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БАЯНДАМАЛАРЫ

ДОКЛАДЫ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

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ENCAPSULATION OF VITAMIN AEVIT OIL SOLUTION WITH β-CYCLODEXTRIN

Abstract. The present work aimed at encapsulation of fat-soluble vitamin Aevit (vitamins A and E, oil) with β-cyclodextrin. Inclusion complex of vitamins A and E with β-cyclodextrin was prepared in an aqueous alcohol medium by ultrasonic treatment. The surface morphology of the resulting clathrate inclusion complexes was described using a scanning electron microscope. The results of thermographic measurements on a differential scanning calorimeter are presented. The spectral properties of the inclusion complex are characterized by ^{1}H and ^{13}C NMR spectroscopy data. The experimental results confirmed the existence of a complex of inclusion of β-cyclodextrin with vitamin Aevit (2:1). The activation energy of the thermooxidation destruction reaction of the clathrate complex β-cyclodextrin:vitamin Aevit was calculated, kinetic parameters of thermal destruction of clathrate were determined. These parameters were determined based on the Freeman-Carroll, Sharpe-Wentworth, Ahar and Coates-Redfern methods. The use of the above models made it possible to graphically establish the thermodynamic parameters of the thermal decomposition of β-cyclodextrin and its clathrate with vitamin. The data of thermographic measurements on a differential scanning calorimeter showed that the thermal destruction of the Aevite clathrate with β-cyclodextrin begins with the removal of water molecules from the β-cyclodextrin cavity, then the "guest" substance and the cyclic oligosaccharide are destroyed.

Key words: cyclodextrins, β-cyclodextrin, encapsulation, clathrate, vitamin.

Introduction. During food processing (including preparation) losses of vitamins might decreses the nutritional quality of foods. In these cases, there is a need for food fortification with vitamins. However, the lipophilicity of many vitamins and other preparations (essential oils, carnosol and fish oil) makes it difficult to use them in technological processes. In recent years, the use of cyclodextrins (Cds) in the food industry has attracted the interest due to their ability to improve solubility and stability of various food components [1-3]. Particularly, CDs can be used to stabilize flavors, vitamins, and essential oils against unwanted changes, to suppress unpleasant odors or tastes, and to achieve controlled release of certain food constituents [1,4]. Additionally, they can decrease the glycemic index of the food and improve the gut microflora [5]. Thus, CDs have applications in many areas including the pharmaceutical, chemical, cosmetic and food industries.

CDs are cyclic oligosaccharides that have an internal hydrophobic cavity and a hydrophilic outer shell. They are products of the biochemical transformation of starch. The CD family includes three main products: α-, β-, and γ-CD, whose macrocircles consist of six, seven, and eight glucopyranose residues, respectively. Hydrophobic molecules are embedded in the internal cavity of the CD, forming supramolecular nanostructured inclusion complexes of the "guest-host" type [5,6]. It provides substantial changes in the physico-chemical properties of molecules associated with CDs: an increase in the stability of the molecule of a "guest" substance that is sensitive to oxygen or light [2,7-11], an increase in the solubility [12,13], a conversion of liquids into powder [12,14] and a suppress of unpleasant smell and taste [2,15,16]. β-CD is a food additive (E459), stabilizer and emulsifier that provides food viscosity and maintains a uniform dispersion of immiscible substances and components [4,8,10].

In the present study we ained at encapsulation of a fat-soluble vitamin mixture Aevit (AE) with β-CD. AE is a complex vitamin preparation with immunostimulating and antioxidant properties and is composed Aevit is composed of two vitamins – A (retinol palmiate) and E (alpha-tocopherol acetate). AE promotes tissue regeneration, has a positive effect on vision, supports the reproductive function of the body, improves blood circulation and restores vascular permeability. Vitamins A and E are relatively termostable, but to air oxygen and ultraviolet light [17-19]. On the industrial scale, fat-soluble vitamins are dissolved in vegetable oil or melted fat and minced meat a few minutes before heating, there is a need to develop methods obtain water-soluble clathrate forms of vitamin AE with β-CD. We hypothesized that the use of an oil solution of vitamins can facilitate their entry into cylindrical hydrophobic cavities of β-CD molecules and formation of a guest-host inclusion complex (figure 1). In addition, in the oil shell, vitamin AE might be better preserved from the effects of oxidants and biological digestibility might be improved.

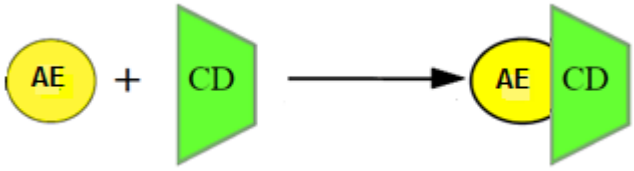

Figure 1 – Schematic representation of the formation of the "guest-host" inclusion complex

Materials and Methods. The following reagents were used: β-CD (99.5%, purchased from Fluka), vitamin complex Aevit (retinol palmitate, 100000 ME, α-tocopherol acetate, 100 IU) in sunflower oil (hereinafter vitamin AE, 200 mg, Medbiopharm, Russia). NMR spectra of ^{1}H and ^{13}C substances were taken in a solution of DMSO-d_6, the remaining reagents had analytical purity. The ^{1}H NMR, ^{13}C NMR measurements were carried out in DMSO-d_6 (Aldrich) solutions. All other chemicals were of analytical grade purity.

The surface morphology of samples of inclusion complexes (clathrates) was studied using a scanning electron microscope (SEM) from Tescon Mira 3 LMN (Czech Republic). The IR spectra were taken on a Cary 600 Series IR Fourier spectrometer manufactured by Agilent Technologies (USA) in the range of 4000-400 cm^{-1}. The samples were prepared from the tested substances and KBr with a mass ratio of 1:100. The ^{1}H and ^{13}C NMR spectra of the resulting clathrates were recorded on a JNM-ECA Jeol 400 spectrometer (frequency 399.78 and 100.53 MHz, respectively) using a DMSO-d_6 solvent. Chemical shifts were measured relative to the signals of residual protons or DMSO-d_6 carbon atoms.

All measurements were made at a resolution of 4.0 cm^{-1}, the number of scans was 40. The melting points of the complexes were determined on the device "Boetius" (Germany). Ultrasonic treatment of solutions was performed at the JY92-IIDN facility (Shanghai, China). Samples of β-cyclodextrin and the inclusion complex with vitamin AE (weight of attachments 12 mg) were analyzed by thermographic method. Thermal properties were determined using a DTA/DTS differential scanning calorimeter (Labsys Evolution). Measurements were performed in dynamic mode in the temperature range of 30-500ºC: temperature range of 30-500°C, the heating rate of samples from 5 to 20 K/min, atmosphere-nitrogen, air, weight of the attachments 12-16 mg and crucible Al_2O_3.

β-CD inclusion complexes with vitamin AE were prepared in an aqueous-alcohol medium (1:1) under ultrasonic treatment [17,18]. β-CD was dissolved in distilled water at a temperature of 80°C in a water bath. The solution was cooled to 60°C and an alcoholic solution of vitamin AE was added drop by drop while stirring. The resulting water-alcohol solution of the β-CD:AE inclusion complex was subjected to

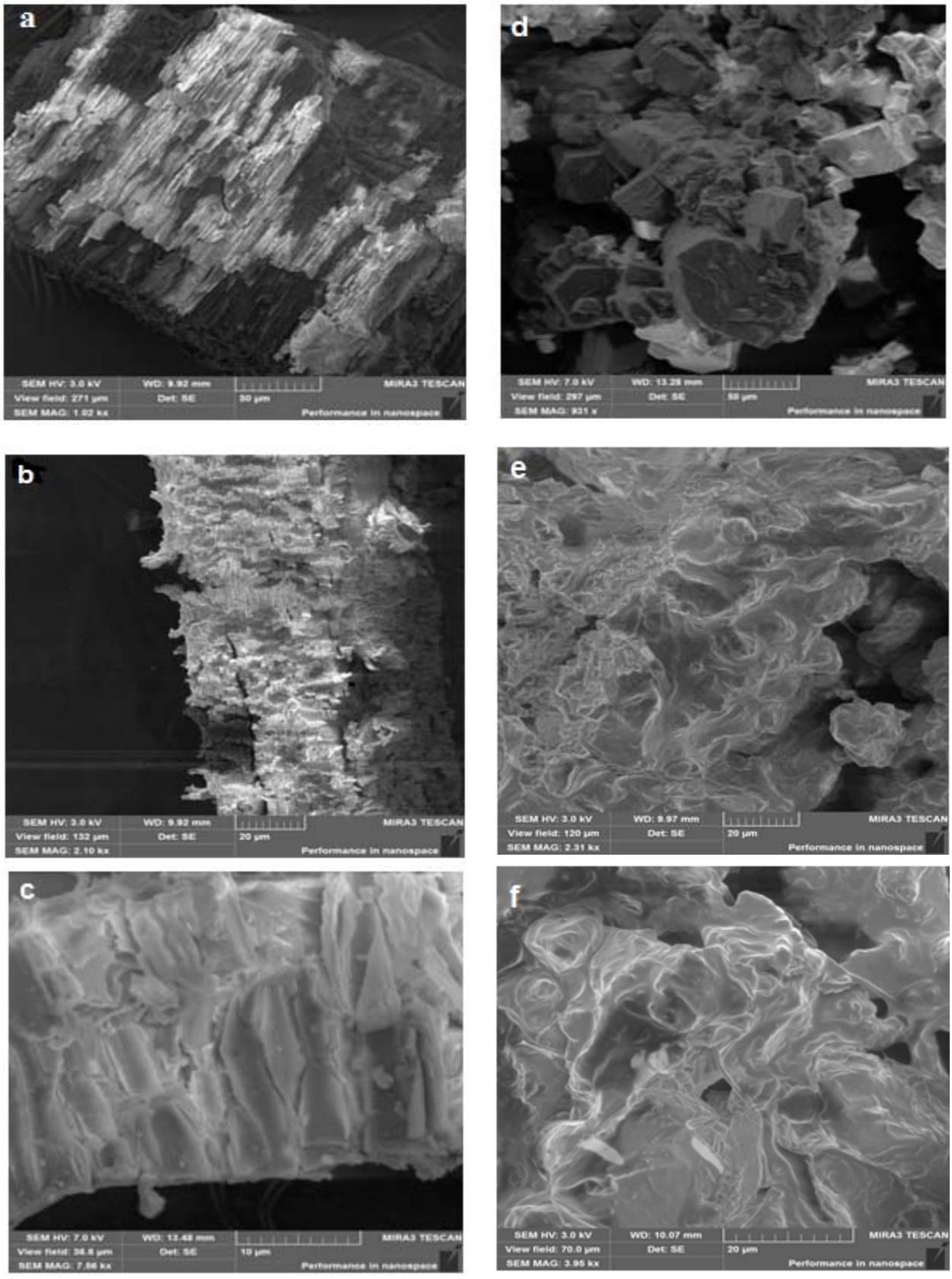

Figure 2 – Scanned electron micrographs of β-cyclodextrin (a-c) and the inclusion complex of β-CD:AE (2:1) (d-f) at various magnifications

ultrasonic treatment (22 kHz) for 30 minutes. At the same time, there was a gradual turbidity of the solution and the formation of fine particles of inclusion complexes. The resulting dry powder was ground to a homogeneous state in a mortar. They were stored in hermetically sealed vials, in a desiccator with $CaCl_2$. The complexes of inclusion of vitamin AE with β-CD were obtained at various ratios: 1:0.2; 1:0.25; 1:0.3 and 1:0.5. Products were obtained in a form of white powders that dissolve in water with the formation of colloidal solutions of milky white color.

Results and Discussion. The determination of the amount of vitamin AE in inclusion complexes was carried out using the gravimetric method. Depending on the ratio of β-CD:AE, different amounts of vitamin AE were included in clathrates. Hexane solvents and 50% dimethyl sulfoxide were used to extract vitamin AE from the clathrate complex. The optimal stoichiometric molar ratios of the components in the β-CD:AE complex were in the range 2:1 - 3:1, which corresponds to the content of vitamin AE in the complex from 8.6 to 9.1%. The solubility of the complex in distilled water was 0.78 ± 0.03%.

The morphology of β-CD particles and binary systems were analyzed by SEM. The SEM method is a qualitative method used to study the structural aspects of the object of study and helps to assess the presence of another component in the resulting preparations. Scanned electron micrographs of the β-CD:A inclusion complex (2:1) are presented in figure 2.

Similar results were reported previously, that changes in the crystal surface morphology are convincing evidence of the formation of an inclusion complex [20-22].

Furthermore, formation of the inclusion complex of vitamin AE with β-CD was confirmed by thermal analysis. Thermoanalytic indicators of β-CD:AE decomposition (2:1) are represented by TG/DTG curves (figures 3 and 4). It should be noted that the total mass loss at five heating rates was 74.9-81.6%. In all the dependences, changes in the relative mass at various heating rates are manifested at temperatures in the range 220-450°C. On the differential curves, several zones of intense mass loss in the temperature range: (50-90)°C, (230-360)°C and (360-440)°C can be distinguished (figure 3). The first zone corresponds to the loss of water by clathrate, the second – to the destruction of the CD ring, the third – to the oxidation of products formed during the destruction of the CD ring.

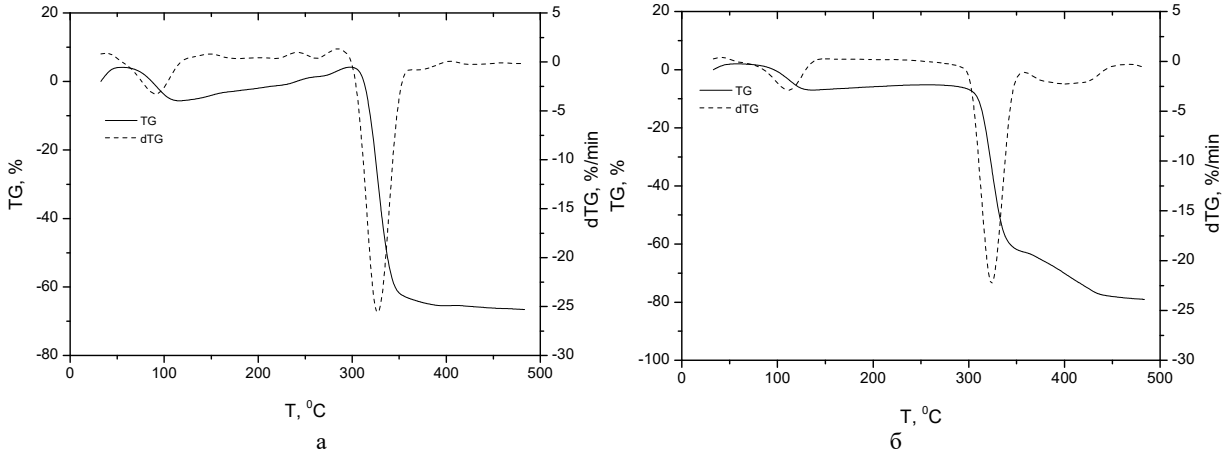

Figure 3 – TG/DTG curves of β-CD (a) and β-CD:AE (1:1) (b) with a constant heating rate of 10 deg/min in nitrogen

The resulting β-CD:AE clathrates contained bound water, as did β-CD. The endothermic peak of dehydration of the samples was in the range of 60-90°C (figure 3). On TG/DTG curves, the peak response is maintained, but a decrease in intensity is observed. The peak heat absorption caused by the activation of thermal destruction of β-CD:AE is in the range of 280-360°C, and for pure β-CD is 270-320°C. A new endothermic effect associated with the decomposition of the vitamin AE molecule appears on the TG curve in the range of 340-450°C. Thermographic analysis data at various heating rates showed that β-CD and β-CD:AE clathrate differ in the temperature of the onset of the thermal decomposition reaction and in the nature of the mass loss of the samples when heated to 500°C. These data may be associated with the

formation of an amorphous inclusion complex through the molecular encapsulation of vitamin AE inside the β-CD cavity [23].

Figure 4 and table 1 show the results of processing TGA β-CD:AE (1:1) with a constant heating rate (10 deg/min in a nitrogen atmosphere) according to the Freeman-Carroll method (a), Sharp-Wentworth (b), Ahara (c) and Coates-Redfern (d) [23].

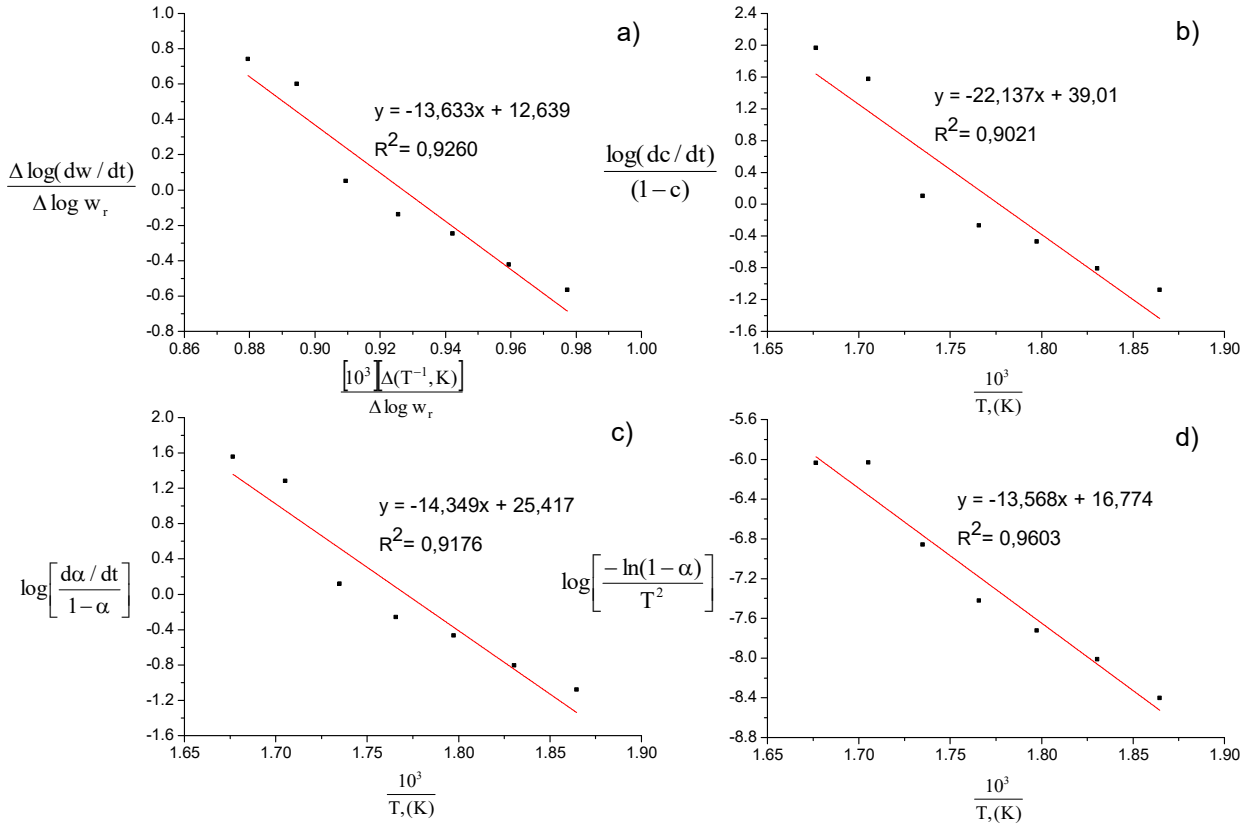

Figure 4 – Graphical results of the analysis of TGA β-CD:AE (1:1), determined by the methods of Freeman-Carroll (a), Sharp-Wentworth (b), Ahar (c) and Coates-Redfern (d) at a constant heating rate (10 deg/min under nitrogen)

Table 1 - Kinetic parameters of thermal destruction of β-CD and β-CD: AE (in nitrogen atmosphere)

Example	Freeman-Carroll method		Sharp-Wentworth method		Ahara method		Coates-Redfern method	
	E, kJ/mol	n	E, kJ/mol	Ax10^{15}, min^{-1}	E, kJ/mol	Ax10^{9}, мин$^{-1}$	E, kJ/mol	Ax10^{5}, min^{-1}
β-CD	548.71	1.4	712.24	1.27	600.84	1.10	458.70	1.32
β-CD:AE	260.69	1.1	423.31	1.46	274.38	1.82	259.45	3.21

In the IR spectra of β-CD and β-CD:AE, stretching vibrations of the O-H bond of hydroxyl groups in the form of a wide band with a maximum at 3387 cm^{-1} are manifested in all binary systems. There is also an absorption band at 2924 cm^{-1} stretching vibrations of CH bonds in the CH and CH_2 groups, 1651 cm^{-1} bending vibrations of the OH bond in the SON groups, and an absorption band at 1423, 1364, 1335 cm^{-1} bending vibrations of the C-H bonds in the CH_2OH and CHOH groups [16,17,20,21]. In the IR spectra of the β-CD:AE complex, absorption bands of C = C, OH hydroxyl bonds, and other AE groups do not appear. This may mean that these groups are masked by very wide and intense β-CD bands in the same wavelength range.

One of the informative methods confirm the formation of inclusion complexes is the ^{1}H NMR spectroscopy method [22,24-27]. The β-CD molecule has the shape of a truncated cone, in the inner hydrophobic binding surface of which protons H-3 and H-5 are located, and on the outer - protons H-2 and H-4 [14,15,19]. This analysis method allows one to fix a pronounced chemical shift in the vibrational spectra of H-3 and H-5 β-CD protons oriented inside the torus cavity, which is due to the placement of the guest molecule in the hydrophobic cyclodextrin cavity. According to our studies [28, 29], the manifestation of six groups of signals in the 3.32–3.35 range is characteristic of the ^{1}H NMR spectrum of individual β-CD; 3.45-3.65; 4.48-4.55; 4.78-4.82; 5.67-5.76 ppm. The most low-field doublet signal in the range of 5.71-5.73 ppm with a splitting of 4 Hz belongs to the proton of the hydroxyl group at the C-2 atom. The proton of the OH group of a neighboring atom (OH-3) located in the internal cavity of the β-CD molecule also resonates in the field of weak field. Doublet signal in the range of 4.78-4.82 ppm corresponds to the proton H-1. The location of this proton in a weaker field compared to the protons of other CH groups is due to the influence of the oxygen atom. In the range of a strong field (3.58-3.65 ppm), signals of H-6a,b of the methylene group are observed. High-intensity signal at 3.46 ppm corresponds to the proton H-3 glucopyranose link. Table 2 also presents six signal groups of ^{13}C NMR nuclei of the elementary unit of the initial β-CD. The signal of the C-6 atom appears at 60.41 ppm. Signals at 72.49, 72.85 and 73.51 ppm. are caused by C-5, C-2 and C-3 atoms, respectively. In the range of 82.02 and 102.41 ppm. signals of carbon atoms C4 and C-1 are observed, which are directly connected to the adjacent glucopyranose link through the oxygen bridge [24, 28, 29-33].

The values of the chemical shift ^{1}H and ^{13}C NMR of β-CD in the free and complexing state are shown in table 2. All six β-CD protons show a pronounced chemical shift towards a strong field. In the ^{1}H NMR spectrum of β-CD:AE, the largest difference in the values of the chemical shift Δδ is characteristic of the intraspheric protons H-3 and H-5, on the basis of which it can be concluded that an internal (inclusive) complex is formed in clathrate [30-32]. In the case of the carbon spectrum, chemical shifts were more pronounced and ranged from 0.05-0.24 ppm. With an increase in the concentration of the guest substance (vitamin AE), a proportional increase in the chemical shift in the ^{1}H NMR vibrational spectra was observed due to a shift in the equilibrium state towards the formation of an inclusion complex. These observations confirmed formation of inclusion complex and suggested that hydrophobic interactions are the driving forces for the formation of an inclusion complex [25].

Table 2 – Chemical shifts of ^{1}H and ^{13}C β-cyclodextrin in the free state and in the inclusion complex

Protons β-CD	δ_0 (^{1}H), ppm.	δ (^{1}H), ppm.	$\Delta\delta = \delta - \delta_0$, ppm.	Atoms C	δ_0 (^{13}C), ppm.	δ (^{13}C), ppm.	$\Delta\delta = \delta - \delta_0$, ppm.
H-1	4,789	4,722	-0,067	C-1	102,43	102,32	-0,11
H-2	3,579	3,554	-0,025	C-2	73,85	72,71	-0,14
H-3	3,795	3,695	-0,100	C-3	73,61	73,45	-0,16
H-4	3,480	3,430	-0,050	C-4	82,16	82,13	-0,03
H-5	3,637	3,565	-0,072	C-5	72,68	72,54	-0,14
H-6	3,576	3,481	-0,095	C-6	60,56	60,49	-0,07

Conclusion. Encapsulated inclusion complexes of β-cyclodextrin with vitamin AE complex were obtained. The synthesized β-CD:AE complexes belong to host-guest inclusion compounds. The decisive role in the formation of the clathrate complex belongs to nonspecific (dispersion and Van der Waals) interactions. SEM, TG and DTA analyzes, as well as ^{1}H NMR, ^{13}C spectroscopy of vitamin AE clathrates with β-cyclodextrin indicate their formation. The complex has potential applications in food industry.

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МАЙЛЫ АЕVIТ ДӘРУМЕНІН β-ЦИКЛОДЕКСТРИНМЕН ҚАПТАУ

Аннотация. Мақалада майда еритін аевит дәруменінің (А және Е дәрумені, май) β-циклодекстринмен (β-ЦД) қапталу үдерісін зерттеу нәтижелері келтірілген. β-циклодекстрин арқылы Аевит дәруменін қаптау арқылы клатратты комплекс алу үдерісі сулы-спиртті ортада ультрадыбыстық өңдеу әдістемесін қолдану арқылы жүргізілді. Алынған клатраттық қосындылардың кешендерінің беткі морфологиясы сканерлеуші электронды микроскоптың көмегімен сипатталған. Дифференциалды сканерлеу калориметріндегі термографиялық өлшеулердің нәтижелері ұсынылған. Қосылыс комплекстерінің спектральді қасиеттері ^{1}H мен ^{13}C ЯМР спектроскопия әдістері арқылы зерттелді. Зерттеу нәтижелері β-циклодекстриннің АЕ дәруменімен комплекс түзетінін дәлелдеуге мүмкіндік берді. В-циклодекстрин клатрат кешенінің термо-тотықтырғыш деструкциясы реакциясының активтену энергиясы есептелді: Аевит витамині есептелді, клатрат термодеструкциясының кинетикалық параметрлері анықталды. Аталған көрсеткіштер Freeman-Carroll, Sharpe-Wentworth, Ahar and Coates-Redfern әдістерін қолдану арқылы анықталды. Жоғарыда келтірілген модельдерді қолдану β-циклодекстриннің және оның витамині бар клатраттың термиялық ыдырауының термодинамикалық параметрлерін графикалық түрде орнатуға мүмкіндік берді. Дифферен-циалды сканерлеу калориметріндегі термографиялық өлшеулер көрсеткендей, Аевит клатратының β-цикло-декстринмен термодеструкциясы β-циклодекстрин қуысынан су молекулаларын шығарудан басталады, содан кейін "қонақ" зат пен циклдік олигосахарид жойылады.

Түйін сөздер: циклодекстриндер, β-циклодекстрин, инкапсуляция, клатрат, дәрумен

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ИНКАПСУЛЯЦИЯ МАСЛЯНОГО РАСТВОРА ВИТАМИНА АЕВИТ β-ЦИКЛОДЕКСТРИНОМ

Аннотация. Настоящая работа направлена на инкапсуляцию жирорастворимого витамина Аевит (витамины А и Е, масло) с β-циклодекстрином. Комплекс включения витаминов А и Е с β-циклодекстрином готовили в водно-спиртовой среде методом ультразвуковой обработки. Морфология поверхности полученных комплексов клатратных включений описана с помощью сканирующего электронного микроскопа. Представлены результаты термографических измерений на дифференциальном сканирующем калориметре. Спектральные свойства комплекса включения характеризуются данными ЯМР-спектроскопии 1H и 13C. Экспериментальные результаты подтвердили существование комплекса включения β-циклодекстрина с витамином Аевит (2:1). Рассчитана энергия активации реакции термоокислительной деструкции клатратного комплекса β-циклодекстрин: рассчитан витамин Аевит, определены кинетические параметры термодеструкции клатрата. Данные параметры определялись на основе методов Freeman-Carroll, Sharpe-Wentworth, Ahar and Coates-Redfern.. Использование приведенных выше моделей позволило графически установить термодинамические параметры термического разложения β-циклодекстрина и его клатрата с витамином. Данные термографических измерений на дифференциальном сканирующем калориметре показали, что термодеструкция клатрата Аевита с β-циклодекстрином начинается с удаления молекул воды из полости β-циклодекстрина, затем разрушаются “гостевое” вещество и циклический олигосахарид.

Ключевые слова: циклодекстрины, β-циклодекстрин, инкапсуляция, клатрат, витамин.

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