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Preparation of encapsulated α-tocopherol acetate and study of its physico-chemical and biological properties

The article discusses the results of research for obtaining encapsulated vitamin E using a water-soluble oligosaccharide (cyclodextrin). The inclusion complexes of β-CD with α-tocopherol were obtained in an aqueous-alcoholic medium by coprecipitation and microwave activation. The highest yields of target clathrate inclusion complexes of vitamin E with cyclodextrin were obtained under microwave synthesis conditions. Molecular modeling of inclusion complexes of α-tocopherol acetate with β-cyclodextrin in the ratios of 1:1, 1:2, 1:3, and 1:4 was performed using the MM+ method. Based on semi-empirical PM3 calculations, without taking into account the influence of the environment, the total energy of the systems under study was estimated. Data on the study of the structure of the clathrate complex of α-tocopherol acetate with β-cyclodextrin was presented. The surface morphology of the resulting "guest-host" clathrate complex was described using a scanning electron microscope. The spectral properties of the inclusion complex were characterized by FT-IR and ^{1}H and ^{13}C NMR spectroscopy data. The study of the ^{1}H NMR and ^{13}C NMR spectra of β-CD in the free and bound state in the form of the β-CD: VE clathrate made it possible to reveal the displacements of the signals of the nuclei (± Δδ) ^{1}H and ^{13}C of the host molecule both in the region of weak and strong fields. The experimental results confirmed the possibility of the formation of inclusion complexes of α-tocopherol acetate with β-cyclodextrin at various ratios. The data on the study of the effect of encapsulated α-tocopherol acetate on the safety of food meat products was presented.

Keywords: α-tocopherol acetate, cyclodextrin, oligosaccharides, vitamin E, starch, inclusion complexes, NMR spectroscopy, clathrate.

Introduction

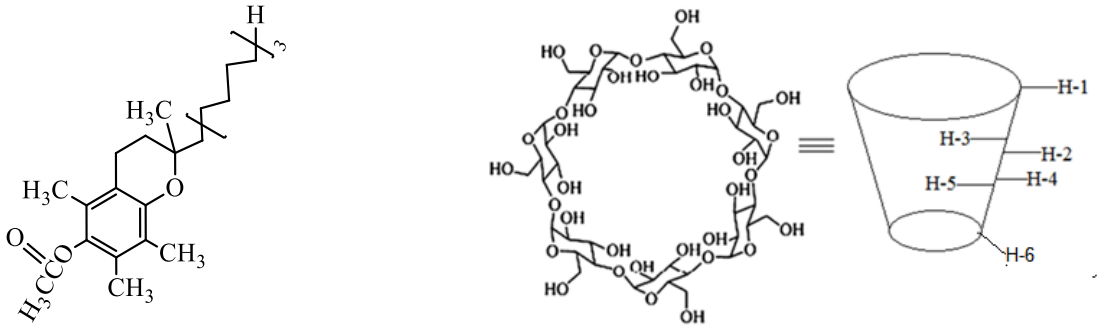
α-Tocopherol (vitamin E) is a fat-soluble vitamin that is necessary for the normal functioning of the human body. It inhibits antioxidant properties and is involved in many metabolic processes. The daily requirement of α-tocopherol is 10–15 IU/day. At present, α-tocopherol acetate (VE) is widely used as an ingredient in food production (Fig. 1). Under production conditions α-tocopherol acetate is easily destroyed under oxygen and ultraviolet rays [1, 2]. Thus, there is a need to obtain its encapsulated water-soluble forms with improved biofunctional properties.

Currently, water-soluble cyclodextrins derived from starch are widely used for encapsulating vitamins and pharmaceuticals. This innovative direction in food and pharmaceutical industry is of high practical importance [5]. Biologically active compounds encapsulated by oligasaccharides make up almost 50 % of all manufactured pharmaceutical and food products in Japan and about 25–30 % in Europe, the USA and Russia [6].

Cyclodextrins (CDs) are enzyme-modified starch derivatives. They are able to form "guest-host" inclusion complexes with molecules of low hydrophilicity due to the hydrophobic inner surface of these ring-shaped molecules. The variants of these cyclic oligosaccharides consist of 6, 7, or 8 glucopyranose units (α-, β -, and γ-CDs, respectively) with different sizes (0.5-0.9 nm in diameter), which determines the geometric arrangement of the guest molecules in the cavity (Fig. 1). VE can be better preserved in the cyclodextrin shell from the actions of oxidizing agents and have improved digestibility.

The process of complexation of VE with β-cyclodextrin (β-CD) has been previously studied [3–7]. The results indicated a possibility to use the β-CD inclusion complexes with VE in the manufacturing confectionery products. The optimal stoichiometric ratio of the components in the "β-CD:VE" complex was shown to be 1:3 mol/mol [3]. The VE inclusion complexes were obtained by grinding in the paste and co-precipitation [3–7].

However, the use of these methods cannot provide the complete formation of a nanostructured complex (clathrates) of the native form of β-CD with VE.



(1) (2)

Figure 1. Structural formulas of α-tocopherol acetate (1) and β-CD (2)

Other research groups used methods of ultrasonic (UV) and microwave irradiation (MW) of a solution of a mixture of VE and β-CD in a ratio of 1:1 to obtain clathrate complexes V, but there are no descriptions of methods for carrying out UV and MW syntheses of inclusion complexes [8–10].

The aim of our work was to develop technological methods for obtaining encapsulated complexes of VE inclusion and to study their physical and chemical properties, as well as its safety in food products. The physicochemical properties and structural features of the obtained "β-CD:VE" complexes were studied using modern physicochemical methods, namely SEM, DSC, IR, NMR^{1}H and ^{13}C spectroscopy.

Experimental

The following reagents were used in the experiments:

– vitamin E (α-tocopherol acetate, VE) $C_{31}H_{52}O_3$, transparent viscous oil of light-yellow color (1 IU of vitamin E = 1 mg). Molar mass of α-tocopherol acetate is 472.76 g/mol, d^{20}_4 = 0.9545–0.9665; n^{20}_4 = 1.4958–1.4972; maximum absorption E = 42.5 at 285.5 nm;

– β-cyclodextrin (99.5 %), (company "Fluka"), white crystalline substance, m.p. 280–299 °C, soluble in water when heated, well soluble in dimethylsulfoxide and pyridine.

The preparation of β-CD inclusion complexes with VE was carried out in an aqueous-alcohol medium. A mixture of calculated amounts of β-CD (mmol) and VE (mmol) in different ratios (1:1, 2:1, 3:1, 4:1) was dissolved in a mixture of solvents water:ethanol (1:1) and heated in a microwave oven for 160–180 seconds in increments of 2 minutes at 80 °C. The microwave activation of the reaction medium was carried out at a power of 850 W using the Anton PaarMonowave 300 device. Under these conditions the highest yield of "β-CD:VE" clathrates was observed at the 2:1 ratio. The resulting products were white powders that are dissolved in water to form colloidal solutions of milky white color. The solubility of the "β-CD:VE" (2:1) complex in water (with a slight heating) was 21–22 ± 0.05 mg/100 ml.

The IR spectra of the "β-CD:VE" inclusion complexes were taken on a Cary 600 Series IR Fourier spectrometer manufactured by Agilent Technologies (USA). The ^{1}H and ^{13}C NMR spectra of the obtained clathrates were recorded on a JNM-ECA Jeol 400 spectrometer (frequency 399.78 MHz, DMSO-d_6). The surface morphology of the samples of the inclusion complexes was studied using a scanning electron microscope (SEM) from Tescon Mira3 LMN (Czech Republic). The results of thermal analysis of samples of the inclusion complexes "β-CD:VE" (2:1 and 4:1) (weight 12 mg) were studied using a differential scanning calorimeter Setaram DTA/DSC and they were described by us in [11].

Molecular modeling of inclusion complexes of VE with β-cyclodextrin was performed by molecular mechanics MM+ using the HyperChem 8.0 software. The initial structure of β-cyclodextrin was taken from the PubcChem database (PubChem SID24892722). First, the structure of the complex was built and its geometry was optimized by the MM+ method. Then the assessment of the geometric and energy parameters of the model was carried out by semiempirical PM3 method using Single Point calculations. All calculations were performed without taking into account the effect of the solvent (gas phase, vacuum).

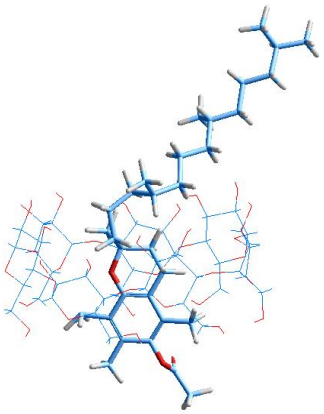
Obtaining meat sausage samples and analysis of quality and safety indicators of VE encapsulated by β-CD as part of a food product were carried out on the basis of the Kazakh Agrotechnical University (Nur-Sultan).

Results and Discussion

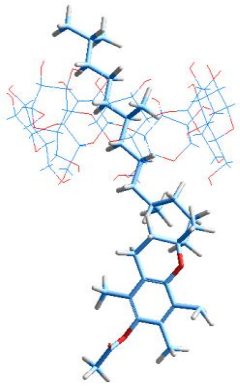
Molecular modeling of complexes of "β-CD:VE" using the HyperChem program. PM3 Calculation method

Assessment of the geometric parameters of the VE and β-cyclodextrin molecules showed the possibility of the inclusion complexes formation between them. The spatial "elongation" of the VE molecule does not exclude the possibility of the formation of β-CD: VE complexes with stoichiometry as 1:1, 1:2, 1:3 and 1:4.

Molecular modeling of "β-CD:VE" inclusion complexes in various ratios was performed. Structures of optimized complexes are shown in Figures 2–4.



E_{total} = –500093 kcal/mol
a) Type I



E_{total} = –500142 kcal/mol
b) Type II

Figure 2. Molecular models of the VE complex with β-CD

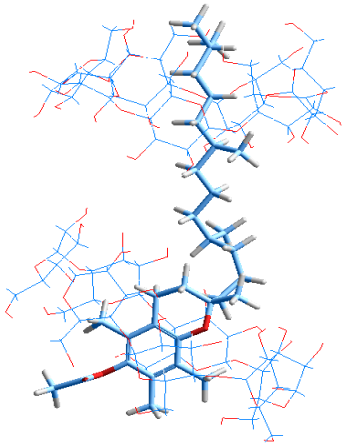
It can be seen from the data presented in Figure 2 that the formation of two types of inclusion complex is possible as a result of the 1:1 interaction of VE with β-cyclodextrin (Fig. 2):

– Type I — due to the penetration of the chroman ring VE into the cavity of the cyclodextrin;

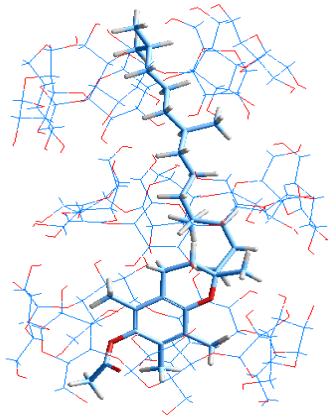
– Type II — due to the penetration of the isoprenoid side chain VE into the cavity of the cyclodextrin.

Comparison of the total energies of these complexes of two types in Figure 2 showed that the formation of the inclusion complex of α-tocopherol acetate with β-cyclodextrin by Type II at ΔE = 49 kcal/mol is thermodynamically more favorable.

The next step was molecular modeling of the "β-CD:VE" inclusion complexes in the ratios of 1:2 and 1:3. Molecular models of "β-CD:VE" complexes obtained as a result of geometry optimization by molecular mechanics in ratios 1:2 and 1:3 are shown in Figure 3.



E_{total} = –876579 kcal/mol
a) complex ratio 1: 2



E_{total} = –1253252 kcal/mol
b) complex ratio 1:3

Figure 3. Molecular model of the "β-CD:VE" complex in the ratios of 1:2 (a) and 1:3 (b)

It can be seen from the molecular models shown in Figure 3 that complexation with two molecules of cyclodextrin does not cause noticeable deformation of the cyclodextrin ring, while complexation with three molecules of cyclodextrin leads to the reversal of some glucoside rings and flattening of the walls of the toroidal cavity, i.e. to conformational deformation.

It was interesting to simulate the inclusion complex of VE acetate with four β-cyclodextrin molecules. As a result of geometry optimization by the MM+ method, a molecular model of the "β-CD:VE" complex in a ratio of 1:4 was obtained (Fig. 4).

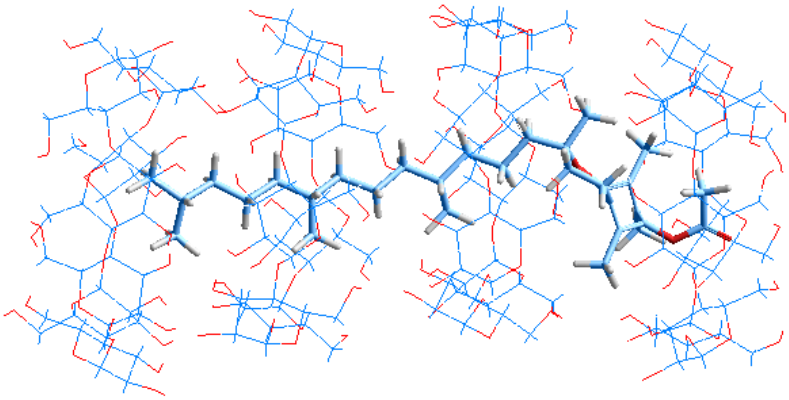


Figure 4. Molecular model of the "β-CD:VE" complex in a ratio of 1:4 (E_{total} = –1629877 kcal/mol)

The analysis of the geometry showed that the bounds between VE and fourth cyclodextrin ring were weakly. Thus it can be concluded that the complexes of the 1:4 composition are quite unstable compared to the complexes with the ratios of 1:1, 1:2 and 1:3.

Study of the morphology of "β-CD:VE" clathrate inclusion complexes

The morphology of the β-CD particles and the "β-CD:VE" inclusion complexes were analyzed using a scanning electron microscope (SEM). Figure 5 shows scanned electronic micrographs of the "β-CD:VE" inclusion complex (2:1). The studied samples of clathrates were sprayed with a conductive layer of carbon. The images were obtained at accelerating voltages of 3 and 7 kV. The magnification in the panels (*a*–*d*) is from 931 to 7560×.

The images of the samples (a, b) show the layered structure of β-cyclodextrin, and the samples (c, d) "β-CD:E" (2:1) show a change in the morphology and shape of the crystals (there is a state of crystallization of the raw material, the layered structure is not visible, the shape of the crystals is different, the crystal forms are covered with a film [12–14].

IR and ^{1}H NMR spectroscopic investigation of the "β-CD:VE" complex

Figure 6 shows the IR spectra of β-CD (a, b) in the free state and in the form of clathrate. The peaks of the carbonyl C=O and aromatic CH groups are clearly visible at 1763 and 2947 cm^{-1}, respectively, in the VE Fourier-IR spectrum. There are fluctuations in the carbon skeleton (C-C bonds) in the region of 1211 cm^{-1}. A comparison of the IR spectra of free β-CD (Fig. 6*a, b*) and the "β-CD: VE" clathrate (Fig. 6*c, d*) shows a slight blurring in the appearance of the characteristic absorption bands of the functional groups of the β-CD molecule, which indicates the absence of covalent interactions between VE and the internal functional groups of the β-CD torus.

However, some characteristic absorption peaks of the C-H, NH, and C-O bonds of the β-CD molecule in the complex have offsets, namely from 3387, 2924, 1651, and 1423 cm^{-1} to 3410, 2929, 1655, and 1469 cm^{-1}, respectively. It should also be noted that a characteristic peak of the carbonyl C=O-group in VE appears in the IR spectrum of the clathrate complex (Fig. 6*c*) at 1759 cm^{-1}. This may mean that VE molecules enter the inner torus of β-CD with their side alicyclic chain. These data indicate a change in the structural framework of the internal torus of the "host" (β-CD) in favor of the formation of the "β-CD:VE" inclusion complex (Fig. 7) [8–10].

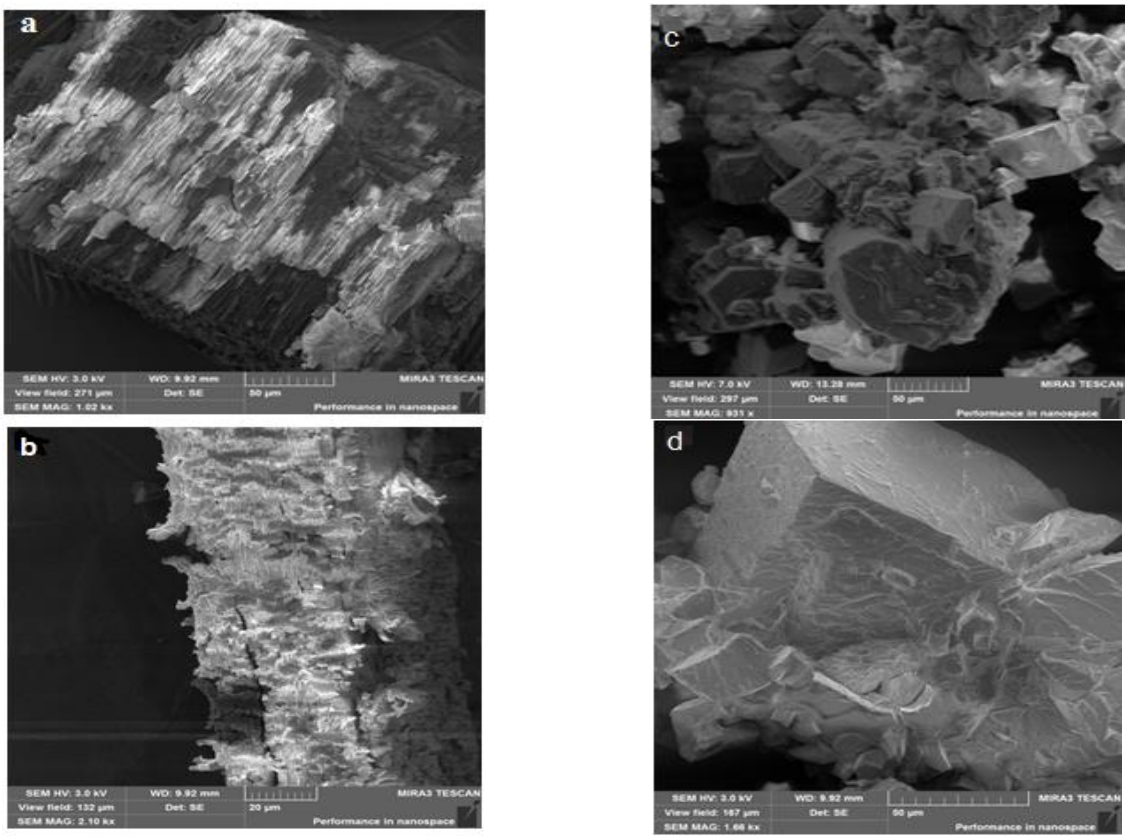


Figure 5. Scanned electron micrographs of β-CD (a, b) and the "β-CD:VE" inclusion complex (2:1) (c, d) at various magnifications

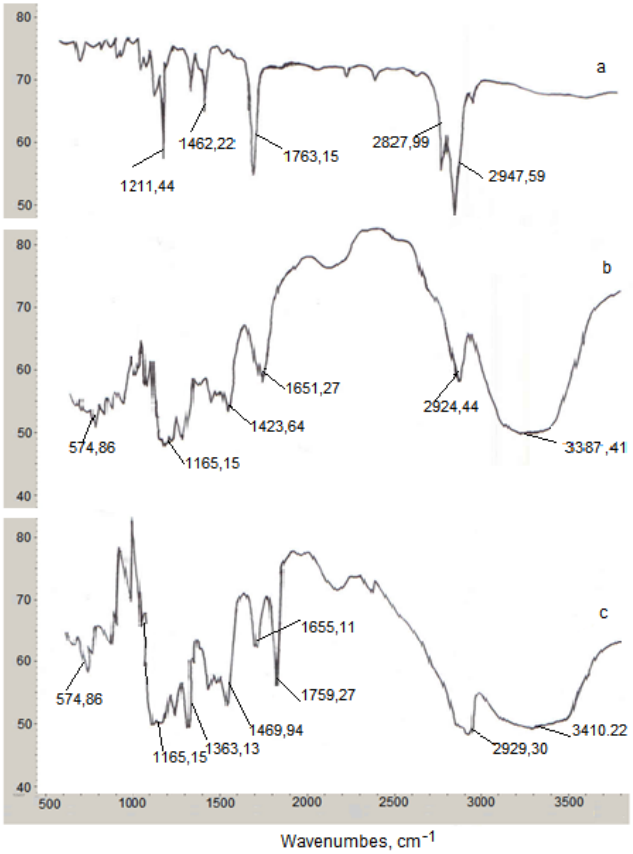


Figure 6. IR-Fourier spectra of VE (a), β-CD (b) and the "β-CD:VE" clathrate complex (KBr) (c)

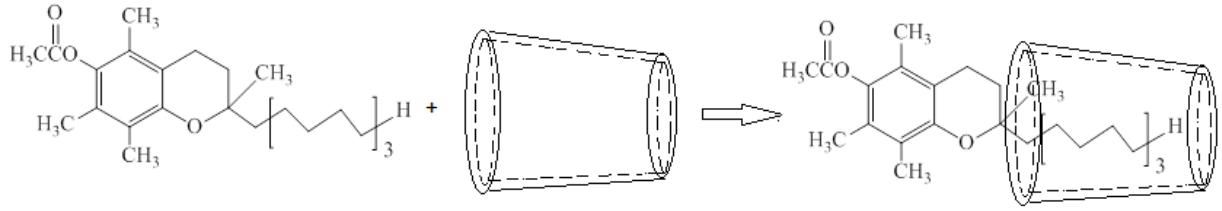


Figure 7. Scheme of the "β-CD:VE" complex formation

The formation of internal and external protons can be distinguished using the NMR spectra of CD and its clathrate complexes. Formation of a substrate complex with CD displaces the proton signals of the initial CD in the NMR spectrum [14]. During the formation of the inner complex shifts of the third and fifth protons are observed, and during the formation of the outer complex shifts of the second and fours protons are observed. One can judge about the formation of internal or external complexes, respectively, according to the magnitude of the chemical shifts of internal or external protons of β-CD.

The shift of the ^{1}H and ^{13}C nuclei ($\pm\Delta\delta$) signals both in the region of weak and strong fields (Table 1) have been observed in the "β-CD:VE" complexes [14, 15].

The study of the ^{1}H (a) and ^{13}C (b) β-CD NMR spectra in the free and bound state in the form of the "β-CD:VE" clathrate (Table 1) revealed the biases of all the signals of the ^{1}H and ^{13}C nuclei of the "host" molecule ($\pm\Delta\delta$) both in the area of weak and strong fields (Table 1). This fact confirms the non-valent binding to the "guest" molecule. In the "β-CD:VE" ^{1}H NMR spectrum, the greatest difference in the values of the chemical shift is characteristic for the intra-atmospheric H-3 protons ($\Delta\delta$ = –0.05 ppm), on the basis of which it can be concluded that an internal (inclusive) complex is formed in the clathrate [9, 15, 16]. In the case of the carbon spectrum there is a less significant difference in the change in chemical shifts, which ranges from –0.01 to 0.01 ppm.

Table 1

Chemical shifts of ^{1}H and ^{13}C NMR of β-cyclodextrin in the free state and in the "β-CD:VE" inclusion complex

Atom no.	The value of δ_0 in the free state, ppm		Value of δ as part of the complex, ppm		Changing the chemical shift, $\Delta\delta = \delta - \delta_0$, ppm	
	$\delta_0(^{1}H)$	$\delta_0\,(^{13}C)$	$\delta(^{1}H)$	$\delta\,(^{13}C)$	$\delta(^{1}H)$	$\Delta(^{13}C)$
H-1	4,77	102,43	4,78	102,44	0,01	0,01
H-2	3,59	73,54	3,57	73,55	-0,02	0,01
H-3	3,55	72,52	3,50	72,53	-0,05	0,01
H-4	3,45	82,00	3,44	82,00	-0,01	0,00
H-5	3,32	72,87	3,30	72,88	-0,02	0,01
H-6	3,60	60,40	3,58	60,39	-0,02	-0,01

Study of the effect of the "β-CD:VE" clathrate complex on some biological properties of a food product

Testing of the proposed solutions with an assessment of the quality and safety indicators of VE encapsulated with *β*-cyclodextrin in the food product was performed. Sausages made from lamb (70 %) and turkey (20 %) were selected as a food model. The basic product for the development of recipes was the Lamb sausage produced according to the GOST 16351-86 (production date 20.09.2020). Organoleptic evaluation of semi-smoked sausages with the "β-CD: VE" clathrate complex was carried out on a 9-point scale according to the GOST 9959-91 "Meat products".

General conditions for organoleptic evaluation. The moisture content was determined according to the GOST 9793-74 by drying the suspension to a constant mass (at 105±3 °C). Physico-chemical and microbiological characteristics of meat product samples with encapsulated vitamin complex "β-CD:VE" were determined in the testing laboratory of "Nuritest" LLP (Almaty, certificate of accreditation KZ.N.02.0043 dated February 08, 2020).

Organoleptic evaluation of the meat sausages demonstrated that the products with the vitamin complex "β-CD:VE" have been characterized by a delicate meat smell, a juicy and tender consistency, and a light brown color. The microbiological parameters of the semi-finished product prototypes meet the requirements of the regulatory documentation according to the results presented in Table 2.

Table 2

Physico-chemical and microbiological characteristics of meat sausage products with encapsulated vitamin complex "β-CD:VE"

Name of indicators	Permissible norms for regulatory documents	Actually received	Designation of regulatory documentation for test methods
Microbiological studies:			
Pathogenic microorganisms, including Salmonella, in 25 g	Not allowed	Not detected	GOST 31659-2012
L. monocytogenes, в 25 г	Not allowed	Not detected	GOST 32031-2012
BGKP (coliforms), in 25 g	Not allowed	Not detected	GOST 9958-81
Staphylococcus aureus, в 1 г.	Not allowed	Not detected	GOST 9958-81
Sulfite-reducing clostridium, in 0.1 g	Not allowed	Not detected	GOST 9958-81
Physical and chemical properties:			
Peroxidenumber, mmol (1/2) / kg	–	3.48±0.35	State Standard (GOST) R 51487-99
Nutritional value, g/100 g:			
Proteins	–	21.64±0.02	25011-81
Fats	–	25.95±0.03	GOST 23042-86
Carbohydrates	–	0.98±0.05	I.M. Skurichin, No.1, 1987
Moisture content	–	49.18±0.24	GOST 9793-74
Ash	–	2.25±0.02	GOST 15113-8-77
Energy value, kcal/kJ/100g	–	324/1355	I.M. Skurichin, No.1, 1987
Vitamins, mg/100g:			
Vitamin E	–	11.28±1.13	I.M. Skurichin, No.1, 1987

Conclusion

The present study proposed the most optimal method for obtaining inclusion complexes of β-CD with VE. The highest yields of target clathrate inclusion complexes of VE with cyclodextrin were obtained under microwave synthesis conditions. Molecular modeling of inclusion complexes of VE with β-CD in ratios of 1:1, 1:2, 1:3, and 1:4 was performed using the MM+ method. The total energy of the systems under study was estimated based on semiempirical PM3 calculations. The study of ^{1}H and ^{13}C NMR spectra of β-CD in a free and bound state in the form of a clathrate "β-CD:VE" made it possible to establish the structural features of supramolecular clathrate complexes of VE. Results of the safety of encapsulated vitamin complex "β-CD:VE" was confirmed by microbiological analysis of a meat product with an encapsulated vitamin complex "β-CD:VE". The microbiological indicators of the meat products correspond to the regulatory documents. The developed scientific approach is of interest for the use of encapsulated vitamins in the production of functional food products.

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Қапталған α-токоферол ацетатының алынуы және оның физикалық-химиялық пен биологиялық қасиеттерін зерттеу

Мақалада суда еритін олигосахаридті (циклодекстринді) қолдана отырып, сыртқы қапталған Е дәруменін алу бойынша зерттеу нәтижелері талқыланған. α-Токоферол ацетатын β-циклодекстринмен қапталған кешенін алу сулы-спиртті ортада тұнбаға бірге түсіру және микротолқынды өңдеу технологиясын қолдана отырып алынған. Е витамині циклодекстринмен кешенді қосылысының ең жоғары шығымы микротолқынды өңдеу жағдайында алынды. ММ+ әдістемесімен α-токоферол ацетатының β-циклодекстринмен 1:1, 1:2, 1:3 және 1:4 қатынастағы комплексті кешендерінің молекулярлы үлгіленулері орындалды. РМ полуэмперикалық РМ3 есептеулері арқылы зерттелуші жүйелердің толық энергиясы реакциялық сұйық ортаның әсерінсіз бағаланды. Олигосахаридпен α-токоферол ацетатының клатраттық кешенінің құрылымын зерттеу бойынша деректер келтірілген. Алынған клатрат кешенінің беткі морфологиясы сканерлеуші электронды микроскоптың көмегімен сипатталған. Қосылу кешенінің құрылыстары ИҚ-Фурье және ЯМР ^{1}Н және ^{13}С спектроскопия деректерімен сипатталады. β-Циклодекстриннің жекелік және клатартты комплекс түріндегі ЯМР ^{1}Н и ЯМР ^{13}С спектрлерін талдау молекулалардағы ^{1}Н және^{13}С ядроларының әлсіз және күшті өріс жақтарға жылжуларын (±Δδ) анықтауға мүмкіншілік жасады. Тәжірибелердің нәтижелері α-токоферол ацетатын β-циклодекстринмен әртүрлі арақатынаста қосу кешенінің қалыптасуын растады. Инкапсуланған α-токоферол ацетатының тағамдық ет өнімдерінің қауіпсіздігіне әсерін зерттеу бойынша деректер келтірілген.

Кілт сөздер: α-токоферола ацетат, циклодекстрин, олигосахаридтер, Е витамині, крахмал, қосылу кешені, ЯМР спектроскопиясы, клатрат.

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Получение инкапсулированного ацетата α-токоферола и исследование его физико-химических и биологических свойств

В статье обсуждены результаты исследования по получению инкапсулированного витамина Е с использованием водорастворимого олигосахарида (циклодекстрина). Получение комплексов включения β-ЦД с α-токоферолом осуществлено в водно-спиртовой среде методами соосаждения и микроволновой активации. Наиболее высокие выходы целевых клатратных комплексов включения витамина Е с циклодекстрином были получены в условиях микроволнового синтеза. Выполнено молекулярное моделирование комплексов включения α-токоферола ацетата с β-циклодекстринами в соотношениях 1:1, 1:2, 1:3 и 1:4 с помощью метода ММ+. На основании полуэмпирических РМ3 расчетов без учета влияния среды выполнена оценка полной энергии исследуемых систем. Приведены данные по изучению структуры клатратного комплекса ацетата α-токоферола с β-циклодекстрином. Морфология поверхности полученного клатратного комплекса «гость–хозяин» описана с помощью сканирующего электронного микроскопа. Спектральные свойства комплекса включения охарактеризованы данными ИК-Фурье и ЯМР ^{1}H и ^{13}C спектроскопии. Изучение спектров ЯМР ^{1}H и ЯМР ^{13}C β-CD в свободном состоянии и связанном в форме клатрата «β-CD:VE» позволило выявить смещения сигналов ядер ($\pm\Delta\delta$) ^{1}H и ^{13}C молекулы «хозяина» как в область слабых, так и сильных полей. Результаты экспериментов подтвердили возможность образования комплексов включения ацетата α-токоферола с β-циклодекстрином при различных соотношениях. Приведены данные по изучению влияния инкапсулированного α-токоферола ацетата на безопасность пищевых мясных продуктов.

Ключевые слова: α-токоферола ацетат, циклодекстрин, олигосахариды, витамин Е, крахмал, комплексы включения, ЯМР-спектроскопия, клатрат.

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