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ВЛИЯНИЕ РАСТВОРИТЕЛЕЙ H_2O-EtOH И H_2O-DMSO НА СОЛЬВАТАЦИЮ γ-ЦИКЛОДЕКСТРИНА

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Циклодекстрины представляют собой циклические молекулы, состоящие из звеньев D-глюкопиранозы, соединенных α-1,4-гликозидными связями. Циклодекстрины уже используются в составе препаратов для повышения растворимости фармакологически активных веществ и все более востребованы в технологиях разработки новых гибридных материалов для различных промышленных процессов. Особенностью строения молекул циклодекстринов является наличие гидрофобной полости, которая способна включать гидрофобные молекулы с образованием молекулярных комплексов как в растворе, так и в твердой фазе. Термодинамические параметры сольватации циклодекстринов необходимы для научного подбора растворителя и прогнозирования реакционной способности циклодекстринов с целью проведения процессов с наибольшей эффективностью. В связи с этим, в данной работе были определены коэффициенты распределения γ-циклодекстрина методом распределения вещества между двумя несмешивающимися фазами: водно-диметилсульфоксидным растворителем переменного состава и н-гексаном, и водно-этанольным растворителем переменного состава и н-гексаном. Полученные значения коэффициентов распределения были использованы для расчета изменений энергии Гиббса переноса γ-циклодекстрина из воды в водные растворы этанола и диметилсульфоксида. Коэффициенты распределения γ-циклодекстрина в смешанных растворителях выше, чем в воде. Изменение энергии Гиббса при переносе γ-циклодекстрина из воды в ее смеси с диметилсульфоксидом и с этанолом свидетельствует об ослаблении сольватации макроцикла. Проведен сравнительный анализ влияния растворителей вода-этанол и вода-диметилсульфоксид с переменным содержанием воды на изменения в сольватном состоянии β-циклодекстрина, гидроксипропил-β-циклодекстрина и γ-циклодекстрина. Сделано предположение, что изменения в сольватном состоянии циклодекстринов оказывают ключевое влияние на устойчивость молекулярных комплексов циклодекстринов с флавоноидами рутином и кверцетином в водно-этанольных средах.

Ключевые слова: водно-органические растворители, комплексы включения, коэффициенты распределения, энергия Гиббса переноса, устойчивость молекулярных комплексов, флавоноиды

EFFECT OF THE H_2O-EtOH AND H_2O-DMSO SOLVENTS ON THE γ-CYCLODEXTRIN SOLVATION

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Cyclodextrins are cyclic molecules that consist of D-glucopyranose units connected by α-1,4 glycoside bonds. Cyclodextrins are already used in the composition of drugs to increase the solubility of active substances and are ever more in demand in technologies for the development of new hybrid materials for various industrial processes. A structural feature of cyclodextrins is the presence of a hydrophobic cavity capable of including hydrophobic molecules with the formation of molecular complexes both in solution and in the solid phase. Thermodynamic parameters of cyclodextrin solvation are necessary for the scientific selection of the solvent and prediction of the reactivity of cyclodextrins for carrying out processes with the greatest efficiency. In this regard, in this work, distribution coefficients of γ-cyclodextrin were determined by the method of distribution of the substance between two immiscible phases with a water-dimethyl sulfoxide (water-ethanol) solvent of variable composition and n-hexane and the changes in the Gibbs energy of re-solvation were calculated. The distribution coefficient of γ-CD in mixed solvents is higher than in water. The change in the Gibbs energy during the transfer of γ-CD from water to its mixture with dimethyl sulfoxide and ethanol indicates a weakening of the macrocycle solvation. A comparative analysis of the effect of H_2O-EtOH and H_2O-DMSO solvents on changes in the solvated state of β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and γ-cyclodextrin was carried out. It was assumed that the changes in the solvated state of cyclodextrins have a major effect on the stability of molecular complexes of cyclodextrins with flavonoids rutin and quercetin in aqueous-ethanol media.

Key words: aqueous-organic solvents, inclusion complexes, distribution coefficient, Gibbs transfer energy, molecular complexes stability, flavonoids

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INTRODUCTION

Cyclodextrins (CD) are cyclic molecules consisting of D-glucopyranose units connected by α-1,4 glycoside bonds. Cyclodextrins containing 6, 7 and 8 subunits and known as α-, β- and γ-cyclodextrins, respectively, have found wide practical application [1, 2]. A structural feature of cyclodextrins (Fig. 1) is the presence of a hydrophobic cavity capable of including hydrophobic molecules with the formation of molecular complexes both in solution and in the solid phase [3]. Due to this property, cyclodextrins are already used in the composition of drugs to increase the solubility of active substances, increase their bioavailability and stability; to reduce undesirable side effects, as well as control the rate of release of drugs and reduce the irritating effect of drugs on the mucous membranes [4-6]. Among natural cyclodextrins, γ-cyclodextrin (γ-CD) has the largest cavity size and the most favourable toxicological profile.

Despite the fact that cyclodextrins are typical biotechnological products, they are increasingly in demand in technologies for the development of new hybrid materials for various industrial processes. For example, cyclodextrins are considered as promising adsorbents of pollutants of various natures from wastewater [7, 8]. To solve this problem, nanocomposites based on covalent conjugation of cyclodextrins with graphene are being developed [9-12].

Being effective solubilizers of hydrophobic molecules, cyclodextrins themselves have relatively low solubility in water (14.5; 1.85; 23.2 g/100 ml for α-, β-, γ-cyclodextrin, respectively) [13]. The problem of increasing the solubility of cyclodextrins can be solved by their chemical modifications. Substitution of hydroxyl groups with substituents such as hydroxypropyl, sulfobutyl ether or glucosyl groups, even hydrophobic fragments, for example, a methyl group, usually increases their solubility in water [5]. The use of non-aqueous media in this context also seems promising [14]. In particular, it was shown that isopropanol is effective as a solvent for starch conversion in cyclodextrin production technologies for the needs of the food, pharmaceutical and agricultural industries [15].

Thermodynamic parameters of cyclodextrin solvation are necessary for scientific selection of the solvent and prediction of the reactivity of cyclodextrins for carrying out processes with the greatest efficiency. In this regard, in this work, the distribution

coefficients of γ-CD in water and its mixtures with ethanol (EtOH) and dimethyl sulfoxide (DMSO) were determined by the method of interfacial distribution of a substance between two immiscible phases (water or mixed solvent and n-hexane). The changes in the Gibbs energy of the transfer of γ-CD from water to mixed solvents H_2O-EtOH and H_2O-DMSO are calculated. A comparative analysis of the effect of H_2O-EtOH and H_2O-DMSO solvents on changes in the solvate state of β-CD, hydroxypropyl-β-cyclodextrin (HP-β-CD) and γ-CD was carried out. An assumption is made about the effect of changes in the solvate state of cyclodextrins on the stability of molecular complexes of cyclodextrins with flavonoids rutin (RUT) and quercetin (QCT) in aqueous-ethanol media. RUT and QCT have antioxidant properties, which mainly explains their biological significance and the importance of their studying. The rutin molecule differs from the quercetin by the presence of two glucorpyranose links, which determines the choice of these molecules for comparing the thermodynamic parameters of their molecular complexation with cyclodextrins (Fig. 1).

The results obtained in this study were used to assess the stability of cyclodextrin inclusion complexes with the flavonoids rutin and quercetin in aqueous ethanol media.

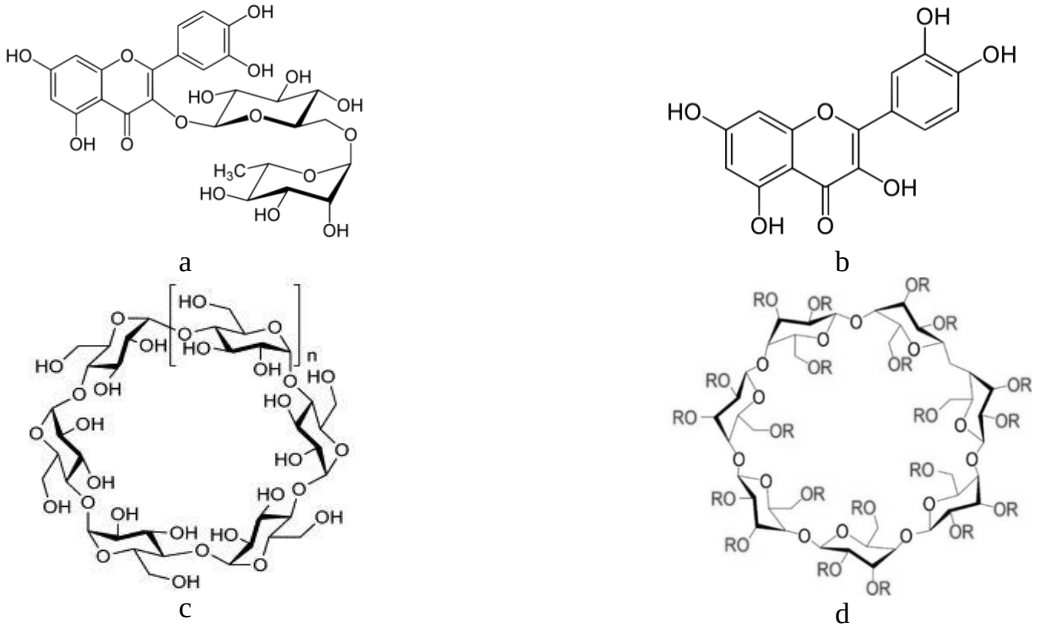

Fig. 1. Structural formulas of rutin (a), quercetin (b), general structure of cyclodextrins molecules: n = 6 – α-CD; n = 7 – β-CD; n = 8 – γ-CD (c), and hydroxypropyl-β-cyclodextrin (d) (R = H, $CH_2CHOHCH$)

Рис. 1. Структурные формулы рутина (a), кверцетина (b), общая структура молекул циклодекстринов: n = 6 – α-ЦД; n = 7 – β-ЦД; n = 8 – γ-ЦД (c) и гидроксипропил-β-циклодекстрин (d) (R = H, $CH_2CHOHCH$)

EXPERIMENTAL

γ-cyclodextrin (γ-CD) produced by Sigma Aldrich with a content of γ-CD ≥ 98 wt.%, n-hexane (JSC Chemreactive) was used without additional purification. Dimethyl sulfoxide (Spektr-Chem, Russia) is purified by distillation under vacuum, residual water concentration (0.56 wt.%) it was controlled by the Fischer method. Ethanol ("rectified") was purified by distillation at atmospheric pressure. The water content was controlled by densimetric (not exceeding 5 wt.%). The residual water content in the solvents was taken into account when preparing solutions.

The solutions were prepared by weight (on analytical scales of the SHIMADZU AUW-220D brand, the weighing accuracy was ± 0.00005 g.) on the basis of freshly distilled aqueous bidistillate (κ = 1.7 mcm/cm, pH 6.6) immediately before the experiment.

The distribution coefficients of γ-cyclodextrin are determined by the method of interfacial distribution of the substance between immiscible phases: an aqueous or aqueous organic solution and n-hexane. The applicability of this method has been confirmed in studies on the effect of solvent on changes in the solvate state of 18-crown-6 ether in binary solvents water-ethanol [15], water-acetone [16] and methanol-dimethylformamide [17], as well as amine and amide ligands in mixtures of non-aqueous [18] and water-organic solvents [19, 20].

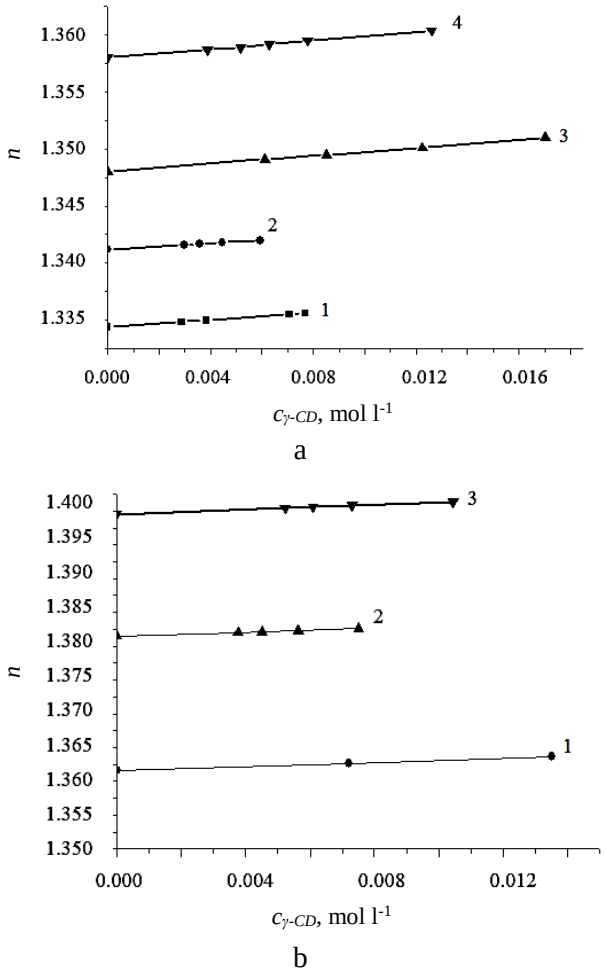

Fig. 2. Calibration graphs of the refractive index dependence of γ-CD solutions on the concentration of the non-aqueous component in the solvents water-ethanol (a), 1 - 0.00 mol. fr. EtOH, 2 – 0.05 mol. fr. EtOH, 3 - 0.10 mol. fr. EtOH, 4 – 0.20 mol. fr. EtOH, and water-dimethyl sulfoxide (b), 1 – 0.05 mol. fr. DMSO, 2 – mol. fr. DMSO, 3 – 0.15 mol. fr. DMSO, T = 298.15 K

Рис. 2. Градуировочные графики зависимостей показателя преломления растворов γ-ЦД от концентрации неводного компонента в растворителях вода-этанол (a), 1 – 0,00 мол.д. EtOH, 2 – 0,05 мол.д. EtOH, 3 – 0,10 мол.д. EtOH, 4 – 0,20 мол.д. EtOH и вода-диметилсульфоксид (b), 1 – 0,05 мол.д. DMSO, 2 – мол.д. DMSO, 3 – 0,15 мол.д. DMSO, T = 298,15 K

During the experiment, equal aliquots of an aqueous organic solution of γ-cyclodextrin and n-hexane were placed in a flask with polished lids. The concentrations of γ-CD ranged from 0.00596 - 0.01703 mol l^{-1}. The contents of the flask were stirred with a magnetic stirrer for 8 h at a constant temperature (298.2 ± 0.1 K) and settled for 15-20 h. After settling, a sample of the lower layer of a heterogeneous system (an aqueous organic solution of cyclodextrin) was collected, in which the equilibrium concentration of γ-CD in aqueous ($c_{(\gamma\text{-CD})^{H_2O}}$), aqueous-ethanol ($c_{(\gamma\text{-CD})^{H_2O\text{-EtOH}}}$) or aqueous-dimethyl sulfoxide layer. To determine the concentration of γ-CD, calibration graphs of the dependence of the refractive index of a solution containing γ-CD with an accurately known concentration were plotted. Approximation equations were used to calculate $c_{\gamma\text{-CD}}$ (1). All measurements were carried out via refractometry method.

The equilibrium concentration of γ-CD in the hexane layer ($c_{(\gamma\text{-CD})^{Hex}}$) was determined by the formula (1, 2), assuming that the volume of the reaction medium remained constant during the experiment:

$$c_{(\gamma\text{-CD})^{Hex}} = c_{(\gamma\text{-CD})^{in}} - c_{(\gamma\text{-CD})^{H_2O}}, \quad (1)$$

$$c_{(\gamma\text{-CD})^{Hex}} = c_{(\gamma\text{-CD})^{in}} - c_{(\gamma\text{-CD})^{H_2O\text{-}X_2}}, \quad (2)$$

where $c_{(\gamma\text{-CD})^{in}}$ is the initial concentration of γ-CD in the water-ethanol layer before the formation of a heterogeneous mixture, mol l^{-1}; $c_{(\gamma\text{-CD})^{H_2O}}$, $c_{(\gamma\text{-CD})^{H_2O\text{-}X_2}}$ are the equilibrium concentrations of γ-CD in water and in water-organic layer of a heterogeneous system, mol l^{-1}, x_2 – is mole fraction of ethanol or dimethyl sulfoxide.

To calculate the Gibbs energy of the transfer of substances from one solvent to another, the values of the distribution coefficients of the studied compounds between two immiscible solvents are used.

Distribution coefficients of γ-CD between immiscible phases and the change in the Gibbs energy of γ-CD during its transfer from water to aqueous dimethyl sulfoxide solutions ($\Delta_{tr}G^0_{\gamma\text{-CD}}$) calculated by the equations:

$$K_1 = c_{(\gamma\text{-CD})^{Hex}}/c_{(\gamma\text{-CD})^{H_2O}}, \quad (3)$$

$$K_2 = c_{(\gamma\text{-CD})^{Hex}}/c_{(\gamma\text{-CD})^{H_2O\text{-}X_2}}, \quad (4)$$

$$\Delta_{tr}G^0_{(\gamma\text{-CD})^{H_2O\text{-}X_2}} = RT\ln(_{(\gamma\text{-CD})^{H_2O}}/_{(\gamma\text{-CD})^{H_2O\text{-}X_2}}) = RT\ln(K_2/K_1), \quad (5)$$

where K_1 and K_2 are the distribution coefficients of γ-CD in hexane-water and hexane-water-ethanol or hexane-water-dimethyl sulfoxide solvents, respectively.

The errors were determined as the standard deviation for three parallel experiments. The obtained values of the Gibbs energy of the γ-CD transfer were taken as standard, due to low concentration conditions and the absence of concentration dependences of the distribution coefficients of γ-CD under experimental conditions.

RESULTS AND DISCUSSION

A quantitative assessment of the transport of biologically active substances through biological membranes, as well as solubility, toxicity, absorption, is given by the distribution coefficient. Changes in the Gibbs energy of the solvation of molecules and ions, calculated on the basis of distribution coefficients, are characteristics of the solvation state of the substances under study in various solvents. The distribution coefficients of γ-CD in H_2O-EtOH and H_2O-DMSO sol-

vents and the Gibbs energy values of the γ-CD solvation calculated on their basis are given in Table. The distribution coefficient of γ-CD in mixed solvents is higher than in water. The change in the Gibbs energy during the transfer of γ-CD from water to its mixture with dimethyl sulfoxide and ethanol indicates a weakening of the macrocycle solvation.

Table

Concentration conditions of the experiment; distribution coefficients of γ-CD between immiscible phases (water (K1), water-ethanol or water-dimethyl sulfoxide solution (K2) and n-hexane; calculated values of the Gibbs energy of the transfer of γ-CD from water in its mixture with ethanol and dimethyl sulfoxide

***Таблица*. Концентрационные условия эксперимента; коэффициенты распределения γ-ЦД между несмешивающимися фазами (вода (K1), водно-этанольный или водно-диметилсульфоксидный раствор (K2) и н-гексан; расчетные значения энергии Гиббса переноса γ-ЦД из воды в ее смесь с этанолом и диметилсульфоксидом**

x_2	$c_{(\gamma\text{-CD})in}$, mmol l^{-1}	$c_{(\gamma\text{-CD})H_2O}$, $c_{(\gamma\text{-CD})H_2O\text{-}X_2}$, mmol l^{-1}	$c_{(\gamma\text{-CD})Hex}$, mmol l^{-1}	K_1	K_2	$\Delta_{tr}G^0_{\gamma\text{-CD}}$, kJ mol^{-1}
			H_2O			
0.00	7.07	6.42	0.655	0.08±0.02	-	0
	7.07	6.42	0.655			
	7.69	7.06	0.628			
	11.02	10.43	0.588			
	6.15	5.63	0.523			
	6.15	5.63	0.523			
			H_2O-EtOH			
0.05	8.96	6.03	2.927	-	0.13±0.06	1.04
	8.96	6.03	2.927			
	5.96	5.19	0.767			
	5.96	5.93	0.026			
	5.96	5.93	0.026			
0.10	12.24	11.46	0.785	-	0.23±0.07	2.48
	12.24	9.74	2.503			
	17.03	12.60	4.430			
	17.03	13.17	3.857			
0.20	10.37	5.29	5.085	-	0.37±0.14	3.62
	10.37	7.43	2.942			
	14.38	9.57	4.807			
	7.79	6.23	1.561			
	7.79	6.23	1.561			
	12.59	8.82	3.768			
			H_2O-DMSO			
0.05	7.22	5.81	1.40		0.16±0.13	1.64
	7.22	6.46	0.76			
	7.22	5.81	1.40			
0.10	7.52	6.52	1.00		0.13±0.06	1.11
	7.52	6.18	1.34			
	7.52	6.52	1.00			
	7.52	6.87	0.65			
0.15	7.24	6.40	0.840		0.12±0.07	0.96
	10.45	9.38	1.073			
	10.45	8.83	1.625			

Fig. 3 shows the Gibbs energy changes during CD transfer from water in its mixture with ethanol (a) and dimethyl sulfoxide (b). The data plotted as lines 1 [21, 22], 2 [23, 24], 3 (this work) were calculated from the results of the interphase transfer method studies; the data 1* [25] and point 3* [13] were calculated from the results of the solubility studies.

In the water-ethanol solvent, a uniform weakening of the solvation of γ-cyclodextrin occurs with an increase in the concentration of ethanol in the system (Fig. 3a). As can be seen from Fig. 3b, the maximum desolvation of γ-cyclodextrin in the solvent water-dimethyl sulfoxide is observed at x_{DMSO} = 0.05. In both aqueous-ethanol and aqueous-dimethyl sulfoxide

solvents, the solvation of β-cyclodextrin and hydroxypropyl-β-cyclodextrin increases somewhat in the concentration range of the non-aqueous component from 0 to 0.2 mol. fractions.

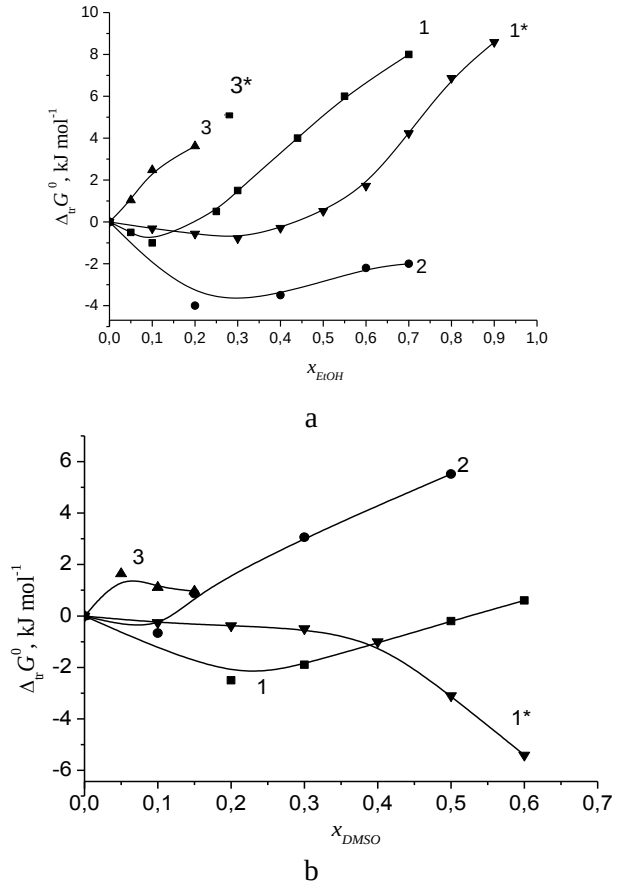

Fig. 3. Dependence of the Gibbs energy transfer of cyclodextrins from water in its mixture with ethanol (a), dimethyl sulfoxide (b): β-cyclodextrin (1) [21, 22], (1*) [25], hydroxypropyl-β-cyclodextrin (2) [23, 24], γ-cyclodextrin (3, 3*) [13]

Рис. 3. Зависимость энергии Гиббса переноса циклодекстринов из воды в ее смеси с этанолом (a), диметилсульфоксидом (b): β-циклодекстрин (1) [21, 22], (1*) [25], гидроксипропил-β-циклодекстрин (2) [23, 24], γ-циклодекстрин (3, 3*) [13]

Fig. 3 also shows the calculated values of the Gibbs energy of the transfer of β-cyclodextrin from water in its mixture with ethanol and DMSO. The calculation was made from data on the solubility of β-cyclodextrin [25] and γ-cyclodextrin [13] in the corresponding solvents. If we compare the two research methods, in aqueous ethanol solutions there is a similar tendency of the dependences of $\Delta_{tr}G^0_{\beta\text{-CD}}$ and $\Delta_{tr}G^0_{\gamma\text{-CD}}$ on x_{EtOH}. Given the significant error of both methods, we can talk about the satisfactory convergence of their results.

It is known that the solvent can influence the equilibrium, rate and mechanism of complexation reactions [26, 27]. To study the role of the solvent in the processes of complexation, a solvation-thermodynamic approach is used [26]. In this context, the thermodynamic characteristics of cyclodextrins solvation are necessary to predict the stability of their molecular complexes in solutions.

It was previously established [23, 24, 28] that during the complexation of RUT with HP-β-CD and quercetin QCT with HP-β-CD, increased solvation of reagents during the transition from water to aqueous ethanol leads to a decrease in the stability of molecular complexes.

The similar dynamics of the change in the Gibbs energy of the HP-β-CD and β-CD solvation in aqueous-ethanol solvents suggests a decrease in the stability of [RUT⊂β-CD] and [QCT⊂β-CD] during the transition from water to aqueous-ethanol mixtures with a low ethanol content (up to $x_{EtOH} = 0.1$ and $x_{EtOH} = 0.2$, respectively) due to increased solvation of both flavonoids and β-CD. A further increase in the ethanol content in the solvent will probably contribute to the hardening of RUT and QCT complexes with β-cyclodextrin derivatives.

With the formation of [RUT⊂γ-CD] and [QCT⊂γ-CD] complexes, it is possible to assume an increase in their stability during the transition from water to ethanol due to the predominant desolvation of γ-CD compared with an increase in the solvation of polyphenols [23, 29, 30].

CONCLUSION

The distribution coefficients of γ-cyclodextrin were determined by the method of distribution of the substance between two immiscible phases with a water-dimethyl sulfoxide (water-ethanol) solvent of variable composition and n-hexane and the changes in the Gibbs energy of recolvation were calculated. During the transition from water to mixed solutions, a weakening of the γ-cyclodextrin solvation is observed. A comparative analysis of the effect of H_2O-EtOH solvents on changes in the solvate state of β-cyclodextrin, hydroxypropyl-β-cyclodextrin and γ-cyclodextrin allowed to make an assumption about H_2O-EtOH solvents influence on the stability of [RUT⊂β-CD] and [QCT⊂β-CD] complexes. The similar dynamics of the change in the Gibbs energy of the HP-β-CD and β-CD solvation suggests a decrease in the stability of [RUT⊂β-CD] and [QCT⊂β-CD] due to increased solvation of both flavonoids and β-CD. For [RUT⊂γ-CD] and [QCT⊂γ-CD] complexes, it is possible to assume an increase in their stability due to the predominant desolvation of γ-CD compared with an increase in the solvation of polyphenols. For a sim-

ilar analysis of the effect of the composition of an aqueous dimethyl sulfoxide solvent on the change in the stability of [RUT⊂γ-CD] and [QCT⊂γ-CD], additional data on changes in the solvate state of flavonoids in aqueous dimethyl sulfoxide media are required, which are not currently presented in the literature.

The results obtained in this study may be of use for evaluating the stability of inclusion complexes of cyclodextrins with polyphenol molecules in non-aqueous solutions or as thermodynamic reference data for developing synthesis technologies of pharmaceutical products.

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

БЛАГОДАРНОСТИ

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