot were plotted as a function of ratio of the molar concentration of the donor: acceptor ($[D]_0$: $[A]_0$) according to the Benesi-Hildebrand equation (Benesi and Hildebrand 1949).

$$\left(\frac{[A]_0}{A} = \frac{1}{K_{CT}\varepsilon_{CT}} \cdot \frac{1}{[D]_0} + \frac{1}{\varepsilon_{CT}}\right) \qquad \text{Eq. 1}$$

Where $[A]_0$ is the initial concentration of the acceptor (CAA), A is the absorbance of the charge transfer band, $[D]_0$ is the initial concentration of the donor (lumefantrine), K_{CT} is the formation constant of the new charge transfer band and ε_{CT} is the molar absorptivity. A plot of $[A]_0$ /A against $1/[D]_0$ will yield intercept as $1/\varepsilon$ and the slope as $1/K\,\varepsilon$ from where the formation constant and the molar absorptivity are obtained. The concentration of the acceptor was kept greater than the donor and fixed so that a wide concentration range could be adopted.

Some other physicochemical properties of the charge transfer bands were estimated such as molar transition energy, oscillator strength , transition dipole, resonance energy, standard free energy and the ionization potential of the donor species; in order to establish the stability or otherwise of the formed complex between lumefantrine and CAA.

Application to dosage forms analysis

Weight uniformity tests were carried out on each of the two brands of the tablets. Standard solutions containing 10 mg of lumefantrine were prepared from the powdered tablet in DMF. The dispersion was mixed thoroughly and then filtered through cotton gauze. A 150 µL aliquot of each stock solution was added into six test-tubes containing 500 µL of CAA. The reaction mixture was processed as before and the absorbance taken at 520 nm on the colorimeter.

Non-aqueous titration using acetous perchloric acid was adopted as the standard procedure for the assay of lumefantrine in these two tablet brands. The results obtained were compared statistically using F-ratio and t-test. A two-tailed probability of less than or equal to 0.05 (95 % confidence interval) was taken as significant.

Interference studies

The effects of commonly adopted tablet excipients on the formation of charge transfer complex was investigated by using 5 mg each of lactose, starch, gelatine, magnesium stearate, talc and a mixture of the excipients. 150 µL aliquots of the lumefantrine stock solution were added into each tube already containing 500 µL of CAA. The reaction mixtures were processed as usual. Four replicate samples were prepared for each excipient.

Results and Discussion

Lumefantrine formed an immediate purple-coloured complex against its light yellow colour and wine colour of CAA. This is an indication of a charge transfer complex formation. The absorption spectra of the three compounds are shown overlaid in Fig. 1 and the visible spectrum is shown in Fig. 2. CAA exhibits prominent peaks at 310 and 430 nm while lumenfantrine exhibits peak at 340 nm. However reaction between CAA and lumefantrine produced a bathochromic shift in the absorption with a peak at 510 nm in addition to peaks at 310 and 400 nm. On the colorimeter optimal difference in absorptivity between CAA and the complex was found at 520 nm and this was adopted as the working wavelength. Lumefantrine is an aromatic fluorene amino alcohol. It possesses two prominent functional groups (butylamino and alcohol groups) that can serve as *n*-electron donors. In particular the tertiary amino group will be more suitable for electron donation. The alkyl substituents are known to have a positive inductive effect (+*I*) and that should make the amino group more electron-rich to donate in a charge-transfer reaction.

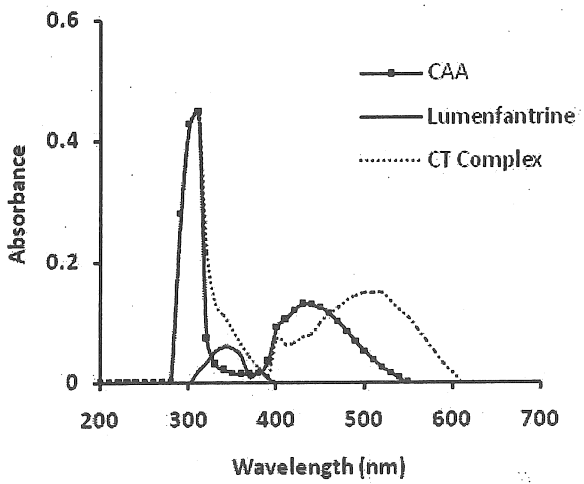

Figure 1. Overlaid absorption spectra of lumenfantrine, CAA and the CT complex

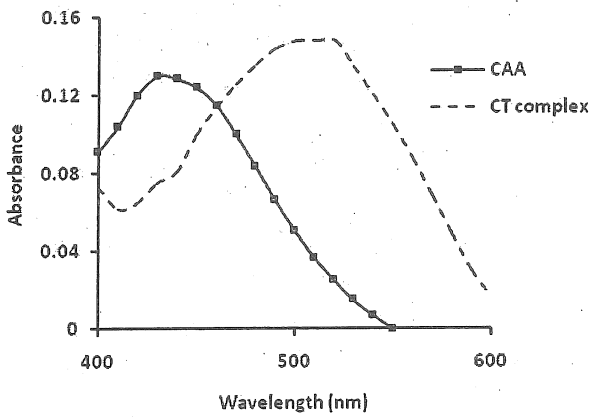

Figure 2. Visible Spectrum of the CT complex overlaid on CAA

The scheme showing the charge-transfer complexation is presented in Fig. 3.

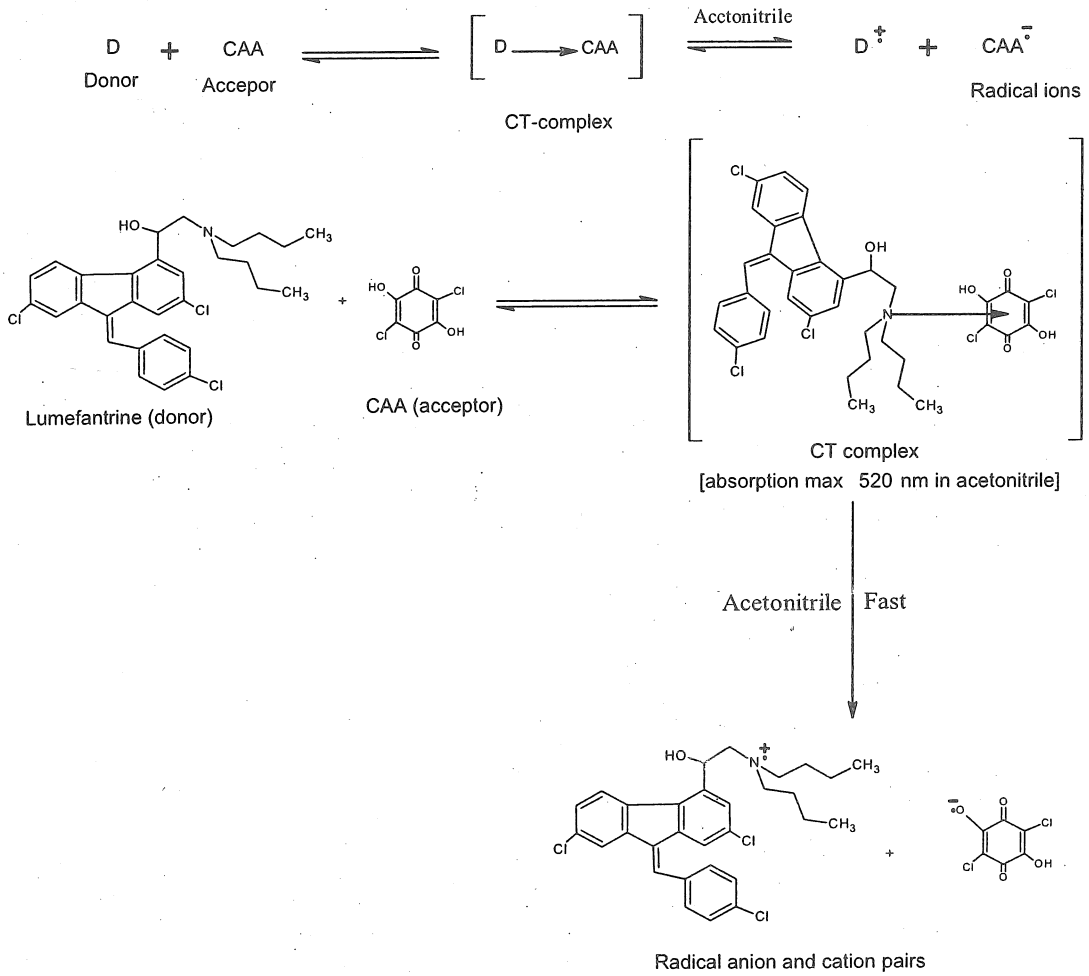

Figure 3. Scheme of complexation reaction between lumenfantrine and chloranilic acid

The reaction was observed to be very fast. Incubation of the reaction at higher temperature led to slight discharge of the colour of the complex. The TLC study showed the presence of a new spot due to the complex completely different from the starting materials.

Optimization of the temperature required for optimal colour formation showed the superiority of 30°C (room temperature) to all other elevated temperatures (Fig. 4).

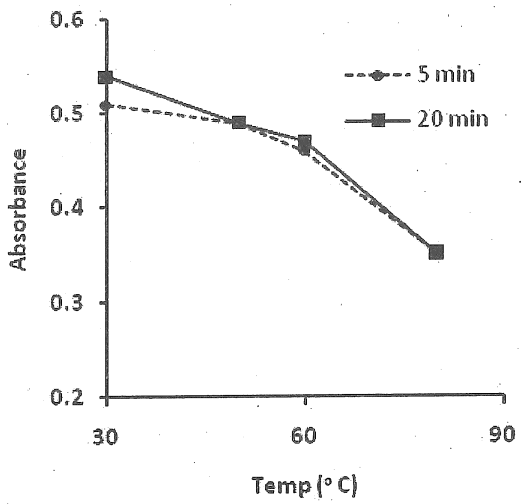

Figure 4. Optimization of reaction temperature for complexation

This is typical of most charge-transfer processes. Since the formation of a new complex is an association reaction of the type,

$$C + B \rightleftharpoons D \qquad \text{Eq. 2}$$

Any factor that will lead to the dissociation of the complex, D will lead to formation of more of the free species C and B. Hence high temperature will favour this. The CAA-lumefantrine was found to be unstable at the higher temperature values adopted implying that an exothermic reaction must be involved in the formation of the complex. However, the molar absorptivities at the higher temperature levels were constant showing the independence of this parameter on temperature. The optimum time required for complex formation was thereafter investigated at 30°C (Fig. 5) and found to be 5 min. Incubation for longer periods was found unnecessary. This will allow for fast sample analysis and the ability to analyse many samples at a short period of time.

The effect of diluting solvent was investigated by using the polar solvents methanol, ethanol, 1,4-dioxan and acetonitrile. The overlaid visible absorption spectrum for the effect of these solvents is shown in Fig. 6. As evident from the plot, acetonitrile gave the optimum absorptivity at 520 nm. Ethanol had another minor peak at 540 nm but the absorptivity is very low.

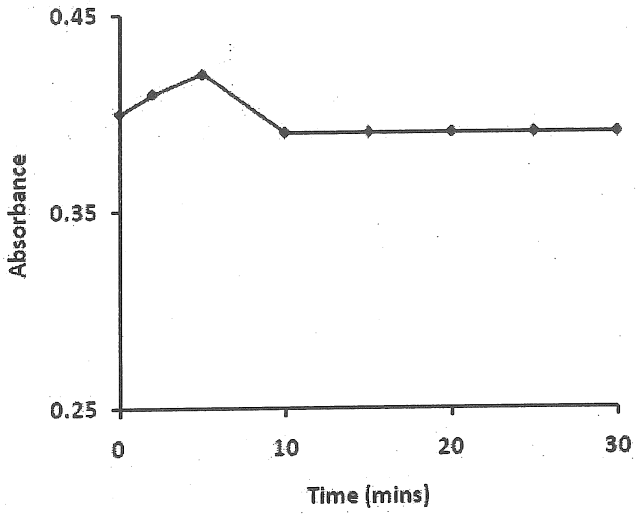

Figure 5. Optimization of reaction time at 30°C

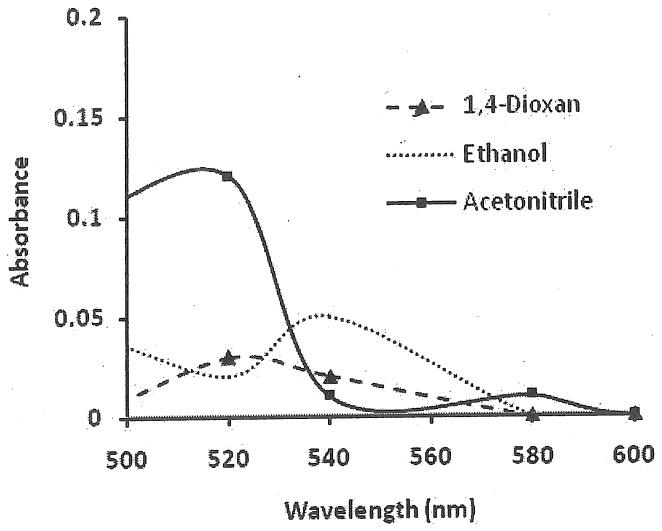

Figure 6. Visible absorption spectra of CT complex in polar solvents

1,4-dioxan also produced a peak at 520 nm but the absorptivity was lower than that produced by acetonitrile. Methanol gave an interesting behaviour; there was no absorptivity in the working visible region of the spectrum. The general dipolarity of methanol is higher than of ethanol, [π^* = 0.60 compared to ethanol 0.54] (Abboud and Notario 1999). Thus the charge-transfer complex formed may be less soluble in a polar solvent such as methanol. The charge-transfer band of chloranilic acid has been attributed to the formation of CAA radical anion resulting from the complete transfer of charge from the donor to CAA according to the reactions shown in the scheme in Fig. 3. The radical anion nature of CAA has been confirmed by electron spin-resonance spectral studies of substituted quinines (Abdel-Hamid et al. 1985). This radical ion gives the purple colour in acetonitrile. Thus acetonitrile provided the best solvation for the

complex compared to the other solvents. Optimum reagent volume was found to be 500 µL and this was adopted as the volume of reagent all through the procedures.

For a constant total concentration of two interacting species, the complex is at its greatest concentration at a point where the two species are combined in the ratio in which they occur in the complex (Alfredet al. 1993). The plot of absorbance against the mole fraction of the chloranilic acid exhibited a change of slope with a maximum absorbance at a mole fraction of 0.5 and decreasing absorption as the value of the mole fraction deviate from 0.5 (Fig. 7). The implication is that better absorbance values will be obtained at equimolar concentrations of the lumenfantrine and chloranilic acid sample. This also signifies that the optimal complexation reaction conditions routinely employed forms the complex by a 1:1 drug to reagent stoichiometric ratio as shown in Fig. 7.

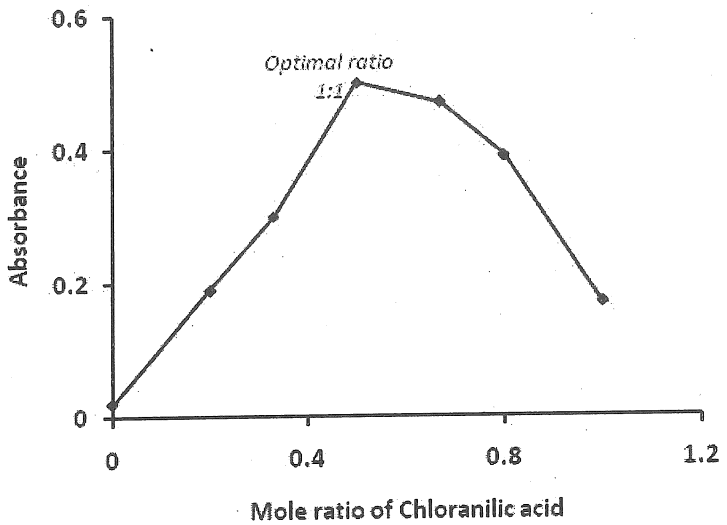

Figure 7. The plot of Job's method for stoichiometric ratio determination

Under the specified optimal reaction conditions obtained, calibration curves were constructed on each of three days and the pooled calibration data was adopted. The regression equations for the results were derived using the least squares method. Beer's law was obeyed in the concentration range of 10-60 µg/mL with small intercept and a good correlation coefficient. The linear regression equation obtained is $y = 0.003 x + 0.064$ ($r = 0.9978$, $r^2 = 0.9960$). The limit of detection was obtained from the expression 3.3σ/slope and a value of 4.917µg/mL was obtained. The Sandell sensitivity was calculated as 33.33ngcm^{-2} per 0.001A. The various analytical and validation parameters are presented in Table 1. Assessment of the three-day accuracy and repeatability of the new procedure gave overall recoveries of 97.64 ± 1.18 (RSD % =1.21). The result of the accuracy data is presented in Table 2. Generally, the precision was better with the higher concentration levels.

Table 1. Analytical and validation parameters for the assay of lumefantrine

Parameter	Value
Analytical wavelength	520 nm
Beer's law limits, (μgmL^{-1})	10 – 60
Limit of detection, (μgmL^{-1})	4.917
Molar absorptivity (Mol^{-1} cm^2)	1.403×10^3
Sandell's sensitivity, (ng cm^{-2} per 0.001 absorbance unit)	33.33
Regression equation[a]	
Intercept, a	0.064
Slope, b	0.003
Correlation coefficient, r	0.9980
Confidence interval of intercept, □	0.0059
Confidence interval of slope, β	0.00037
Formation constant[b], K	4.677×10^9

[a] *Y = bX + a, where Y is the absorbance for concentration X μgmL^{-1}*
[b] *estimated from Benesi-Hildebrand plot*

Table 2. Assessment of accuracy and repeatability of the new procedure

Concentration	Day 1*		Day 2*		Day 3*		Inter-day statistics	
(μgmL^{-1})	%Mean recovery	% RSD	%Mean recovery	% RSD	%Mean recovery	% RSD	%Mean recovery	% RSD
10	97.49±1.53	1.57	99.01±2.17	2.19	98.15±1.75	1.78	103.82±1.77	1.75
30	95.84±0.51	0.53	97.45±2.60	2.67	96.09±0.28	2.91	100.43±2.17	1.39
50	98.60±0.44	0.45	99.08±1.21	1.22	97.07±1.24	1.28	105.17±1.69	0.86

** n=12, Regression equation: y=0.003x +0.064 (R^2=0.9960), overall recovery for lumefantrine is 97.64 ± 1.18 (RSD % =1.21)*

Based on the electronic spectrum of the CT complex formed between lumefantrine and CAA at the various concentrations of the donor for a fixed concentration of the acceptor, the formation constant $K_{CT}$and the molar absorptivity ε_{CT} were estimated using the Benesi-Hildebrand (BH) equation (Eq. 1). The BH plot is presented in Figure 8 and the two physicochemical parameters were estimated from an assessment of the slope and the intercept. The results are presented in Table 1.

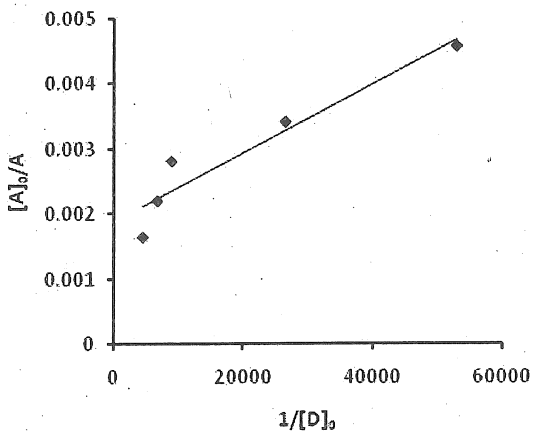

Figure 8. Benesi-Hildebrand's plot for the CT complex

The immediate formation of the purple-coloured CT complex can be explained by the large formation constant of 4.677×10^9 which demonstrates a greater propensity for the forward reaction to proceed with ease. The higher value of both K and ε confirmed the high stability of the CT complex as a result of the presence of lone pair of n-electrons on the nitrogen atom. This is in spite of the bulky dibutyl substituents linked to the nitrogen. It is anticipated that the molecule should be able to adapt an orientation that will favour the exposure of the lone pair of electrons to the CAA molecule. Further studies conducted on the CT complex were the calculations of the various physicochemical parameters as a way of evaluating the energetics and the immediate formation of the complex observed.

The oscillator strength (f) is a dimensionless quantity used to express the transition probability of the CT band and the transition dipole moment (μ_{EN}) of the CT complex (Tsubomura and Lang 1961). Both parameters are obtained from equations 3 and 4 respectively.

$$f = 4.32 \times 10^{-9} [\varepsilon \Delta\nu_{1/2}] \qquad \text{Eq. 3}$$

$$\mu_{EN} = 0.095 \left[\frac{\varepsilon_{CT} \Delta\nu_{1/2}}{\Delta\nu}\right]^{1/2} \qquad \text{Eq. 4}$$

Where $\Delta\nu_{1/2}$ is the half-width i.e. the width of the band at the half the maximum absorption, and $\Delta\nu \approx$wavenumber at the absorption maximum. The oscillator strength, f and the transition dipole moment obtained are 6.06 and 8.13 Debye respectively.

The standard free energy changes of the complexation (ΔG^0) was calculated from the charge transfer formation constant K_{CT} according to equation 5 (Person1962),

$$-\Delta G^0 = 2.303\ RT \log K_{CT} \qquad \text{Eq. 5}$$

Where ΔG^0 *is* the free energy of the CT complex (KJ Mol^{-1}), R is the gas constant (8.314 $JMol^{-1}$ K^{-1}) and K is the absolute temperature. ΔG^0 was calculated to be 5.795 KJ Mol^{-1}.

Another physicochemical parameter calculated was the transition energy of the complex which is obtained from the expression $h\nu_{CT}$ where h is Planck's constant and ν_{CT} is the wavenumber of the absorption peak of the CT complex. The transition energy was found to be 2.303 eV.

The ionization potential, I_D, of the donor in the charge transfer complex is calculated using the empirical equation derived by Aloisi and Pigantoro (1972) (Eq. 6).

$$I_{D\,(eV)} = 5.76 + 1.53 \times 10^{-4} \nu_{CT} \qquad \text{Eq. 6}$$

Where ν_{CT} is the wavenumber of the CT band in cm^{-1}. I_D was found to be 8.7eV.

The resonance energy of the complex (R_N) in the ground state is obtained from the theoretical equation derived by Briegleb and Czekalla (Briegleb 1961), given in Eq. 7.

$$\varepsilon_{CT} = 7.7 \times 10^4 / [h\nu_{CT}]/R_N - 3.5 \qquad \text{Eq. 7}$$

Where ε_{CT} is the molar absorptivity of the complex at the maximum of the CT absorption, $h\nu_{CT}$ is the transition energy of the complex .The resonance energy was calculated as 3.945 eV.

The dissociation energy (W) of the formed CT complex between lumefantrine and CAA was calculated from the transition energy($h\nu_{CT}$), ionization potential of the donor (I_D) and the electron affinity of CAA (E_A = 1.1) using the relationship (McConnell et al. 1953).

$$h\nu_{CT} = I_D - E_A - W \qquad \text{Eq. 8}$$

The dissociation energy was found to be 5.297 eV.

The various physicochemical parameter obtained are summarised in Table 3.

Table 3. Various physicochemical parameters of the CT complex between lumefantrine and CAA

Solvent	CT λ_{max} (nm)	$h\nu_{CT}$(eV)	f	μ_{EN} (Debye)	R_N(eV)	ΔG^0(KJMol^{-1})	I_D(eV)	W(eV)
Acetonitrile	520	2.303	6.061	8.1316	3.945	-5.795 x 10^4	8.7	5.297

A cursory look at the values obtained points to the good stability of the complex formed between CAA as acceptor and lumefantrine as donor. The ionization potential of the donor gave a high value of 8.7 eV showing lumefantrine is a good *n*-electron donor. The transition energy is about two times less than this ionization energy of lumenfantrine, hence, the energy is readily surmounted and the complex is produced readily. I_D was also found to be higher than the dissociation energy, W. Thus the spontaneous decomposition of the CT complex will be minimal. The high dissociation energy also implies that decomposition of the complex will require an externally applied energy which was noticed with increasing temperature. Likewise, the high values of the oscillator frequency and the resonance energy point to the good stability observed for the complex. Indeed the complex was stable for days in the laboratory environment. The standard free energy gave a negative value pointing to the exothermic nature of the complex formation. This thus explains why higher temperature values led to decrease in the absorbance of the complex. The transition dipole moment having a high value suggests the existence of a good ion pair which was readily solvated and stabilized by acetonitrile as a solvent.

The optimized procedure was adapted to analyse the lumefantrine content of the two artemether-lumefantrine tablet dosage forms sampled. The results are presented in Table 4. Recoveries of lumefantrine ranged from 100 to 102 % from the tablets by both methods. There was found to be no significant difference in content of active ingredient between the new method proposed in this work and the classical non-aqueous titration ($p>0.05$).

Table 4. Analysis of Lumefantrine in tablet dosage forms

Drug formulation	New Method (%±S.D.)	95% C.I.[b]	Non-aqueous titration (%±S.D.)	p-value[a]	
				F-test	t-test
Coartem® Tablet	102.78±1.92	32.18± 0.96	100.37±2.35	0.73	0.28
Lonart® Tablet	100.00±0.91	30.68 ±1.55	100.22±2.39	0.16	0.81

[a] *statistical analyses done between the results obtained from the proposed method and the classical non-aqueous titration*

[b] *confidence interval calculated for 30 µg/mL of lumefantrine*

One other major advantage of the new procedure is the lack of potential interference from commonly used tablet excipients. The recoveries of quality control samples of lumefantrine in the presence of excipients are; 96.56±1.00 (lactose), 96.31±1.29 (starch), 97.39±1.66 (gelatine), 101.81±0.06 (magnesium stearate), 102.15±0.64 (talc) and 99.14±0.78 (mixture of excipients).

The new method described in this report is simple and with the adoption of lumefantrine as first line combination therapy in treatment of malaria, this charge transfer procedure will be a readily adaptable method especially in the poor resource economies where utilization of a colorimeter will be an advantage.

Conclusion

The new procedure described in this study is fast and it is the first of such report for the quantitative derivatization of lumefantrine in dosage forms. It is simple and could be readily adapted for the quality control of this important antimalarial agent, especially with the utilization of a colorimeter.

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