IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 11, Issue 11 Ver. I (November. 2018), PP 24-34
www.iosrjournals.org

Characterisation and solubility studies of Quinine sulphate and Hydroxychloroquine sulphate inclusion complexes with α – cyclodextrin

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Abstract: *Cyclodextrins are cyclic oligo saccharides which have recently been recognized as useful pharmaceutical excipients. The molecular structure of these glucose derivatives generate a hydrophilic exterior surface and a non -polar cavity interior. Such cyclodextrin can interact with appropriate size drug molecules which lead to the formation of inclusion complexation. The aim of present investigation was to improve the solubility and ultimate bioavailability of Quinine sulphate and hydroxychloroquine sulphate, an antimalarial drug by encapsulating them in α-cyclodextrin. Effect of these complexes was studied by UV- VIS spectroscopy, Fluorescence spectroscopy, phase solubility study, FTIR spectroscopy. The water solubility of these drugs were increased by inclusion with α-CD according to phase solubility diagram. The results obtained from FTIR and ^{1}HNMR spectroscopy confirmed the formation of inclusion complexation into α-cyclodextrin cavity.*

Keywords: *Quinine sulphate, Hydroxychloroquinesulphate, cyclodextrins, inclusion complex.*

Date of Submission: 09-11-2018 Date of acceptance: 24-11-2018

I. Introduction

Quinine sulphate($C_{40}H_{54}N_4O_{10}S$) is an antimalarial drug obtained from Chinchona park, which is still widely used in many countries for treating uncomplicated malaria, but suffer from poor water solubility, bioavailability`and metabolic stability, which limit their use in clinic[1,2,3]. Hydroxychloroquine sulphate ($C_{18}H_{26}ClN_3O.H_2SO_4$) is a synthetic quinine derivative commonly used as chemotherapeutic agent that acts against erythrocytic forms of malarial parasites. It is sparingly soluble in water and insoluble in organic solvents such as chloroform,ether etc. So it requires extensive study as to improve the physicochemical parameters of both the drugs render them much favorable for clinical application. One of the approach is to prepare inclusion complexes with CD.

Cyclodextrins are cyclic oligo saccharides of 6,7or 8-D-glucopyranose units with a relatively hydrophobic central cavity and hydrophilic outer surface [4,5]. The hydrophobic CDs inner cavitry forms inclusion complexes with a wide range of guest molecules [6,7,8] while the hydrophilic exterior enhances CD solubility in water[9].The stability of inclusion complexes is provided by non-covalent interactions such as Vander Waals forces, electronic effects hydrophobic interactions and steric factors [10]. Encapsulation with CDs leads to increasing the aqueous solubility , enhancing dissolution rate, membrane permeability and bioavilability low solubility compounds[11]. This chapter deals with the identification and characterization of quinine sulphate and hydroxychloroquine sulphate. The effect of α-CD on the absorption and fluorescence spectra of quinine sulphate and hydroxychloroquine sulphate have been investigated in this chapter. Different analytical techniques such as Fourier transform Infrared spectroscopy (FT-IR) , Nuclear magnetic resonance spectroscopy (NMR) and phase solubility studies have been used to confirm the inclusion complex formation.

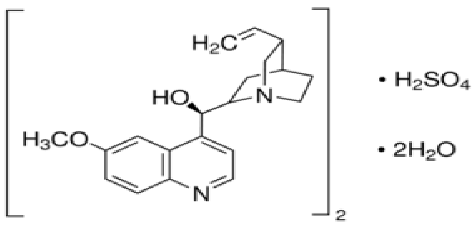

Fig.1: Quinine sulphate

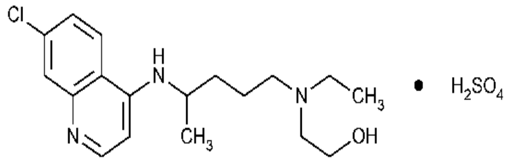

Fig.2 :Hydroxychloroquine sulphate

II. Material and methods

Quinine sulphate and hydroxychloroquine sulphate were obtained as gift sample from Ipca laboratories ltd. Mumbai, India. α-CDwas purchased from Sigma Aldrich. Both were used as received with no further purification. All other reagents and chemicals were of analytical grade.

Preparation of liquid inclusion Complex

The liquid inclusion complex was prepared by adding constant volume of quinine sulphate and hydroxychloroquine sulphate drugs separately into 10ml volumetric flask containing the absence and presence of increasing concentrations (2-10mM) of α-CD .

UV- Visible Spectral analysis

The UV-Visible spectra were carried out with systronic Double beam spectro photometer-2203. All UV – visible spectra were taken with reference to the corresponding blank solution.

Fluorescence emission

Fluorescence spectral measurements were carried out with JASCO Spectrofluorometer FP-8200.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Cornors12. Quinine sulphate and hydroxychloroquine sulphate in amounts that exceeded its solubility , were taken into vials to which were added 15ml of distilled water (pH 6.8) containing various concentration of α-CD (2-10mM).These flasks were sealed and shaken at room temperature for 5 days to reach equilibrium and the sample were filtered immediately through a 0.45µ nylon disc filter and appropriately diluted. A portion of the sample was analysed by UV spectrophotometer against blank prepared in the same concentration of α-CD in water so as to cancel any absorbance that may be exhibited by the α-CD.

4.Preparation of solid inclusion complex

Solid dispersion / Co- evaporated dispersion method

The solid inclusion complex of quinine sulphate and hydroxychloroquin esulphate with α-CD in1:1 molar ratio were prepared by dissolving the drugs in methanol and α-CD is dissolved in water separately[13,14]. The α-CD solution is added to drug solution and stirred for about 48 hours at room temperature to attain equilibrium.The resulting solution was evaporated to dryness.

Fourier Transform Infrared Spectroscopy

Infra – Red spectroscopy is used to estimate the interaction between cyclodextrin and the guest molecules in the solid state [15,16]. FTIR spectra were obtained using JASCO FT 761 photometer at SIC-SFRC. The sample of pure drug quinine sulphate, hydroxychloroquinesulphate, α-CD and solid inclusion complexes were previously grounded and thoroughly mixed with KBr. The KBr disks were prepared by compressing the powder blend. The FTIR spectra were executed at a resolution of 1cm^{-1}(from 4000-400 cm^{-1}).

NMR Spectroscopy

^{1}HNMR analysis was carried out in Sophisticated Test and Instrumentation Centre (STIC) Cochin University,Cochin,Kerala. Solutions of α-CD, quinine sulphate, hydroxychloroquine sulphate and inclusion complexes in D_2O were placed in NMR tubes with a Coaxial NMR tube containing a solution of $CDCl_3$ – TMS as an external reference.

III. Results and discussion

Absorption Study

` Table no1 and fig 3 and fig 4 represents the absorption spectra of quinine sulphate and hydroxychloroquine sulphate with varying concentration of α-CD. Hypsochromic (blue shift) or bathochromic shift (red shift) or increase in absorptivity have been considered as evidence for interaction between cyclodextrin and the drug in the formation of the complex. A bathochromic shift with an increase in the absorbance is observed for the absorption spectrum of quinine sulphate by increasing the concentration of α-CD (from 233.2nm to 236.4nm). In the case of hydroxychloroquine sulphate a bathochromic shift with increase in the absorbance is noticed for the absorption spectrum.(from 328nmto330.6nm). These results show that both the drug quinine sulphate and hydroxychloroquine sulphate are entrapped in α-CD to form inclusion complexes.

Table no 1 : Absorption maxima of Quinine sulphate and Hydroxychloroquine sulphate at different concentration of α-CD

α-CD concentration	Quinine sulphate		Hydroxychloroquine sulphate	
	λmax(nm)	Absorbance	λmax(nm)	Absorbance
0	233.2	0.760	328	0.495
0.002	234.6	0.896	328.8	0.592
0.004	234.8	0.949	329.2	0.604
0.006	235.4	1.089	329.8	0.608
0.008	235.6	1.169	330	0.634
0.01	236.4	1.246	330.6	0.685

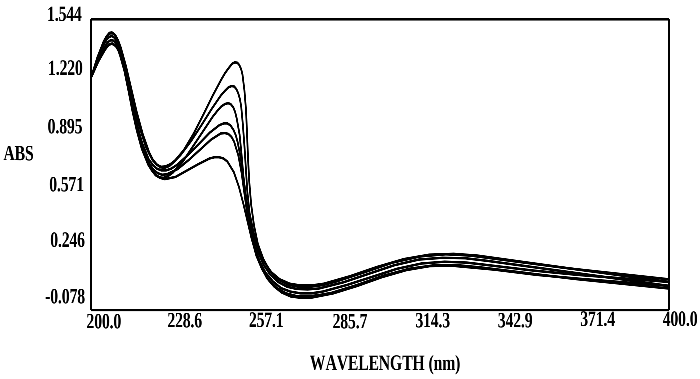

Fig.3: Absorption spectra of Quinine sulphate with α-CD

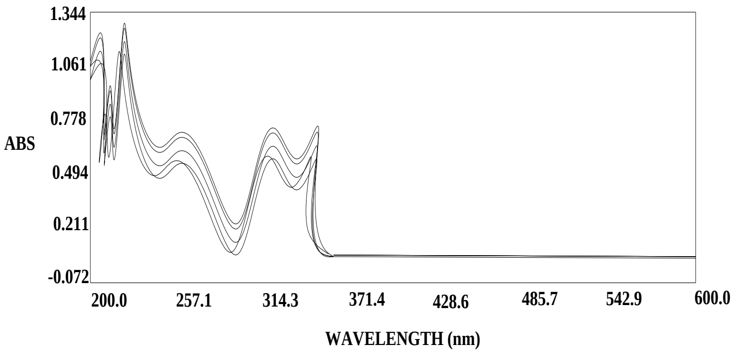

Fig4. Absorption spectra of Hydroxychloroquine sulphate with α-CD

Fluorescence Study

Table no2 and fig 5,6 represents the effect of α-CD on the fluorescence spectra of quinine sulphate and hydroxychloroquine sulphate . A hypsochromic shift is observed in the emission spectrum of both the drugs quinine sulphate(from 390nm to 384nm) and hydroxychloroquine sulphate from (395nm to 390nm) by increasing the concentration of α-CD. An increase in fluorescence intensity is also observed in both the cases.

Table no 2: Fluorescence maxima of Quinine sulphate and Hydroxychloroquine sulphate at different concentration of α-CD

α-CD concentration	Quinine sulphate		Hydroxychloroquine sulphate	
	λflu(nm)	Intensity	λflu(nm)	Intensity
0	390	205.65	395	146.41
0.002	388	313.07	393	260.71
0.004	386	357.55	393	312.80
0.006	385	368.95	392	373.01
0.008	385	392.42	392	396.45
0.01	384	414.66	390	408.56

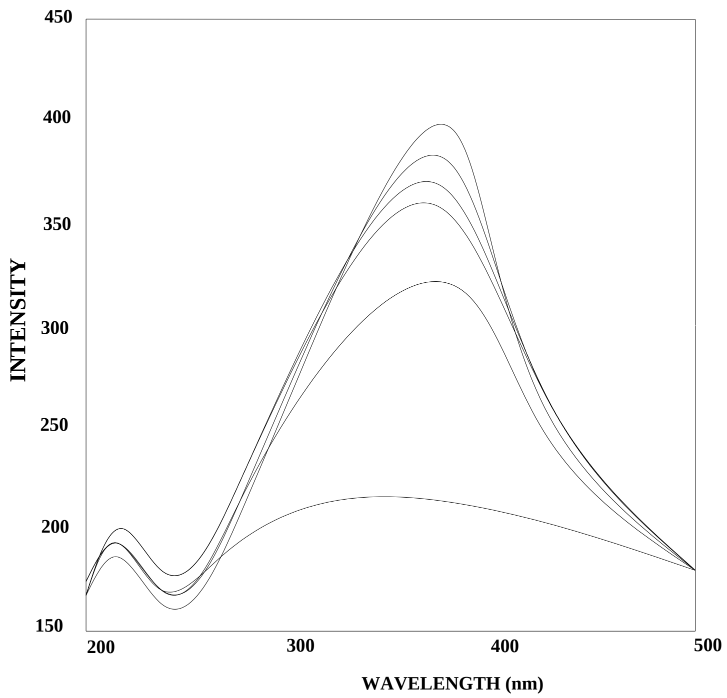

Fig.5: Emission spectra of Quinine sulphate with α-CD

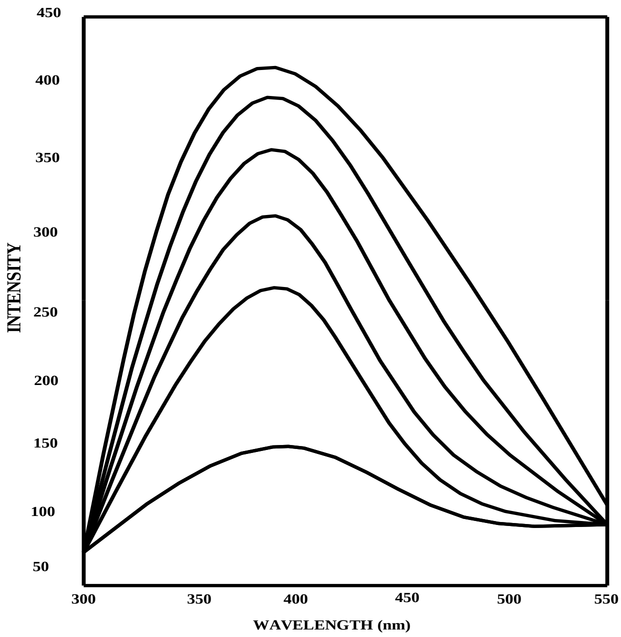

Fig.6: Emission spectra of Hydroxychloroquine sulphate with α-CD

The association constant (K) for the formation of inclusion complexes is determined from the changes in the absorption and fluorescence intensity of the guest molecule with increasing the concentration of α-CD by using Benesi- Hildebrand equation [17]. The equation for 1:1 complexes are

Absorption

$$\frac{1}{A-A_0} = \frac{1}{A-A_0} + \frac{1}{K(A-A_0)[\alpha-CD]}$$

Fluorescence

$$\frac{1}{I-I_0} = \frac{1}{I-I_0} + \frac{1}{K(I-I_0)[\alpha-CD]}$$

In the above equation A_0/I_0 is the intensity of absorbance/ fluorescence of quinine sulphate and hydroxychloroquine sulphate without α-CD,

A/I is the absorbance/ fluorescence intensity with a particular concentration of α-CD. A good linear correlation is obtained from the graph drawn between concentration of α-CD and intensity of absorbance / emission.

The association constant for absorption and emission is determined from the slope of the graph.

For absorption

$K = \dfrac{1}{Slope(A-A_0)}$ =386.7 for quinine sulphate :α-CD and 375.93 for hydroxychloroquine sulphate : α-CD inclusion complexes.

For emission

$K = \dfrac{1}{Slope(I-I_0)}$ = 451.4 for quinine sulphate : α-CD and 317.8 for hydroxychloroquinesulphate : α-CD inclusion complexes.

This analysis reveals that both the drug molecules quinine sulphate and hydroxychloroquine sulphate form 1:1 inclusion complexes with α-CD.

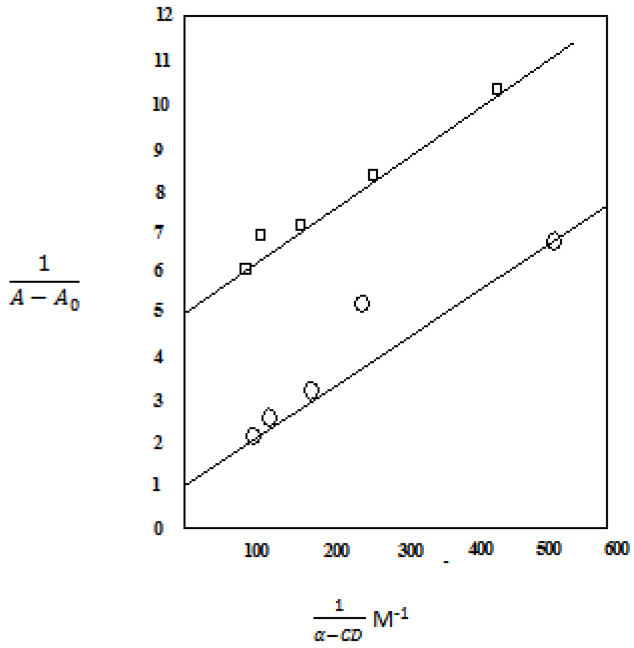

Fig.7:Plot of $\frac{1}{A-A_0}$ Vs $\frac{1}{\alpha-CD}$ M^{-1} for Quinine sulphate and Hydroxychloroquine sulphate

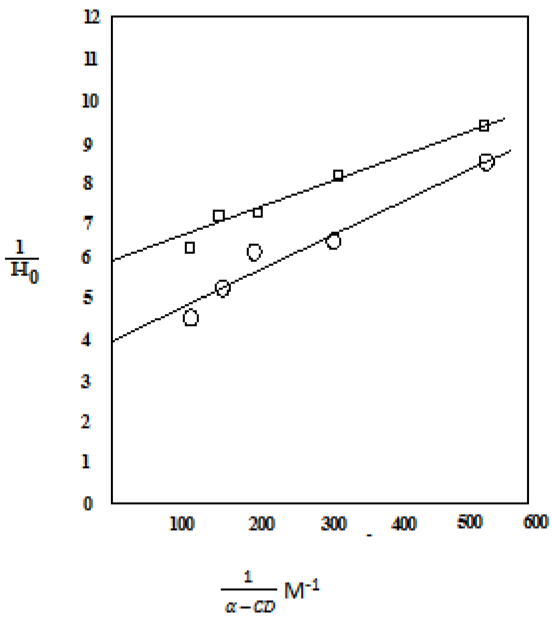

Fig.8 : Plot of $\frac{1}{I-I_0}$Vs $\frac{1}{\alpha-CD}$ M^{-1} for Quinine sulphate and Hydroxychloroquine sulphate

Phase solubility study

Fig.9 and fig.10 represent the phase solubility diagram of α-CD: quinine sulphate and α-CD: hydroxy chloroquine sulphate liquid inclusion complexes. From the diagram it is observed that the drug solubility increases linearly by increasing α-CD concentration.The diagrams are considered as A_L type according to the model proposed by Higuchi and Carnors. The apparent stability constant (Ks) are found to be 217.8M^{-1} and 206M^{-1} for α-CD: quinine sulphate and α-CD : hydroxychloroquine sulphate complexes respectively.

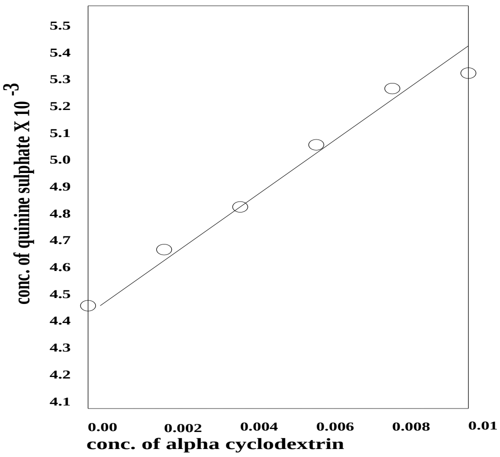

Fig.9: Phase solubility diagram of α-CD and Quinine sulphate

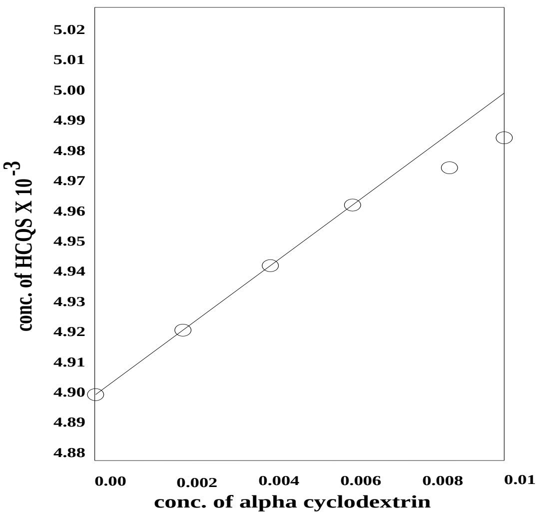

Fig.10: Phase solubility diagram of α-CD and Hydroxychloroquine sulphate

Fourier Transform Infrared (FTIR) Spectroscopic study

The FTIR spectra of pure α-CD (fig11) shows characteristic peak at 3382.91cm^{-1} (O-H stretching vibration), 2925.81 cm^{-1} (C-H), 1641.31 cm^{-1} (H-O-H bending), 1155.28 cm^{-1} (C-O) and 1029.92 cm^{-1} (C-O-C). The FTIR spectra of quinine sulphate and the solid inclusion complexes are shown in fig. 12 and 13. The –OH stretching frequency at 3211.0 cm^{-1} 1 in the original sample is shifted to 3217.27 cm^{-1} in the solid inclusion complex the aromatic C=C stretching frequency at 1510.16 cm^{-1} in the sample is shifted to 1512.19 cm^{-1} in the α-CD/quinine sulphate solid inclusion complex. The C-O stretch at 1242.07 cm^{-1} in the original sample is shifted to 1234.44 cm^{-1} in the solid inclusion complex. Similarly the C-N band at 1083.92 cm^{-1} showed a marked shift to 1080.14 cm^{-1} for the inclusion complex. The alkene stretching frequency 1620.07 cm^{-1} of the original sample is appeared almost at the same frequency 1620.21 cm^{-1} in the solid inclusion complex.

The FTIR spectra of hydroxychloroquine sulphate and the solid inclusion complex are shown in fig.14 and fig.15. The –OH stretching frequency appeared at 3217.27 cm^{-1} in the original complex is shifted to 3387.00 cm^{-1} in the solid inclusion complex. Whereas the aromatic C-H stretching frequency at 2916.37 cm^{-1} in the sample is shifted to 2924.09 cm-1 in the α-CD:hydroxychloroquinesulphate solid inclusion complex. The aromatic C=C stretching frequency occurs in two region 1612.49 cm^{-1} and 1450.47 cm^{-1} in the original sample is shifted to 1635.64 cm^{-1} and 1458.18 cm^{-1} in the solid inclusion complex. Similarly, the C-Cl stretching frequency at 1033.85 cm^{-1} also showed a marked shift to 1056.99 cm^{-1} in the solid inclusion complex. The C-N bending frequency at 1111.00 cm^{-1} occurs in the original sample is shifted to 1157.29 cm^{-1} in the inclusion complex. The above changes in the FTIR spectra of α-CD, quinine sulphate, hydroxychloroquine sulphate and solid inclusion complex are significant. These result indicates both the guest molecules are included in the α-CD cavity.

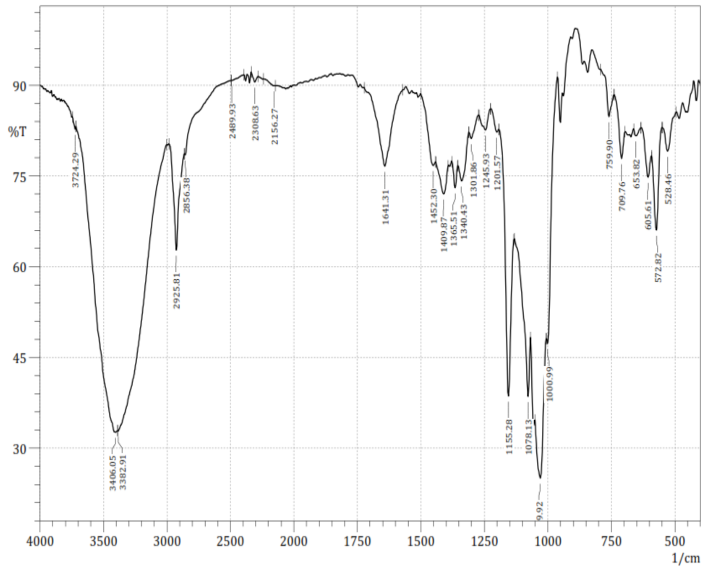

Fig11: FTIR Spectra of α-CD

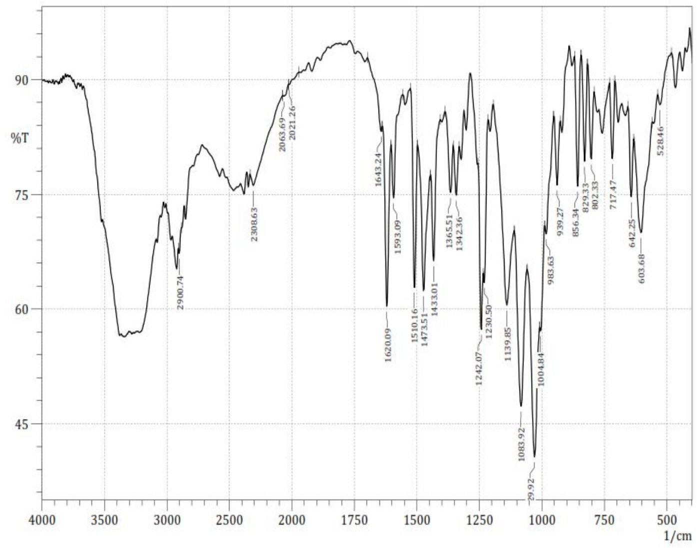

Fig. 12: FTIR Spectra of quinine sulphate

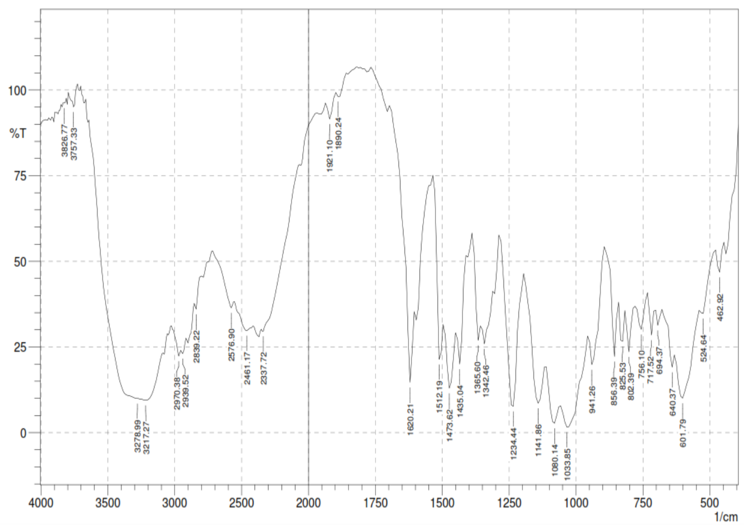

Fig.13: FTIR spectra of α-CD : quinine sulphate inclusion complex

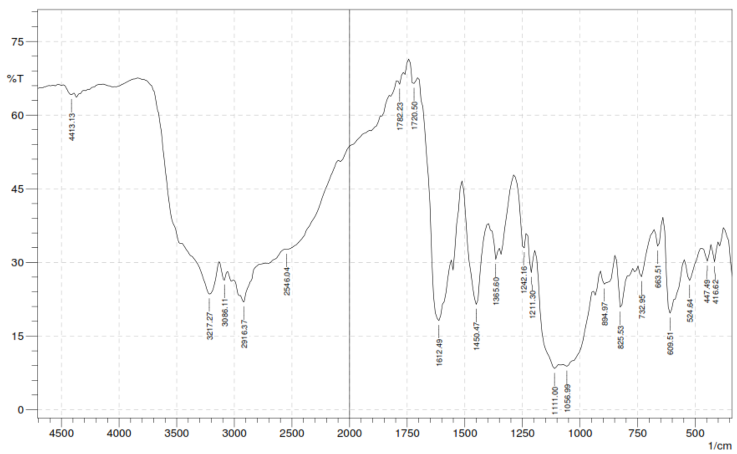

Fig.14:FTIR spectra of Hydroxychloroquine sulphate

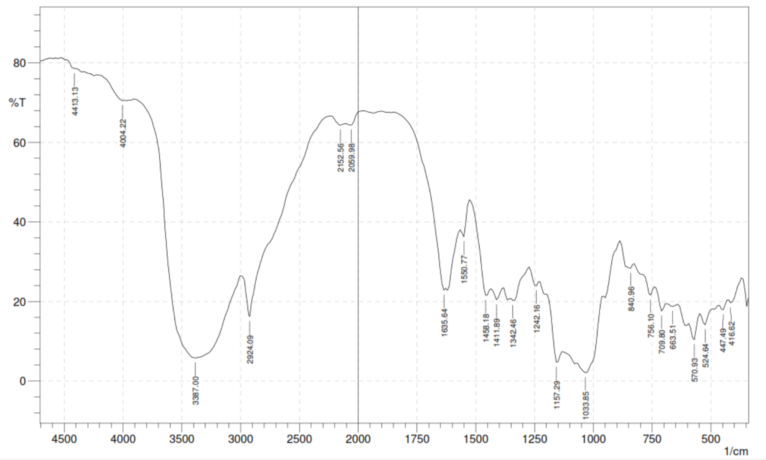

Fig..15:FTIR spectra of α-CD:Hydroxychloroquine suphate inclusion complex

^{1}HNMR spectral study

NMR spectroscopic characterization of α-cyclodextrin with Quinine sulphate and Hydroxychloroquine sulphate

Proton nuclear magnetic resonance 1HNMR spectroscopy has proved to be a powerful tool in the study of inclusion complexe[18]. Inclusion of a guest molecule into the hydrophobic cavity of the α-cyclodextrin will result in the chemical shift of guest and host molecules in the NMR spectra. Generally the chemical shift observed at H3 and H5 proton which are located in the inner cavity of α-cyclodextrin due to inclusion complex is considered[19]. The chemical shift change (Δδ) which is defined as the difference in the chemical shift change , positive sign means a downfield shift and negative sign means an upfield shift [20]. Table no 3 and table no4 shows the peak assignments for α-cyclodextrin and the inclusion complex of quinine sulphate - α-cyclodextrin and hydroxychloroquine sulphate - α-cyclodextrin.

Fig 16, 17 and 18 shows the 1HNMR spectra of α-CD, α-CD : Quinine sulphate and α-CD : hydroxy chloroquinesulphate inclusion complex. Table 3and 4 shows the chemical shift observed for H1,H2,H3,H4,H5 and H6 and also the chemical shift change (Δδ). Addition of Quinine sulphate / Hydroxychloroquine sulphate to a α-CD solution resulted in the shielding of H3 and H5 protons positioned on the inner surface of α-CD. The H6 proton located on the cavity rim at the narrow end of the molecule also gets shielded. From the table no.3 it is clearly identified that the chemical shift change (Δδ) for H5 proton is greater than that of H3 proton that proves the formation of inclusion complexes between α-CD and quinine sulphate / hydroxychloroquinesulphate. Similarly from the table no 4, it is noticed that the chemical shift change (Δδ) for H5 proton is greater than that of H3 proton which proves that the formation of inclusion complexes between α-CD and hydroxychloroquine sulphate.

Table no3 : Chemical shift for the protons of α-CD :Quinine sulphate inclusion complex.

H	δ α-CD	δ α-CD / Quinine sulphate	Δδ
H1	5.00	5.054	0.054
H2	3.58	3.564	-0.016
H3	3.91	3.883	-0.027
H4	3.563	3.535	-0.028
H5	3.597	3.564	-0.033
H6	3.914	3.908	-0.006

Table no 4 : Chemical shift for the protons of α-CD : Hydroxychloroquine sulphate inclusion complex.

H	δ α-CD	δ α-CD /Hydroxychloroquinesulphate	Δδ
H1	5.00	5.53	0.53
H2	3.58	3.47	-0.11
H3	3.91	3.87	-0.04
H4	3.563	3.06	-0.503
H5	3.597	3.74	0.143
H6	3.914	4.51	0.596

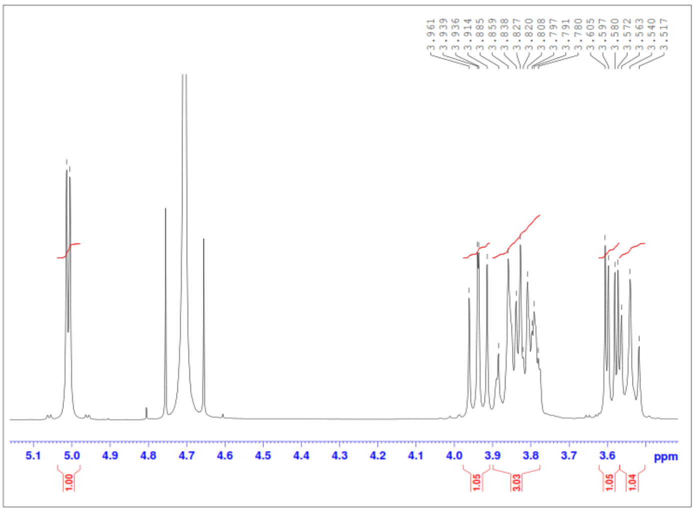

Fig.16: NMR spectra of α-CD

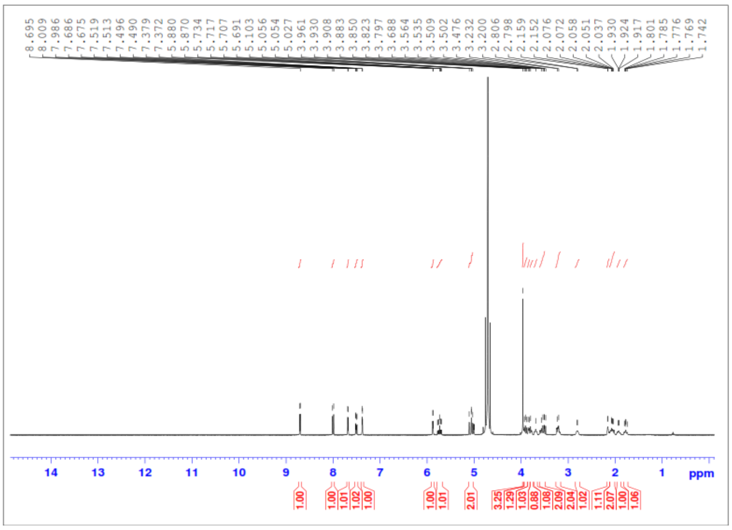

Fig.17:NMR spectra of α-CD :Quinine sulphate inclusion complex

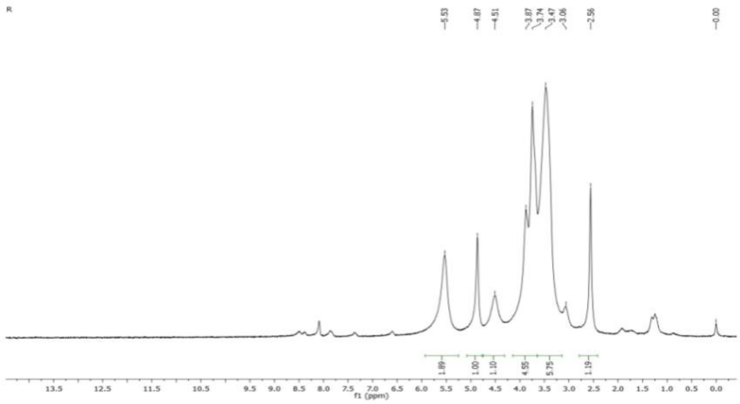

Fig.18.NMR spectra of α-CD :Hydroxychloroquine sulphate inclusion complex

IV. Conclusion

Inclusion of quinine sulphate and hydroxychloroquine sulphate with α-CD shows almost the same features. Due to the presence of the Cl in hydroxychloroquine sulphate the absorbance and emission wavelength is higher than that of quinine sulphate.The association constant for absorbance and emission are higher for Quinine sulphate than hydroxychloroquine sulphate. The stability constant value is higher for quinine sulphate: α-CD complex than hydroxychloroquinesulphate : α-CD complex. The ^{1}HNMR study of the inclusion complexes shows that both the drug molecules are fully included in the α-CD cavity. The FTIR spectroscopy study also confirms the formation of 1:1 complexes. From these observations it can be concluded that the formation of inclusion complexes of quinine sulphate and hydroxychloroquine sulphate with α-CD increases the solubility and stability of the guest molecules.

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M.Shirly Treasa. "Characterisation and solubility studies of Quinine sulphate and Hydroxychloroquine sulphate inclusion complexes with α – cyclodextrin" IOSR Journal of Applied Chemistry (IOSR-JAC) 11.11 (2018): 24-34.