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Novel inclusion complex of ibuprofen tromethamine with cyclodextrins: Physico-chemical characterization

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ABSTRACT

Guest–host interactions of ibuprofen tromethamine salt (Ibu.T) with native and modified cyclodextrins (CyDs) have been investigated using several techniques, namely phase solubility diagrams (PSDs), proton nuclear magnetic resonance (^{1}H NMR), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffractometry (XRPD), scanning-electron microscopy (SEM) and molecular mechanics (MM). From the analysis of PSD data (A_L-type) it is concluded that the anionic tromethamine salt of ibuprofen ($pK_a = 4.55$) forms 1:1 soluble complexes with all CyDs investigated in buffered water at pH 7.0, while the neutral form of Ibu forms an insoluble complex with β-CyD (B_S-type) in buffered water at pH 2.0. Ibu.T has a lower tendency to complex with β-CyD ($K_{11} = 58\,M^{-1}$ at pH 7.0) compared with the neutral Ibu ($K_{11} = 4200\,M^{-1}$) in water. Complex formation of Ibu.T with β-CyD ($\Delta G^\circ = -20.4$ kJ/mol) is enthalpy driven ($\Delta H^\circ = -22.9$ kJ/mol) and is accompanied by a small unfavorable entropy ($\Delta S^\circ = -8.4$ J/mol K) change. ^{1}H NMR studies and MM computations revealed that, on complexation, the hydrophobic central benzene ring of Ibu.T and part of the isobutyl group reside within the β-CyD cavity leaving the peripheral groups (carboxylate, tromethamine and methyl groups) located near the hydroxyl group networks at either rim of β-CyD. PSD, ^{1}H NMR, DSC, FT-IR, XRPD, SEM and MM studies confirmed the formation of Ibu.T/β-CyD inclusion complex in solution and the solid state.

1. Introduction

Ibuprofen [Ibu; (±)-2-(4-*iso*butylphenyl) propionic acid] is used as an anti-inflammatory agent that also exhibits analgesic and antipyretic activity. It is available in different dosage forms including soft capsules, suspensions, chewable tablets, and film-coated tablets. In addition, it is available as a parenteral injection under the brand name NeoProfen® (5 mg/ml Ibu as the lysinate salt) for ovation. It is practically insoluble in water and approximately 80% of an oral dose of Ibu is absorbed from the GI tract [1]. Its aqueous solubility is pH dependent; it is insoluble at low pH, but is readily soluble in basic media. In the solid state, it is highly stable when incubated at stress condition of heat, humidity and light. Less than 0.1% degradants were observed upon exposure over several months. In the solution phase, Ibu is also relatively stable upon exposure to stress conditions in 1 M NaOH, 1 M HCl and 50% H_2O_2. The decarboxylation and oxidation degradants of less than 0.1% include isobutylacetophenone and 2-(4-isobutyrylphenyl)-propionic acid [2].

Ibu exhibits a chemesthetic (irritant effect) on the oral cavity, throat, and pharynx and this makes pharmaceutical oral dosage forms containing Ibu unpleasant, and therefore less likely to meet the need for consumer compliance. Therefore, there is still a need (in pharmaceutical formulations) for ingredients capable of eliminating the unacceptable properties of Ibu and thereby contributing towards a deliverable oral form. The general approaches to overcome the aforementioned limitations include:

(a) Conversion of Ibu to alkali salts, such as those of sodium or potassium, or the use of alkylammonium salts, i.e., lysine or

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tromethamine [3–6]. However, some of its salts may exhibit limited solubility that is insufficient for achieving the target concentration, especially in oral and parenteral solutions, and do not mask its unacceptable taste. Conventional salt formation is therefore often inadequate (e.g., for stability and processing reasons).

(b) Esterification of the carboxylic acid groups [7,8].

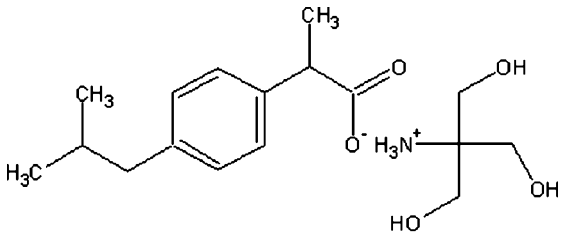
(c) Preparation of mixed anhydrides of carboxylic acid-bearing drugs [9] to produce lipophilic and non-irritating prodrug forms, provided that the parent bioactive agent can be released from the prodrug at its sites of activity.

(d) Formulation in microspheres containing cellulose acetate and polyethylene glycol [10] to control the release of Ibu, or

(e) complexation with CyD [11–13].

For example, patent WO96/14839A1 [11] describes a pharmaceutical composition of a non-steroidal anti-inflammatory drug (NSAID) included into CyD, by kneading and use of an alkali agent, that is claimed to provide rapid absorption with minimized gastrointestinal irritation. These improvements were achieved by using the alkali agent in excess (the molar ratio the alkali agent to NSAID exceeds 1:1), which is capable of forming an alkaline diffusion layer around the composition in the GI tract. Consequently, this mechanism is only limited to capsule and tablet dosage forms. Patent WO97/18245A1 [12] describes a ternary inclusion complex of naproxen, preferably its sodium salt, with a CyD and a hydroxylamine. The complex is prepared by kneading two components of the ternary system together then adding the third component and drying the formed paste; or by precipitation from a buffered solution to be followed by spray- or freeze-drying. The resultant complex may be formulated for oral, parenteral, ophthalmic, nasal, rectal or vaginal application. In order to achieve the taste masking effects of the complex in oral formulations, high levels of hydroxylamine are used. Nevertheless, the utilization of an alkali agent in the formulation may lead to a competition with the hydroxylamine towards binding with naproxen, and subsequently enhance the dissociation of the ternary complex due to the formation of naproxen sodium salt, which exhibits no significant complexation at pH 7 or higher. Patent EP1129709A2 [13] describes an improvement in Ibu solubility and its organoleptic properties by using the Ibu lysinate salt in combination with CyD. The product is formed by dry mixing using a high shear mixer, and the resulting mixture is finally mixed with pharmaceutically acceptable excipients. Following these steps a true inclusion complex may not be formed. Moreover, it is also highly likely that the product is a very fine, well-mixed physical mixture of ibuprofen lysinate and CyD and, since Ibu lysinate is highly soluble in water, no driving force exists for complex formation. As a result, it is expected that this type of formulation may not significantly affect the organoleptic properties of Ibu and its lysinate salt. Therefore, the absence of inclusion of Ibu lysinate into the CyD cavity would introduce no taste masking effect to the bitter and irritant Ibu salt tastes.

Recently, novel formulations containing Ibu, tromethamine and CyD have been developed in order to eliminate Ibu's unacceptable taste and to produce a deliverable oral form [14]. In the present study, complex formation of Ibu.T salt with natural CyDs and with a modified β-CyD, namely (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD) is reported. The complexation thermodynamic parameters were also measured in order to evaluate the driving forces for complex formation. ^{1}H NMR, DSC, FT-IR, XRPD, SEM and MM techniques have been utilized to ascertain whether inclusion complex formation takes place, and to explore possible guest–host interaction sites.



Chemical structure of ibuprofen tromethamine salt.

2. Experimental

2.1. Materials

Ibu (99.6%; Dr. Reddy's, India), tromethamine (99.8%; Acros Organics, Belgium), α-CyD (99.3%), β-CyD (101.0%) and γ-CyD (98.7%), all from Wacker Chemie, Germany, and HP-β-CyD (with a degree of substitution of 6.3, Yiming Fine Chemicals (China)) were used as received. All other chemicals were of analytical grade and obtained from Merck (Germany) or Acros Organics (Belgium).

2.2. Preparation of ibuprofen tromethamine salt

Ibu and tromethamine (4.8 mol each) were separately dissolved by heating at 50 °C (RCT Basic, IKA Labortechnik, Germany) in ethanol and water (500 ml each), respectively. Then, the tromethamine aqueous solution was added to the Ibu ethanolic solution with vigorous stirring. The precipitate was filtered and dried at 80 °C (UT 6200, Heraeus/Germany) overnight. The solid was collected and analyzed for Ibu content by using first derivative ultraviolet–visible spectrophotometry at 276 (Du-650i, Beckman, USA, speed 1200 nm/min, smoothing 15 points). It should be noted that this method was consistently used throughout this work following careful examination of absorption spectra against CyD concentration, which showed the absence of interference at this wavelength. The calibration curve, constructed by using Ibu reference standard in 0.1 M NaOH, was linear (R^2 = 0.9998) within the concentration range 0.3–2.2 mM. The measurements at five levels of concentration were found repeatable with the relative standard deviation (RSD) range 0.1–0.5%. The average molar absorptivity (ε) of the five levels of concentrations was 48.2 (RSD = 1.6%). The limit of quantitation (LOQ = 10 × standard error of intercept/slope) was 0.1 mM. The loss on drying was measured using a halogen moisture analyzer at 120 °C (HR 73, Mettler, Switzerland).

2.3. Preparation of solid ibuprofen tromethamine/β-CyD complex and physical mixture

The Ibu.T/β-CyD complex was prepared by dissolving a mixture of Ibu, tromethamine and β-CyD (equal molarity) in a sufficient, known, amount of water, and then freeze-dried (Heto PowerDry PL9000, Thermo Fisher Scientific-Inc., Waltham-MA, USA). The solid was collected and analyzed for Ibu content by using first derivative ultraviolet–visible spectrophotometry at 275 nm. The loss on drying was measured using a halogen moisture analyzer at 120 °C. Aqueous solutions of β-CyD (12 mM) and Ibu.T (20 mM) were separately freeze-dried and the resultant solids were used to prepare the physical mixture for comparison in the DSC, FT-IR, SEM, and XRPD studies. The freeze-dried solids of Ibu.T and β-CyD were physically mixed in a molar ratio of 1:1 using mortar and pestle. For solid complex characterization, wherever the terms Ibu.T and β-CyD appear anywhere in the text, they mean the freeze-dried components.

2.4. Phase solubility studies

Solubility studies were performed as described by Higuchi and Connors [15]. Excess amounts of the drug (~50 mg and ~3 g of Ibu and Ibu.T, respectively) were added to flasks containing 50 ml of aqueous solutions having different CyD concentrations. In the case of β-CyD, it was added in amounts far in excess of its optimal solubility in water (18 mM at 30 °C) ranging from 0 to about 140 mM. The samples were mechanically shaken (~200 rpm) in a thermostatic bath shaker (1086, GFL, Germany) connected to a chiller (23 DT 662-1, Heto-Holten, Denmark). Following equilibrium, an aliquot was centrifuged (when necessary) and filtered using a 0.45 μm filter (cellulose acetate or cellulose nitrate, Advantec MFS Inc., Duplin, USA). The final pH of each solution was measured by pH-meter (3030, Jenway, England). The drug assay was conducted as indicated in Section 2.2. The phase solubility diagrams (PSDs) were analyzed to obtain estimates of the complex formation constants of soluble complexes following rigorous procedures described earlier [16,17]. By assuming the formation of 1:1 (SL) and 1:2 (SL_2) soluble Ibu.T/CyD complexes, the individual complex formation constants of SL and SL_2 complexes defined as K_{11} and K_{12}, respectively, are given by the following expressions:

$$K_{11} = \frac{[SL]}{[S][L]} \tag{1}$$

$$K_{12} = \frac{[SL_2]}{[SL][L]} \tag{2}$$

The solubility (S_{eq}) of Ibu.T in aqueous CyD solutions of variable concentrations is given by the expression:

$$S_{eq} = [S] + [SL] + [SL_2] = [S] + K_{11}[S][L] + K_{11}K_{12}[S][L]^2 \tag{3}$$

where $[S]$ and $[L]$ denote the concentrations of free Ibu.T and CyD, respectively. Since the solutions are saturated with Ibu.T, $[S] = S_0$ which is the solubility of Ibu.T at zero CyD concentration, while $[SL]$ and $[SL_2]$ represent the concentrations of 1:1 and 1:2 Ibu.T/CyD complexes, respectively. Eq. (3) reduces to:

$$S_{eq} = S_0 + [SL] + [SL_2] = S_0 + K_{11}S_0[L] + K_{11}K_{12}S_0[L]^2 \tag{4}$$

The value of $[L]$ was estimated from the total concentration of CyD in solution (L_{eq}) and can be expressed as

$$L_{eq} = [L] + [SL] + 2[SL_2] = (1 + K_{11}S_0)[L] + 2K_{11}K_{12}S_0[L]^2 \tag{5}$$

and thus:

$$L = \frac{-b + \sqrt{b^2 - 4ac}}{2a} \tag{6}$$

where

$$a = 2K_{11}K_{12}S_0, \quad b = 1 + K_{11}S_0 \quad \text{and} \quad c = -L_{eq}$$

Non-linear regression of experimental data corresponding to each PSD was conducted to obtain the best estimates of S_0, K_{11}, and K_{12} by minimizing the sum of squares of errors (SSE) given by

$$\text{SSE} = \sum (S_{eq}^P - S_{eq})^2 \tag{7}$$

where S_{eq}^P is the predicted equilibrium solubility of Ibu.T.

2.5. Estimation of thermodynamic parameters

Gibbs and van't Hoff equations were used to estimate the thermodynamic parameters ΔH°, ΔS° and ΔG° according to [17]:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{8}$$

$$\ln(Y) = \frac{\Delta S^\circ}{R} - \frac{\Delta H^\circ}{RT} \tag{9}$$

A plot of $\ln(Y)$ versus $1/T$ produces:

$$\text{slope} = -\frac{\Delta H^\circ}{R} \quad \text{and} \quad \text{intercept} = \frac{\Delta S^\circ}{R}$$

Y represents either K_{11}^x or S_0^x, and x denotes the mole fraction standard state (the values of K_{11} and S_0, which were initially obtained in molar concentration units, were converted to the dimensionless mole fraction units K_{11}^x and S_0^x).

2.6. ^1H nuclear magnetic resonance spectroscopy (^1H NMR)

Solutions of Ibu.T, β-CyD and the Ibu.T/β-CyD complex (~15 mM each) were prepared in 99.98% D_2O and filtered before use. ^1H NMR spectra were obtained at 500 MHz and 25 °C (GSX500, JEOL, Japan). Chemical shifts are quoted relative to sodium 3-trimethylsilyl [D_4] propionate at 0.0 ppm but spectra were calibrated via the known position of the residual HOD resonance, both of which were obtained as external references in D_2O.

2.7. Differential scanning calorimetry (DSC)

The thermal behaviors of freeze-dried Ibu.T, β-CyD, a physical mixture of Ibu.T and β-CyD, and Ibu.T/β-CyD complex were examined using differential scanning calorimetry (910S, TA instrument, USA). An accurately weighed sample of each solid, equivalent to 5 mg Ibu.T, was heated in a sealed aluminum pan, using an empty pan sealed as reference, over the temperature range from 30 to 300 °C, at a rate of 10 °C/min. An indium standard was used for temperature calibration.

2.8. Fourier transform infrared spectroscopy (FT-IR)

Thin pellets containing 1 mg of each sample dispersed in 100 mg of KBr were used for FT-IR measurements. The spectra were recorded at room temperature as an average of 30 scans using FT-IR spectrophotometer (Paragon 1000, PerkinElmer, England) in the 600–4000 cm^{-1} range with a spectral resolution of 1 cm^{-1}. In order to minimize the effects of traces of CO_2 and water vapour from the atmosphere of the sample compartment, the spectrometer was purged with N_2.

2.9. X-ray powder diffractometry (XRPD)

The XRPD patterns were measured with an X-ray diffractometer (Philips PW 1729, Japan). Radiation generated from a Co Kα source and filtered through Ni filters with a wavelength of 1.79025 Å at 40 mA and 35 kV was used. The instrument operated over the 2θ range 5–55°.

2.10. Scanning-electron microscopy (SEM)

The morphology of the samples was determined using scanning-electron microscopy (Quanta 600, FEI, Holland) operated at an accelerating voltage of 25 kV. The sample (0.5 mg) was mounted onto a 5 mm × 5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 40 s at a beam current of 38–42 mA/dm^3 with a 100 Å layer of gold/palladium alloy.

2.11. Molecular mechanics (MM)

MM computations were conducted using the Hyperchem® molecular modeling software (release 6.03, Hypercube Inc., Waterloo, Canada) and employing an Amber force field. The initial molecular geometry of β-CyD was obtained using X-ray diffraction data [18], while Ibu.T structure was built up with standard bond lengths and bond angles. Partial atomic charges for both β-CyD

and Ibu.T were computed using the semi-empirical AM1 method. Each single molecule was then optimized using the Amber force field. Energy minimization was performed using the Polak–Ribiere conjugate gradient algorithm using 0.01 kcal $Å^{-1}$ mol^{-1} as the convergence criterion. A dielectric constant of 78 was used in the current calculations to simulate solvent effects. The binding energy ($E_{binding}$) of each minimized complex was calculated by using the expression:

$$E_{binding} = E_{complex} - (E_{\beta\text{-CyD}} + E_{Ibu.T}) \quad (10)$$

Interaction energies were computed for the Ibu.T approaching from its carboxylate side through the narrow and wide rims of the β-CyD cavity to access the most probable optimal configurations for the 1:1 complex formed.

3. Results and discussion

3.1. Interaction of ibuprofen tromethamine with CyD in solution

3.1.1. Phase solubility diagrams (PSDs)

The phase solubility diagrams (PSDs) of neutral Ibu and Ibu.T salt with CyD in buffered water at pHs 2.0 and pH 7.0 at 30 °C are shown in Fig. 1a and b, respectively. Neutral Ibu (pK_a = 4.55 [2]) showed a B_S type PSD with β-CyD in water indicating insoluble complex formation. However, anionic Ibu.T formed soluble complexes (A_L type PSDs) with all CyDs in water (pH = 7.0). The complex stoichiometry and complex formation constants which were estimated through rigorous non-linear regression [16,17] are listed in Table 1. The results indicate that neutral Ibu with inherent solubility measured in the absence of β-CyD in water (S_0 = 0.059 mM) exhibits higher affinity for β-CyD (K_{11} = 4200 M^{-1} at pH 2.0) than anionic Ibu.T species (S_0 = 50 mM, K_{11} = 58 M^{-1} at pH 7.0), which indicates a significant contribution of the hydrophobic effect towards complex stability. The K_{11} values for Ibu.T/CyD systems are 15, 54, 58, and 60 M^{-1} for α-CyD, γ-CyD, β-CyD, and HP-β-CyD, respectively (Table 1). The low K_{11} values for α-CyD is most likely due to its relatively small cavity size, which reduces the probability of sequestering the bulky groups of Ibu.T [19].

It is interesting to note that the solubility of β-CyD increases beyond its solubility limit (18 mM in water at 30 °C) in the presence of Ibu.T (Fig. 1b) leading to the formation of a highly soluble complex. The same phenomenon was previously observed in studies of the interaction of the acidic drug nimesulide with β-CyD in the presence of L-lysine [20]. This paved the way for the utilization of multicomponent complexation techniques in pharmaceutical formulation, which allows a significant reduction in the amounts of CyDs required for achieving target formulations [21–23]. Since the K_{11} values presented in Table 1 clearly show that, to within experimental error, β-CyD, γ-CyD and HP-β-CyD exert the same level of solubilization onto Ibu.T (see also Fig. 1b), β-CyD was selected for further investigation.

3.1.2. Stoichiometry of ibuprofen tromethamine/β-CyD complex

Non-linear regression of experimental data corresponding to each phase diagram in Fig. 1 indicates that anionic Ibu.T forms 1:1 soluble complexes. In contrast, neutral Ibu forms an insoluble

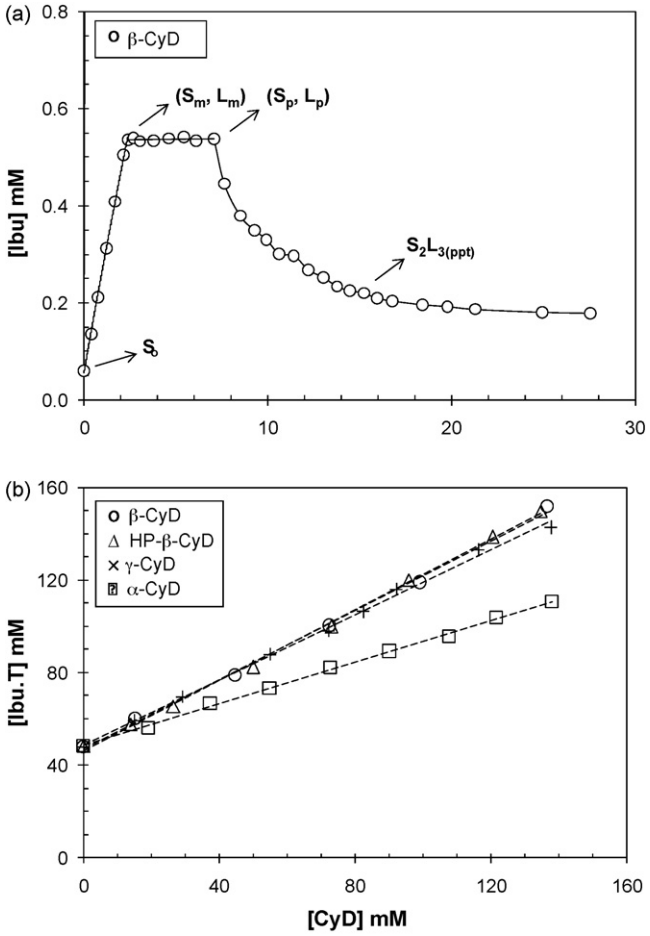


Fig. 1. Phase solubility diagrams of (a) neutral Ibu/β-CyD in buffered water (pH = 2.0) and (b) anionic Ibu.T/CyD in buffered water (pH = 7.0) at 30 °C.

complex with β-CyD in buffered water at pH = 2.0 as indicated by the B_S-type PSD shown in Fig. 1a. The stoichiometry of the complex, which precipitated from solution, may be calculated from the plateau region of the PSD in Fig. 1a as follows [24,25]. The amount of β-CyD (L_c) included in the precipitated complex is equal to that entering during the plateau region. The corresponding amount of Ibu (S_c) in the complex is equal to that which appears as free undissolved Ibu at the point (S_m, L_m).

Therefore,

$$S_c = S_i - S_m = 4.8\,mM - 0.5\,mM = 4.3\,mM \quad (11)$$

$$L_c = L_p - L_m = 7.1\,mM - 2.4\,mM = 4.7\,mM \quad (12)$$

where S_i is the excess amount of Ibu added to construct the PSD (50 mg per 50 ml solution, which is equivalent to 4.8 mM). From Eqs. (11) and (12), the ratio of S_c to L_c represents the stoichiometry

Table 1
Estimates of the complex formation constants (K_{11}) for the Ibu/β-CyD and Ibu.T/CyD systems obtained in aqueous solution at 30 °C. S_0 is the solubility in the absence of CyD. Numbers in parentheses denote absolute errors estimated for a 95% confidence level.

System	CyD	PSD type	K_{11} (M^{-1})	K_{12} (M^{-1})	S_0 (mM)
Ibu/β-CyD in buffered water (pH = 2.0)	β-CyD	B_S	4200 (300)	82 (10)	0.059 (0.01)
Ibu.T/CyD in buffered water (pH = 7.0)	α-CyD	A_L	15 (1)	–	50 (1)
	γ-CyD	A_L	54 (5)	–	50 (1)
	β-CyD	A_L	58 (8)	–	50 (2)
	HP-β-CyD	A_L	60 (8)	–	50 (2)

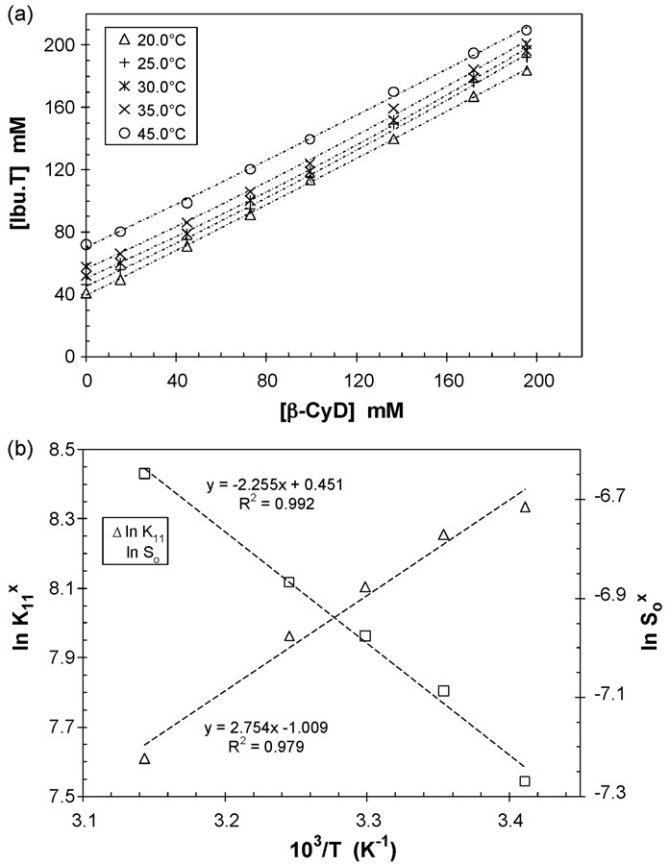


Fig. 2. (a) Phase solubility diagrams of Ibu.T/β-CyD systems in buffered water (pH = 7.0) at different temperatures and (b) van't Hoff plots of $\ln K_{11}^{x}$ and $\ln S_0^{x}$ against $1/T$ (x denotes the mole fraction standard state).

of the Ibu/β-CyD complex precipitated, i.e.

$$\text{The molar ratio of } S_c \text{ to } L_c = \frac{S_c}{L_c} = \frac{4.3}{4.7} = 0.9 \quad (13)$$

This value indicates that the precipitate of the complex has the formula S_1L_1, This finding is in agreement with what was reported earlier [26], where the neutral Ibu forms a 1:1 Ibu/β-CyD complex based on Job plots (the continuous variation method). However, the results of the chemical analysis of the complex precipitated at high concentration of β-CyD in the descending region of Fig. 1a (at the point labeled as ($S_2L_{3(ppt)}$) indicated the complex system had a stoichiometric ratio of 2:3 (Ibu:β-CyD), which may reflect contributions from more than one type of complex precipitating at high concentration of β-CyD [27]. The crystalline complex with a stoichiometric ratio of 1:2 (Ibu:β-CyD) was successfully isolated by recrystallization in water after 2 weeks [28]. This stoichiometric ratio was obtained by the elemental analysis and conformed by single crystal X-ray diffraction. From the above results, it can be concluded that neutral Ibu forms inclusion complexes with different stoichiometric ratio, which depends on the experimental conditions (i.e., method of preparation).

3.1.3. Thermodynamics

The PSDs of Ibu.T/β-CyD obtained in water (pH 7.0) at different temperatures are shown in Fig. 2a. The corresponding complex formation constants (K_{11}) and the solubility of Ibu.T in the absence of β-CyD (S_0) are listed in Table 2. van't Hoff plots of $\ln K_{11}^{x}$ and $\ln S_0^{x}$ against $1/T$ are shown in Fig. 2b, while the thermodynamic parameters (ΔH°, ΔS° and ΔG°) are listed in Table 2.

The results suggest that Ibu.T/β-CyD complex formation ($\Delta G^\circ = -20.4$ kJ/mol) is largely driven by enthalpy ($\Delta H^\circ = -22.9$ kJ/mol), which is attributed to van der Waals interactions, H-bonding between the guest and host, or due to loss of water on complexation. The corresponding negative entropy change ($\Delta S^\circ = -8.4$ J/mol K) is attributed to a reduction in the translational and rotational degrees of freedom of the guest molecule rather than to solvent disordering [25]. In contrast, Ibu.T solubility ($\Delta G^\circ = 17.6$ kJ/mol) is largely impeded by enthalpy ($\Delta H^\circ = 18.8$ kJ/mol), but slightly. The positive enthalpy indicates that energy is needed to split a molecule away from its pure phase and break the structure of water in the bulk to form a vacant space or "cavity" for the incoming molecule, while the solubility is only slightly favored by entropy changes ($\Delta S^\circ = 3.7$ J/mol K) leading to a more random structure [29].

3.1.4. ^{1}H nuclear magnetic resonance (^{1}H NMR)

The ^{1}H NMR spectra of the aliphatic β-CyD protons and aromatic Ibu.T protons measured in D_2O before and after complexation are shown in Fig. 3, while their corresponding proton assignments are listed in Table 3. The results show upfield chemical shift displacements ($\Delta\delta$) upon complexation for all β-CyD protons suggesting that a hydrophobic interaction is dominant between Ibu.T and β-CyD. The most significant upfield shifts were observed for the inner cavity protons H_5 (−0.2193 ppm) and H_3 (−0.1092 ppm), and also for H_6 (−0.0787 ppm) proton extending from the primary (narrow) rim of the β-CyD cavity. This clearly indicates inclusion of the hydrophobic benzene ring of Ibu.T where the cavity protons (H_3, H_5) are affected by anisotropic shielding due to the aromatic ring [30], while the primary H_6 protons are shielded by the carboxylate anion located in between. On the other hand, the relatively low upfield shifts (−0.0061 to −0.0300 ppm) exhibited by protons at the outer surface of the β-CyD torus (H_1, H_2 and H_4) indicate lower interactions with the guest molecule. For Ibu.T, both aromatic (d and e) protons exhibit significant upfield displacements with the aromatic (d) proton showing the largest upfield shift (−0.1621 ppm). This suggests deep inclusion of the benzene ring to interact with the inner β-CyD cavity protons (H_3 and H_5). The neighboring aliphatic protons (b and c) exhibit less significant upfield displacements, which is likely due to their being located near the cavity rim. On the other hand, protons a, f and g undergo significant downfield displacements (+0.0341, +0.0270 and +0.0134 ppm, respectively) on complexation, thus indicating that the methyl groups (a and g) and the methine proton (f) are located close to the hydroxyl group networks situated at both rims of the β-CyD cavity. The tromethamine protons (h) are slightly upfield shifted on complexation (+0.0081 ppm)

Table 2
Estimates of complex formation constants (K_{11}) of the Ibu.T/β-CyD system obtained in buffered water at pH 7.0 and different temperatures, and the thermodynamic parameters corresponding to inherent Ibu.T solubility (S_0 obtained in the absence of β-CyD) and complex formation constants (K_{11}) obtained from van't Hoff plots. Numbers in parentheses denote absolute errors estimated for a 95% confidence level.

T (°C)	S_0 (mM)		K_{11} (M^{-1})
20.0	38.6 (0.8)		75.1 (4.1)
25.0	46.3 (1.7)		69.3 (8.3)
30.0	51.5 (1.7)		59.6 (6.9)
35.0	57.7 (1.8)		51.8 (6.0)
45.0	71.9 (1.2)		36.3 (2.7)
	ΔG° (kJ/mol)	ΔH° (kJ/mol)	ΔS° (J/mol K)
Ibu.T/β-CyD complex	−20.4 (6.1)	−22.9 (6.1)	−8.4
Solubility of Ibu.T (S_0)	17.6 (3.1)	18.8 (3.1)	3.7

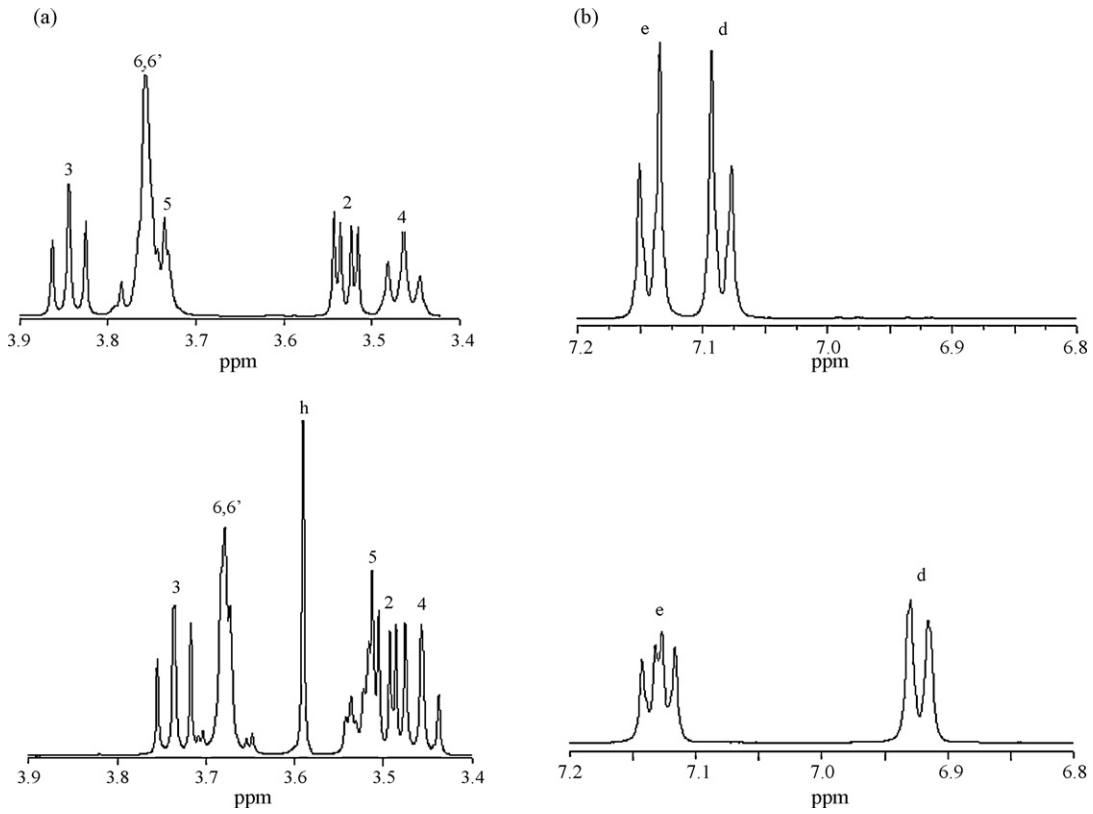
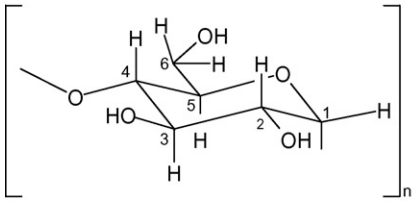


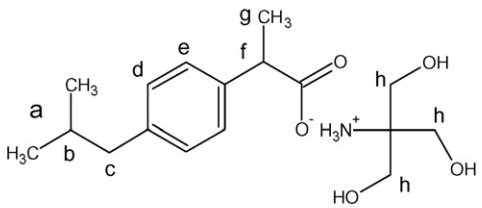
Fig. 3. ^{1}H NMR spectra of the Ibu.T/β-CyD system in D_2O at 25 °C (a) for protons of β-CyD and (b) for aromatic protons of Ibu.T before (upper traces) and after (lower traces) complexation.

suggesting that the counter cation is positioned outside but opposite to one of the β-CyD cavity rims. This is in agreement with the data reported earlier for terfenadine/citric acid/β-CyD, ketoconazole/tartaric acid/β-CyD, econazole/malic acid/α-CyD ternary systems [31–33], where the counter anion is located outside of the CyD cavity. However the downfield shift of (h) proton might indicate slight interaction of tromethamine with the hydrophilic, exterior edges of β-CyD.

Table 3
^{1}H NMR chemical shifts (in ppm) of β-CyD and Ibu.T protons in the absence (δ_{free}) and presence of β-CyD ($\delta_{complex}$) obtained in D_2O at 25 °C. n_H denotes the number of protons while $\Delta\delta$ is the corresponding chemical shift displacement ($\delta_{complex} - \delta_{free}$).



β-CyD (n=7)



Ibu.T

Assignment	n_H	Multiplicity	δ_{free}	$\delta_{Complex}$	$\Delta\delta$
β-CyD protons					
H_1	7	Doublet	4.9496	4.9231	−0.0265
H_2	7	2 doublets	3.5291	3.4991	−0.0300
H_3	7	Triplet	3.8445	3.7353	−0.1092
H_4	7	Triplet	3.4632	3.4571	−0.0061
H_5	7	Triplet	3.7356	3.5163	−0.2193
$H'_{6,6}$	14	Multiplet	3.7578	3.6791	−0.0787
Ibu.T protons					
a	6	Doublet	0.7496	0.7837	+0.0341
b	1	Multiplet	1.7123	1.7063	−0.0060
c	2	Doublet	2.3528	2.3452	−0.0080
d	2	Doublet	7.0848	6.9227	−0.1621
e	2	Doublet	7.1427	7.1297	−0.0133
f	1	Quartet	3.4855	3.5125	+0.0270
g	3	Doublet	1.2620	1.2754	+0.0134
h	6	Singlet	3.5824	3.5905	+0.0081

3.2. Characterization of ibuprofen tromethamine/β-CyD solid complex

3.2.1. Differential scanning calorimetry (DSC)

Fig. 4a–d presents the thermal behavior of Ibu.T, β-CyD, the corresponding 1:1 physical mixture and inclusion complex. Ibu.T has an endothermic peak at about 175 °C, which is retained in the 1:1 Ibu.T:β-CyD physical mixture, but is absent in the thermogram of the 1:1 Ibu.T/β-CyD complex thus indicating that Ibu.T is included into the β-CyD cavity.

3.2.2. Fourier transform infrared spectroscopy (FT-IR)

Fig. 5a–d depicts segments of the FT-IR spectra (1700–1300 cm^{-1}) of Ibu.T, β-CyD, the corresponding 1:1 physical mixture and the inclusion complex, respectively, where variations in some IR absorption bands are more clearly indicative of inclusion complex formation. For example, the $-CO_2^-$ asymmetric stretching vibration, which occurs at 1559 cm^{-1} in both Ibu.T (Fig. 5a) and the physical mixture (Fig. 5c) is shifted to 1562 cm^{-1} in the complex. In addition, the band depicting anti-symmetric deformation of the two isobutyl CH_3 groups at 1449 cm^{-1}, which occurs sharp for Ibu.T and as a shoulder in the physical mixture, shifts to morph into that of the iso-propionate CH_3 group anti-symmetric deformation, a sharp peak occurring at 1460 cm^{-1} in the complex. In other words, the iso-propionate CH_3 group anti-symmetric deformation band, which occurs only as a shoulder at 1460 cm^{-1} in both Ibu.T and the physical mixture, morphs with that of the two isobutyl CH_3 groups into a sharp peak at the same frequency (1460 cm^{-1}) in the complex. Moreover, the band depicting deformation of the ammonium group ($-NH_3^+$) in tromethamine, which occurs at 1632 cm^{-1} in Ibu.T, and the intense H_2O symmetric bending band corresponding to β-CyD water of hydration at 1654 cm^{-1} in β-CyD, merge into a band at 1643 cm^{-1} in the physical mixture; this band (1643 cm^{-1}) appears as intense as that of the $-CO_2^-$ asymmetric stretching vibration located at 1559 cm^{-1}, in the physical mixture. However, on complexation, the band corresponding to deformation of the ammonium group ($-NH_3^+$) which occurs at 1632 cm^{-1} in Ibu.T is significantly shifted to 1636 cm^{-1} on complexation, while the intense H_2O symmetric bending band corresponding to β-CyD water of hydration at 1654 cm^{-1} in β-CyD disappears altogether.

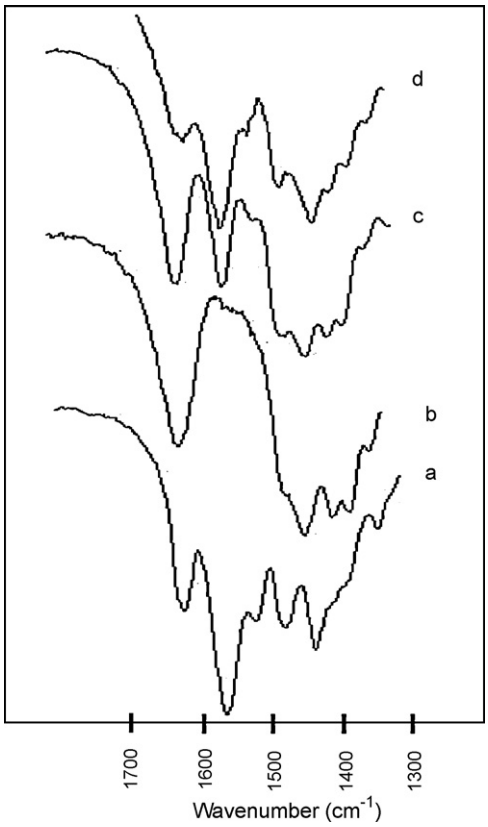


Fig. 5. FT-IR spectra of (a) Ibu.T, (b) β-CyD, (c) a physical mixture of Ibu.T and β-CyD, and (d) the Ibu.T/β-CyD complex.

Those significant shifts of the IR vibrational bands corresponding to the anti-symmetric stretching of $-CO_2^-$, the symmetric deformation of CH_3 groups, and deformation of the $-NH_3^+$ group of Ibu.T to higher frequencies, on complexation with β-CyD, is indicative of restrictions on their vibrational motion imposed by interactions with β-CyD. This when coupled with the disappearance of

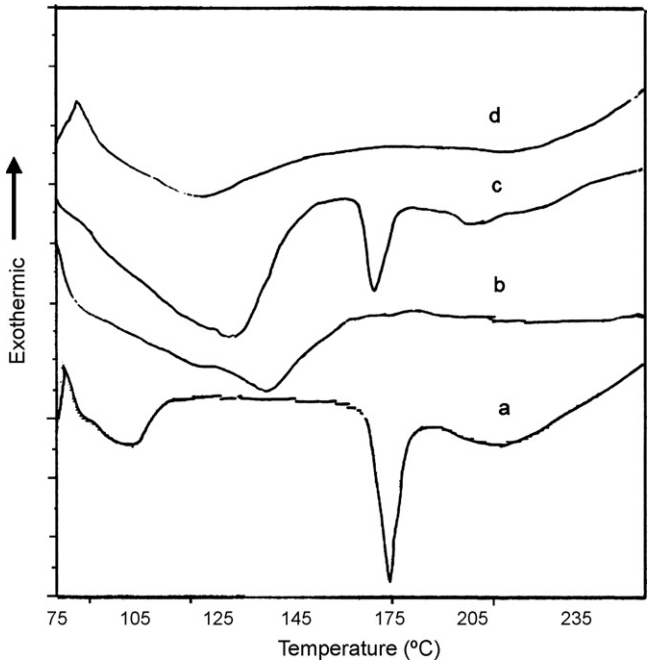


Fig. 4. DSC thermograms of (a) Ibu.T, (b) β-CyD, (c) a physical mixture of Ibu.T and β-CyD, and (d) the Ibu.T/β-CyD complex.

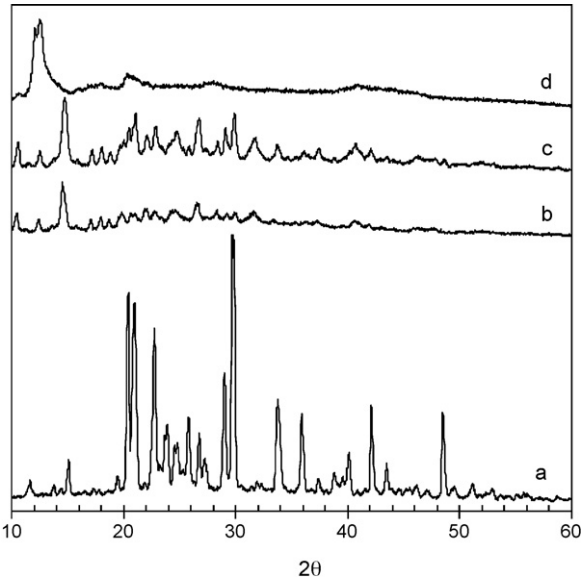


Fig. 6. XRPD patterns of (a) Ibu.T, (b) β-CyD, (c) a physical mixture of Ibu.T and β-CyD, and (d) the Ibu.T/β-CyD complex.

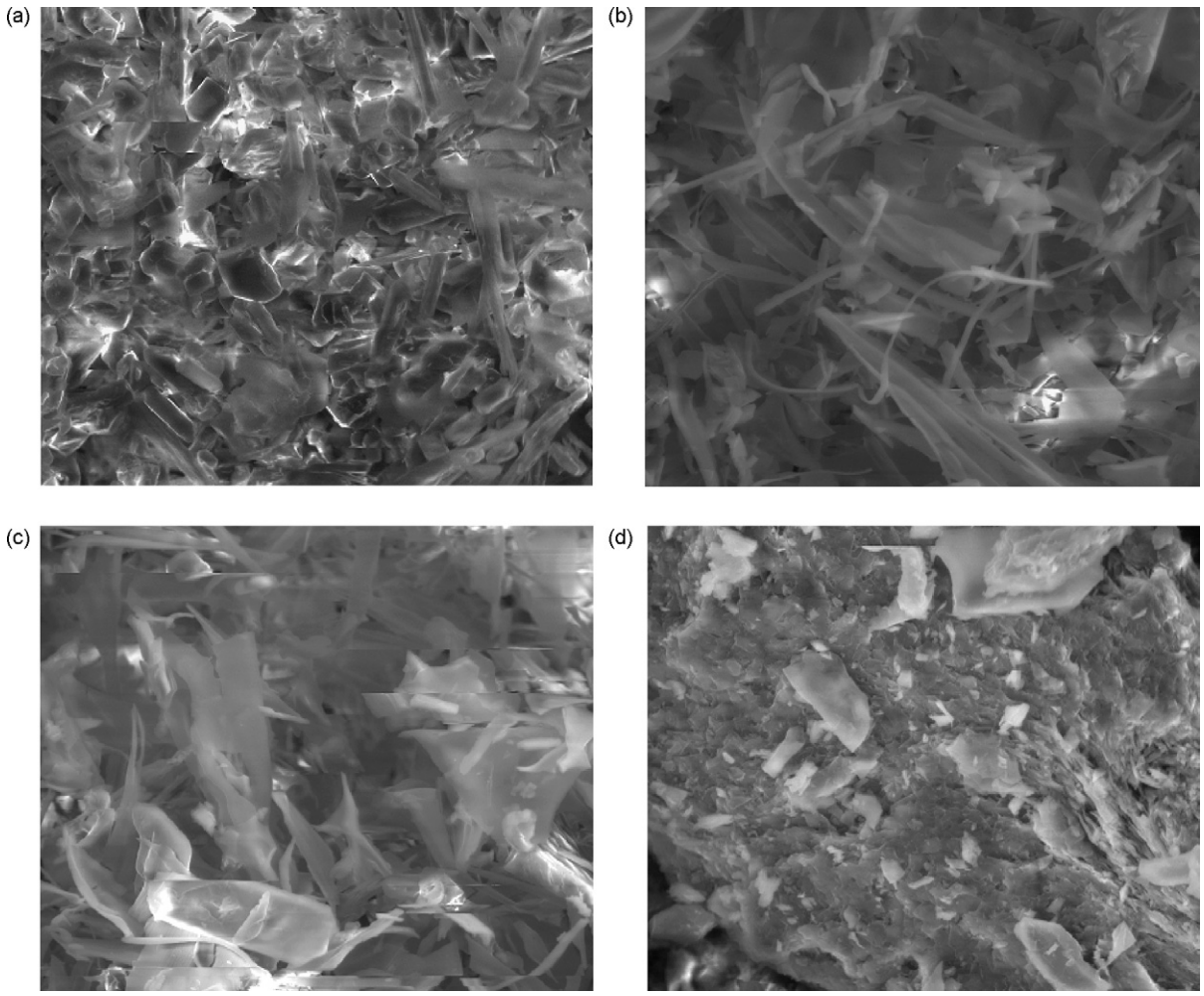


Fig. 7. SEM images of (a) Ibu.T, (b) β-CyD, (c) a physical mixture of 1:1 Ibu.T and β-CYD, and (d) 1:1 Ibu.T/β-CyD complex.

the band at 1654 cm^{-1} corresponding to water of hydration of β-CyD clearly suggests a displacement of cavity water with Ibu.T, and hence inclusion complex formation. This FT-IR evidence of solid state Ibu.T/β-CyD inclusion complex formation confirms the same conclusion arrived at from the ^1H NMR spectral measurements in aqueous solution (D_2O) discussed in Section 3.1.4 above.

It should be pointed out that within the resolution of the FT-IR instrument (1 cm^{-1}) used, it was not possible to obtain further information from the IR bands corresponding to –N–H, –O–H, C–H and C–C stretching vibrations, nor was it possible to obtain useful information from those corresponding to $–CH_2$, –C–H, and C–C bending vibrations, which is apparently due to their complete

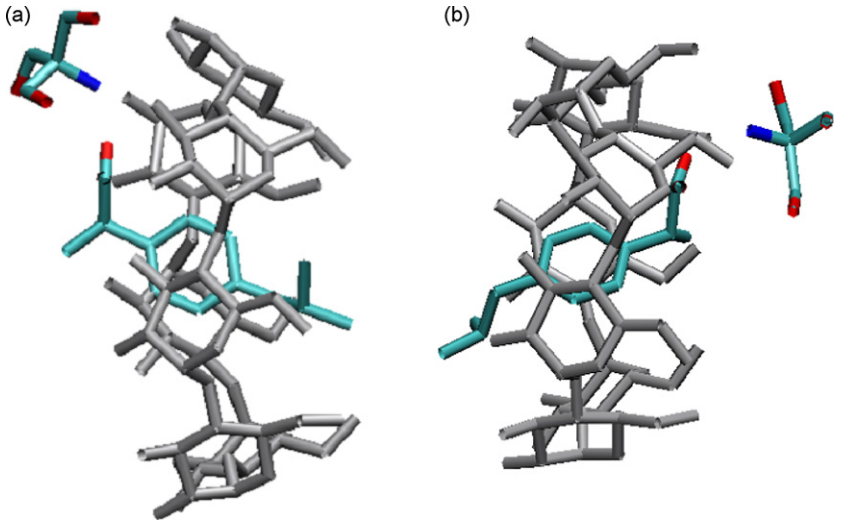


Fig. 8. Side views of the most probable 1:1 Ibu.T/β-CyD inclusion complex configurations where the carboxylate group is oriented to (a) the wide and (b) the narrow rims of β-CyD.

overlap with the overwhelmingly dominant vibrational bands of β-CyD, which appeared highly broadened in both the Ibu.T/β-CyD complex and the corresponding physical mixture.

3.2.3. X-ray powder diffraction (XRPD)

Fig. 6a–d presents the XRPD patterns of Ibu.T, β-CyD, the corresponding 1:1 physical mixture and inclusion complex, respectively. It is clear that the XRPD pattern of the physical mixture of Ibu.T and β-CyD is almost a superposition of the patterns contributed by Ibu.T and β-CyD. The dominance of the principal peaks of β-CyD in the physical mixture is a result of its high percentage in the mixture (78%, w/w). In contrast, the diffraction pattern of Ibu.T/β-CyD complex showed the complete disappearance of the principal diffraction peaks apparent in the XRPD patterns of Ibu.T and β-CyD, which suggests the formation of a real inclusion complex consisting of a new solid phase (e.g., amorphous structure). It should also be noted that in the present study, the two components (Ibu.T and β-CyD) were freeze-dried prior to preparation of their physical mixture. Therefore, the Ibu.T/β-CyD complex isolated by freeze-drying of the co-precipitated product is an inclusion complex and not just a dispersed mixture of the two amorphous components [17,26,34–36]. On screening what was previously published in the literature [37–42], it was observed that guest and host components used to prepare complexes were not similarly treated, for example, by freeze-drying, co-precipitation, kneading, microwaving, or fluid-bed coating prior to measurements. As a result, changes in component responses measured by the analytical techniques (DSC, PXRD, SEM, etc.) may not necessarily be indicative of inclusion complex formation unless, of course, each component was similarly treated for reference.

3.2.4. Scanning-electron microscope (SEM)

Fig. 7a–d presents the SEM images of Ibu.T, b-CyD, the corresponding 1:1 physical mixture and inclusion complex, respectively. In the physical mixture, the morphologies of individual compounds are maintained with the dominant particles being those of β-CyD. In contrast, it was not possible to recognize individual component particles in the SEM image of the Ibu.T/β-CyD complex thus indicating effective interaction between Ibu.T with β-CyD. Therefore, SEM results, along with those of DSC, FT-IR and XRPD, confirm the presence of inclusion complex in the solid state.

3.3. Molecular mechanics (MM)

Fig. 8a and b depicts side views of the two optimized 1:1 Ibu.T with β-CyD inclusion complex configurations obtained from MM computations in a medium with a dielectric constant of 78. The computed binding energies ($E_{binding}$, Eq. (10)) suggest that the most stable complex structure is that of Fig. 8a with a binding energy (−48.0 kcal/mol) that is significantly lower than that of Fig. 8b (−43.4 kcal/mol). Fig. 8a clearly shows that the benzene ring of Ibu.T is deeply included into the β-CyD cavity, while each of the isobutyl and iso-propionate groups is oriented close to one of the two hydroxyl group networks located at either rim of the β-CyD cavity. This explains the ^{1}H NMR downfield chemical shift displacements exhibited by the methyl protons of the isobutyl and iso-propionate groups on complexation. Moreover, it explains the highly significant upfield chemical shift displacements exhibited by benzene proton (d) and inner β-CyD cavity protons H_1 and H_3 due to their mutual hydrophobic interaction on inclusion of Ibu.T into the β-CyD cavity.

4. Conclusion

The results of this study on Ibu.T/β-CyD complexation under different conditions reveal the following. Ibu.T salt forms aqueous soluble 1:1 type complexes with each of the CyDs investigated in this work. In contrast, neutral Ibu forms an insoluble complex with β-CyD complex (B_S-type). The inherent ionization of Ibu.T, at pH 7, lowers the affinity of the more soluble anionic Ibu toward complex formation with CyDs as compared to the much less soluble neutral Ibu, which forms a more stable complex. However, the neutral Ibu/β-CyD complex has very low solubility in water. To within experimental error, β-CyD, γ-CyD and HP-β-CyD exert the same level of solubilization onto Ibu.T. Moreover, the solubility of β-CyD in water increase tremendously in the presence of Ibu.T to form a highly water soluble Ibu.T/β-CyD complex. Ibu.T/β-CyD complex formation is largely favored by enthalpic contribution but slightly retarded by a relatively small entropic change. All data obtained from the PSDs, ^{1}H NMR, DSC, FT-IR, XRPD and SEM studies confirm Ibu.T/β-CyD inclusion complex formation in solution and in the solid state.

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