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Cu–Fe nanoparticles containing nanocomposites: synthesis, stabilization and antibacterial activity

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Abstract: Currently, soft hydrogels with antimicrobial properties are widely used in biomedical applications as dressings and wound healing agents. In the present work, Cu–Fe nanoparticles with different component ratios were obtained by the joint electric explosion of iron and copper wires in an argon atmosphere. Bimetallic nanoparticles had a clear interface between the iron and copper phases at the particle level. Cu–Fe nanoparticles had high antibacterial activity against a wide bacterial spectrum. In connection with dusting and entrainment of nanoparticles, for the convenience of biomedical application, compositions were created based on non-toxic biocompatible polymers – polyvinyl alcohol, polyacrylic acid, and polyacrylamide. The suspension of nanoparticles was pretreated with ultrasound for 5 min at a frequency of 22.4 kHz. Polyvinyl alcohol was used as a nanoparticle stabilizer. The stability of the suspension was investigated by the sedimentation method. The resulting compositions effectively inhibited the growth of *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 6538, methicillin-resistant *Staphylococcus aureus* ATCC 43300 (*MRSA*), and *Pseudomonas aeruginisa* ATCC 9027.

Keywords: bimetallic nanoparticles; polymers; biocidal composition; antibacterial activity.

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Биоцидный гидрогель, содержащий наночастицы Cu–Fe: получение, стабилизация и антибактериальная активность

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Аннотация: В настоящее время мягкие гидрогели с антимикробными свойствами находят широкое биомедицинское приложение в качестве перевязочных и ранозаживляющих средств. В настоящей работе совместным электрическим взрывом железной и медной проволочек в атмосфере аргона получены наночастицы Cu–Fe с различным соотношением компонентов. Биметаллические наночастицы имели четкую границу раздела железной и медной фаз на уровне частицы. Наночастицы Cu–Fe обладали высокой антибактериальной активностью в отношении широкого бактериального спектра. В связи с пылением и уносом наночастиц для удобства биомедицинского применения созданы композиции на основе нетоксичных биосовместимых полимеров – поливинилового спирта, полиакриловой кислоты и полиакриламида. Суспензию наночастиц предварительно обрабатывали ультразвуком в течение 5 минут при частоте 22,4 кГц. В качестве стабилизатора наночастиц использовали поливиниловый спирт. Стабильность суспензии исследовали седиментационным методом. Полученные композиции эффективно подавляли рост бактерий *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 6538, устойчивых к метициллину *Staphylococcus aureus* ATCC 43300 (*MRSA*) и *Pseudomonas aeruginisa* ATCC 9027.

Ключевые слова: биметаллические наночастицы; полимеры; биоцидная композиция; антибактериальная активность.

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1. Introduction

Despite the rapid development of science and technology the problem of the antibiotic-resistant bacterial strains formation remains relevant. According to the World Health Statistic Report 2019, in the world about 700 thousand people died in 2019 from bacterial infections. In this regard, the creation of new materials with antimicrobial activity is currently a promising and most intensively developing area of nanotechnology. Currently, antimicrobial hydrogels are widely used in biology and medicine as a means for drug delivery [1], filling hygiene products, contact lens material and dressing components [2] due to their three-dimensional structure, structural stability and moisture capacity. For the creation of dressings based on hydrogels, an important indicator is their ability to maintain a constant moisture level in the area around the wound, which promotes the growth of connective tissue and accelerates the production of collagen [3]. However, a humid environment is often favorable for the reproduction of microorganisms [4]. In this regard, the creation of compositions based on polymers containing nanoparticles with antimicrobial properties is a promising way to solve this problem.

In most cases, silver nanoparticles (NPs) are used for antibacterial modification of polymer gels [5]. However, the use of silver is limited by the aggregation of NPs, which leads to a significant decrease in their activity [6], and proven cyto- and genotoxicity [7]. To reduce the toxic effect on the human body, it is advisable to use NPs of biologically active metals (Ca, Na, K, Mg, Fe, Cu, Zn, Mo, Mn, etc.). Such NPs introduced into eukaryotic cells, having less toxicity, can even stimulate the mechanisms of regulation of the microelement composition and the activity of antioxidant enzymes [8].

To increase the antibacterial activity of NPs of biologically active metals, the use of bimetallic nanoparticles is promising [9]. One of the main mechanisms of the antibacterial activity of NPs is the release of ions into the solution [10]. The nanoscale state, the large area of the accessible surface, and the presence of electrochemical pairs in the bulk of bicomponent nanoparticles make it possible to regulate the solubility of metals, the ions of which will interact with the components of the cell wall. The most effective are copper-containing NPs. The authors of [11] attributed the synergistic effect in the antibacterial activity of bimetallic Cu/Zn nanoparticles to the slow simultaneous release of metal ions, while copper NPs interacted with the bacterial membrane, changing its permeability, which enhanced the effect of zinc. Cu–Ni NPs synthesized by a chemical method for dental applications, in contrast to copper NPs, exhibited the same antibacterial effect in relation to all tested strains [12], provided by the release of copper ions. Cu–FeO NPs 90–220 nm in size, synthesized by the hydrothermal method, had a less pronounced antibacterial activity compared to Cu_2O, which had a size of about 24.5 nm [13], which was associated with a lower concentration of released Cu^{2+} ions.

In this work, an electric explosion of wires (EEW) was used to obtain Cu–Fe NPs [14]. EEW allows one to obtain NPs with different structures and phase compositions, which can be controlled by the synthesis conditions. In addition, EEW has a number of advantages over other physical methods, such as high efficiency of energy transfer, the ability to vary the process parameters and, accordingly, the powders properties, a relatively narrow NPs size distribution function, low cost and equipment simplicity.

In this research, biocidal composites were obtained based on solutions of water-soluble polymers of polyacrylamide, polycarboxylate, and polyvinyl alcohol and electroexplosive Cu–Fe NPs, which have antibacterial activity against gram-positive and gram-negative microorganisms. The influence of the polymer and the NPs solubility on their antibacterial activity was studied in model liquids.

2. Materials and methods

2.1. Synthesis of nanocomposites

To obtain Cu–Fe NPs, an electric explosion of iron and copper wires in an oxygen-containing atmosphere was used. The technical details of the NPs synthesis process and the scheme of the experimental setup are presented in [15]. The parameters of NPs synthesis are given in Table 1. The ratio of the weights of metals in the powder was controlled by the geometric dimensions of the wires.

Table 1. Conditions for the Cu–Fe bimetallic nanoparticles preparation

Sample	d_{Cu}	d_{Fe}	l	w_{Cu}(%), calc.		w_{Fe}(%)		U, kV	C, μF
	mm			wt. %	atm. %	wt. %	atm. %		
Cu72–Fe28	0.30	0.20	65	71.9	69.3	28.1	30.7	34	1.6
Cu53–Fe47	0.20	0.20	60	53.2	50.1	46.8	49.9	26	1.2
Cu28–Fe72	0.20	0.35	65	27.1	24.7	72.9	75.3	32	1.2

The choice of polymer matrices for preparing the compositions was due to the possibility of creating on their basis soft dosage forms like gels containing NPs. Polyacrylamide TOSN (Russian Standard 17622–72) with a molecular weight of 5100 g·moL^{-1} was chosen as polymer matrices; polyvinyl alcohol MOWIOL® grade 10–98 with a molecular weight of 10^{-6} g·moL^{-1}; carbopol ETD 2020 is a homopolymer and copolymer of acrylic acid crosslinked with polyalkenyl polyester (BASF, Germany) with a viscosity of 1 % aqueous gels of at least 45–77 Poz. NPs in the form of stable suspensions were introduced into the polymer matrix. Deagglomeration of aqueous suspensions of nanoparticles was carried out using a Hilscher UP-100M submersible ultrasonic homogenizer with a frequency of 30 kHz, varying the processing time t and the power N of the disperser. Ultrasonic treatment is the most effective method for deagglomeration of electroexplosive nanopowders [17]. The processing time was chosen up to 10 minutes, because with a further increase, the suspension was heated at any exposure power, which can lead to sintering of the processed NPs.

2.2. Methods of the nanocomposites properties investigation

Cu–Fe NPs were studied by X-ray diffraction analysis (diffractometer Shimadzu XRD 6000 with CuKa radiation), transmission (JEOL-2100F, Japan), and scanning (LEO EVO 50, Zeiss, Germany) electron microscopy. To determine the number average size of nanoparticles, TEM images were used (no less than 2400 particles). The study of the chemical composition of the surface of the samples was carried out on a photoelectron spectrometer (SPECS Surface Nano Analysis GmbH) equipped with a PHOIBOS-150-MCD-9 hemispherical analyzer, an XR-50 X-ray source of characteristic radiation with a double Al/Mg anode. The release of ions from bimetallic nanoparticles was studied under conditions corresponding to standard methods for assessing the antibacterial activity of substances, i.e. with 24-hour cultivation in water and in an environment favorable for the bacterial culture life – sterile 0.9 % NaCl solution, according to the requirements [16]. A series of samples were placed in conical flasks containing 30 ml of water or NaCl solution and kept with constant shaking using an orbital shaker at 37 °C for 24 hours. Further exposure time increase is impractical, since the vital activity of bacterial cultures decreases within 24 hours and all bacterial experiments are usually limited to 18–24 hours. The study of the degradation of nanoparticles in nutrient broths, as the most favorable media for incubation, was not carried out due to the fact that the use of organic compounds as a dispersion medium makes it impossible to use highly sensitive methods of analytical chemistry. A mechanical mixture of electroexplosive monometallic NPs of iron and copper in the same ratios as in bicomponent NPs was used as reference samples.

2.3. Antibacterial properties of research objects

To assess the antibacterial activity of nanoparticles, the method of radial diffusion into agar was used. For 20 mL Mueller–Hinton agar was poured into sterile Petri dishes (90 mm diameter) and allowed to solidify. After solidification, wells were made using sterile cylinders. 200 μL of a suspension of nanoparticles in 0.85 % NaCl at a concentration of 100 μg·mL^{-1} was added to the wells. Petri dishes were incubated at 37 °C for 24 h. Antibacterial activity was determined by measuring the diameters of growth inhibition zones around the wells.

The antibacterial activity of the compositions was evaluated using test cultures – bacteria *Escherichia coli* ATCC 25922, antibiotic-resistant *MRSA* ATCC 43300, *Pseudomonas aeruginosa* ATCC 9027 and *Staphylococcus aureus* ATCC 6538, provided by Biolot (Russia) and the All-Russian collection of industrial microorganisms. To determine the minimum inhibitory concentration (MIC) of gels, at which the growth of the studied bacterial cultures is completely inhibited, the method described in [18]

was used Mueller–Hinton broth (RCP, St. Petersburg) was used as a nutrient medium. To assess the dynamics of the growth of microorganisms, a microplate variation of the method was used with an assessment of the optical density of the bacterial suspension by the spectrophotometric method (Multiskan FC, ThermoFisher Scientific, USA, $\lambda = 620$ nm). MICs were determined from the results of a series of 3 experiments containing at least 3 parallel samples.

3. Results and Discussion

NPs production and properties.

With a joint electrical explosion of copper and iron wires in an argon atmosphere, the so-called. Janus nanoparticles, that is, particles with a clear interface between the phases of the components. Taking into account the phase diagrams, the Cu–Fe metal system is characterized by the absence of mutual solubility in the solid and liquid states. The solubility of iron in copper does not exceed 2.5wt% at a temperature of 1025 °C. In this system, the formation of three regions of primary crystalline phases is observed: γ (850 °C), ε (1083 °C) and δ (1500 °C). In a number of works summarized in [19], the solubility of copper in α-Fe is given; depending on temperature, it is in the range of 0.1 ÷ 1.8 % (at.).

According to the phase analysis data, only the phases of iron (α–Fe) and metallic copper are found in the synthesized bimetallic Cu–Fe nanoparticles. However, the data obtained in the study of the surface of nanoparticles by X-ray photoelectron spectroscopy confirm the presence of Fe^{3+} and Cu^{2+} on the surface of the particles (Fig. 1).

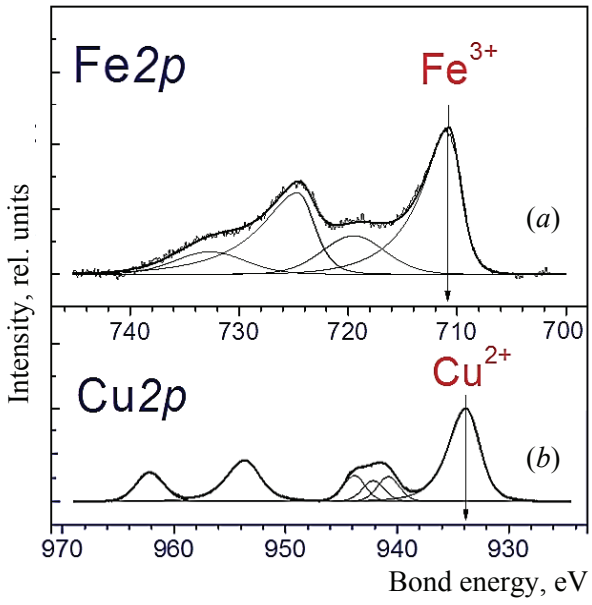


Fig. 1. XPS analysis of Cu50–Fe50 nanoparticles

The spectra of Fe2*p* nanoparticles are shown in Fig. 1*a*. Two main peaks at ≈ 711.5 eV with a shift towards lower binding energies and 724.5 eV with a shift towards lower binding energies can be attributed to $Fe2p_{3/2}$ and $Fe2p_{1/2}$, respectively [20]. According to the literature data [21], iron, which is a part of the oxides, is characterized by the values of the binding energy $Fe2p_{3/2}$ in the ranges 709.5–710.2 eV (for FeO), 710.1–710.6 eV (for Fe_3O_4) and 710.7–711.2 eV (Fe_2O_3). The high value of the binding energy and the presence of satellites, which are 5.7, 8.5, and 8.8 eV away from the main peak of $Fe2p_{3/2}$, made it possible to assert that iron in these samples is in the Fe^{3+} state. In the spectrum of copper (Fig. 1*b*), regardless of the composition of nanoparticles, there was an intense peak in the region of 933.9 eV, which can be attributed to $Cu2p_{3/2}$ [22]. The peak at 952.8 eV can be considered as Cu^0 with a weak satellite peak in the region up to 946.7 eV, which is associated with Cu^+ particles [23]. Thus, an X-ray amorphous oxide film is present on the surface of nanoparticles.

Depending on the ratio of the components, D_{cir} of metal phases, calculated by the Williamson–Hall method, linearly correlated with the content of the corresponding metal in all exploded wires (Fig. 2).

The resulting Cu–Fe nanoparticles have a spherical shape and an average size of 63-72 nm (Fig. 3*a*). Moreover, the average size of nanoparticles is practically independent of the composition of the particles. In a detailed study of the particles by the method of energy dispersion analysis (Fig. 3), it was found that, regardless of the ratio of the components, copper and iron are unevenly distributed over the particle, there are areas enriched in one of the components with clear phase boundaries.

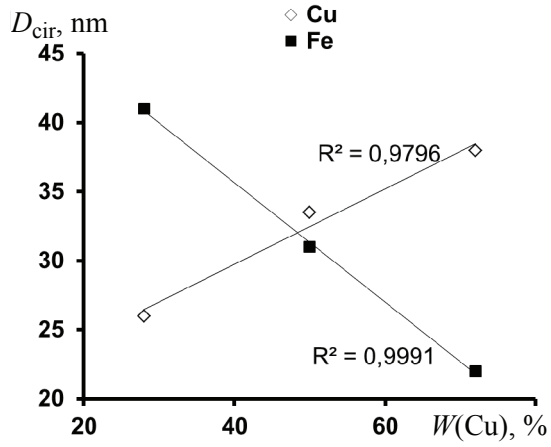
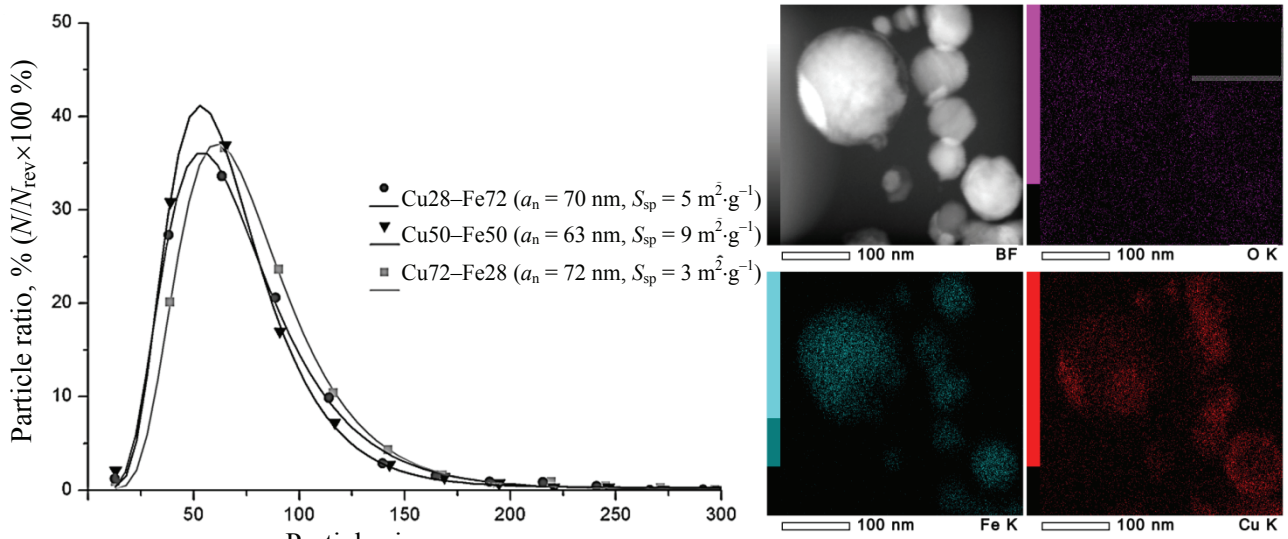


Fig. 2. Coherent scattering region dependences for copper and iron on the Cu–Fe nanoparticles composition



(*a*) (*b*)

Fig. 3. Particle size distribution functions (*a*) and TEM-image and EDX-analysis (*b*) of Cu–Fe nanoparticles

Antibacterial activity of NPs.

The release of ions when NPs are placed in a physiological solution (electrolyte) plays an important role in their antibacterial activity. It is known that the bacterial membrane consists of anionic polar molecules of acidic phospholipids (phosphatidylethanolamine – 66 %, cosfatidyl-glycerol – 18 %, cardiolipin – 12 % for *E. coli*), lipopolysaccharide and teichoic acids, which easily interact with metal ions, for example, by adding one ion metal (II) to two adjacent phosphate groups of membrane-forming organic molecules, which leads to the destruction of the bacterial membrane [24]. | In addition, ions of silver, iron and copper bind to sulfur-containing amino acids that make up the proteins of the cell wall, mainly with the polar acid cysteine. When Cu^{2+} interacts with *E. coli* membrane proteins, disulfide bonds that form a tertiary protein structure are broken, as a result of which nonspecific conduction channels for cations are opened. The nanoscale state, and, accordingly, the large area of the accessible surface and the presence of electrochemical pairs in Cu–Fe NPs can lead to an increase in the solubility of metals, the ions of which will interact with the components of the cell wall. The release of ions in aqueous media from bicomponent NPs obtained by an electric explosion has hardly been studied.

Degradation of Cu–Fe NPs can be represented from the point of view of electrochemical corrosion, which occurs in a neutral medium with oxygen depolarization:

(A) $Fe - 2e \rightarrow Fe^{2+}$ – oxidation

(K) $2H_2O + O_2 + 4e \rightarrow 4OH$ – recovery.

Short-circuited galvanic cell circuit:

$$A\ (-)\ Fe|H_2O,\ O_2|Cu\ (+)\ K.$$

The following reactions take place at the metal surface in the electrolyte:

$$Fe^{2+} + 2OH^- \rightarrow Fe(OH)_2;$$

$$Fe(OH)_2 + O_2 + 2H_2O \rightarrow 4Fe(OH)_3.$$

It was found that the amount of Cu^{2+} and Fe^{2+} ions released from NPs into water depends on the ratio of metals in the nanopowder. In Fig. 4 shows the curves of changes in the content of iron and copper during exposure to Cu–Fe NPs in a model medium versus time. Depending on the content of metals in nanopowders, the amount of released Cu^{2+} and Fe^{2+} ions changes. The largest amount of Fe^{2+} ions is released upon exposure to Cu50–Fe50 nanopowder (Fig. 4*a*). At this ratio of metals, the galvanic effect of the pair is most pronounced – a decrease in the solubility of copper in the presence of iron.

The release of copper ions is most significant in the Cu72–Fe28 NPs (Fig. 4*b*). This difference in the release of ions from bicomponent nanoparticles can be explained from the point of view of the NPs structure. At a high copper concentration, the number of nanoparticles with a core-shell structure increases. The formation of a copper shell prevents the diffusion of water to the iron core and, accordingly, the reaction of water and NaCl with iron. With an equal ratio of components, nanoparticles with a symmetric shape are mainly formed. Both iron and copper are in contact with water. The area of the metal interface is maximal in this case. As a result, at this ratio, the

galvanic effect plays the main role in the formation of ions. Galvanic effects occurring at the copper-iron interface prevent the release of copper into the reaction medium. Therefore, we observed an increase in the release of Fe^{2+} ions and a decrease in the release of Cu^{2+} ions. With a further increase in the iron content, the copper fragments decrease, and the iron fragments increase. The data on the release of ions correlate with the antibacterial activity of the nanoparticles (Table 2).

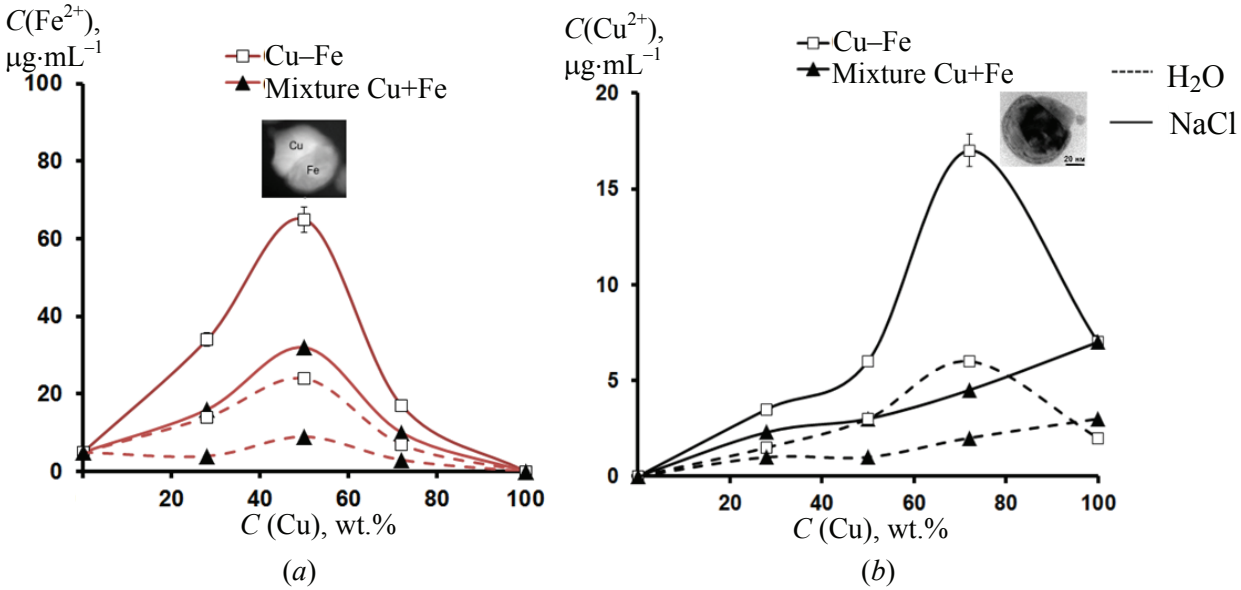


Fig. 4. Concentration of copper and iron ions after 24 h exposure of Cu–Fe NPs in water (*a*) and 0.9 wt. % NaCl solution (*b*)

Table 2. Antibacterial activity of Cu–Fe nanoparticles

NPs	$C(Fe^{2+})$	$C(Cu^{+})$	$C(Cu^{2+} + Fe^{+})$	Growth retardation zone, mm		
		$\mu g \cdot mL^{-1}$		*E. coli* ATCC 25922	*S. aureus* ATCC 6538	*MRSA* ATCC 43300
Cu28–Fe72	34	3.5	37.5	23.5 ± 0.4	23.5 ± 0.5	23.5 ± 0.2
Cu50–Fe50	65	6	71	24.4 ± 0.5	23.5 ± 0.2	23.5 ± 0.1
Cu72–Fe28	17	17	34	22.4 ± 0.3	26.5 ± 0.8	24.2 ± 0.1
Fe (92 nm)	5	–	–	10.1 ± 0.2	10.0 ± 0.0	10.1 ± 0.2
Cu (80 nm)	7	–	–	11.4 ± 0.0	12.7 ± 0.1	11.6 ± 0.3

Obtaining biocidal compositions with bicomponent NPs.

The main problem of using NPs as antibacterial agents is their high dispersion, tendency to agglomeration, which leads to dusting, entrainment by a liquid or gas flow, contact with mucous membranes, decreased activity, etc. The choice of polymers for the creation of composites is determined by many factors: the necessary functional requirements for finished materials and products, their operational reliability and safety of use, compatibility and mutual influence of components, manufacturability of processing, availability and cost. When choosing polymer matrices, first of all, the possibility of creating on their basis soft dosage forms in the form of gels or ointments modified with NPs was taken into account. In this regard, the preparation technique included the formation of a single-phase hydrophilic system, well sorbed on the surface of wounds, in which bicomponent

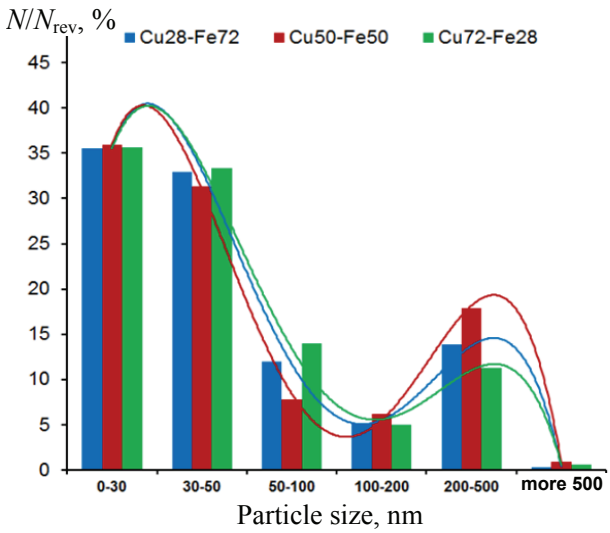


Fig. 5. Size distribution of Cu–Fe NPs and agglomerates in an aqueous suspension

nanoparticles are evenly distributed. As a hydrophilic base were chosen 1 wt. % aqueous solutions of polymers with low toxicity, hypoallergenicity, promoting a slow release of the antimicrobial component, not interfering with gas exchange of the skin and not disrupting the activity of the glands.

The main problem with the introduction of NPs to obtain biocidal compositions is associated with their agglomeration. When NPs are produced by an electric explosion of wires, the nanoparticles come into contact with each other, forming agglomerates and aggregates. During aggregation, metal NPs are bound by weak adhesion forces of Van der Waals, and during agglomeration, as a rule, strong agglomerates of individual particles are formed, which are firmly connected by necks. Aggregates of nanoparticles are easily destroyed by external influences, for example, by ultrasonic dispersion. Destroying strong agglomerates of mechanically bonded nanoparticles is a much more difficult task. The size distribution of NPs and agglomerates of Cu–Fe nanoparticles determined by the sedimentation method is shown in Fig. 5.

Samples with different Cu–Fe ratios had a similar weight average distribution with a maximum in the region of 40–50 nm. In this case, about 80 % of the particles had a size of 100 nm. There are Cu–Fe agglomerates larger than 500 nm. The largest weight of large agglomerates was typical for the Cu50–Fe50 sample.

When dispersing a suspension of NPs by ultrasound for 5 min, the suspension did not settle for 3 min, which was sufficient for the introduction of particles into the polymer matrix. As a result, biocidal compositions were obtained in the form of gels, which were well applied and evenly distributed on the skin. In addition, due to the gel texture, a uniform distribution of bicomponent nanoparticles in the bulk of the base was achieved and their aggregation was prevented. The compositions are homogeneous in structure, the pH is in the range from 6.0 to 6.5, which is close to the physiological pH of human skin.

To determine the antibacterial activity of the biocidal compositions, the suspension method described above was used. The antibacterial activity of the compositions is given in Table 3.

Table 3. Antibacterial activity of compositions containing bimetallic Cu-Fe nanoparticles

Sample	MIC, mg·L^{-1}			
	E. coli ATCC 25922	*S. aureus* ATCC 6538	*P. aeruginosa* ATCC 9027	*MRSA* ATCC 43300
		Polyvinyl alcohol		
Cu28–Fe72	62.5	31.3	125	125
Cu50–Fe50	31.3	7.8	62.5	62.5
Cu72–Fe28	62.5	7.8	125	62.5
		Carbopol		
Cu28–Fe72	31.3	15.6	125	31.3
Cu50–Fe50	31.3	7.8	62.5	31.3
Cu72–Fe28	62.5	15.6	125	62.5
		Polyacrylamide		
Cu28–Fe72	250	125	>250	125
Cu50–Fe50	125	62.5	250	62.5
Cu72–Fe28	250	125	>250	125

The obtained experimental data on the antibacterial activity of samples of biocidal compositions, in which Cu–Fe nanoparticles were used as an antimicrobial component, exhibited high antimicrobial activity against *MRSA*. The most effective composition was carbopol + Cu–Fe. The least activity was demonstrated by compositions based on polyacrylamide. As shown by theoretical studies of the authors [25], a strong interaction takes place in the iron-iron oxide-polyacrylamide system and the polymer chain is adsorbed on the surface of nanoparticles, which can lead to a decrease in ion release and a significant decrease in antibacterial activity. The results of antibacterial activity of biocidal compositions with bimetallic Cu–Fe NPs exceed the values obtained for silver-containing hydrogels based on gelatin and chitosan modified with silver nanoparticles [26], which indicates that the obtained samples are promising.

4. Conclusion

Thus, water-based composites modified with bimetallic Cu–Fe nanoparticles can be promising for the creation of antibacterial agents for treating wounds, as an alternative to silver-containing nanomaterials. Wound dressings based on composite hydrogel are able to maintain a moist environment for a long period of time, as well as protect the wound from any microbial infections that may arise. Controlled release of ions of bioactive metals copper and iron provide high antibacterial activity of the obtained composites.

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6. Conflict of interests

The authors declare no conflict of interest.

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