COMPLEXAÇÃO DE PRAZIQUANTEL COM α -, β - E γ -CICLODEXTRINAS EM SOLUÇÕES HIDROALCOÓLICAS

COMPLEXATION OF PRAZIQUANTEL WITH α -, β - AND γ -CYCLODEXTRINS IN AQUEOUS-ALCOHOLIC SOLUTIONS

КОМПЛЕКСООБРАЗОВАНИЕ ПРАЗИКВАНТЕЛА С α -, β - И γ -ЦИКЛОДЕКСТРИНАМИ В ВОДНО-СПИРТОВЫХ РАСТВОРАХ

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RESUMO

Hoje, a percentagem de infecções por doenças invasivas (parasitárias) é bastante grande, portanto, o tratamento das helmintíases é um problema urgente em medicina veterinária. Os vermes parasitas infligem danos significativos ao gado, levando à morte de animais, escassez de carne, produtos lácteos e lã. O objetivo deste trabalho foi estudar a complexação do praziquantel com α -, β - e γ -ciclodextrinas em soluções hidroalcoólicas. A interação de um medicamento anti-helmíntico, praziquantel, com α -, β - e γ -ciclodextrinas em soluções hidroalcoólicas foi estudada pelo método de espectroscopia ultravioleta. Verificou-se que a adição de ciclodextrinas às soluções hidroalcoólicas de praziquantel leva a alterações espectrais, indicando a presença de interações intermoleculares e complexação. O método da série isomolar mostrou que em soluções diluídas o praziquantel forma compostos complexos com as ciclodextrinas de composição 1:1, ou seja, há uma molécula de praziquantel por uma molécula de α -, β - ou γ -ciclodextrina. As constantes de estabilidade dos complexos resultantes foram calculadas usando o método da razão molar. É mostrado que na faixa de 296-316 K a composição dos compostos complexos permanece inalterada (1:1), e sua estabilidade diminui com o aumento da temperatura. O estudo das dependências das constantes de estabilidade com a temperatura possibilitou determinar os valores padrão das variações da energia de Gibbs, entalpia e entropia de complexação.

Palavras-chave: medicamentos anti-helmínticos, praziquantel, doenças parasitárias, substâncias contendo nitrogênio, lei de Beer-Lambert-Bouguer.

ABSTRACT

Currently, the percentage of infections with invasive (parasitic) diseases is quite large; therefore, the treatment of helminthiases is an urgent problem in veterinary medicine. Parasitic worms inflict significant damage on animal husbandry, leading to the death of animals, shortage of meat, dairy products, and wool. The most common active ingredient in anthelmintics is praziquantel, which is well known as an effective broad-spectrum anthelmintic. At the same time, praziquantel has low solubility in water and a pronounced bitter taste, which represents a significant obstacle in developing liquid forms of drugs that are convenient for administration to animals. One way to solve these problems is the complexation of medicinal substances with various (natural and synthetic) compounds. In this regard, this paper aims to study the complexation of praziquantel with α -, β -, and γ -cyclodextrins in aqueous-alcoholic solutions. The studies were carried out by the method of ultraviolet spectroscopy. It was found that the addition of cyclodextrins to aqueous-alcoholic solutions of praziquantel leads to spectral changes indicating the presence of intermolecular interactions and complexation. The isomolar series method showed that in dilute solutions, praziquantel forms complex compounds with cyclodextrins 1:1, that is, one molecule of praziquantel falls on one molecule of α -, β - or γ -cyclodextrin. The stability constants of the resulting complexes were calculated using the molar ratio method. It is shown that in the range of 296-316 K, the composition of complex compounds remains unchanged (1:1), and their stability decreases with increasing temperature. The study of the temperature dependences of the

stability constants made it possible to determine the standard values of changes in the Gibbs energy, enthalpy, and complexation entropy.

Keywords: *anthelmintic drugs, praziquantel, parasitic diseases, nitrogen-containing substances, Bouguer-Lambert-Beer law.*

АННОТАЦИЯ

На сегодняшний день процент заболевания инвазионными (паразитарными) болезнями достаточно велик, поэтому лечение гельминтозов является актуальной проблемой ветеринарии. Значительный ущерб паразитические черви наносят животноводству, приводя к гибели животных, недополучению мясной и молочной продукции, шерсти. Целью настоящей работы явилось изучение комплексообразования празиквантела с α -, β - и γ -циклодекстринами в водно-спиртовых растворах. Методом ультрафиолетовой спектроскопии исследовано взаимодействие антигельминтного препарата – празиквантела – с α -, β - и γ -циклодекстринами в водно-спиртовых растворах. Установлено, что добавление циклодекстринов к водно-спиртовым растворам празиквантела приводит к спектральным изменениям, свидетельствующим о наличии межмолекулярных взаимодействий и комплексообразования. Методом изомольных серий показано, что в разбавленных растворах празиквантел образует с циклодекстринами комплексные соединения состава 1:1, то есть на одну молекулу α -, β - или γ -циклодекстрина приходится одна молекула празиквантела. С помощью метода молярных отношений рассчитаны константы устойчивости образующихся комплексов. Показано, что в интервале 296-316 К состав комплексных соединений остается неизменным (1:1), а их устойчивость с ростом температуры падает. Изучение температурных зависимостей констант устойчивости позволило определить стандартные значения изменений энергии Гиббса, энтальпии и энтропии комплексообразования.

Ключевые слова: *антигельминтные препараты, празиквантел, паразитарные болезни, азотсодержащие вещества, закон Бугера-Ламберта-Бера.*

1. INTRODUCTION:

Currently, the percentage of infections with invasive (parasitic) diseases is quite large; therefore, the treatment of helminthiasis is an urgent problem in veterinary medicine. Unlike microorganisms such as unicellular, fungi, viruses, and bacteria, which have a rather delicate and soft cover, most helminths, especially nematodes, have a multi-layered muscle cuticle that sufficiently protects the organs of the parasite. Great economic damage is inflicted on animal husbandry due to the widespread of nematodes, leading to the death of animals, shortage of meat and dairy products, and wool. Lack of treatment for invasive diseases can lead to severe damage to internal organs up to death. Also, some helminthiasis are dangerous to humans. It should be noted that annually in the Russian Federation alone, more than 20 million people fall ill with parasitic diseases, and most often, they are residents of rural areas (Butko *et al.*, 2018). In this regard, invasive (parasitic) diseases are of great importance today, which leads to an increase in demand for veterinary drugs used to treat them.

Praziquantel-2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one is often used as an active component of antihelmintics. This drug is known as an effective broad-spectrum anthelmintic agent (Subbotin *et al.*, 2000). It is a broad-spectrum drug used to treat many parasitic infections, including cysticercosis, tapeworm disease, and clonorchiasis (Zhang *et al.*, 2020). Praziquantel is considered a relatively low-toxic drug that does not possess embryotoxic, mutagenic, and teratogenic properties and does not affect the postnatal development of the body (Demidov, 1982; Engasheva, 2011; Garcia *et al.*, 2011; Zolotareva and Zeynalov, 2015; Harvie *et al.*, 2019; Liu *et al.*, 2019; Nono *et al.*, 2020). At the same time, with all the listed advantages, praziquantel has several disadvantages: 1) low solubility in water and, as a result, limited bioavailability of this substance in liquid compositions; 2) lack of the necessary activity concerning the roundworms; 3) the lack of complete clearance of praziquantel from the body, which, with prolonged use, can lead to increased toxicity to animals; 4) pronounced bitter taste, which is a significant obstacle in the development of medicinal products for oral administration and, in particular, their liquid

forms intended for dogs and cats (Subbotin *et al.*, 2000; Xu *et al.*, 2009; Sousa-Figueiredo *et al.*, 2012; Zolotareva and Zeynalov, 2015).

One way to solve these problems is the complexation of medicinal substances with various (natural and synthetic) compounds. The prospects of this approach are confirmed by data on the study of the complexation of some nitrogen-containing, including medicinal, substances (derivatives of uracil, 4- and 5-aminosalicylic acids) with polyfunctional acids (see, for example, (Baltina *et al.*, 2001; Chernyshenko, 2008; Myshkin *et al.*, 2009; Borisova *et al.*, 2013; Gimadieva *et al.*, 2014; Wangchuk *et al.*, 2016a; Zimin *et al.*, 2017), and the sources cited there). It should be borne in mind that complexation can eliminate some of the disadvantages of medicinal substances and introduce new beneficial properties. In recent years, biologically degradable, non-toxic, and relatively cheap cyclodextrins are built from glucose residues, which have a hydrophilic outer surface and a volumetric hydrophobic inner cavity comparable to many substrates (organic and inorganic), are often used as a complexing agent (Szejtli, 1998; Crini *et al.*, 2018). Due to their structure, cyclodextrins can form "host-guest" complexes with various types of molecules (Uekama *et al.*, 1998; Pandey *et al.*, 2010; Crini *et al.*, 2018). The formation of such complexes can significantly change the physicochemical and biological properties of the "guest" molecule, which determined their relevance as an object and tool of the modern chemical and pharmaceutical technologies (Fedorova *et al.*, 2011). Complexation with cyclodextrins makes it possible to increase the selectivity and, therefore, the dose efficiency of pharmacologically active substances; stabilize compounds sensitive to the action of light, heat, and oxygen in the air; multiply the solubility of substances hardly soluble in water and increase their bioavailability; prolong the effects of drugs, ensure their targeted transport in the body; prevent the irritating effect of drugs on mucous membranes; reduce toxicity; mask unpleasant tastes and smells (Uekama *et al.*, 1998; Pandey *et al.*, 2010; Fedorova *et al.*, 2011). In connection with the above, the purpose of this paper is to study the complexation of praziquantel with α -, β - and γ -cyclodextrins in aqueous-alcoholic solutions.

2. MATERIALS AND METHODS:

The complexing agents were natural

cyclic oligosaccharides, cyclodextrins produced by the company "AppliChem" (Darmstadt, Germany). Of the huge family of cyclodextrins, this study was used three main, most studied and widespread products: α -cyclodextrin (α -CD), β -cyclodextrin (β -CD), and γ -cyclodextrin (γ -CD), the macrorings of which consist of 6, 7, and 8 glucopyranose residues, respectively. These cyclodextrins have the following empirical formulas: α -CD - $C_{36}H_{60}O_{30}$, β -CD - $C_{42}H_{70}O_{35}$, and γ -CD - $C_{48}H_{80}O_{40}$. Praziquantel (PR) was provided by the research and production company "Ecohimtech" (Ufa), where a unique scheme for the synthesis of this drug was developed. The solvent was a water-alcohol mixture with a volume ratio of water and alcohol 1:1.

The complexation of praziquantel with α -, β - and γ -cyclodextrins was studied by UV spectroscopy in the temperature range from 296 to 316 K. Since cyclodextrins, when transmitted by UV light, do not give absorption peaks in the wavelength range of 190-360 nm. Therefore, all studies were carried out at the maximum absorption wavelength of praziquantel. Complex compounds were obtained under equilibrium conditions at low concentrations of the starting reagents (10^{-4} – 10^{-3} mol/L) in aqueous-alcoholic solutions. UV spectra of praziquantel and complex compounds were recorded on a UV-2401 PC spectrophotometer (Shimadzu, Japan) in temperature-controlled quartz cells 1 cm thick relative to the solvent - aqueous-alcoholic mixture.

To determine the composition of the resulting complexes, the isomolar series method was used (Bulatov and Kalinkin, 1986; Beck and Nadpal, 1989). This method is based on determining the ratio of isomolar concentrations of the interacting substances, which corresponds to the maximum yield of the resulting complex compound. In this case, the curve of the dependence of the yield of the complex and the change in optical density on the composition of the solution should be characterized by an extremum point. Such a point will indicate the maximum possible concentration of the complex, and its position on the abscissa axis will correspond to the stoichiometric ratio of the reactants. Based on the above, experiments were prepared and carried out, the essence of which was as follows. Aqueous-alcoholic solutions of praziquantel and α -, β - or γ -cyclodextrin of the same molar concentration ($1 \cdot 10^{-3}$ mol/L) were mixed in inverse relation (from 1:9 to 9:1) while

maintaining the total volume of the solution unchanged. In this case, the total number of moles of both components in the solution also remained constant. After 1 hour, the optical densities of the solutions were measured. The comparison cuvette was filled with a solvent, a water-alcohol mixture (1:1 by volume). By measuring the optical densities of the prepared solutions of the isomolar series, a graph of the dependence of the change in optical density on the ratio of the concentrations of the components were plotted, and the position of the absorption maximum on the isomolar curve was determined. The maximum light absorption is possessed by a solution in which the content of the resulting complex compound is biggest. The extreme point on the isomolar diagram was used to determine the composition of the resulting complex (Bulatov and Kalinkin, 1986; Beck and Nadpal, 1989).

To determine the stability constants (K) of complex compounds, molar ratios were used (Bulatov and Kalinkin, 1986; Beck and Nadpal, 1989). This method is based on establishing the dependence of the change in optical density (ΔA) on the concentration of one of the components at a constant concentration of the second component, and vice versa. The experiments were carried out as follows. Aqueous-alcoholic solutions of praziquantel (PR) and cyclodextrin (CD) (α -, β -, or γ -) with the same molar concentration of $1 \cdot 10^{-3}$ mol/L were prepared. In 10 volumetric flasks, 2 ml of PR solution and from 0.5 to 8 ml of CD solution were poured. Then the total volume of each flask was brought up to 10 ml with a water-alcohol mixture. The resulting solutions were thoroughly mixed and left for 1 hour at room temperature, after which the optical densities were measured at the maxima of the absorption wavelength of praziquantel. To find the stability constants, graphs of $[PR]/\Delta A$ versus $1/[CD]$ were built, from which the K values were calculated from the ratio of cut-offs to the slope tangents

3. RESULTS AND DISCUSSION:

The UV spectrum of praziquantel has three characteristic absorption bands at 193 nm, 263 nm, and 271 nm. Studies have shown that the most convenient were the last two absorption bands (at wavelengths $\lambda = 263, 271$ nm), used for further study. At the first stage of research, the range of working concentrations of praziquantel was determined. For this, was

applied the Bouguer-Lambert-Beer law (Equation 1). Where A – optical density of aqueous-alcoholic solutions of praziquantel; ϵ_λ – extinction coefficient of praziquantel at wavelength λ ($\text{mol/L}^{-1} \text{ cm}^{-1}$); $[PR]$ – concentration of praziquantel (mol/L); l – sample cell thickness ($l = 1 \text{ cm}$).

It was found that the linear relationship between the optical density of praziquantel and its concentration in a water-alcohol solution is fulfilled up to $[PR] = 1 \cdot 10^{-3}$ mol/L. Thus, for further studies, praziquantel concentrations not exceeding $1 \cdot 10^{-3}$ mol/L were used. The extinction coefficient of praziquantel in an aqueous-alcoholic solution was calculated from the slope of the dependence (Equation 2).

In this study, it was found that the addition of cyclodextrins (α -CD, β -CD, or γ -CD) to aqueous-alcoholic solutions of praziquantel leads to the following changes in its UV spectra: a shift of the absorption band maxima to shorter wavelengths and a decrease in the intensities of the absorption peaks. The observed changes are due to intermolecular interactions that take place in the reaction systems “ α -CD+PR”, “ β -CD+PR” or “ γ -CD+PR”, and lead to the formation of complex compounds (most likely, inclusion complexes (Uekama *et al.*, 1998; Wangchuk *et al.*, 2016b; Pandey *et al.*, 2010; Fedorova, 2011; Crini *et al.*, 2018; Park *et al.*, 2019; Cunha *et al.*, 2020)). Figure 1 shows the UV spectra of aqueous-alcoholic solutions of praziquantel and its complex with α -cyclodextrin.

The complexation of praziquantel with α -, β - and γ -cyclodextrins is also evidenced by isomolar diagrams obtained by the method of isomolar series (Bulatov and Kalinkin, 1986; Beck and Nadpal, 1989). So, Figure 2 shows the isomolar diagram for the complex compound formed by praziquantel and α -cyclodextrin.

An analysis of this diagram suggests that the dependence (Equation 3) passes through a maximum with an increase in the concentration of the optically active substance (PR). This fact confirms the existence of interactions between praziquantel and α -cyclodextrin, otherwise, a different (not extreme) character of the dependence would be observed.

The isomolar diagram (Figure 2) was used to determine the composition of the complex formed in the reaction system “ α -CD +

PR". The maximum change in optical density (ΔA) observed at a ratio of isomolar solutions equal to 0.5 indicates the formation of a 1:1 complex compound in dilute aqueous-alcoholic solutions. It should be noted that in the reaction systems " β -CD + PR" and " γ -CD + PR", similar dependences were obtained, indicating a ratio of components in the complexes equal to 1:1. Thus, in the considered complex compounds, one molecule of α -, β - or γ -cyclodextrin accounts for one molecule of praziquantel.

The stability constants of complex compounds were calculated according to the studies of Bulatov and Kalinkin (1986), Beck and Nadpal (1989). According to this method, spectral changes in the investigated reaction systems " α -CD + PR", " β -CD + PR" and " γ -CD + PR" are described by the Equation 4. Where [PR] – concentration of praziquantel in an aqueous-alcoholic solution (mol/L); A and A_0 – optical densities of praziquantel solutions in the presence and absence of cyclodextrins ($A - A_0 = \Delta A$); ϵ and ϵ^0 – molar extinction coefficients of the complexes and praziquantel, respectively (mol/L⁻¹ cm⁻¹); K is the stability constant of the complex compound (mol/L); [CD] – concentration of cyclodextrins (α -, β - or γ -). To find the stability constants, a dependency diagram of [PR]/ ΔA versus 1/[CD] was built (Figure 3), from which the K values were calculated from the ratio of cut-offs to the slope ratio.

Studies were carried out on the temperature effect on the composition and stability of the resulting complexes. It was found that in the studied temperature range of 296-316 K, the complex compounds retain their composition (1:1), i.e., there is always one praziquantel molecule for every single α -, β - or γ -cyclodextrin molecule. Simultaneously, the stability of the resulting complexes decreases with increasing temperature (Table 1).

Having processed the data of the dependences (Equation 5) in the coordinates of the equation (Equation 6) (Poltorak, 1991). Standard thermodynamic parameters (changes in entropies ΔS° and enthalpies ΔH°) of the reactions of formation of praziquantel with α -, β - and γ -cyclodextrins in aqueous-alcoholic solutions were calculated (Table 2). The standard values of changes in Gibbs energies ΔG° at a certain temperature were found according to (Equations 7, 8) (Poltorak, 1991). Table 2 shows that the values of all thermodynamic parameters have a negative

sign. A negative value of ΔS° indicates a decrease in entropy, which is associated with restrictions on the freedom of vibrational and rotational motions of molecules that arise during complexes formation. Negative values of ΔH° and ΔS° indicate, respectively, the exothermicity and spontaneity of complexation processes in the investigated temperature range (296-316 K).

Based on the data obtained on the composition, stability, and thermal stability of the studied complex compounds, a procedure was developed for the synthesis of an individual complex (a complex of α -cyclodextrin with praziquantel), a prototype of this compound was developed, and its solubility in water was studied. In addition, the complex of α -cyclodextrin with praziquantel was transferred to the research and production company "Ecochimtech" (Ufa) for biological tests.

The complex compound α -CD...PR was synthesised by mixing equimolar amounts of the starting reagents (α -cyclodextrin and praziquantel) in a water-alcohol solution. The reaction mixture was stirred for eight days at a temperature of 297 K, after which the water was removed by evaporation under reduced pressure. As a result, the complex compound was obtained in quantitative yield. Below are the spectral characteristics of the α -CD...PR complex in aqueous solution (Equation 9).

In this study, the extinction coefficient of the complex formed by α -cyclodextrin and praziquantel was determined. Using the Bouguer-Lambert-Beer formula (Equation 1), the authors studied the dependence of the optical density of aqueous solutions of complex compound (A) on its initial concentration. The extinction coefficient of the investigated complex in an aqueous solution (Equation 10) was calculated from the tangent of the slope of the dependence (Equation 11).

To confirm the formation of the inclusion complex of praziquantel with α -cyclodextrin and to reveal the nature of the bonds formed in it, the method of IR spectroscopy was used. In the IR spectrum of the initial substrate, praziquantel (Figure 4), the most informative are the regions 1700 - 1600 cm⁻¹, where vibrations of the R-CN-R group (1650 and 1627 cm⁻¹) and stretching vibrations of the carbonyl group C=O (1668 cm⁻¹). The absorption bands at 2900-2800 cm⁻¹ belong to the stretching vibrations of CH groups.

A characteristic functional group inherent in α -cyclodextrin is a hydroxyl group. Therefore, in its IR spectrum (Figure 5), it is possible to observe a band of O-H bond vibrations, which manifests itself in a wide range of wave numbers $3537\text{--}3265\text{ cm}^{-1}$ and is quite intense. The absorption bands at $2900\text{--}2800\text{ cm}^{-1}$ belong to the stretching vibrations of C-H groups. In the IR spectrum of the complex compound (Figure 6), absorption maxima at 1668, 1650, and 1627 cm^{-1} disappear and one band appears at 1635 cm^{-1} , and a broadened band at 863 cm^{-1} is formed, which is characteristic of plane bending N-H vibrations bonds. At the same time, it should be noted that the complex is characterised by a decrease in the intensity of the bands of the hydroxyl group. This data indicates the participation of the O-H groups of praziquantel in the formation of the inclusion complex. Based on the IR spectroscopy data, it can be concluded that the complexation of α -cyclodextrin and praziquantel occurs due to the formation of intermolecular bonds, in which participate the C=O and CN groups of praziquantel and the O-H groups of cyclodextrin.

At the final stage, studies were carried out to determine the solubility of the complex of α -cyclodextrin with praziquantel synthesised by the authors. The solubility of the complex compound was determined by a visual method. For this, a weighed portion of the synthesised complex was dissolved in 50 ml of a solvent (double-distilled water), after which the resulting mixture was shaken for 1-2 minutes at room temperature (297 K). Then the solubility was checked against a white sheet of paper and under additional lighting. If suspended particles of a substance were found in the solution, another 50 ml of water was added, the solution was shaken and checked again for solubility. Thus, this procedure was repeated until suspended particles of the α -cyclodextrin complex with praziquantel were found in the solution. The complex compound was considered dissolved in the absence of substance particles.

Studies have shown that for the complete solubility of praziquantel with a mass of 0.0016 g, 2100 ml of double-distilled water is required, while a complex compound of the same mass is completely dissolved in 100 ml of water. Thus, the solubility of praziquantel was $2.38 \cdot 10^{-6}\text{ mol/L}$, and the solubility of the compound was $5 \cdot 10^{-5}\text{ mol/L}$, i.e., it increased 21 times. In addition, it was found that the

synthesised complex compound $\alpha\text{-CD}\cdots\text{PR}$ is characterised by the absence of odour and a significant decrease in bitterness.

Thus, the complexation of praziquantel with cyclodextrins allows to get rid of a number of disadvantages inherent in PR (see the introduction). So, for example, the solubility of praziquantel in the composition of the complex compound $\alpha\text{-CD}\cdots\text{PR}$ increased more than 20 times, which opens up possibilities for creating a drug in liquid compositions. In addition, the absence of odour and a significant reduction in bitterness found for the $\alpha\text{-CD}\cdots\text{PR}$ compound will remove the obstacle to the creation of a medicinal product for oral administration and, in particular, its liquid form intended for pets (dogs and cats).

4. CONCLUSIONS:

In this study, using the method of ultraviolet spectroscopy, the possibility of complexation of an anthelmintic drug, praziquantel, with natural oligosaccharides (α -, β -, and γ - cyclodextrins) in aqueous-alcoholic solutions was investigated. The choice of solvent is due to the extremely low solubility of praziquantel in water. According to the Bouguer – Lambert-Beer law, the extinction coefficient of praziquantel in a water-alcohol mixture was determined at an equal ratio of the volumes of H_2O and $\text{C}_2\text{H}_5\text{OH}$. It was found that the addition of cyclodextrins (α -, β - or γ -) to aqueous-alcoholic solutions of praziquantel leads to the following changes in its UV spectra: a shift of the absorption band maxima to shorter wavelengths and a decrease in the intensities of the absorption peaks. The observed changes are caused by intermolecular interactions in the reaction systems under study and lead to the formation of complex compounds (most likely, inclusion complexes).

By the method of isomolar series, it was shown that in dilute aqueous-alcoholic solutions, praziquantel forms complex compounds with cyclodextrins 1:1, that is, one molecule of praziquantel falls on one molecule of α -, β - or γ - cyclodextrin. Using the method of molar ratios in the temperature range 296-316 K, the stability constants of the resulting complex compounds are calculated. The findings indicated that praziquantel forms relatively unstable complexes with the studied cyclodextrins: the values of the stability constants in the studied temperature range vary

within $(1 \div 7) \cdot 10^2$ mol/L. It was found that an increase in temperature does not affect the composition of complex compounds, while the stability of the complexes decreases with increasing temperature. The study of the temperature dependencies of the stability constants made it possible to determine the standard values of changes in the Gibbs energy (ΔG°), enthalpy (ΔH°), and entropy (ΔS°) of complexation.

It follows from the results obtained that the values of all thermodynamic parameters have a negative sign. The negative value of ΔG° indicates the spontaneous occurrence of complexation processes in the studied temperature range (296-316 K). A negative value of ΔH° indicates exothermicity of the complex compounds' formation processes. The negative value of ΔS° indicates a decrease in entropy during complexation, which is associated with the restrictions on the freedom of vibrational and rotational motions of molecules that arise during the complexation.

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$$A = \varepsilon_{\lambda} \cdot [\text{PR}] \cdot l, \quad (\text{Eq. 1})$$

$$A = f([\text{PR}]): \varepsilon_{\lambda} = (2.6 \pm 0.2) \cdot 10^3 \text{ mol/L}^{-1} \text{ cm}^{-1} (\lambda = 263 \text{ nm}) \quad (\text{Eq. 2})$$

$$\Delta A = f([\text{PR}] / ([\text{PR}] + [\alpha\text{-CD}])) \quad (\text{Eq. 3})$$

$$\frac{[\text{PR}]}{(A-A_0)} = \frac{1}{(\varepsilon-\varepsilon_0)} + \frac{1}{((\varepsilon-\varepsilon_0) \cdot K \cdot [\text{CD}])}, \quad (\text{Eq. 4})$$

$$K = f(T) \quad (\text{Eq. 5})$$

$$\ln K = \frac{\Delta S^\circ}{R} - \frac{\Delta H^\circ}{R} \cdot \frac{1}{T}, \quad (\text{Eq. 6})$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ. \quad (\text{Eq. 7})$$

$$\varepsilon_{\lambda} = (2.6 \pm 0.2) \cdot 10^3 \text{ mol/L}^{-1} \text{ cm}^{-1} (\lambda = 263 \text{ nm}) \quad (\text{Eq. 8})$$

$$\text{UV spectrum (H}_2\text{O)} (\lambda, \text{ nm}): \max^1 = 197, \max^2 = 264, \max^3 = 271 \quad (\text{Eq. 9})$$

$$A = f([\alpha\text{-CD} \cdots \text{PR}]) \quad (\text{Eq. 10})$$

$$\varepsilon_{\lambda} = (5.5 \pm 0.1) \cdot 10^3 \text{ L mol}^{-1} \text{ cm}^{-1} (\lambda = 264 \text{ nm}) \quad (\text{Eq. 11})$$

Table 1. Temperature dependences of the stability constants of complex compounds formed by praziquantel and α -, β -, and γ -cyclodextrins

T, K	$K \cdot 10^{-2}$, mol/L		
	α -CD...PR	β -CD...PR	γ -CD...PR
296	7.1 ± 0.8	5.7 ± 0.7	4.6 ± 0.6
301	5.6 ± 0.7	4.6 ± 0.6	3.9 ± 0.5
306	4.0 ± 0.5	3.8 ± 0.5	3.1 ± 0.4
311	2.7 ± 0.3	3.0 ± 0.4	2.0 ± 0.2
316	1.1 ± 0.1	2.1 ± 0.2	1.8 ± 0.2

Table 2. Thermodynamic parameters of the complexation reactions of praziquantel with α -, β - and γ -cyclodextrins

Reaction systems	ΔS° , kJ/mol $^{-1}$ K $^{-1}$	ΔH° , kJ/mol	ΔG° (298 K), kJ/mol
α -CD + PR	-180 ± 20	-70 ± 8	-16 ± 2
β -CD + PR	-70 ± 8	-35 ± 4	-14 ± 2
γ -CD + PR	-80 ± 9	$-40 \pm$	-16 ± 2

Figure 1. UV spectra of aqueous-alcoholic solutions of praziquantel (1) and its complex with α -cyclodextrin (2), 296 K, $[PR] = [\alpha\text{-CD}] = 5 \cdot 10^{-4}$ mol/L

Figure 2. Isomolar diagram for the complex of praziquantel with α -cyclodextrin; 296 K, $[PR] + [\alpha\text{-CD}] = 1 \cdot 10^{-3} \text{ mol/L}$

Figure 3. Dependency diagram of $[PR]/\Delta A$ versus $1/[\alpha\text{-CD}]$ for a complex formed by praziquantel and α -cyclodextrin; 296 K, $[PR] = 2.0 \cdot 10^{-4} \text{ mol/L}$, $[\alpha\text{-CD}] = (0.5 \div 8.0) \cdot 10^{-4} \text{ mol/L}$

Figure 4. IR spectrum of praziquantel

Figure 5. IR spectrum of α -cyclodextrin

Figure 6. IR spectrum of the complex of α -cyclodextrin with praziquantel