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SYNTHESIS AND STUDY OF NANO-SIZED COMPLEX OF Fe(III) WITH ETHYLENEDIAMINEDISUCCINIC ACID.

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In this work, the $FeEDDS_{NP}$ nanocomplex was synthesized by dissolution peptization of a freshly precipitated sol of iron hydroxide $Fe(OH)_3$ in an aqueous solution of the racemic form of H_4EDDS. The complex was characterized by electron absorption spectroscopy and IR spectroscopy. It was shown that the structure of the nanocomplex is identical to the structure of the FeEDDS complex obtained using a two-stage technology. The position of the absorption maxima of iron nanoparticles practically does not change depending on the storage time at room temperature, which indicates the stability of the synthesized nanocomplex. The nanodispersed $FeEDDS_{NP}$ complex is more soluble in water (275 g/l) compared to the FeEDDS complex obtained by the classical method (150 g/l), which greatly facilitates its use as a biologically active compound. To determine the stability of the system depending on the pH, the electrokinetic potential was measured to select the optimal pH of the medium and concentrations to obtain stable dispersed systems. It is shown that at low pH (1.5–4.0) there is a drop in the electrokinetic potential, and when the pH increases, the ξ-potential changes its sign, which is due to the recharging of the colloidal particle and the decrease in the size of the particles. The system is stable in the range of pH 4.5–7.5 and a wide range of concentrations ($1 \cdot 10^{-1}$–$1 \cdot 10^{-3}$ M). At a metal concentration of 6–8 wt.%, the system is thixotropic-reversible and does not require additional stabilization, since EDDS itself has surface activity. Using the methods of dynamic light scattering and scanning electron microscopy, a study of the dispersion of $FeEDDS_{NP}$ complex nanoparticles, their distribution by radii, shape and morphology was carried out. It is shown that the particles of the nanocomplex have a morphology close to spherical with dimensions of ~30 nm.

Keywords: iron (III), nanoparticles, synthesis, peptization, colloidal solution, ethylenediaminedisuccinic acid.

INTRODUCTION. Biocoordination compounds of vital metals (microelements) as medical and biological agents form the basis of modern socially and technologically significant innovative developments. Combining metal ions with an organic compound enables the production of supramolecular associates, which are inherently close to the endogenous coordination compounds that exist in the living organism and in general in biosystems. They are less toxic than their constituents and usually have a wide range of biological activity [1–3]. The effectiveness of the effect of a microelements on any living organism directly depends on the form in which the trace element is. The twenty-first century is the period of use in various bio-medical fields of effective preparations of microelements based on chelated compounds, which are easily absorbed by living organisms. The most promising chelating agents are aminopolycarboxylic acids, for example ethylenediaminediansuccinic acid (H_4EDDS), which contains fragments of aspartic and succinic acids in the molecule, known as adaptogens. In a living organism, it performs not only the function of delivering trace elements but also carries a biologically active load. Under the action of enzymes in the living organism, EDDS breaks down into essential amino acids (arginine, leucine, isoleucine, valine, histidine, asparagine, alanine), which are components of the metabolic chain [4, 5]. EDDS forms fairly stable complexes with biogenic metals in a wide pH range (3–10), which in terms of biochemical structure and chemical purity are very similar to organometallic compounds that are synthesized in plant or animal cells. Therefore, upon entering a living cell, these substances will be perceived by it not as foreign elements, but as "its own", which will ensure their biogenic compatibility and accordingly, high digestibility [1, 6, 7]. For example, complexes of metals with ethylenediaminedisuccinic acid have an antimicrobial effect against fungi and bacteria [8] and an antiviral effect against cytomegalovirus [9]. They can be used in homeopathic doses on all types of soil for any plants, or as feed additives for animals, without harming nature [10–12].

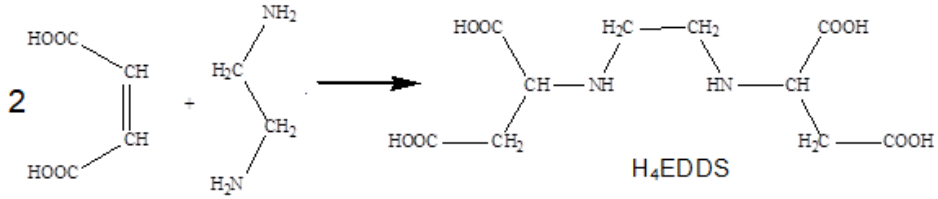
With the development of modern technologies for the synthesis of nanomaterials, interest has arisen in studying the properties of metals in the ultradisperse range in the form of powders, solutions and suspensions [13–15]. Of particular interest to researchers are nanosystems of a given composition with predictable properties and a certain size of nanoparticles, since the permeability, activity, solubility and toxicity of nanoparticles depends on this [16, 17]. The targeted production of metal complexes in the nano-range with a certain size, degree of aggregation and particle shape for the creation of new functional materials (optical and nanoelectronic devices, chemical and biological sensors, catalysts) is an important task, since many physicochemical characteristics of materials depend on these parameters [18, 19].

Among the various forms of nanosized materials for various fields of biology, veterinary medicine and medicine, solutions of nanoparticles of metal complexes are of interest. Their advantage lies in a relatively narrow distribution of particles in size and shape, and a long period of preservation of biological activity. However, the main problem in obtaining nanodispersed metal complexes is that nanoparticles are unstable in solution and tend to form large aggregates. To obtain stable nanoparticles of a certain size and shape in the form of colloidal solutions, it is necessary to contain

stabilizing agents (surfactants) in aqueous dispersions, which, when adsorbed on the surface of the particles, prevent their association for several months [20–22]. Various organic compounds are often used as such stabilizers – thiols, thiourea derivatives, amines, thiocyanates, carboxylates, etc. Stabilizers are sorbed on the surface of growing particles and reduce their surface energy, thereby reducing the likelihood of aggregation and precipitation [23–26].

The purpose of this work is to develop a method for the synthesis of biologically active Fe(III) complexes with ethylenediaminesuccinic acid in the nanoscale range (30–200 nm), which will facilitate the effective penetration of the microelement through the cell membranes of living organisms by endocytosis.

EXPERIMENT AND RESULTS DISCUSSION. The classic version of the synthesis of 3d-metal complexes with ethylenediaminedisuccinic acid is a two-stage process consisting of the condensation reaction of ethylenediamine and maleic acid in an alkaline medium (1) and an exchange reaction between an organic molecule and an inorganic metal salt (2) (Fig. 1) [27, 28].

(1) 

(2) $$H_4EDDS + M^{n+} \rightarrow MH_{4-n}EDDS + nH^+ \quad M^{n+} = Mn^{2+}, Fe^{3+}, Co^{2+}, Cu^{2+}, Zn^{2+}$$

Fig. 1 – Scheme of the synthesis of 3d-metal complexes with ethylenediaminedisuccinic acid.

This method for the synthesis of Fe(III) ethylenediaminedisuccinates is the most common. However, the size of complex particles cannot be controlled due to the high rate of the reaction. With today's development of nanotechnology, the task of obtaining biologically active compounds in the form of nanosystems becomes urgent, since nanoparticles are the most acceptable forms of perception of biogenic metals by a living cell. Based on these considerations, we synthesized a Fe(III) nanocomplex with EDDS from a freshly precipitate iron hydroxide sol. The synthesis is based on the process of dissolution peptization of $Fe(OH)_3$ in an aqueous solution of the racemic form of ethylenediaminedisuccinic acid.

The synthesis of $FeEDDS_{NP}$ was carried out according to the following scheme:

1. Preparation of highly dispersed iron(III) hydroxide.

To a hot (60^0C) supersaturated solution containing 3 moles (252 g) of $NaHCO_3$ in 1 liter of distilled water, with vigorous stirring, 1 mole of a hot solution of iron(III) chloride $FeCl_3 \cdot 6H_2O$ (270 g), dissolved in 500 ml of water, was slowly added. The reaction proceeds according to the equation:

$$3NaHCO_3 + FeCl_3 = Fe(OH)_3 + 3NaCl + 3CO_2.$$

The mixture was stirred for 10 minutes, then the solution was cooled to room temperature. After cooling, the resulting precipitate of

$Fe(OH)_3$ was separated from the mother solution by centrifugation and washed repeatedly with distilled water using the suspension-centrifugation method until the wash water reacted negatively to Cl^- ions.

2. Preparation of a colloidal solution of the Fe(III) complex with ethylenediaminedisuccinic acid.

An equimolar amount of dry H_4EDDS (292 g) was added to the wet $Fe(OH)_3$ gel quantitatively transferred into a 1-liter beaker. The mixture was stirred and left for 20–30 minutes until completely liquefied. After this, the solution was heated to a temperature of 50–60 ^{0}C with intense stirring. The pH of the medium was adjusted using dry sodium carbonate to 7.0–7.5. In this case, the surface layer of the sediment dissolved, resulting in the formation of the monoprotonated FeHEDDS complex, which is the electrolyte necessary for the peptization of the rest of the sediment:

$$Fe(OH)_3 + H_4EDDS \rightarrow FeHEDDS + 3H_2O.$$

Then peptization of the sediment was carried out – loosening the sediment and transforming it into a stable colloidal solution. To do this, 50 ml of solution was diluted with 0.001 M NaOH solution to 1000 ml and pH = 8.5. The colloidal solution was filtered through a 0.45 μm hydrophilic filter (to eliminate polydispersity). When dissolving peptization, it is very important to introduce the peptizing agent gradually in small portions, since its sudden introduction or excess will lead to complete dissolution of the precipitate and the formation of a true molecular ionic solution. Since, in this case, the peptizer is a monoprotonated complex formed in the solution, a slow process at a constant temperature guarantees a positive result. This synthesis does not require the selection of a separate stabilizer to increase the stability of the disperse system, since EDDS has a diphilic structure and is an internal surfactant in a wide range of pH (3.2–8.5) and concentrations.

As is known, a measure of the stability of a colloidal system is the electrokinetic potential (ξ), which depends on the pH of the medium, the influence of electrolytes and temperature. Therefore, studies were carried out on the stability of the system and changes in particle size depending on the pH of the solution (Fig. 2, Table 1). The ξ-potential and particle size were determined by dynamic light scattering using a Zeta Sizer Malvern device at a temperature of 25^{0}C. To do this, 15 ml of the solution was placed in an autotitrator tube and measurements were carried out with a pH interval of 0.5, titrating the test system with a solution of 0.25 M HCl.

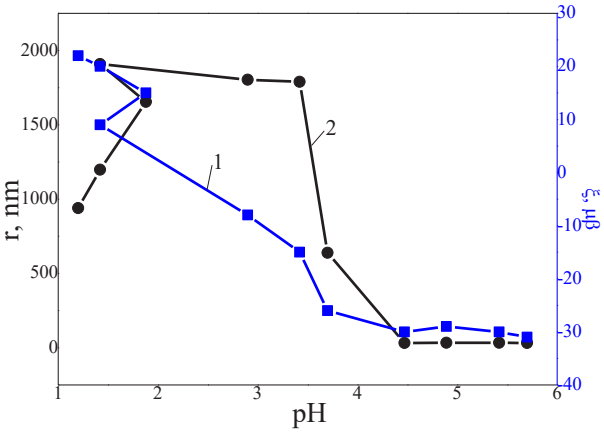


Fig. 2 – Change in ξ-potential (1) and particle size (2) depending on the pH of the medium in the Fe(III) – EDDS system.

As can be seen from Fig. 2, the system is stable at pH≥4.5 (|ξ|≥30 mV). At low pH, a drop in the electrokinetic potential is observed, and, as a consequence, coagulation of the col-

loidal system occurs. With increasing pH, the ξ-potential changes sign, which may be due to both recharging of the colloidal particle and a decrease in particle size due to decoagulation. There is evidence in the literature that a polymolecular layer can form on the surface of a particle [29], but in our case such a statement is doubtful, since polymolecular adsorption from solutions is impossible.

In Fig. 3 and Table 1 show the size distribution of $FeEDDS_{NP}$ nanoparticles.

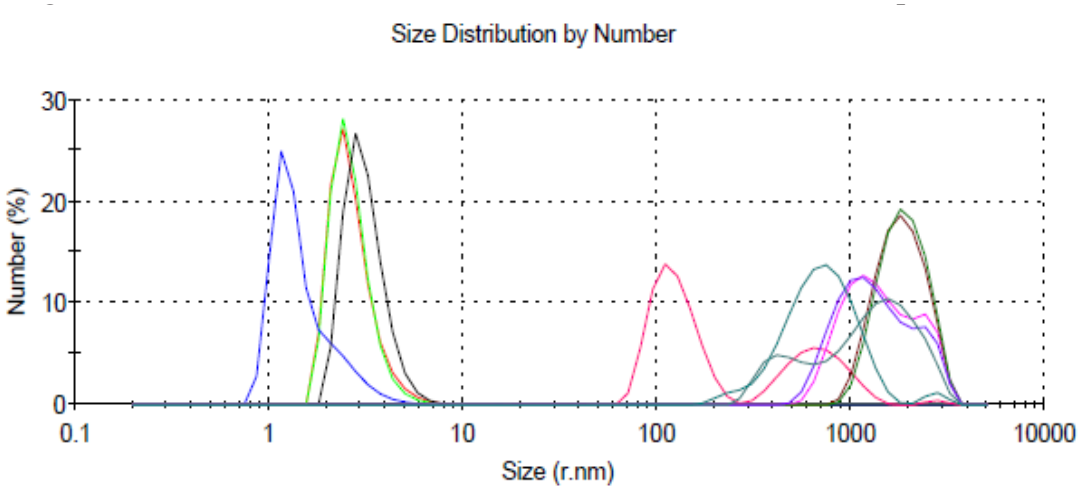


Fig. 3 – Size distribution of $FeEDDS_{NP}$ nanoparticles.

An analysis of the distribution of nanoparticles shows that in this system there are two regions with a predominant radius of particles of approximately the same size. In the region of low pH values (1.2–3.7), large particles (940–1900 nm) are formed with a wide distribution among fractions. In this case, a drop in the electrokinetic potential occurs due to compression of the electrical double layer, which, in turn, is associated with the sensitivity of the ξ-potential to the pH of the medium for systems containing amphoteric compounds. Recharging a particle under the influence of pH, unfortunately, leads to coagulation processes and a decrease in the stability of the entire dispersed system. In the pH range = 4.5–7.5, the system is dominated by nanoparticles with sizes of ~ 32 nm, that is, the system is monodisperse and quite stable. Based on the charge of the dzeta potential, we can assume the following micelle formula:$\{[(mFeLn[FeL]^{-}(n-x)K^{+}]\cdot xK^{+}\}$. As can be seen from the formula, the potential-determining ion (PDI) is the complex particle $[FeL]^{-}$, which is typical for nanodispersed systems based on organic ligands with surface-active properties.

In a more acidic environment, protonated (usually poorly soluble) complexes are present. Therefore, at pH = 1.5–4.0, the particle size increases significantly, and the electrokinetic potential drops sharply. In this case, at pH <1.5, the particle is recharged in the system both due to a sharp decrease in pH and under the influence of ions of a non-indifferent electrolyte, which is ferric chloride. There are several different protonated forms of the complex in

solution, making their identification difficult. Due to the fact that the electrokinetic potential in the acidic region changes its sign, and it is determined by the sign of the POI charge, then, obviously, the micelle formula takes on the following form:{[(mFeLnFe^{3+}3(n–x)Cl^{-}] 3xCl^{-}}.

Based on the data in Fig. 3 and table. 1 we can talk about a fairly high aggregative stability of the dispersed system in the pH range 4.0–7.5 in a wide range of concentrations ($1\cdot10^{-1}$–$1\cdot10^{-3}$ M). In most cases, when the critical micelle concentration is reached, smaller thermodynamically stable particles are formed that are less prone to coagulation [30]. It should be noted that at a metal concentration of 6–8 wt.%, the system is thixotropic-reversible. It is known that thixotropic transformations, as a rule, do not destabilize the system; sometimes, on the contrary, such systems are more stable. This is due to the formation of rigid gel-like structures, where the particles are fixed at a certain distance from each other, which eliminates coagulation processes. The dispersity of the system practically does not change during thixotropic transformations.

When it comes to the sensitivity of the system to the pH of the environment, the situation is slightly different. In particular, everything depends on the charge and size of the potential-determining ion. As a rule, when a particle is recharged due to the pH of the medium, agglomeration takes place in the system, and, consequently, a change in dispersion, which is confirmed by the results of the study. Thus, the presented results indicate the stability of the $FeEDDS_{NP}$ nanodisperse complex in the pH range = 4.5–7.5, the particle size is optimal (the possibility of toxic effects of small particles is excluded), which allows its use as a biologically active additive for living organisms.

Table 1.

Changes in particle size and electrokinetic potential depending on the pH of the medium in the FeEDDS system.

№	pH	r, nm	ξ,mV
1	7.5	32.04	-31
2	6.2	3.31	-31
1	5.7	32.29	-31
2	5.42	34.38	-30
3	4.89	33.03	-29
4	4.47	32.78	-30
5	3.7	639.6	-26
6	3.42	1789	-15
7	2.9	1804	-8
8	1.42	1909	9
9	1.88	1654	15
10	1.42	1198	20
11	1.2	940	22

It should be noted that the nanodispersed $FeEDDS_{NP}$ complex has a higher solubility (275 g/l) compared to the FeEDDS complex obtained using two-stage technology (150 g/l), which greatly facilitates its use as a biologically active compound.

The $FeEDDS_{NP}$ nanodisperse complex isolated from solution was analyzed by electron absorption spectroscopy, IR spectroscopy and scanning electron microscopy (SEM). Electronic absorption spectra were recorded on a Specord M-40 UV-VIS spectrometer in quartz cuvettes (l = 1 cm) in the range of 50000–11000 cm^{-1}. IR spectra were recorded on a Specord M-80 spectrometer in the region of 4000–400 cm^{-1} in tablets with KBr. Microphotographs were recorded on a Tescan Mira 3 LMU scanning electron microscope (SEM).

The electronic absorption spectra of $FeEDDS_{NP}$ are similar to the spectra of Fe(III) ethylenediaminedisuccinate synthesized using the classical method (Fig. 4).

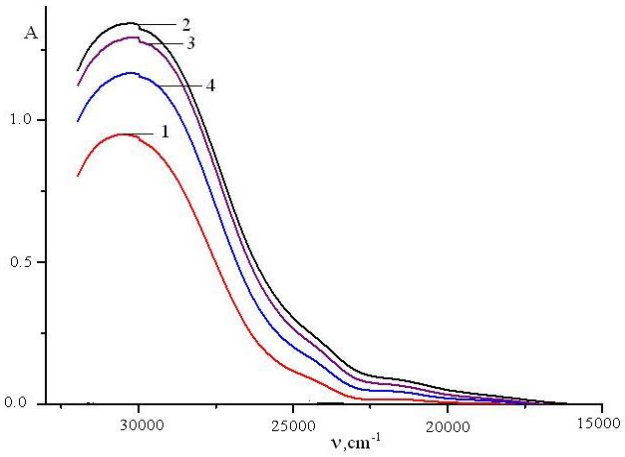


Fig. 4 – UV-VIS spectra of FeEDDS (1) and $FeEDDS_{NP}$ depending on storage time (2 – 3 days, 3 – 1 month, 4 – 6 months). $C_{Fe}=5\cdot10^{-3}$ mol/l, pH=6.5, T= $22^0C\pm 3^0C$.

Absorption maxima (ν_{max}) at 24600 and 29840 cm^{-1} relate to d-d transitions ($^6A_{1g}\rightarrow{}^4A_{1g}$ and $^6A_{1g}\rightarrow{}^4T_{1g}$, respectively) of the Fe^{3+} ion in an octahedral environment [31]. A small splitting ν_{max} at ~30000 cm^{-1} is due to the overlap of the charge transfer band from the metal to the ligand (30960 cm^{-1}) and the $^6A_{1g}\rightarrow{}^4T_{1g}$ term. At the same time, the intensity of the absorption bands and the position of the absorption maxima of iron nanoparticles practically did not change depending on the storage time at room temperature, which indicates the stability of the synthesized nanocomplex.

The IR spectra of the complexes obtained by different methods are almost identical (Fig. 5, Table 2).

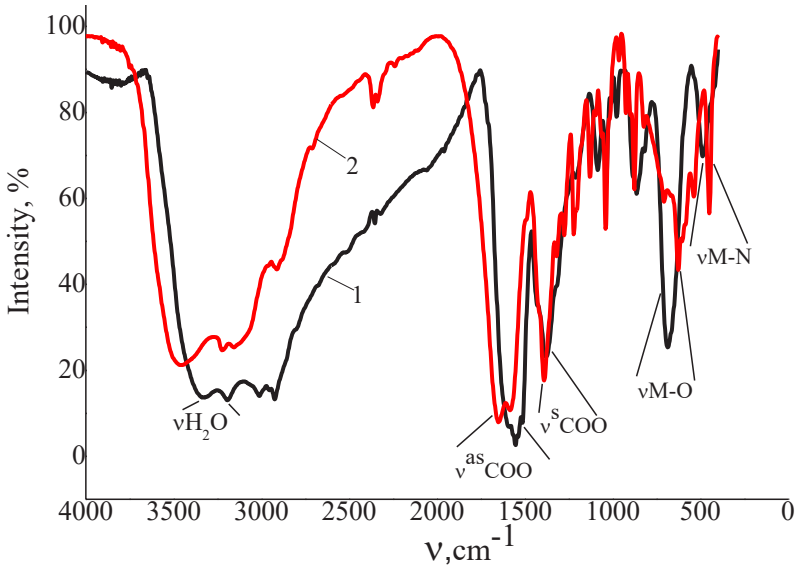


Fig. 5 – IR spectra of FeEDDS (1) and $FeEDDS_{NP}$ (2) complexes.

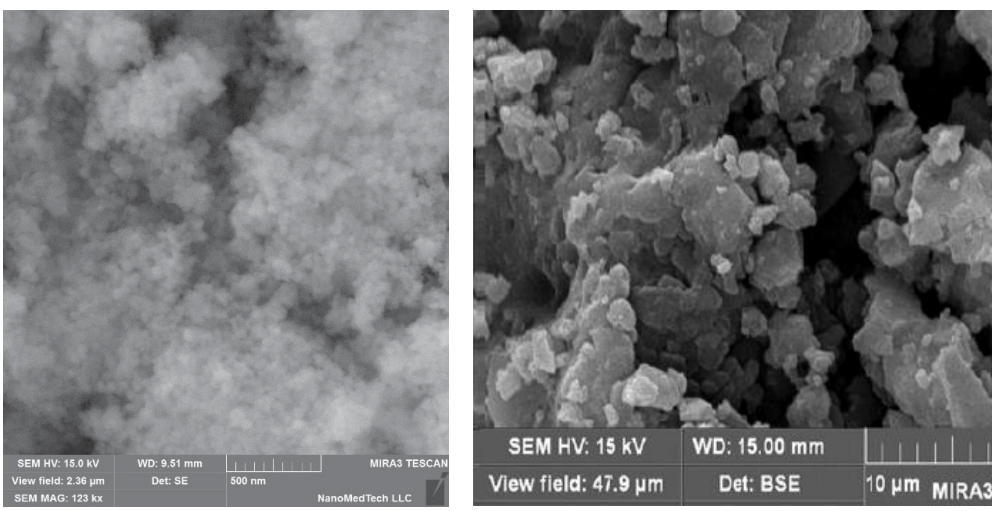
The absorption bands $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ have values of ~1600 and 1400 cm^{-1}, respectively, which indicates the ionic type of bond of the Fe^{3+} ion with the oxygen atoms of ionized carboxyl groups. A slight shift of these bands in the spectrum of $FeEDDS_{NP}$ to the high-frequency region compared to FeEDDS indicates an increase in the ionicity of the bond in the nano-complex. This is also evidenced by a decrease in the bond energy ν(M-N) in $FeEDDS_{NP}$ relative to FeEDDS [32].

Table 2.

Basic vibrational frequencies (cm^{-1}) and their assignments in the IR spectra of complexes FeEDDS.

band assignment	FeEDDS	$FeEDDS_{NP}$
ν (COOH)	–	–
ν_{as}(COO)	1602	1655
	1553	1575
	1515	
ν_{s}(COO)	1433	1446
	1379	1389
	1305	1316
ν(M—O)	559	537
	656	626
	602	603
	707	711
ν(M—N)	457	449
$\nu(H_2O)_{intra}$	3192	3224
$\nu(H_2O)_{inter.}$	3424	3460

Analysis of micrographs (Fig. 6, a) indicates that the synthesized $FeEDDS_{NP}$ complex is nanosized, with the particle size being ~30 nm. In addition, it should be noted that the resulting compounds have a homogeneous chemical composition and a morphology close to spherical. Microphotographs of the FeEDDS complex (Fig. 6, b) indicate that the complex consists of irregularly shaped particles with sizes up to 10 μm. Those, for iron ethylenediminedisuccinate synthesized using the classical method, compared to the nano-complex, the particle size increases and their shape changes, which is associated with the speed of the complex formation reaction.



a **b**

Fig. 6 – SEM micrographs of the $FeEDDS_{NP}$ complex, scale mark 500 nm (a) and FeEDDS complex(b), scale mark 10 μm(b).

CONCLUSIONS. A procedure has been developed for the synthesis of a nanosized Fe(III) complex based on ethylenediaminedisuccinic acid using a freshly precipitated Fe(III) hydroxide sol. The synthesis is based on the process of dissolution peptization of $Fe(OH)_3$ in an aqueous solution of the racemic form of EDDS. The use of bipolar substances with a zwitterionic structure (namely, EDDS) as a dispersant makes it possible to introduce such systems in the form of suspensions not only into aqueous phases, but also into fatty phases. This is one of

the conditions for introducing nanocomplexes into animal feed (premixes). To determine the stability of the system depending on pH, the electrokinetic potential was measured to select the optimal pH of the medium and concentrations to obtain stable dispersed systems. It has been shown that at low pH there is a drop in the electrokinetic potential, and with increasing pH the ξ-potential changes sign, which is due to the recharging of the colloidal particle and a decrease in particle size. The system is stable in the pH range 4.5–7.5 and in a wide range of concentrations ($1\cdot10^{-1}$–$1\cdot10^{-3}$ M). At a metal concentration of 6–8 wt.%, the system is thixotropic-reversible and does not require stabilization, since EDDS itself has surface activity. The methods of dynamic light scattering and scanning electron microscopy were used to study the dispersion of nanoparticles of the $FeEDDS_{NP}$ complex, their distribution by radius, shape and morphology. It was shown that the particles of the nanocomplex have a morphology close to spherical with a size of ~30 nm.

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СИНТЕЗ І ДОСЛІДЖЕННЯ НАНОРОЗМІРНОГО КОМПЛЕКСУ Fe(III) З ЕТИЛЕНДИАМІНДИБУРШТИНОВОЮ КИСЛОТОЮ

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З огляду на сучасний розвиток нанотехнологій перед фахівцями постало завдання отримати біологічно активні сполуки у вигляді наносистем, оскільки саме наночастинки є найбільш прийнятними формами сприйняття біогенних металів живою клітиною. Таким чином актуальним стає пошук нових шляхів формування монодисперсних систем із контрольованим розміром наночастинок. У роботі представлено результати із синтезу та дослідження нанорозмірного комплексу Fe(III) на основі етилендиаміндибурштинової кислоти. В основу синтезу покладено процес дисолюційної пептизації свіжоосадженого золю $Fe(OH)_3$ у водному розчині рацемічної форми EDDS. Використання в ролі диспергатора біполярних речовин цвіттер-іонної будови (а саме такою речовиною є EDDS) дозволяє вводити такі системи у вигляді суспензій не тільки у водні фази, але й у жирові. Це є однією з умов введення нанокомплексів у корми (премікси) для тварин. Для визначення стійкості системи залежно від pH було виміряно електрокінетичний потенціал для вибору оптимального pH середовища та концентрацій для отримання стабільних дисперсних систем. Показано,

що за низьких pH (1.5–4.0) спостерігається падіння електрокінетичного потенціалу, а при збільшенні pH ξ-потенціал змінює знак, що зумовлено перезарядженням колоїдної частинки та зменшенням розміру частинок. Система стабільна в діапазоні pH 4.5–7.5 і широкому діапазоні концентрацій ($1 \cdot 10^{-1}$–$1 \cdot 10^{-3}$ М). При концентрації металу 6–8 мас.% система є тиксотропно-оборотною і не потребує додаткової стабілізації, оскільки сама EDDS має поверхневу активність. Методами динамічного розсіювання світла та скануючої електронної мікроскопії проведено дослідження дисперсності наночастинок комплексу $FeEDDS_{NP}$, їхній розподіл за радіусами, формою та морфологією. Показано, що частинки нанокомплексу мають морфологію, близьку до сферичної з розмірами ~30 нм.

Ключові слова: залізо(III), наночастинки, синтез, пептизація, колоїдний розчин, етилендиаміндибурштинова кислота.

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