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ORIGINAL ARTICLE

Encapsulation of rifampicin by natural and modified β-cyclodextrins: characterization and thermodynamic parameters

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Abstract
Introduction Encapsulation of rifampicin by β-cyclodextrin and its methyl and hydroxy-propyl derivatives was studied in solid and solution phase.
Materials and Methods The inclusion phenomenon was evidenced by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) analysis and fourier-transform infrared (FT-IR) spectroscopy and supplemented by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. The host–guest stoichiometry (1:1) and stability constant were determined by solution calorimetry.
Results The inclusion of drug was found to be exothermic process accompanied by small negative value of Gibbs free energy ($\Delta G°$) and small positive value of entropy ($\Delta S°$).
Conclusion The magnitude of equilibrium constant (K) indicates that methyl-β-cyclodextrin has the best complex formation ability. Solubility, dissolution and partition coefficient studies also support the most effective behavior of methyl-β-cyclodextrin.

Keywords β-Cyclodextrins · Rifampicin · Inclusion complex · Calorimetry · Thermodynamic parameters · Stoichiometry

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Introduction

Tuberculosis is a ubiquitous, highly contagious chronic granulomatous bacterial infection and has been righteously declared as a global emergency by World Health Organization (WHO). An integral part of strategy to fight the disease is the use of quality first-line drugs like rifampicin, isoniazid, ethambutol and pyraniazid. However, rifampicin is most widely used because of its use in both the initial as well as continuation phase of the treatment [1]. Unfortunately, the efforts to counter the disease through the use of rifampicin have not been free from the problems because of its poor solubility in water [2]. Moreover, its absorption has been reported to be adversely affected by food [3]. Rifampicin alone, in solid state, is stable but its stability in the presence of moisture/acidic stomach conditions [4, 5] and other anti-tubercular drugs [6] together is questionable. It is highly desirable to improve the solubility of rifampicin and also to protect it against oxidation and interaction with other drugs. Inclusion of the drug in the hydrophobic cavity of cyclodextrin is one of the appropriate approaches to solve such problems.

Cyclodextrins, the cyclic oligosaccharides discovered in 1891 are still regarded as novel excipients of unexplored potential. The new cyclodextrin based technologies are constantly being developed. The drug formulations containing cyclodextrins have been approved for marketing in Japan, Europe and in US [7].

There have been several [2, 8, 9] attempts to prepare inclusion complexes of rifampicin but the detailed analysis giving thermodynamic parameters and the exact geometry of the complex are lacking. Solution calorimetry is the one of the most important techniques described in the literature for directly measuring the enthalpy changes associated with the encapsulation [10, 11]. The

present work deals with the determination of the thermodynamic parameters of complexation of rifampicin with β-CD, M-β-CD and HP-β-CD by solution calorimetry and characterization of these complexes by DSC [12, 13], FT-IR [14, 15], PXRD [16, 17], ^{1}H-NMR [18–20] methods. Further, phase solubility [21, 22] partition coefficient determination [23] and the dissolution studies [24] have also been performed.

Experimental

Materials

Rifampicin was obtained as a gift sample from Themis Medicare Ltd., Mumbai, India. β-CD and M-β-CD were obtained from Sigma-Aldrich and HP-β-CD from Roquette, France. All the above materials were employed without any further purification.

Buffers

Phosphate buffers were prepared by mixing solutions of appropriate sodium salts of phosphoric acid in suitable ratio according to the given procedures [25]. The ionic strength of all phosphate buffers was 0.05 M. The pH value of the buffers were measured using a pH meter (Elico, India) standardized with solutions of pH 4.0, 7.0 and 9.2.

Phase solubility studies

Phase solubility studies were carried according to method described by Higuchi and Connors [26]. Excess amount of drug was added to aqueous solution containing increasing concentration of β-CDs (1×10^{-2} M to 1×10^{-3} M). The flasks were sealed and shaken with a speed of 100 rpm at 37 ± 0.5 °C for 48 h to ensure equilibrium. The shaker was switched off and temperature of bath maintained for 6 h to avoid forced solubility due to shaking. The samples were then filtered through 0.2 µm filters and suitably diluted and content of rifampicin was determined spectrophotometrically at 473 nm using Perkin Elmer UV/VIS spectrophotometer.

Preparation of inclusion complexes

Inclusion complexes were prepared by kneading method. The method involved the formation of paste of cyclodextrin with drug molecules by using small quantity of water to form the kneaded mass which was dried in dark at 37 °C for 48 h, pulverized and sieved from 150 µm mesh.

Characterization of the inclusion complexes

Differential scanning calorimetry (DSC) analysis

DSC analysis of pure rifampicin, β-CD, M-β-CD, HP-β-CD and their inclusion complexes was performed using DSC, Mettler, Toledo, Switzerland. Indium was used to calibrate the instrument. Each sample was scanned at a speed of 10 °C/min in the temperature range of 25–400 °C.

Powder X-ray diffraction (PXRD) analysis

X-ray diffraction spectra were obtained in a Bruker AXS D8 Advance X-ray diffractometer using Cu as tube anode. Analysis was performed at generator tension (voltage) 40 kV, generator current 30 mA, a scanning speed 2° min^{-1}.

Fourier-transform infrared (FT-IR) spectroscopic studies

FT-IR spectra were obtained in KBr disks using a Perkin–Elmer RX-I FT-IR Spectrophotometer. The scanning range was between 4,000 and 450 cm^{-1}.

Proton NMR spectroscopic studies

Bruker Advance II 400 NMR Spectrometer operating at 400 MHz was used for studying ^{1}H-NMR spectra of all the samples in D_2O solvent.

Solution calorimetry

Isoperibol solution calorimeter (ISC) model 4300 (Calorimetry Science Corporation, Utah, USA) was used for thermal measurements. The calorimeter consists of thin walled 25 mL silvered Dewar flask in a constant temperature bath (37.00 ± 0.0001 °C). It is a semi-adiabatic calorimeter with temperature resolution, after noise reduction, close to 1 µK, which corresponds to a heat resolution of 1–4 mJ in a 25 mL reaction vessel. The time constant of the system is 2.05 h. The drug was filled into the batch adaptor, sealed on both sides with 'O' rings and cover glass which was then inserted into Dewar flask containing buffer. The speed of glass stirrer was 100 rev/min and was allowed to equilibrate for 90 min. The ampoule was shattered automatically by means of plunger and temperature change noted. The performance of the system was tested by measuring enthalpy of solution of Potassium Chloride (17.301 kJ/mol) in triple distilled water, which was in good agreement with known enthalpy of solution of 17.322 kJ/mol. The precision of any individual measurement was better than ±0.03 KJ/mol for three consecutive experiments.

Complexation thermodynamics of rifampicin with β-CD and its derivatives were determined by measuring the enthalpy of solution of drug in pure buffer (pH 7) and in

aqueous solutions of cyclodextrins (pH 7). The solutions of CDs were prepared over a range of 0.0493–1.1031 mM. The enthalpy of interaction was calculated by the equation:

$$\Delta H_{\text{int(exp)}} = \frac{\Delta H_{(\text{CD})} - \Delta H}{v(l)} \quad (1)$$

$\Delta H_{\text{int(exp)}}$, enthalpy of interaction between drug and cyclodextrin per liter of solution; ΔH, $\Delta H_{(\text{CD})}$, enthalpy of solution of drug in buffer and in buffered aqueous solution of cyclodextrins, respectively; $v(l)$, volume of sample cell in liters (0.025 L).

Dissolution studies

The dissolution profile of inclusion complexes were obtained using USP XII apparatus equipped with paddle type tribune. Dissolution media consisted up of 900 mL of phosphate buffer of pH 7. The media were previously filtered, degassed and maintained at 37 ± 0.5 °C according to USPXXVIII. The stirring speed was set at 100 rpm. Inclusion complexes equivalent to 50 mg of rifampicin were filled in hard gelatin capsules. Sample was withdrawn after every 5 min for a period of 3 h and analyzed spectrophotometrically. Three replicates have been made for each experiment.

Determination of partition coefficient

The log partition coefficient '*P*' of rifampicin alone as well as in the presence of CDs was determined using octanol as lipophilic phase and phosphate buffer solutions of pH 2, 5, and 8 as hydrophilic phase. Each phase was presaturated by the other by mixing equal volumes, vigorous shaking and funnel separation. Equimolar amount of rifampicin and cyclodextrins was solubilized in the buffer solutions by stirring for 2 h. Equal volumes (5 mL) of buffered solution of free drug or complexed drug were mixed with octanol and shaken for 30 min with a horizontal agitator. The two phases were separated by centrifugation at 9,000×*g* for 15 min and assayed spectrophotometrically. The partition coefficient was expressed as the logarithm of the ratio of the drug concentration in the organic phase to that in the aqueous phase.

Results and discussion

Phase solubility studies

The solubility of the drug increases monotonically as the function of cyclodextrin concentration and followed an A_L type curve approximately (Fig. 1) indicating the formation of water soluble complexes. The initial slope was calculated and found to be less than unity for all the CD complexes indicating 1:1 stoichiometry.

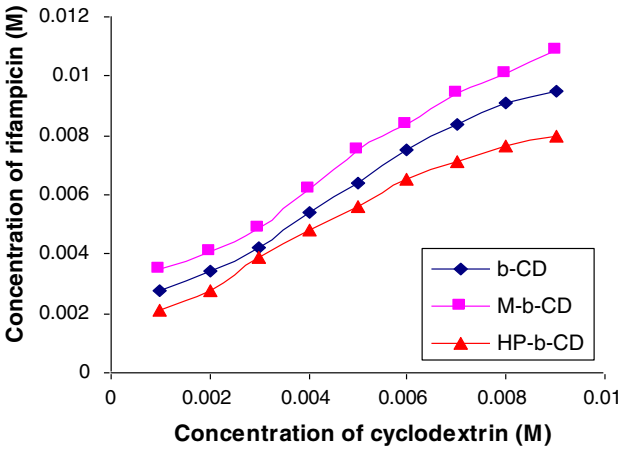

Fig. 1 Phase solubility curve of rifampicin with *β*-CD and its derivatives at 37 °C

Characterization of inclusion complexes

Differential scanning calorimetry (DSC) analysis

DSC, a thermal analysis technique of choice is frequently used because of its ability to provide detailed information about both the physical and energetic properties of a substance. The DSC curve of rifampicin shows a characteristic fusion endothermic peak at 188.5 °C corresponding to its melting point and is followed by a broad decomposition peak at 253.65 °C. The DSC curves of pure *β*-CD, M-*β*-CD and HP-*β*-CD showed broad endothermic effect around 60 and 100 °C associated with the crystal water losses (Fig. 2). Considering the kneaded systems, rifampicin endothermic fusion disappears in the M-*β*-CD complex and a substantial size reduction and a broadening are observed in case of *β*-CD and HP-*β*-CD complexes indicating true inclusion. Interestingly, the decomposition peak is reduced to great extent further supporting that the encapsulation of the drug has enhanced its physical stability. The absence of rifampicin melting point in DSC of M-*β*-CD complex indicates stronger interaction of drug with this cyclodextrin as compared to *β*-CD and HP-*β*-CD.

Powder X-ray diffraction (PXRD) analysis

The PXRD diffraction patterns of pure components (rifampicin, *β*-CD, M-*β*-CD and HP-*β*-CD) and inclusion complexes are shown in Fig. 3. The PXRD of rifampicin revealed its crystalline character showing major peaks at $2\theta^\circ = 9.90$, 11.08, 12.56, 15.67, 17.93, 19.85, 21.21 and 26.13. The PXRD pattern of *β*-CD revealed several diffraction peaks indicative of its crystalline nature while absence of any peak in diffraction patterns of M-*β*-CD and HP-*β*-CD comproved their amorphous state. However, a diffused pattern was obtained for all the three

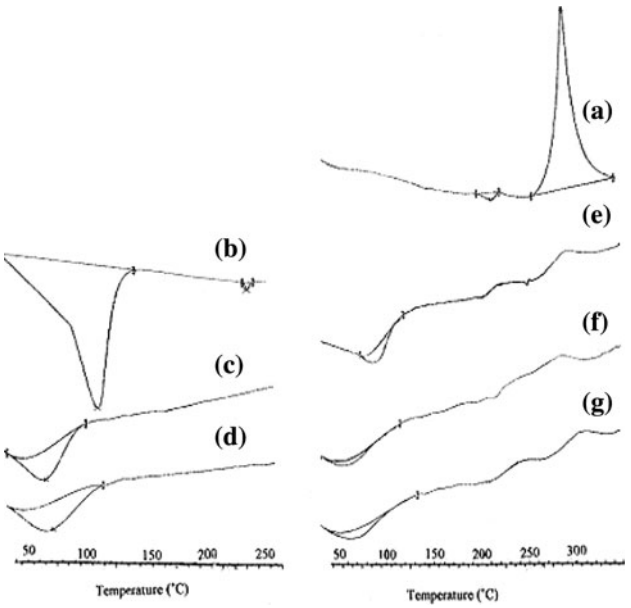

Fig. 2 DSC thermograms of rifampicin-CD solid systems **a** rifampicin, **b** β-CD, **c** M-β-CD, **d** HP-β-CD, **e** rifampicin: β-CD complex, **f** rifampicin: M-β-CD complex, **g** rifampicin: HP-β-CD complex

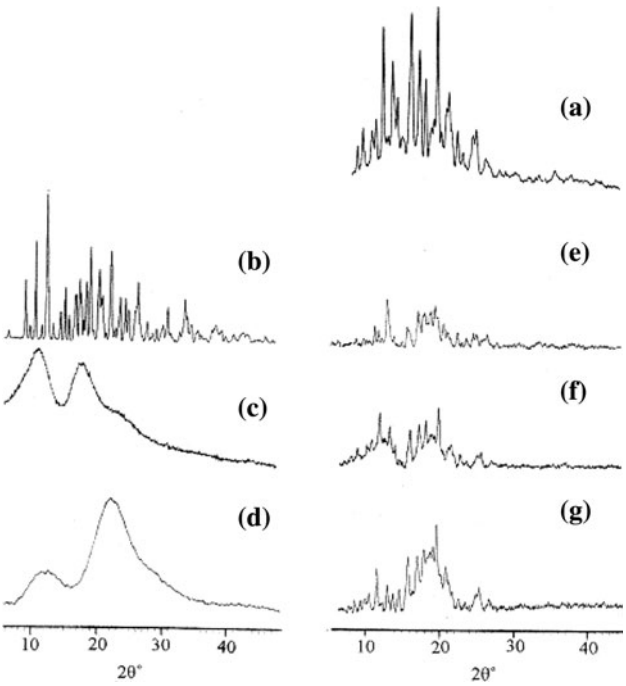

Fig. 3 XRD pattern of rifampicin-CD solid systems **a** rifampicin, **b** β-CD, **c** M-β-CD, **d** HP-β-CD, **e** rifampicin: β-CD complex, **f** rifampicin: M-β-CD complex, **g** rifampicin: HP-β-CD complex

complexes. Comparison of these diffraction patterns with those of pure components shows a reduced number of signals, with remarkably lowered intensity. This suggests a decreasing of crystallinity which can be attributed to the reciprocal interactions between host and the guest in the solid state. Besides this decrease in particle size during kneading is also responsible for the decrease in peak intensities. In particular, the peaks at $2\theta°$ value of 9.90, 11.08 and 25.48 nearly disappeared supporting inclusion of the drug.

Fourier-transform infrared (FT-IR) spectroscopic studies

Supporting evidence for the complexation of a guest molecule with cyclodextrin can be obtained by monitoring in the FTIR spectra, the changes in some guest molecule bands relative to those observed in spectra of complexes. Upon complexation, a significant shift was observed in the characteristic peaks of the guest molecule to either a higher or lower frequency. The O–H stretch of rifampicin shifts from 3422.5 to 3400.1, 3427.6 and 3398.9 cm^{-1} in β-CD, M-β-CD and HP-β-CD complexes, respectively. These shifts in the frequency of functional groups indicate the formation of hydrogen bond with hydroxyl group of cyclodextrin which results in lengthening of O–H bond. The >C=O stretch of α, β-unsaturated carboxylic acid shifts from 1714.5 to 1733.6/1712.0, 1721.2 and 1734.3/1712.2 cm^{-1} and >C=N stretch shifts from 1651.2 to 1654.0, 1652.3 and 1654.3 cm^{-1} in β-CD, M-β-CD and HP-β-CD complex, respectively (Fig. 4). These observations suggest that the side chain, 4-methyl piperazin-1-ylimino-methyl may be included in the core of β-CD while other some groups interact with the cyclodextrin by way of formation of hydrogen bonds.

Proton NMR spectroscopic studies

Proton-magnetic resonance spectroscopy plays a vital role in predicting the exact geometry of complex. Insertion of the guest molecule into the hydrophobic cavity of the host molecule results in the modification of ^{1}H-NMR frequencies. The ^{1}H-NMR spectrum of complexes showed no new peaks but some changes in the chemical shifts occurred throwing light on the interaction, position and orientation of the guest molecule (Table 1). The downfield shifts of protons b–d (Fig. 5a) indicate the penetration of piperazine ring into the cavity and variation in chemical shift of proton e is attributed to the association with oxygen on the outside of cyclodextrin cavity. The reported internal cavity diameter of β-CD (6.2 A°) and depth (7.8 A°) can easily accommodate the piperazine ring while the other portion remains outside the ring as shown in Fig. 5b. There can be every possibility that the methyl group is protruding out from the narrow side of the β-CD cavity while remaining inside the methyl and hydroxypropyl-β-CD cavity as the substitution enlarges the cyclodextrin cavity.

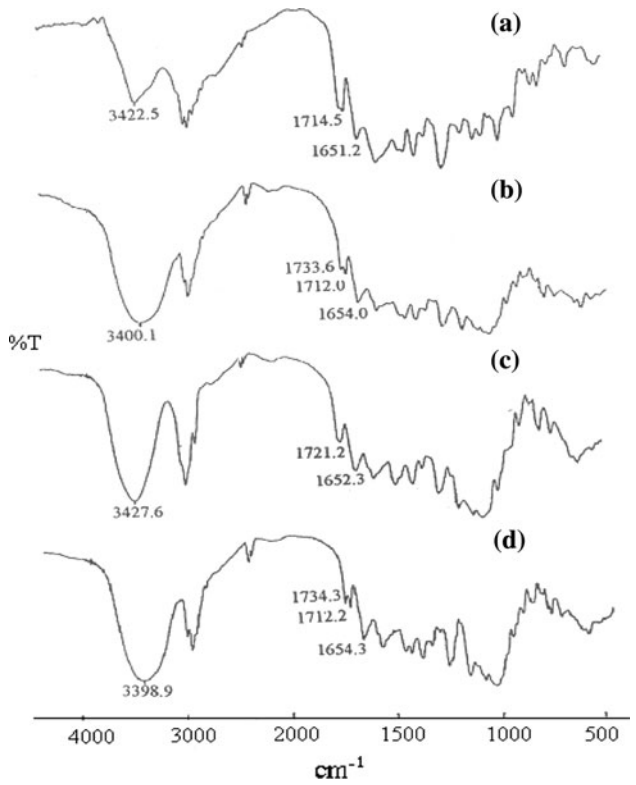

Fig. 4 FTIR spectra of rifampicin-CD solid systems **a** rifampicin, **b** rifampicin: β-CD complex, **c** rifampicin: M-β-CD complex, **d** rifampicin: HP-β-CD complex

Table 1 Variation of ^{1}H chemical shifts before and after inclusion

	a	*b*	*c*	*d*	*e*
δ (free)	2.2654	2.5023	3.0832	8.1415	2.1039
β-CD, δ (complex)	2.2634	2.5291	3.0912	8.1461	2.1610
$\Delta\delta$	−0.002	0.0268	0.0080	0.0046	0.0571
M-β-CD, δ (complex)	2.2697	2.5098	3.0981	8.1465	2.1126
$\Delta\delta$	0.0043	0.0075	0.0149	0.005	0.0087
HP-β-CD, δ (complex)	2.2674	2.5086	3.0882	8.1462	2.1121
$\Delta\delta$	0.0020	0.0063	0.0050	0.0047	0.0082

$\Delta\delta = \delta$ (complex) − δ (free)

Solution calorimetry

Solution calorimetry has been employed to confirm the stoichiometry as well as to evaluate the stability constants and thermodynamic parameters associated with the binding process. The molar enthalpy of solution of rifampicin ($\Delta H_{(M)}$) was determined in buffered aqueous solution at pH 7 and was found to be exothermic (−34.281 kJ mol^{-1}). The molar enthalpy of solution of rifampicin in presence of β-CD ($\Delta H_{(M)(\mathrm{CD})}$) was found to be more exothermic than molar enthalpy of solution of pure drug in buffer which is attributed to interaction between drug and cyclodextrin.

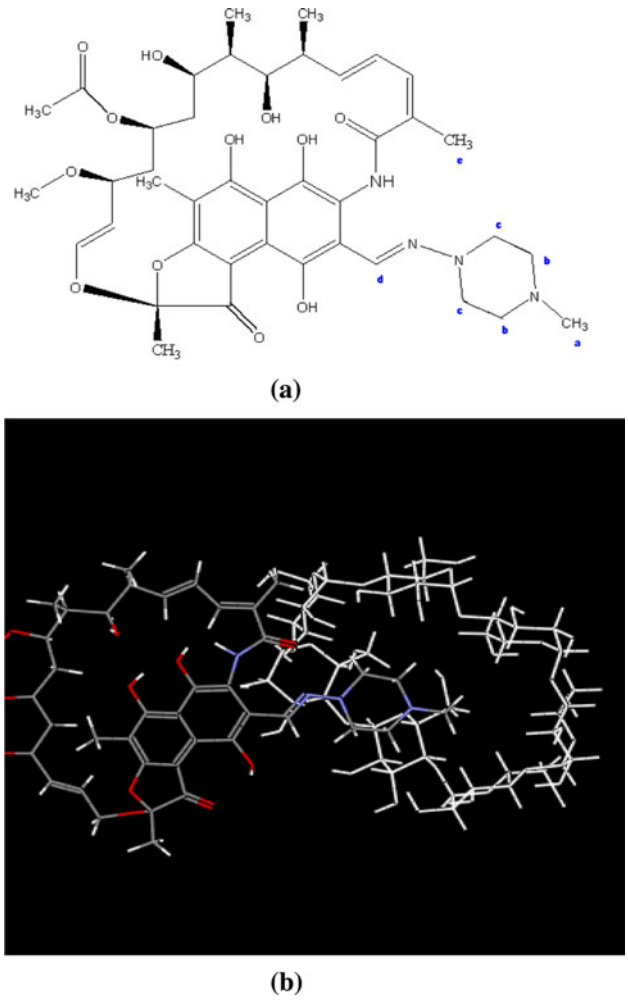

Fig. 5 **a** Chemical structure of rifampicin. **b** Molecular representation of inclusion complex of rifampicin with β-cyclodextrin

The magnitude of difference depends upon the concentration of the drug as well as cyclodextrin. Enthalpy of interaction per mole of drug and cyclodextrin ($\Delta H_{\mathrm{int}(M)}$) were calculated from Eq. 2 and are presented in Table 2. Similar results were obtained for methyl-β-CD and HP-β-CD.

$$\Delta H_{\mathrm{int}(M)} = \frac{\Delta H_{\mathrm{int(exp)}}}{a+b} = \frac{\Delta H_{(M)\cdot(\mathrm{CD})} - \Delta H_{(M)}}{1 + x_2/x_1} \quad (2)$$

a and b, initial molar concentration of drug and cyclodextrin; x_1 and x_2, apparent mole fractions of the drug and cyclodextrin ignoring the concentration of buffers.

The stoichiometry of the complex was ascertained utilizing continuous variation method (Job's plot) [27] by plotting ($\Delta H_{\mathrm{int}(M)}$) versus ($x_2$) (Fig. 6). It can be seen that the minima occurs at $x_2 = 0.5$. This indicates that complex has 1:1 stoichiometry and supports the proposed stoichiometry as predicted by the differences in chemical shifts in the NMR.

Table 2 Thermodynamic parameters of inclusion complexes of rifampicin with β-cyclodextrin at pH 7

x_2	M_{Rifa} (a) (mM)	$M_{\beta\text{-CD}}$ (b) (mM)	$\Delta H_{(\text{CD})}$ (J)	$\Delta H_{\text{int(exp)}}$ (J/L)	$\Delta H_{\text{int}(M)}$ (kJ/mol)
0.1018	0.4666	0.0529	−0.4057	−0.2323	−0.4473
0.1519	0.4131	0.0740	−0.3615	−0.2966	−0.6088
0.1986	0.3839	0.0952	−0.3381	−0.3581	−0.7474
0.2479	0.3742	0.1233	−0.3320	−0.4484	−0.9012
0.3004	0.3694	0.1586	−0.3306	−0.5596	−1.0600
0.3502	0.3597	0.1938	−0.3247	−0.6570	−1.1870
0.4026	0.3451	0.2326	−0.3145	−0.7467	−1.2927
0.4488	0.3159	0.2573	−0.2898	−0.7593	−1.3248
0.4969	0.2819	0.2784	−0.2601	−0.7396	−1.3200
0.5499	0.2624	0.3207	−0.2445	−0.7815	−1.3401
0.6015	0.2381	0.3595	−0.2238	−0.7865	−1.3160
0.6493	0.2284	0.4229	−0.2172	−0.8567	−1.3152
0.6988	0.2187	0.5075	−0.2109	−0.9379	−1.2916
0.7654	0.2138	0.6978	−0.2115	−1.1287	−1.2381
0.8005	0.2089	0.8388	−0.2098	−1.2250	−1.1692
0.8502	0.1944	1.1031	−0.1997	−1.3230	−1.0197
0.9010	0.1847	1.6811	−0.1957	−1.4945	−0.8010

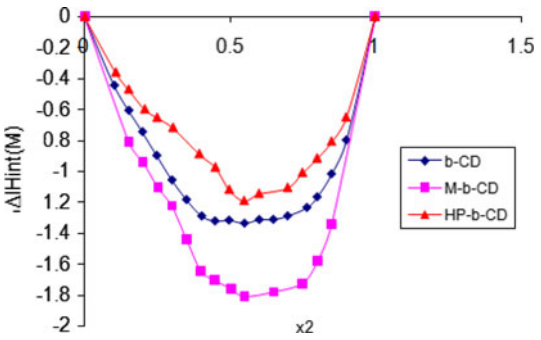

Fig. 6 Plot between $\Delta H_{\text{int}(M)}$ versus mole fraction (x_2) of β-CD, M-β-CD and HP-β-CD at pH 7

After the stoichiometry has been established the thermodynamic constants are calculated assuming the following equilibria.

$$\text{CD} + \text{drug} \leftrightarrow \text{CD} : \text{drug} \tag{3}$$

The experimentally calculated enthalpy of interaction ($\Delta H_{\text{int(exp)}}$) is proportional to the product of molar concentration of drug–cyclodextrin complex in the solution at equilibrium (c) and enthalpy of binding per mole of drug (ΔH°)

$$\Delta H_{\text{int(exp)}} = \Delta H^\circ \times c \tag{4}$$

Assuming the activities are equal to their molarities the following equation can be written for the above equilibrium (3)

$$K = (c)/(a-c)(b-c) \tag{5}$$

K is the equilibrium constant.

Rearranging Eq. 5 we obtain the quadratic Eq. 6

$$c^2 - (a+b+1/K)c + ab = 0 \tag{6}$$

The physically acceptable solution for the above quadratic equation is:

$$c = [(a+b+1/K) - \sqrt{\{(a+b+1/K)^2 - (4ab)\}}]/2 \tag{7}$$

Putting, $A = a + b + 1/K$, the concentration of complex [c] will correspond to Eq. 8

$$c = [A - \sqrt{\{(A)^2 - 4ab\}}]/2 \tag{8}$$

Putting Eq. 8 in Eq. 4,

$$\Delta H_{\text{int(exp)}} = \Delta H^\circ \times [(A - \sqrt{\{(A)^2 - 4ab\}})/2] \tag{9}$$

The binding constant K and enthalpy of binding (ΔH°) were computed from the experimentally calculated enthalpy of interaction ($\Delta H_{\text{int(exp)}}$) and are given in Table 3. The calculations were done by our computer program utilizing an iterative non-linear least square regression method to minimize the value of $\Sigma(\Delta H_{\text{int(exp)}} - \Delta H_{\text{int(calc)}})^2$.

The values of free energy of inclusion (ΔG°) and entropy of inclusion (ΔS°) were calculated from the following equations:

$$\Delta G^\circ = -RT \ln K \tag{10}$$

$$\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T \tag{11}$$

The association constant for 1:1 inclusion complexation of rifampicin with β-CD, M-β-CD and HP-β-CD has been found to be within the range of 500–5,000 M^{-1} which is considered adequate for the formation of inclusion complex

Table 3 Thermodynamic parameters of rifampicin with β-CD, M-β-CD and HP-β-CD at pH 7, determined using solution calorimetry

System	K (M^{-1})	$\Delta H°$ (kJ/mol)	$\Delta G°$ (kJ/mol)	$\Delta S°$ (J/mol.K)
Rifampicin + β-CD	1,240 ± 12	−12.30 ± 0.09	−18.36 ± 0.03	19.54 ± 0.30
Rifampicin + M-β-CD	1,564 ± 8	−14.17 ± 0.07	−18.96 ± 0.02	15.43 ± 0.22
Rifampicin + HP-β-CD	1,038 ± 11	−11.64 ± 0.12	−17.89 ± 0.03	20.19 ± 0.39

(Table 3). Very high value of equilibrium constant (>5,000 M^{-1}) may lead to very slow release of the drug from the complex while very low value (<200 M^{-1}) reduces the effect that inclusion complexation has on the bioavailability of the drug. However, the absolute value of K decreases in the order of HP-βCD < β-CD < M-β-CD. The interaction with M-β-CD is found better and sterically favored as compared to other cyclodextrins. The intermolecular hydrogen bonding between O(2)H of hydroxyl group and O(3)H of adjacent glucopyranose unit in β-CD making it less soluble and more rigid, is absent in M-β-CD. Thus, the methylation makes the environment more hydrophobic as well as allows the increased adaptability of cyclodextrin towards the guest through enhanced flexibility. The value of association constant is least in case of HP-β-CD because the hydroxyl groups make the cyclodextrin cavity partially hydrophilic leading to lesser affinity as reflected by the lower values of $-\Delta G°$ and accompanied by less negative value of $\Delta H°$. This trend in the equilibrium constant values is consistent with the hydrophobic nature of host–guest interaction.

Dissolution studies

The dissolution profiles for the systems under study are presented in Fig. 7. The dissolution rate was found to be highest for M-β-CD complex followed by that of β-CD and HP-β-CD. The probable cause for the low dissolution rate of HP-β-CD complex may be due to its wettability.

Partition coefficient

The lipophilicity values (log P) were determined at various pH for rifampicin alone and in the presence of equimolar

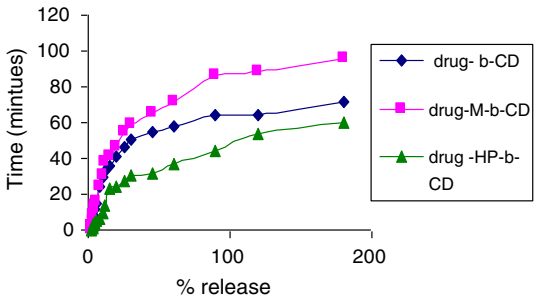

Fig. 7 Dissolution profile of rifampicin and its inclusion complexes

Table 4 Log P values of rifampicin alone and in the presence of different cyclodextrins at different pH

	pH 2	pH 5	pH 8
Rifampicin	0.804 ± 0.093	1.647 ± 0.002	0.592 ± 0.030
Rifampicin + β-CD	0.539 ± 0.008	1.444 ± 0.010	0.465 ± 0.005
Rifampicin + M-β-CD	0.532 ± 0.007	1.423 ± 0.003	0.454 ± 0.013
Rifampicin + HP-β-CD	0.578 ± 0.014	1.490 ± 0.003	0.525 ± 0.001

amounts of different cyclodextrins (Table 4). The apparent lipophilicity of rifampicin was lower in the presence of different cyclodextrins than rifampicin alone at all three pH values, confirming the capability of cyclodextrins to enhance the hydrophilicity of rifampicin via the formation of the complex. The effect is found to be maximum with M-β-CD and minimum for HP-β-CD. This is in agreement with the values of the stability constants.

Conclusion

The results obtained from DSC, PXRD and FTIR studies show some host–guest interactions between rifampicin and β-CD as well as its derivatives. Phase solubility and ^{1}H-NMR indicate a 1:1 stoichiometry. The solution calorimetry allowed us obtained exact stoichiometry, standard enthalpy changes ($\Delta H°$) and equilibrium constant (K) directly from the experimentally determined enthalpy of interaction ($\Delta H_{int(exp)}$) between drug and cyclodextrin. The magnitude of calculated thermodynamic parameters reveals that M-β-CD because of higher hydrophobicity of its cavity has better complexing properties for rifampicin than the parent β-CD and HP-β-CD. Dissolution and partition coefficient studies further confirm better solubility and hydrophilicity of rifampicin on complexation with M-β-CD.

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