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# ЭНТАЛЬПИЙНЫЕ ХАРАКТЕРИСТИКИ СОЛЬВАТАЦИИ ГИДРОКСИПРОПИЛ-β-ЦИКЛОДЕКСТРИНА И ЕГО МОЛЕКУЛЯРНОГО КОМПЛЕКСООБРАЗОВАНИЯ С РУТИНОМ И КВЕРЦЕТИНОМ В ВОДНО-ЭТАНОЛЬНЫХ РАСТВОРИТЕЛЯХ

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***Энтальпии растворения гидроксипропил-β-циклодекстрина (HPβCD) в воде и в водно-этанольных смешанных растворителях были определены методом изотермической калориметрии растворения. При переходе от воды к водно-этанольным растворителям экзотермичность растворения гидроксипропил-β-циклодекстрина уменьшается: $\Delta_{sol}H°_{(HP\beta CD)}$ = -53,91; -41,14; -17,84; -22,07; -26,13; -28,28 кДж/моль при X(EtOH) = 0; 0,05; 0,1; 0,2; 0,6; 0,9 мол. д. соответственно. С использованием литературных данных и результатов, полученных в данной работе, проведен анализ сольватационных вкладов реагентов в изменение энтальпии реакций молекулярного комплексообразования между HPβCD рутином и кверцетином в водно-этанольных растворителях состава 0,0-0,1 мол.д. этанола. Установлено, что эндотермичность энтальпии переноса циклодекстринов превышает изменения энтальпии переноса реакций в водно-этанольном растворителе изученного состава. Аналогичная тенденция наблюдается для молекулярных комплексов аминокислот с 18-краун-6 (18C6): во всех ранее изученных системах эндотермичность переноса 18C6 превышает экзотермичность энтальпий реакции максимум в два раза во всем диапазоне составов водно-этанольного растворителя. Для комплексообразования HPβCD с RUT и QCT эндотермичность энтальпий переноса HPβCD превышает изменения энтальпии переноса реакций образования молекулярных комплексов [RUT⊂HPβCD] и [QCT⊂HPβCD] примерно в 10 раз. Анализ изменений энтальпии сольватации и реакций образования молекулярных комплексов между аминокислотами и 18C6 показал, что увеличение концентрации неводного сорастворителя преимущественно влияет на энтальпии реакции за счет увеличения положительных значений энтальпии переноса 18C6. Можно предположить, что в случае комплексообразования HPβCD с RUT и QCT энтальпийный вклад HPβCD будет определять изменение энтальпии комплексообразования [QCT⊂HPβCD] и [RUT⊂HPβCD] во всем диапазоне составов водно-этанольных растворителей.***

**Ключевые слова:** гидроксипропил-β-циклодекстрин, сольватация, термодинамика сольватации и комплексообразования, водно-этанольные растворители, полифенолы

## ENTHALPIC CHARACTERISTICS OF SOLVATION OF HYDROXYPROPYL-β-CYCLODEXTRIN AND ITS MOLECULAR COMPLEXATION WITH RUTIN AND QUERCETIN IN WATER-ETHANOL SOLVENTS

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***The enthalpies of dissolution of hydroxypropyl-β-cyclodextrin (HPβCD) in water and in water-ethanol mixed solvents were determined by isothermal solution calorimetry. When transitioning from water to water-ethanol solvents, the exothermicity of hydroxypropyl-β-cyclodextrin dissolution decreases: $\Delta_{sol}H°_{(HP\beta CD)}$ = -53.91; -41.14; -17.84; -22.07; -26.13; -28.28 kJ/mol in X(EtOH) = 0; 0.05; 0.1; 0.2; 0.6; 0.9 mol. fr. respectively. Using literature data and the results obtained in this work, an analysis of the solvation contributions of the reactants to the change in enthalpy of molecular complexation reactions between HPβCD and rutin (RUT) and quercetin (QCT) was conducted in water-ethanol solvents with composition of EtOH 0.0÷0.1 mol. fraction. The endothermicity of the transfer enthalpy of cyclodextrins exceeds the changes in the transfer enthalpy of the reactions. A similar trend is observed for amino acid with 18-crown-6 (18C6) molecular complexes: in all previously studied systems, the endothermic transfer of 18C6 was at most twice the exothermicity of reaction enthalpies. For the investigated HPβCD complex formation with RUT ([RUT⊂HPβCD]) and QCT ([QCT⊂HPβCD]), the maximum disparity between absolute solvation enthalpy values of the HPβCD and reaction enthalpies exceeds 10-fold. Analysis of solvation enthalpy changes and molecular complex formation reactions between amino acids and 18C6 in prior studies revealed that increasing non-aqueous cosolvent concentration predominantly affects reaction enthalpies by rising positive transfer enthalpy values of 18C6. It can be assumed that in the case of HPβCD complexation with RUT and QCT, the enthalpy contribution of HPβCD will determine the change in the enthalpy of [QCT⊂HPβCD] and [RUT⊂HPβCD] complexations in all range of aqueous-ethanol solvents compositions.***

**Keywords:** hydroxypropyl-β-cyclodextrin, solvation, thermodynamics of solvation and complexation, aqueous-ethanol solvents, polyphenols

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## INTRODUCTION

The development of encapsulation and vector delivery methods for hydrophobic drug substances is one of the current challenges in pharmaceuticals. To enhance the solubility of hydrophobic biomolecules in biological media, cyclodextrins are traditionally used [1-5]. The mechanism of increasing the solubility of hydrophobic biomolecules involves the formation of molecular complexes with cyclodextrins through the inclusion of the biomolecule or their hydrophobic moiety into the cyclodextrin cavity. The enhancement of hydrophobic biomolecules' solubility through hydrophobic binding by cyclodextrins also leads to increase bioavailability and stability of the biomolecules, enables controlled drug release rates, and reduces the irritant effects of drugs on mucous membranes [6-13]. Despite being effective solubilizers of hydrophobic molecules, cyclodextrins themselves exhibit relatively low water solubility [14, 15]. Their solubility can be enhanced through chemical modifications, such as substituting hydroxyl groups with methyl, hydroxypropyl, sulfobutyl ether, or glucosyl moieties [7, 16, 17]. One of the most promising derivatives for practical applications is hydroxypropyl-β-cyclodextrin (Fig. 1).

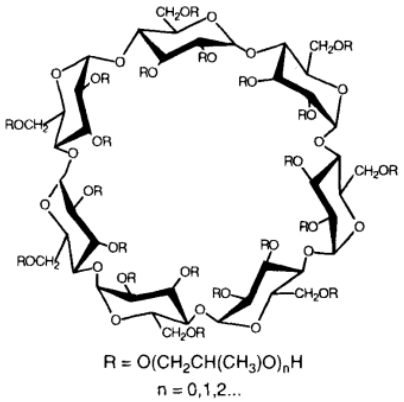


Fig. 1. Structural formula of cyclodextrins with seven D-glucopyranose units linked by α-1,4 glycosidic bonds: β-cyclodextrin (R = H) and hydroxypropyl-β-cyclodextrin (R = $CH_2CHOHCH_3$) [5]
Рис. 1. Структурная формула циклодекстринов, состоящих из семи единиц D-глюкопиранозы, соединенных α-1,4-гликозидными связями: β-циклодекстрин (R = H) и гидроксипропил-β-циклодекстрин (R = $CH_2CHOHCH_3$) [5]

The use of water-miscible cosolvents such as ethanol or dimethyl sulfoxide in pharmaceutical synthesis can provide an additional solubilizing effect during complexation of hydrophobic molecules with cyclodextrins. However, the solubility of cyclodextrins themselves decreases when transitioning from pure water to water-ethanol or water-DMSO solvent systems [16-18].

It is known that the solvent can affect the equilibrium, rate, and mechanism of complexation reactions [19-21]. Therefore, to effectively conduct molecular complexations involving cyclodextrins and biomolecules and predict their reactivity in solutions, it is essential to understand the thermodynamic parameters of their solvation state [22].

In our previous studies, we investigated the effects of aqueous-organic solvents on the thermodynamic parameters of molecular complex formation reactions between β-cyclodextrins and rutin (RUT) or quercetin (QCT) - hydrophobic polyphenols of natural origin with large pharmacological properties [23-25] (Fig. 2). It was found that the addition of small amounts of ethanol or dimethyl sulfoxide to water decreases the stability of these molecular complexes and reduces the exothermicity of the formation reactions.

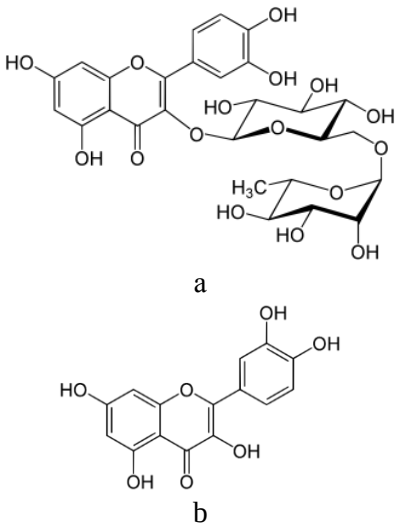


Fig. 2. Structural formulas of rutin (a) and quercetin (b)
Рис. 2. Структурные формулы рутина (a) и кверцетина (b)

From the solvation approach perspective, an analysis of solvation contributions of the reagents to the changes in stability and complexation enthalpy was also performed. However, this analysis remained incomplete due to the lack of data on changes in solvation enthalpy characteristics of the reagents in aqueous-organic solvents.

In this context, in the present work the dissolution enthalpies of hydroxypropyl-β-cyclodextrin in water and in water-ethanol mixed solvents were determined by isothermal solution calorimetry. Using literature data on the Gibbs energy change for HPβCD transfer from water to water-ethanol solvents [23], the entropic characteristics of HPβCD solvation were calculated. The obtained results were compared with literature data for related systems. The obtained solvation enthalpy characteristics of HPβCD were then used to analyze the solvation contributions of reagents to the enthalpy changes in "host-guest" molecular complexation reactions of HPβCD with rutin as well as with quercetin in water-ethanol solvents.

## MATERIALS AND METHODS

Hydroxypropyl-β-cyclodextrin (97.0% by weight) from «ACROS ORGANICS» was used without additional purification. Rectified ethyl alcohol was purified by distillation at atmospheric pressure before use. The residual amount of water in ethanol (no more than 5% by weight) was taken into account when preparing water-ethanol solvents. Mixed water-ethanol solvents were prepared using bidistilled water by the gravimetric method. Determination of the heat effects of dissolution of 2-hydroxypropyl-β-cyclodextrin in water and in water-ethanol solvents of composition 0.05, 0.1, 0.2, 0.6 and 0.9 mole fractions of ethanol (mol. fr.) was carried out at $T$ = 298.15 K on an ampule solution calorimetric with an isothermal shell. The design of the calorimetric cell is similar to those described previously [26]. The chemical calibration of the calorimeter was made by the enthalpy of dissolution of crystalline potassium chloride in water. The value obtained was $\Delta_{sol}H^0$(KCl, $\infty H_2O$, 298.15 K) = = 17.22 ± 0.04 kJ·mol$^{-1}$ and it is satisfactorily coincides with the most reliable literary value 17.243 ± ± 0.018 kJ·mol$^{-1}$ [27].

Based on calorimetric data, the enthalpies of dissolution of 2-hydroxypropyl-β-cyclodextrin in water and in water-ethanol solvents were calculated.

During the experiment hydroxypropyl-β-cyclodextrin was introduced into a calorimetric cell containing solvent by breaking a sealed glass ampoule containing the test substance. The sample mass was weighed with an accuracy of ±0.0001 g.

## RESULTS AND DISCUSSION

Concentration conditions for calorimetric experiments, molar and standard dissolution enthalpies of hydroxypropyl-β-cyclodextrin in water and water-ethanol solvents are presented in the Table. The absence of concentration dependence in molar dissolution enthalpies and experimental conditions approaching infinite dilution allowed us to consider the average $\Delta_{sol}H^m$ values in each solvent as standard enthalpies ($\Delta_{sol}H^0$).

***Table***

**Concentration conditions for calorimetric experiments, molar and standard dissolution enthalpies of hydroxypropyl-β-cyclodextrin in water and water-ethanol solvents at T = 298,15 K**

***Таблица.* Концентрационные условия для калориметрических экспериментов, молярные и стандартные энтальпии растворения гидроксипропил-β-циклодекстрина в воде и водно-этанольных растворителях при T = 298.15 K**

| $\chi_{(EtOH)}$, mol. fr. | $m_{HP\beta CD}$, g | $C_{HP\beta CD}\cdot10^{-4}$, mol/L | $\Delta_{sol}H^m_{(HP\beta CD)}$, kJ/mol | $\Delta_{sol}H^0_{(HP\beta CD)}$, kJ/mol |
|---|---|---|---|---|
| 0.00 | 0.0138 | 1.34 | -52.10 | -53.91 ± 2.40 |
| | 0.0122 | 1.21 | -53.30 | |
| | 0.0262 | 2.60 | -54.77 | |
| | 0.0554 | 5.49 | -55.47 | |
| 0.05 | 0.0360 | 3.63 | -40.23 | -41.14 ± 3.0 |
| | 0.0179 | 1.92 | -40.69 | |
| | 0.0153 | 1.45 | -42.51 | |
| 0.10 | 0.0293 | 3.26 | -15.97 | -17.84 ± 4.07 |
| | 0.0313 | 3.49 | -19.02 | |
| | 0.0297 | 3.31 | -18.54 | |
| 0.20 | 0.0173 | 2.03 | 20.90 | -22.07 ±3.04 |
| | 0.0330 | 4.04 | 22.96 | |
| | 0.0279 | 3.41 | 24.29 | |
| | 0.0201 | 2.01 | 20.11 | |
| 0.6 | 0.0180 | 1.83 | 23.55 | -26.13 ± 6.67 |
| | 0.0181 | 1.73 | 25.92 | |
| | 0.0180 | 1.72 | 28.91 | |
| 0.9 | 0.0211 | 2.20 | 25.99 | -28.28 ± 5.32 |
| | 0.0165 | 1.72 | 30.23 | |
| | 0.0208 | 2.17 | 28.62 | |

The exothermicity of hydroxypropyl-β-cyclodextrin dissolution decreases with EtOH additions. In proton-donor media, hydrogen bonding between the oxygen atoms of cyclodextrin and solvent hydrogen atoms contributes to stabilization of the macrocycle's solvation shell. Thus, it can be inferred that the weakened solvation of HPβCD upon transition from water to water-ethanol solvents results from reduced proton-donating capacity of the solvent system with increasing concentration of EtOH.

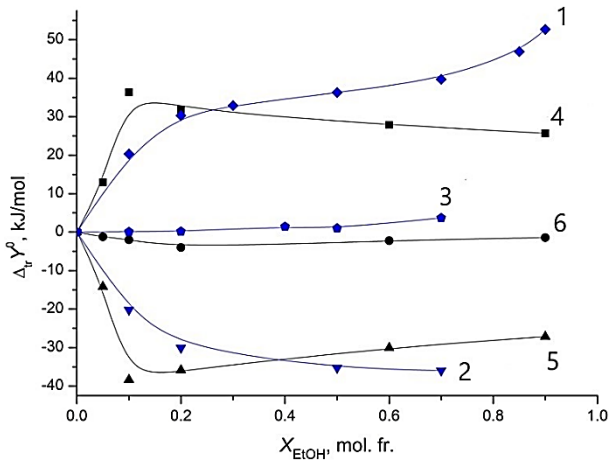


Fig. 3. Thermodynamic transfer functions of HPβCD: $\Delta_{tr}H^0$ – (4); {-T$\Delta_{tr}S^0$} – (5); $\Delta_{tr}G^0$ – (6) and 18C6 [31]: $\Delta_{tr}H^0$ – (1); {-T$\Delta_{tr}S^0$} – (2); $\Delta_{tr}G^0$ – (3) in $H_2O$ – EtOH solvents

Рис. 3. Термодинамические функции переноса HPβCD: $\Delta_{tr}H^0$ – (4); {-T$\Delta_{tr}S^0$} – (5); $\Delta_{tr}G^0$ – (6) и 18C6 [31]: $\Delta_{tr}H^0$ – (1); {-T$\Delta_{tr}S^0$} – (2); $\Delta_{tr}G^0$ – (3) в системе $H_2O$ – EtOH

The quantitative influence of a solvent composition on the thermodynamic parameters of "host-guest" complexation and reagent solvation can be described within the solvation approach by the following equations [28]:

$$\Delta_{tr}Y_r = \Delta_rY_{(solvent)} - \Delta_rY_{(water)} \quad (1)$$

$$\Delta_{tr}Y(Z) = \Delta Y(Z)_{(solvent)} - \Delta Y(Z)_{(water)} \quad (2)$$

$$\Delta_{tr}Y_r = \Delta_{tr}Y_{([complex])} - \Delta_{tr}Y_{(«host»)} - \Delta_{tr}Y_{(«guest»)} \quad (3)$$

where $\Delta_{tr}Y_r$ – change in thermodynamic parameters ($\Delta_{tr}H$, $\Delta_{tr}G$, $T\Delta_{tr}S$) of the reaction ($\Delta_{tr}Y_r$), reagents solvation and complex particle ($\Delta_{tr}Y(Z)$) upon transfer from water to aqueous-organic or non-aqueous solvents; $\Delta Y(Z)$ – solvation thermodynamic parameters ($\Delta H$, $\Delta G$, $T\Delta S$) for "guest", "host", and "host-guest" complex molecules.

Using experimental data (Table 1) and Equation (1), we calculated the transfer enthalpies of HPβCD from water to water-ethanol solvents ($\Delta_{tr}H^0$). Combining obtained transfer enthalpies with previously reported Gibbs energies of HPβCD resolvation in water-ethanol systems ($\Delta_{tr}G^0$) [29], we derived the entropic terms of resolvation ($T\Delta_{tr}S^0$) from the equation:

$$\Delta_{tr}G^0 = \Delta_{tr}H^0 - T\Delta_{tr}S^0 \quad (4)$$

Changes in thermodynamic functions of HPβCD resolvation in water-ethanol solvents are presented in Fig. 3. The Gibbs energy changes for HPβCD transfer from water to water-ethanol solvents are close to zero, resulting from enthalpy-entropy compensation effect.

Previous work [30] investigated the solvation state of crown ether 18-crown-6 in water and water-ethanol mixed solvents of varying composition. Unlike HPβCD, 18C6 possesses a cyclic structure with a hydrophilic cavity. In water, the exothermicity of 18C6 dissolution (-21.8 ± 0.2 kJ/mol [30]) is lower than that of HPβCD. Despite these differences, the influence of ethanol additions on solvation characteristics is identical for both macrocycles (Fig. 3).

The solvation enthalpy characteristics of HPβCD were used to analyze its solvation contributions to enthalpy changes in "host-guest" molecular complex formation reactions of HPβCD with rutin and with quercetin in water-ethanol solvents. The data reported in [23] shows that RUT and QCT complexations with HPβCD in water-ethanol systems are enthalpy-driven processes. The full analysis of enthalpy reagent contributions to the reactions enthalpy of [RUT⊂HPβCD] and [QCT⊂HPβCD] complexations are limited due to lacking solvation enthalpy data for quercetin and rutin. The combination of solvation characteristics applied for this analysis is presented as:

$$\Delta_{tr}Y_r = \{\Delta_{tr}Y_{([complex])} - \Delta_{tr}Y_{(«host»)}\} - \Delta_{tr}Y_{(«guest»)} \quad (5)$$

The enthalpy characteristics for both the molecular complex formations [RUT⊂HPβCD] and [QCT⊂HPβCD] as well as the reagents solvation in $H_2O$-EtOH solvents are presented in Fig. 4 and 5.

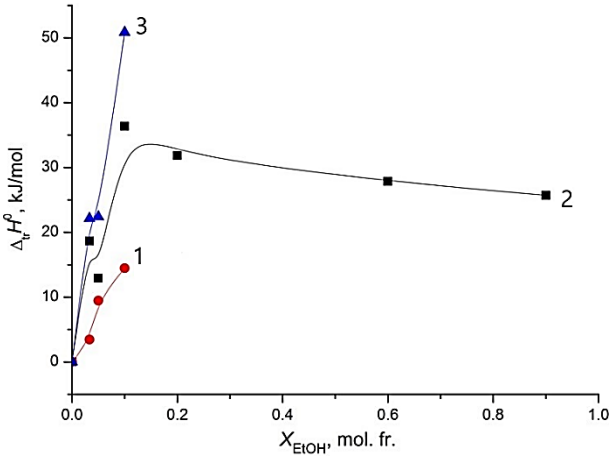


Fig. 4. Influence of water-ethanol solvent composition on enthalpy changes for [RUT⊂HPβCD] complex formation (1) and reagents solvation: $\Delta_{tr}H^0_{HP\beta CD}$ – (2) and {$\Delta_{tr}H^0_{[RUT\subset HP\beta CD]}$ - $\Delta_{tr}H^0_{RUT}$} – (3) at transfer from $H_2O$ to $H_2O$-EtOH mixed solvents

Рис. 4. Влияние состава водно-этанольного растворителя на изменения энтальпии реакции образования комплекса [RUT⊂HPβCD] (1) и сольватации реагентов: $\Delta_{tr}H^0_{HP\beta CD}$ – (2) и {$\Delta_{tr}H^0_{[RUT\subset HP\beta CD]}$ - $\Delta_{tr}H^0_{RUT}$} – (3) при переносе из $H_2O$ в смешанные растворители $H_2O$-EtOH

Our experimental results show that the endothermicity of HPβCD transfer enthalpies exceeds the enthalpy changes of the complexation reactions. A similar trend is observed for amino acid-18C6 molecular complexes, though in all previously studied systems, the endothermic transfer of 18C6 was at most

twice the exothermicity of reaction enthalpies [20]. For the investigated HPβCD complexes with RUT and QCT, the maximum disparity between absolute solvation enthalpy values of the host molecule and reaction enthalpies exceeds 10-fold, particularly in hydroxypropyl-β-cyclodextrin-quercetin complexation.

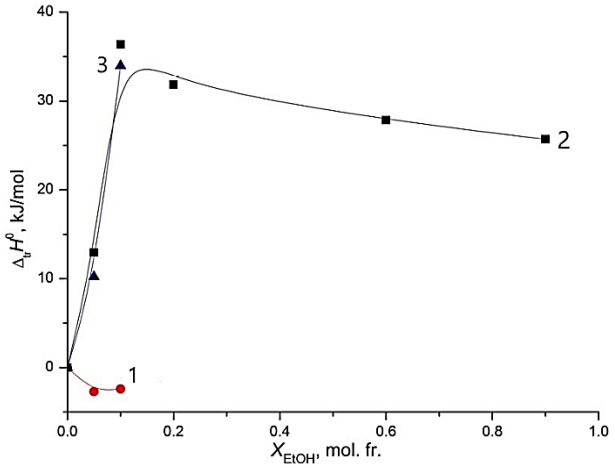


Fig. 5. Influence of water-ethanol solvent composition on enthalpy changes for [QCT⊂HPβCD] complex formation (1) and reagents solvation: $\Delta_{tr}H^0_{HP\beta CD}$ – (2) and $\{\Delta_{tr}H^0_{[QCT\subset HP\beta CD]} - \Delta_{tr}H^0_{QCT}\}$ – (3) at transfer from $H_2O$ to $H_2O$-EtOH mixed solvents

Рис. 5. Влияние состава водно-этанольного растворителя на изменения энтальпии реакции образования комплекса [QCT⊂HPβCD] (1) и сольватации реагентов: $\Delta_{tr}H^0_{HP\beta CD}$ – (2) и $\{\Delta_{tr}H^0_{[QCT\subset HP\beta CD]} - \Delta_{tr}H^0_{QCT}\}$ – (3) при переносе из $H_2O$ в смешанные растворители $H_2O$ -EtOH

Analysis of solvation enthalpy changes and molecular complex formation reactions between amino acids and 18C6 in prior studies [32-35] revealed that increasing non-aqueous cosolvent concentration predominantly affects reaction enthalpies through rising positive transfer enthalpy values of 18C6. It can be assumed that in the case of HPβCD complexation with RUT and QCT, the enthalpy contribution of HPβCD will determine the change in the enthalpy of [QCT⊂HPβCD] and [RUT⊂HPβCD] complexations in all range of aqueous-ethanol solvents compositions.

## CONCLUSION

Experimental determination of thermodynamic parameters for cyclodextrin-polyphenol intermolecular complexation is constrained by low aqueous solubility of polyphenols, and limited cyclodextrin solubility in non-aqueous media. Consequently, the thermodynamic characteristics obtained within narrow water-ethanol solvent composition ranges namely $\Delta_{sol}H^0$(HPβCD) = = -53.91; -41.14; -17.84; -22.07; -26.13; -28.28 kJ/mol in X(EtOH) = 0; 0.05; 0.1; 0.2; 0.6; 0.9 mol. fr. respectively hold significant scientific and practical value.

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## CONFLICTS OF INTERESTA

*The authors declare the absence a conflict of interest warranting disclosure in this article.*

*Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.*

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