



Formation & specification of host–guest inclusion complexes of an anti-malarial drug inside into cyclic oligosaccharides for enhancing bioavailability

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Abstract

The purpose of this novel research is to explore the formation of inclusion complexes of a drug, namely, chloroquine diphosphate with cyclic oligosaccharides. The solubility, versatility and bioavailability of the drug are enhanced and some of its side effects are reduced after encapsulation. Various sophisticated approaches have been employed to synthesize and characterize the inclusion phenomenon, which confirm the 1:1 stoichiometry of the complexes. The association constant is found higher in case of β -cyclodextrin which was explicated based on their molecular structure. The work explores the enhancement of overall bioavailability of this essential biologically active molecule.

Keywords Cyclodextrin · Chloroquine diphosphate · Inclusion complex · Thermodynamics · Bioavailability

Introduction

Cyclodextrins (CD) are the most fascinating host molecules in supramolecular chemistry [1]. They have the capacity to construct stable encapsulated complexes (inclusion complex, IC) with various guest molecules on account of their exceptional truncated cone structure [2–7]. Stabilisation by hydrophobic interaction between the cavity of the cyclodextrin and hydrophobic part of the guest molecule is responsible for the formation of this type of steady host–guest encapsulated complexes. The weak intermolecular forces acting between the host and guest molecules are mainly van der Waals force, dipolar interaction, electrostatic and hydrogen bonding attractions [8]. They are broadly used in the pharmaceutical production as drug carrier to modify the bioavailability of biologically active molecules [9]. They are non-poisonous and can be taken safely by humans. Cyclodextrin based inclusion is the best method to develop inclusion

complexes to improve the physicochemical properties of the drug molecule [10]. CDs are macro cyclic water soluble oligosaccharides composed of six (α -CD), seven (β -CD) and eight (γ -CD) glucopyranose units linked through α -(1–4) bond [11]. Primary hydroxyl groups are situated at narrow end and secondary hydroxyl groups are placed around the wider end (Scheme 1) [12]. This type of unique structure permits them to enclose comprehensive guest molecules.

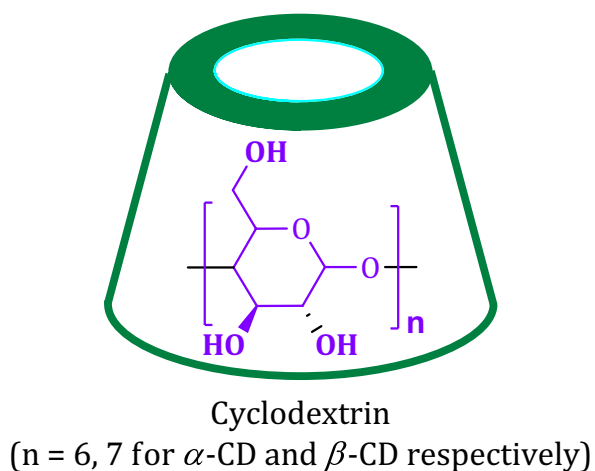
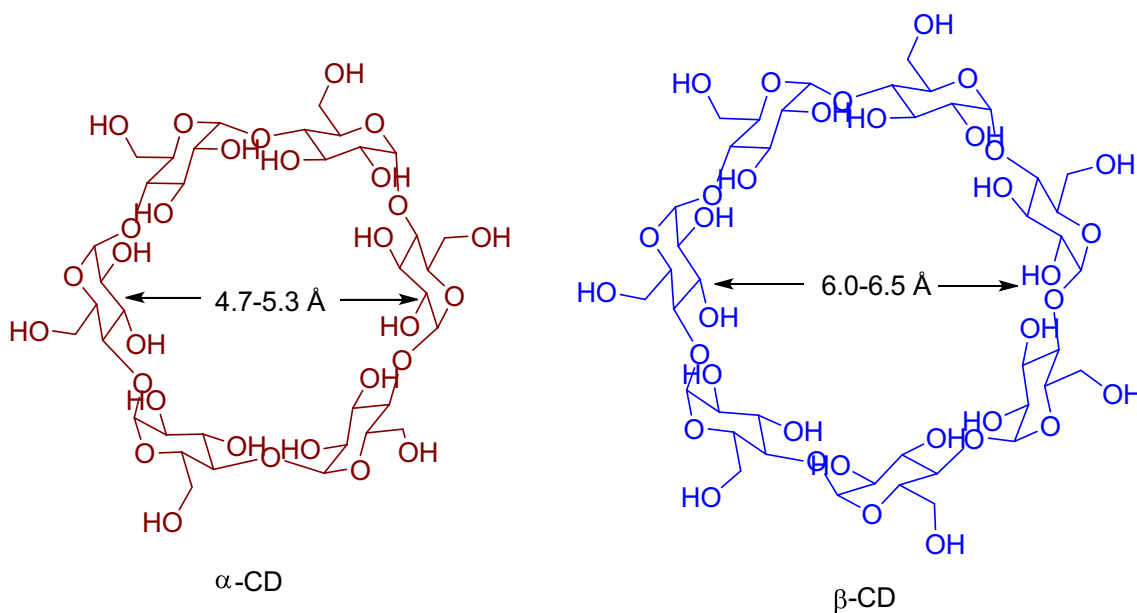
The drug chloroquine diphosphate (CDP) is a medicine that is primarily used to prevent and treat malaria (Scheme 2). Certain types of complicated cases of malaria typically require additional medication. CDP is occasionally used for amebiasis, rheumatoid arthritis and lupus erythematosus. [13, 14] It is a component of drug class 4-aminoquinoline. It appears to be safe during pregnancy time. It works in opposition to the asexual form of malaria inside red blood cell. This drug has some ordinary side effects including muscle problems, loss of hunger, diarrhea and skin complaint [15]. Controlled release of this drug using CD as the encapsulating agent can minimize these side effects and the drug molecule should be able to penetrate the lipophilic membrane to facilitate its biological activity. By forming inclusion complex CD can transport the drug to the physiological spot without losing any of its bioactivity [9].

In this article we endeavor to explore the formation and nature of IC of CDP with two cyclic oligosaccharides in aqueous environment with the help of spectroscopic and

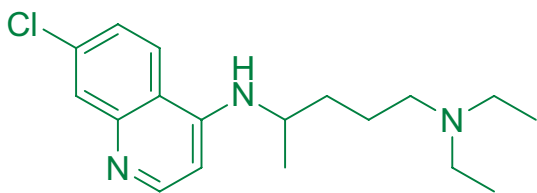
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Scheme 1 Structure of cyclodextrin molecules



Scheme 2 Molecular structure of chloroquine

physicochemical studies keeping in mind that the drug molecule must retain its biological activity.

Experimental section

Source and purity of samples

Chloroquinediphosphate, α -CD and β -CD of puriss grade were purchased from Sigma-Aldrich, Germany and used in the experiment as it received. The mass fraction purity of CDP, α -CD and β -CD were ≥ 0.98 , ≥ 0.99 and ≥ 0.98 respectively.

Apparatus and procedure

Triple distilled & degassed water was utilized for checking the solubility of the drug CDP, α -CD and β -CD. The drug and both the CD molecules are completely soluble in water. The solutions were set up by mass at 298.15 K. Solutions were made with proper care to avoid weight loss by evaporation.

^1H NMR was done at 300 MHz in D_2O solution using Bruker Avance machine at 298 K. Signals are shown as δ in ppm using solvent signals (HDO: δ 4.79 ppm) as internal standard.

Surface tension experiment was done by tensiometer (K9, KRUSS; Germany) by platinum ring detachment at 298.15 K. During experiment the temperature of the system was kept constant by thermostat water circulating through double wall glass vessel enclosing the solution.

The conductances of the solutions were determined by MT Seven Multi conductivity meter. The uncertainty of the result was approximately $\pm 1.0 \mu\text{S m}^{-1}$. The experiments were done in a thermostat water bath keeping the temperature fixed at 298.15 K.

Ultra-violet visible spectra were recorded by spectrophotometer (JASCO V-530), with an uncertainty ± 2 nm. A digital thermostat was used to keep the temperature constant.

Fourier transform IR spectra were taken on a spectrometer (Perkin Elmer) applying the KBr disk procedure. Samples were formulated as KBr disks with complex (1 mg) and KBr (100 mg). The scanning range was 4000–400 cm^{-1} at normal temperature.

HRMS were performed with Q-TOF instrument (high resolution) by positive mode electro-spray ionization.

ICs (α -CD + CDP and β -CD + CDP) were also prepared in the solid state taking 1:1 mol ratio of the drug CDP and each CD. For this purpose 1.0 mmol CD was dissolved in 20 mL water and 1.0 mmol drug CDP was dissolved in 20 mL water. These two solutions are allowed to stir separately in a magnetic stirrer for 3 h. The aqueous solution of the drug was added dropwise into the aqueous solution of the cyclodextrin. Then the mixture is constantly stirred for 4 days at 40–45 $^\circ\text{C}$. The solution was filtered at that temperature, then cooled to 5 $^\circ\text{C}$ and kept for 24 h. The resulting suspension was filtered and the white polycrystalline powder was found, it was dried in air.

Result and discussion

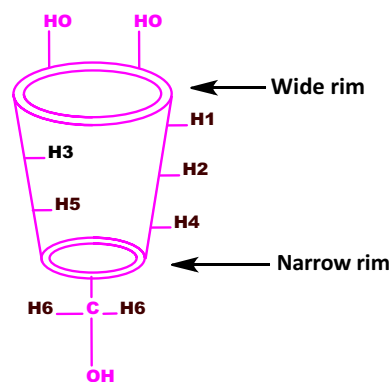
^1H NMR spectra analysis

The formation of IC and stoichiometry is verified by ^1H NMR study. When the drug molecule is encapsulated into the hydrophobic cavity of CD molecule it consequences the

shift of protons of the CDP and CD molecules [16, 17]. The aromatic ring of CDP molecule produces diamagnetic shielding of protons present in it according to the interaction with the CD protons after encapsulation. The location of various protons in the CD molecules are illustrated in Scheme 3. The protons H3 and H5 are located within the cone of CD close to the wider rim and narrower rim respectively. The remaining H1, H2 and H4 protons have their positions at the outer surface of the CD molecule [18–20]. The chemical shift (δ) values of the drug CDP, α -CD, β -CD and ICs are mentioned in table S1. The signals of the protons of the host and aromatic ring of the drug shifted towards upfield in the resulting inclusion complex of the drug and CD (Figs. 1, 2). Chemical shift indicates that the aromatic moiety of the drug interact with the H3 than H5 protons signifying that the drug molecule enter into the hydrophobic cavity from wider rim. The change in δ value of CDP and CD is mainly because of change of environment after inclusion complex formation. The upfield shift is basically due to formation of hydrogen bond of the guest with rim hydroxyl groups of CD. The shielding of H3 and H5 protons are due to ring current effect as the aromatic part of the ring was positioned perpendicular to the to the cyclodextrin molecule cavity [2]. These results show the formation of inclusion complex.

Surface tension study

Surface tension study nicely explains the formation of IC [21, 22]. CDs being hydrophobic in nature do not express considerable change of surface tension (γ) of aqueous solution [23]. The drug molecule CDP exist as charged structure and behave like surface active molecule. Therefore when CDP forms IC with the host molecule notable modification in surface tension is detected. The γ value of the aqueous solution of this drug is less than that of water. In this article the γ value of various solutions of CDP with gradual addition of α and β -CD were determined at 298.15 K (Tables



Scheme 3 Truncated conical structure of cyclodextrin

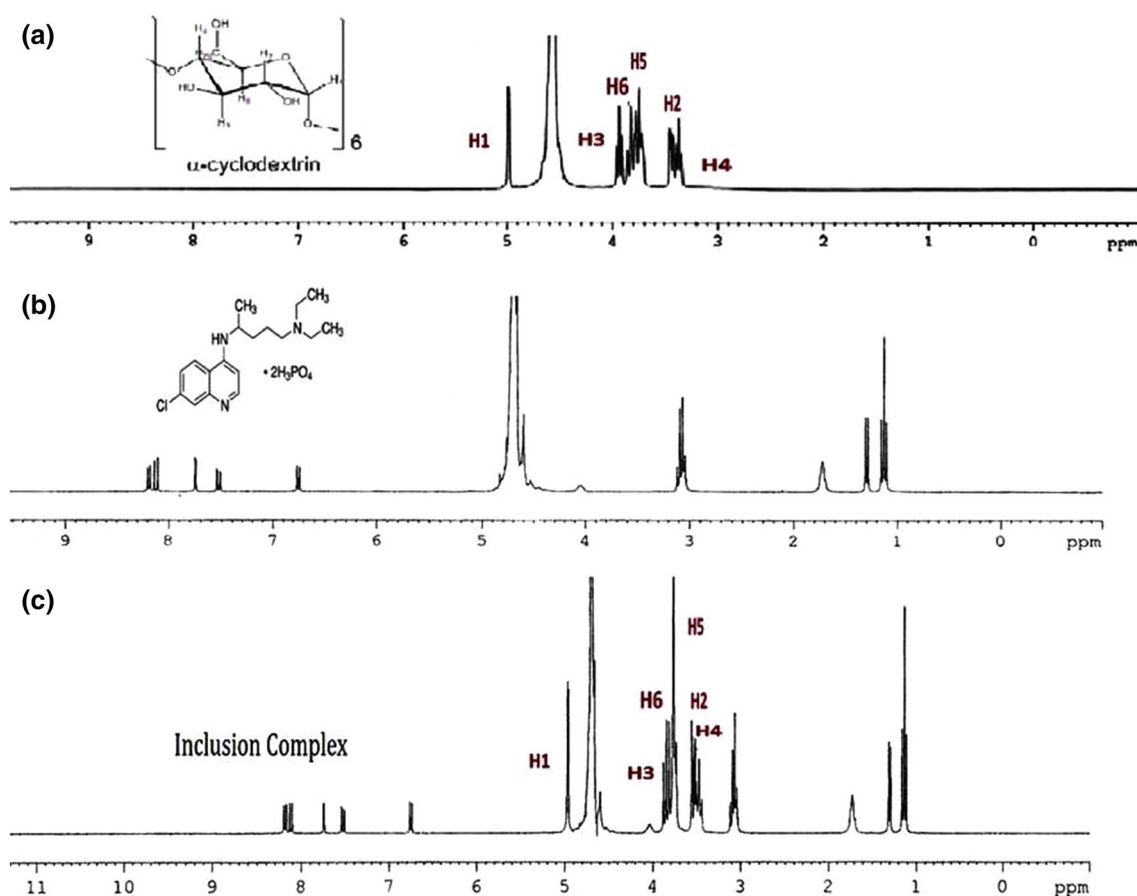


Fig. 1 ^1H NMR spectra of (a) α -CD (b) CDP and (c) IC of α -CD+CDP in D_2O in 298.15 K

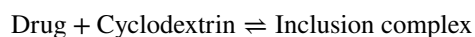
S4, S5). The γ regularly increases for both the CDs, perhaps owing to the inclusion of the surfactant like drug molecules from solution to the hydrophobic cavity of the CDs (Scheme 4). There is a solo noticeable break in both the plots (Fig. 3) which propose the formation of IC [24, 25]. The concentration ratios of the CDs and CDP at the break point (Table 1) are roughly 1:1 which surely indicate the stoichiometric ratio of the IC to be 1:1. If more than one break point would be detected in the surface tension plot it would indicate other stoichiometry of the IC.

Conductivity study

Conductivity (κ) provides important information concerning the stoichiometry of the IC [26, 27]. The aqueous solution of the drug CDP is conductive in nature as it can exist as a charged structure. For this purpose the conductivity of a sequence of solutions of this drug with gradual addition of α and β -CD were determined at 298.15 K. When dropwise CD solution is added to the drug solution the conductivity value regularly decreases and there is an appearance of a sharp break point after that the conductivity value do not

show any change (Tables S6, S7). α and β -CD show same type of tendency in their conductivity values (Fig. 4). The manifestation of sharp break points imply the formation of IC [3, 28]. The decreasing κ value is mainly due to the insertion of the guest drug molecule in the conical cavity of CD. The values of κ and subsequent concentration of the CD molecules are mentioned in Table 1 which proposes that the ratio of concentration of CDP and the CD at the break point is around 1:1. This confirms the stoichiometry of the IC to be 1:1.

The break point is the point at which the conductivity value corresponds to the maximum inclusion of the drug molecules in CD molecule cavity [18]. There exists an active equilibrium between the free and encapsulated drug molecules.



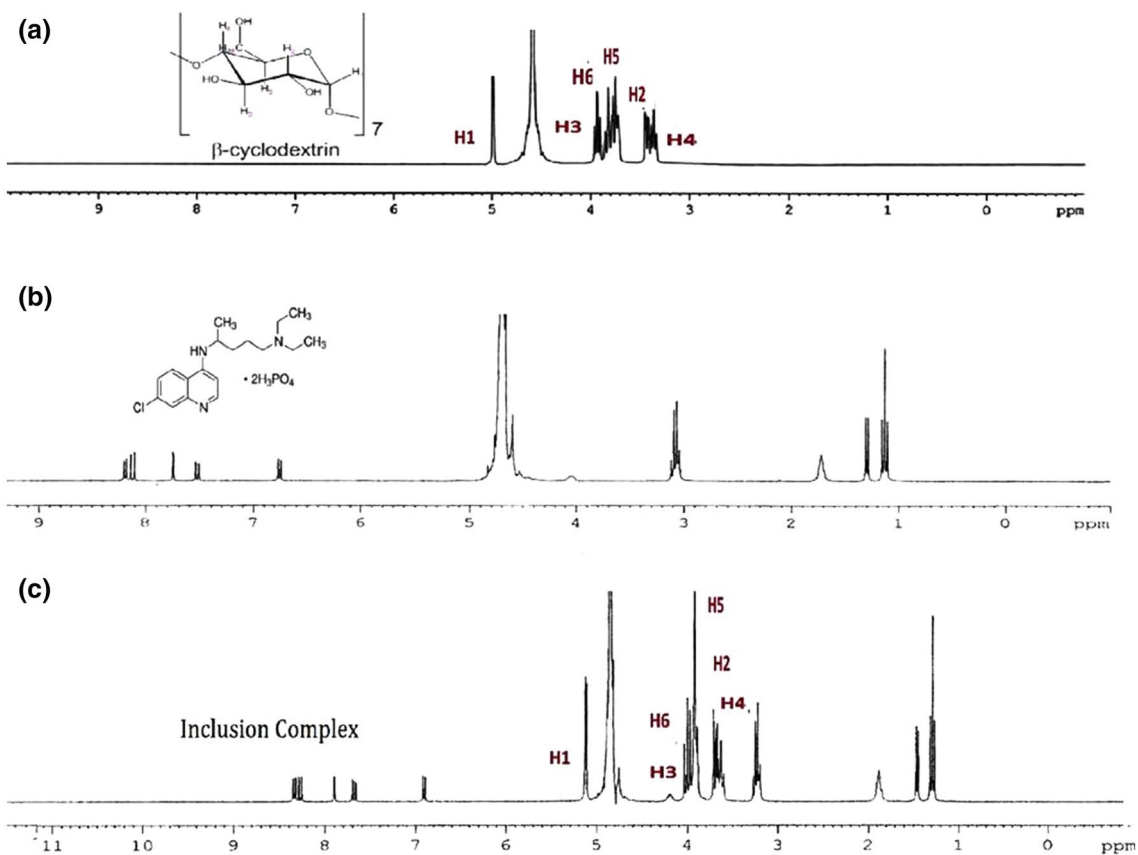
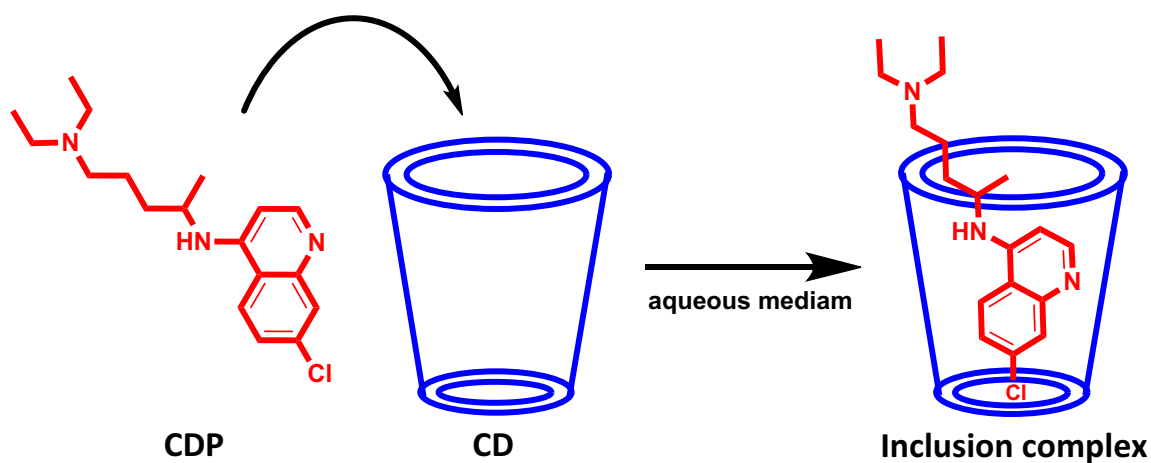


Fig. 2 ^1H NMR spectra of (a) β -CD (b) CDP and (c) IC of β -CD+CDP in D_2O in 298.15 K



Scheme 4 Probable mechanism of encapsulation of CDP into α and β -cyclodextrins

Job plots confirm the stoichiometric ratio

Job's method can be utilized to recognize the stoichiometry of the ICs formed [29, 30]. Job plots are constructed by the continuous variation method by UV–Visible

spectroscopy. For this purpose a series of solutions for the drug CDP and both the CDs were prepared with the variation of the mole fraction of the drug molecule (Tables S2, S3). $\Delta A \times \Delta R$ was plotted against R to obtain these plots where ΔA is the difference in the absorbance of the drug without and with the presence of host CDs and $R = [\text{CDP}] /$

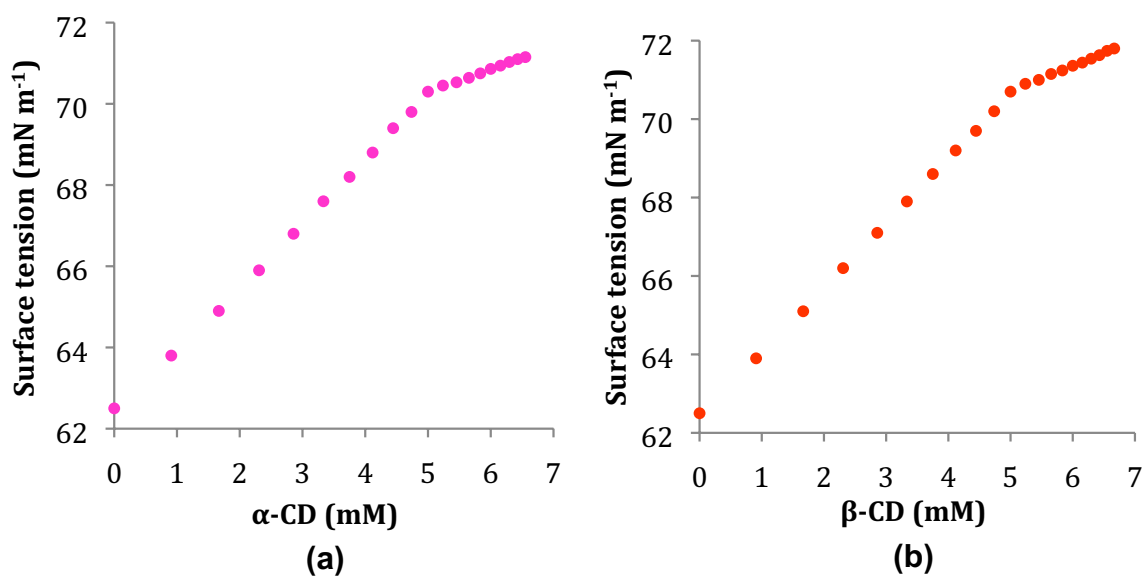


Fig. 3 Change of surface tension of aqueous CDP solution with rising concentration of **a** α -CD **b** β -CD correspondingly at 298.15 K

Table 1 Values of surface tension (γ) and conductance (κ) data the break point with subsequent concentration of α and β -CD at 298.15 K

CDP			
α -CD		β -CD	
Surface tension concentration/mM	γ/mNm^{-1}	Surface tension concentration/mM	γ/mNm^{-1}
5.08	70.34	5.07	70.75
Conductivity concentration/mM	κ/mSm^{-1}	Conductivity concentration/mM	κ/mSm^{-1}
5.01	0.512	5.0	0.490

Standard uncertainties (u): temperature: $u(T) = \pm 0.01$ K, surface tension: $u(\gamma) = \pm 0.1$ mNm⁻¹, conductivity: $u(\kappa) = \pm 0.001$ mSm⁻¹

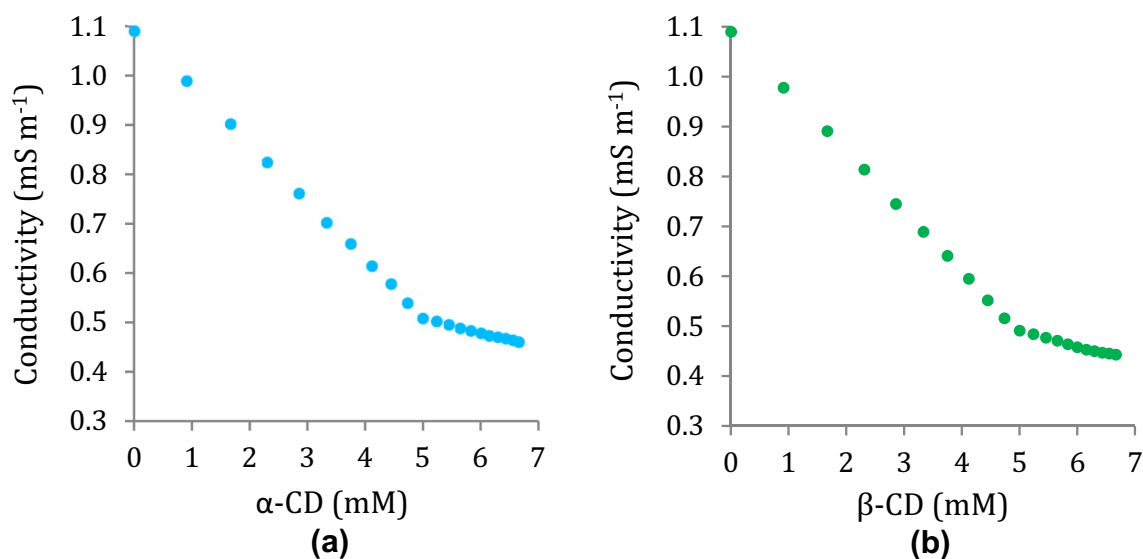


Fig. 4 Change of conductivity of aqueous CDP solution with rising concentration of **a** α -CD **b** β -CD respectively at 298.15 K

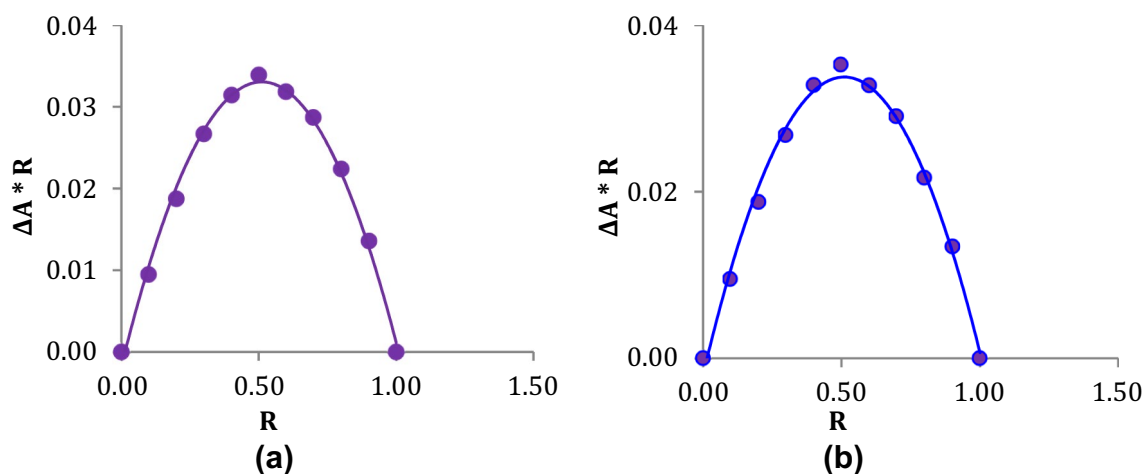


Fig. 5 Job plot of **a** CDP- α -CD system at $\lambda_{\max}=254$ nm **b** CDP- β -CD system at $\lambda_{\max}=254$ nm at 298.15 K. $R=[\text{CDP}]/([\text{CDP}]+[\text{CD}])$, ΔA =absorbance difference of CDP without and with CD

($[\text{CDP}] + [\text{CD}]$) [21, 31]. Absorbance values were recorded at the respective λ_{\max} for each of the solutions at 298.15 K. The stoichiometry of the inclusion complex was found from the R values at maximum deviation, that is the ratio of host and guest at $R=0.5$ is for 1:1 complex; $R=0.33$ for 1:2 complex; $R=0.66$ for 2:1 complex [8]. From Fig. 5, it has been found that the maxima is at $R=0.5$ for each plot which confirms the 1:1 stoichiometry of the ICs.

Association constant and thermodynamic parameters

Association constants were determined for both the CDP-CD ICs from UV–Visible spectra [32]. When the drug molecule is encapsulated in the CD cavity there is a change

from polar aqueous environment to the apolar hydrophobic cavity. As a result the change in molar absorptivity ($\Delta\epsilon$) of the drug molecule changes after inclusion. The difference in absorbance intensity (ΔA) of the drug is observed as a function of concentration of both the CD molecules to find out the K_a value (Tables 2, S2 and S3). Double reciprocal plots were generated on the basis of Benesi–Hildebrand method for 1:1 host–guest ICs [8, 33] (Figs. S1, S2, Eq. 1)

$$\frac{1}{\Delta A} = \frac{1}{\Delta\epsilon[\text{CDP}]K_a} \times \frac{1}{[\text{CD}]} + \frac{1}{\Delta\epsilon[\text{CDP}]} \quad (1)$$

The aforementioned equation is a linear one and the K_a was calculated dividing intercept by slope from double-reciprocal plots for both the ICs [34].

Table 2 K_a , ΔH° , ΔS° and ΔG° of various CDP-CD ICs

	CDP				
	Temp (K) ^a	$K_a \times 10^{-3} (\text{M}^{-1})^b$	$\Delta H^\circ (\text{kJ mol}^{-1})^b$	$\Delta S^\circ (\text{J mol}^{-1} \text{K}^{-1})^b$	$\Delta G^\circ (\text{kJ mol}^{-1})^b$ (298.15 K)
CDP + α -CD	288.15	1.99			
	293.15	1.71			
	298.15	1.50	-22.19	-13.78	-18.08
	303.15	1.28			
	308.15	1.08			
CDP + β -CD	288.15	2.38			
	293.15	2.13			
	298.15	1.89	-19.06	-1.35	-18.65
	303.15	1.64			
	308.15	1.42			

^aStandard uncertainties in temperature u are: $u(T) = \pm 0.01$ K

^bMean errors in $K_a = \pm 0.02 \times 10^{-3} \text{ M}^{-1}$; $\Delta H^\circ = \pm 0.01 \text{ kJ mol}^{-1}$; $\Delta S^\circ = \pm 0.01 \text{ J mol}^{-1} \text{ K}^{-1}$, $\Delta G^\circ = \pm 0.01 \text{ kJ mol}^{-1}$

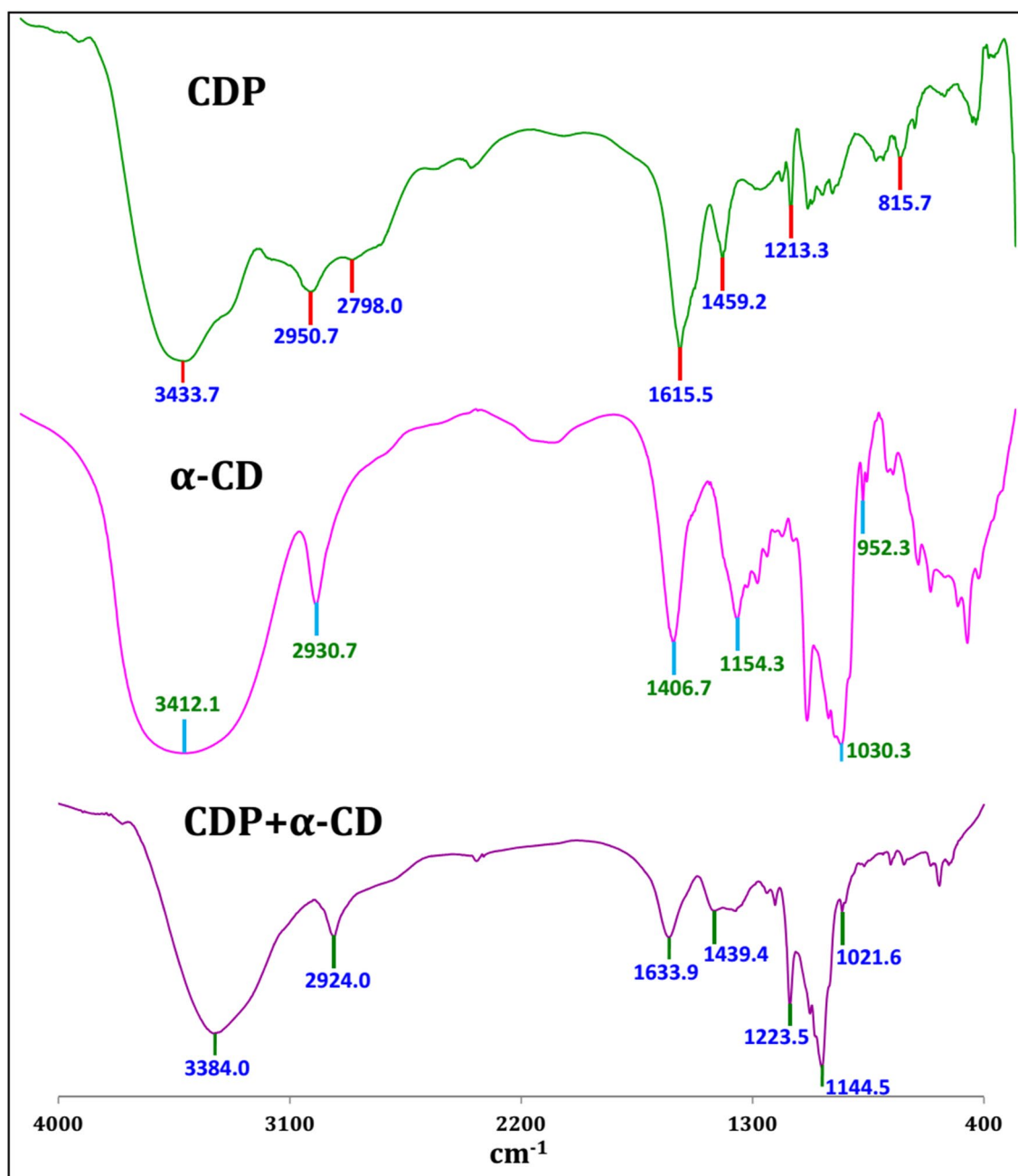


Fig. 6 FTIR spectra of CDP, α-CD and CDP+α-CD IC

The thermodynamic parameters can also be evaluated using the K_a values found at various temperatures on the basis of above method using van't Hoff equation mentioned below [35].

$$\ln K_a = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \quad (2)$$

Linear relationship exists between $\ln K_a$ and $1/T$. The slope of the plot of equilibrium constant at various temperatures gives a negative value for ΔH° , thus indicating that the process is exothermic [31]. The thermodynamic parameters are listed in Table 2. The negative values of ΔG° for both systems indicate that the formation of inclusion complexes is spontaneous. The decrease in ΔS° value implies that the process is entropy controlled but not

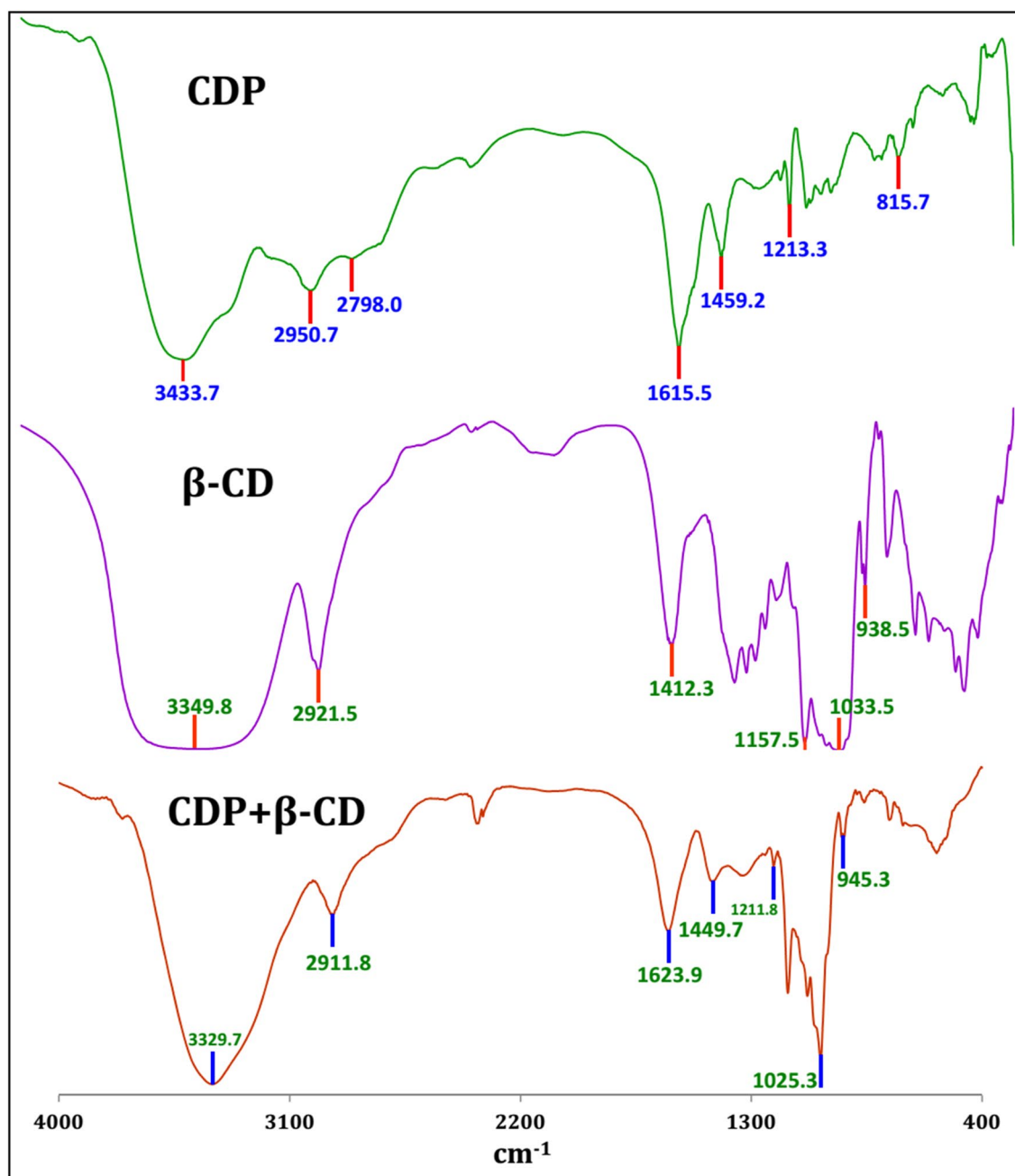


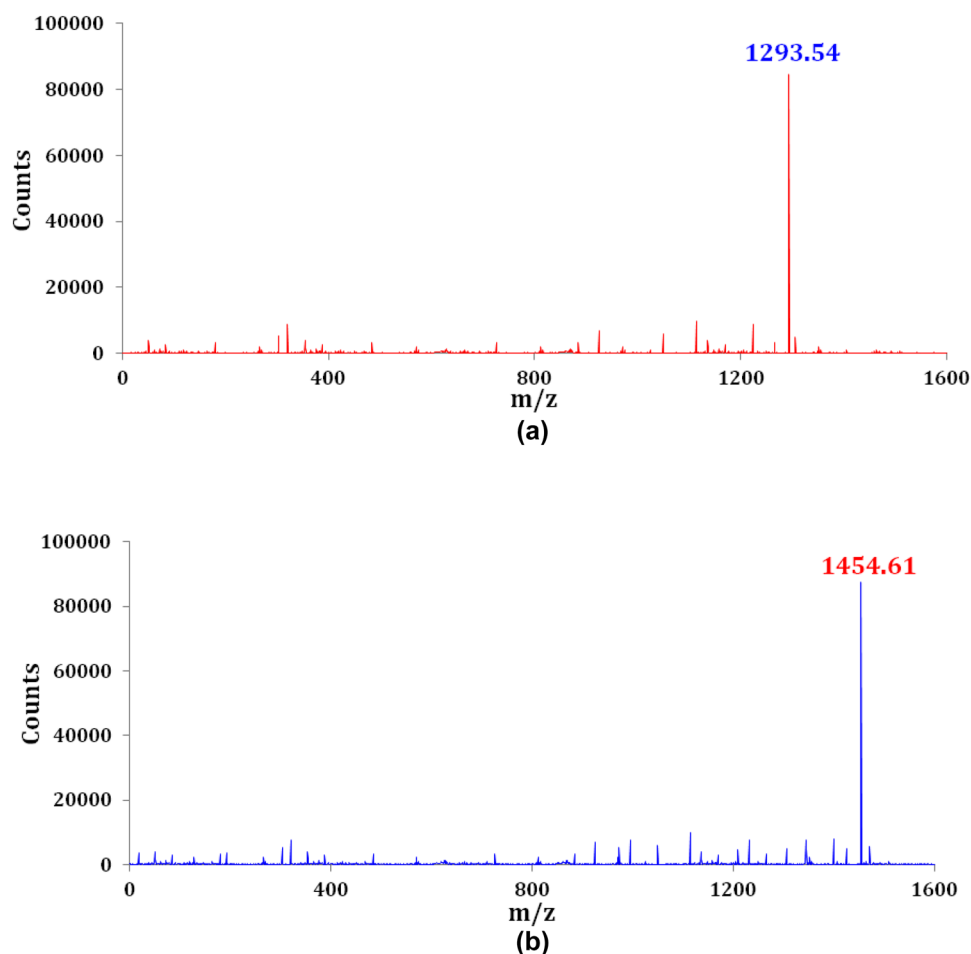
Fig. 7 FTIR spectra of CDP, β -CD and CDP + β -CD IC

entropy driven. The negative value of ΔS° , unfavorable to the inclusion process, is overcome by the negative value of ΔH° , leading to an overall thermodynamically favorable process.

The entropic contribution for β -CD is less unfavorable compared to α -CD as found from the spectroscopic studies. This may be attributed to the fact that both α and β -CD comprise of few water molecules inside the cavity.

While the hydrophobic guest enters into the cavity of CD, these water molecules are released into the bulk increasing the overall entropy of the system. Now, as found from the other studies that β -CD has higher tendency for the formation of inclusion complex, it is typical that the drop of entropy would be much less in case of β -CD as respect to α -CD.

Fig. 8 ESI mass spectra of **a** CDP + α -CD and **b** CDP + β -CD ICs



FT-IR spectra analysis

FT-IR spectral study helps to determine the interaction between the host and guest in the IC [36, 37]. The drug CDP and the CDs form solid inclusion complexes by other than covalent interactions such as hydrophobic interactions, van der Waals interaction and hydrogen bonding. After encapsulation of the drug molecule by the CDs, the resulting absorption bands from the encapsulated part of the guest have been shifted in their position [38, 39]. The FT-IR spectrum of pure CDP, α -CD, β -CD and the two ICs are shown in the Figs. 6 and 7. The different frequencies of the above mentioned compounds are reported in table S10. The spectrum of CDP is characterised by peaks of -N-H , -C=N , -C-N , -C-Cl , aromatic -C=C , -C-H of -CH_2 and -CH_3 etc. The broad -O-H stretching frequency for α -CD and β -CD was observed at 3412.11 cm^{-1} and 3349.85 cm^{-1} respectively. In the ICs the -O-H frequency shifted to lower region i.e., 3384.08 and 3329.76 cm^{-1} for α -CD and β -CD respectively. This shift occurs probably due to participation of the -O-H groups of both the CDs in hydrogen bonding with the guest drug molecule. The peaks of -C=N , -C-N , aromatic -C=C of the drug CDP are shifted in the spectra of the ICs. The

changes in the FT-IR spectra of ICs are due to the restriction of the vibration of free CDP molecules as the quinoline part of the drug with Cl groups is encapsulated in the hollow space of CD molecules [40, 41]. No additional peaks are found in the spectra of the ICs. This fact again confirms that only non covalent interaction exists between the host and guest, only Vanderwaal's interaction are present.

HRMS study

ESI-MS study is a extensively acknowledged practice to describe host-guest IC [42, 43]. The result of ESI-MS study can simply be matched up with other experiments, for instance Job Plot titration obtained from UV-Visible spectra. The solid ICs synthesized by the method mentioned in the experimental section are used for MS study. Figure 8a, b show the mass spectra of the two CDP-CD ICs. The strong peaks at m/z 1293.54 and 1454.61 refers to the proton adduct of CDP + α -CD IC and CDP + β -CD IC. Since no additional intense peak was detected at higher values the ESI-MS experiment verifies the 1:1 stoichiometry of the ICs [44, 45].

Conclusion

It can be concluded from the present study that chloroquine diphosphate form ICs with α -CD and β -CD in aqueous solution and in solid phase, thus enhances the bioavailability of the drug. These two inclusion complexes have found applications for controlled release of this drug. The inclusion phenomenon is explained by $^1\text{H-NMR}$ study whereas surface tension, conductivity and Job plot variation suggest the 1:1 stoichiometry of the ICs. FTIR and HRMS also support the formation of IC. The binding constants and thermodynamic data are determined by UV–Visible spectroscopy which is come across to be higher for β -CD. In general the inclusion process is thermodynamically approving. These two ICs have potential application in the pharmaceutical industries and biomedical fields.

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Compliance with ethical standards

Conflict of interest The authors announce they have no conflict of interest.

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