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OPTIMIZATION OF SYNTHESIS CONDITIONS OF BIOCOMPATIBLE COLLOID SOLUTIONS OF COPPER METAL PARTICLES.

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The work presents a comprehensive selection of conditions for the synthesis of nanosized Copper particles in an aqueous oxidizing environment using a biocompatible amino acid – L-Cysteine as a stabilizer, a reducing agent – sodium tetraborate, and the application of the method of mathematical experimental planning the Scheffe method.

The use of the mathematical planning method made it possible to predict the additive effect of the ratio between precursors in the studied medium on the value of the optical absorption edge of the obtained colloidal solutions of copper nanoparticles, their stability over time and the effect on test cultures of microorganisms P.aeruginosa, C.albicans, B.subtilitis.

The ratio between the starting reagents that lead to the formation of stable colloidal solutions of copper nanoparticles at pH=6 and temperature of 20°C in an oxidizing reaction medium has been established.

A mathematical model was constructed in the form of a projection onto the plane of an equilateral triangle of the dependence of the value of the optical absorption edge of colloidal solutions of metallic copper nanoparticles on the ratio between the precursors. A mathematical equation was obtained – a fourth-degree polynomial that describes the dependence of the value of the optical absorption edge of colloidal solutions of copper nanoparticles on the ratio between three independent variables – crystal-forming components of time-stable particles in the reaction medium.

The antibacterial activities of a series of test solutions were investigated by the micromethod of serial dilutions in accordance with the procedures of the European Committee for Susceptibility Testing against reference strains of bacteria (P.aeruginosa, C.albicans, B.subtilitis.). Using the Scheffe mathematical model, the concentration regions and ratios between the components of the studied system were determined, which had the highest impact on the action of test cultures of microorganisms.

Keywords: nanoparticles, optical indicators, copper, microorganisms P.aeruginosa, C.albicans, B.subtilitis.

INTRODUCTION. Active scientific development of research in the field of nanomaterials, which is aimed at obtaining and applying nanoparticles (NPs) as new materials in various fields of science, began in the twentieth century. In most countries of the world, intensive research and implementation of nanotechnology results into practical activities are being carried out. The synthesis, research and application of nanoscale materials are the subject of study of several interdisciplinary fields of science at once. In particular, one of the results of such complex research and cooperation is the implementation of nanotechnology in medicine and pharmacy.

The use of NPs in medicine and pharmacy is a very promising direction of modern science. A special place among the studied NPs in the field of medicine and pharmacy is occupied by metal nanoparticles (Ag, Au, Pt, Cu, etc.), which are used as antimicrobial, bactericidal and antitumor drugs [1–9]. Recently, quite intensively, researchers have been working on studying the effectiveness of the action of nanoparticles (NPs) on pathogens of infectious and inflammatory processes of various localization and, accordingly, the search and creation of highly effective antimicrobial drugs of a wide spectrum of action.

Copper NPs are especially promising and economically advantageous (in comparison with silver NPs) for these purposes [9–11].

Researchers are particularly interested in studying the synthesis conditions (the influence of different copper salts, different reducing agents, synthesis temperature) of stable copper nanoparticles and their effect on antibacterial and antifungal properties [12–13].

Attention is also paid to the study of copper NPs obtained using biocompatible reagents and non-toxic reaction by-products, which exhibit lower environmental risks for living organisms [14–15].

In the work [16], a detailed analysis of the synthesis methods of copper nanoparticles, the study and comparison of their antibacterial properties, toxicity and prospects for their application with other metal particles, was carried out. It is important to note that Copper NPs exhibit antimicrobial activity against gram-positive and gram-negative bacteria, including Bacillus subtilis. This work presents cases of better bactericidal properties of copper nanoparticles compared to silver nanoparticles. Also described are studies in which copper NPs are used as a fungicide against a wide range of plant fungi.

Studies of the antimicrobial and fungicidal properties of copper NP substances on clinical isolates of pathogens of infectious and inflammatory processes: bacteria S.aureus, E.coli, Proteus mirabilis, K.pneumoniae, Enterobacter aerogenes, P.aeruginosa and fungi of the genus Candida, namely, C.albicans, Candida non-albicans and other micromicelles showed that the copper nanoparticle substance used in the work has pronounced antimicrobial and fungicidal activity against all pathogenic test cultures and against the effect on clinical isolates of pathogens of infectious and inflammatory processes of various locations [17].

The mechanisms of antimicrobial and antifungal action of copper NPs have not been fully studied, however, these processes are based on damage and destruction of the corresponding bacterial and fungal cells.

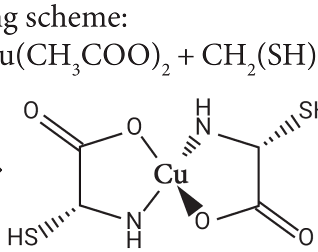
One of the important characteristics of colloidal solutions of Cu NPs is the stability of particles over time [1, 9–11], especially in a potentially oxidizing environment and without deaeration of the initial solutions. Cuprum nanoparticles are of great interest to scientists, despite the increased instability of copper to oxidation with the formation of copper oxide, the possibility of the formation of its complex compounds in aqueous solutions, toxic starting reagents and synthesis products, in order to find conditions for the synthesis of copper nanoparticles that are stable over time and that will exhibit antimicrobial and antifungal properties.

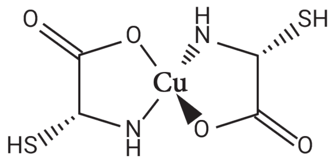
Purpose of the work: selection of conditions for the synthesis of colloidal solutions of copper nanoparticles stabilized by the biocompatible amino acid L-Cysteine in an oxidizing environment at a synthesis temperature of 20^0C. Study of the effect of Cu NPs on test cultures of microorganisms P.aeruginosa, C.albicans, B.subtilitis.

EXPERIMENT AND DISCUSSION OF RESULTS. Colloidal solutions of copper nanoparticles were obtained in aqueous solution without prior deaeration of the starting solutions, using the following components: $Cu(CH_3COO)_2 \cdot H_2O$, sodium tetrahydroborate $NaBH_4$ and as a stabilizer a solution of amino acid – L-Cysteine $HO_2CCH(NH_2)CH_2SH$, (all purchased from Sigma Aldrich) were used for synthesis without changes. The synthesis was carried out observing the value of hydrogen index 6.0.

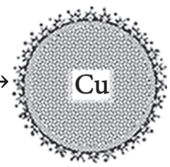
The order of introduction of the components was carried out according to the following scheme:

$Cu(CH_3COO)_2 + CH_2(SH)CH(NH_2)COOH \rightarrow$

→ 



$+ NaBH_4 \rightarrow$

→ 

The reliability of the formation of copper nanoparticles was recorded using optical absorption spectra of colloidal solutions (appearance of surface plasmon resonance bands of copper nanoparticles at 470–520 nm in the absorption spectra of colloidal solutions and the absence of bands of the copper complex with cysteine and cuprous oxide in the region of 620–800 nm) [18]. The study of the optical properties of the solutions was carried out at a temperature of 298±5 K using spectrophotometers MDR-4 and USB-650 (Ocean Optics). The optical density of the solutions was measured within the range of 0.01–2 with increasing wavelength in the range of 350–1000 nm. The absorption of NP solutions was studied in quartz and polystyrene cuvettes 1 cm thick, using a stabilizer solution – L-Cysteine for comparison.

The study of antibacterial activity was carried out by the micromethod of serial dilutions in accordance with the procedures of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Janowska, Andrzejczuk, Gawryś Wujec, 2023). The minimum bacteriostatic (fungistatic) and bactericidal (fungicidal) concentrations of the tested solutions were determined in relation to reference strains of bacteria (P.aeruginosa, C.albicans, B.subtilitis.). A solution of the amino acid L-Cysteine was taken as a negative control.

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Analysis of the literature devoted to the study of the synthesis conditions of Cu NPs showed that some researchers are making attempts to generalize the influence of the ratio between the components on the properties of the synthesized particles. Unfortunately, it is impossible to predict the properties of nanoparticles and their stability over time as a function of the composition in a wide range of concentrations of crystal-forming components of the solution.

In the practical and scientific research activities of a researcher in the field of pharmacy, medicine or chemistry, the results of research and analysis require the maximum number of effective responses with the performance of the minimum number of experimental studies. That is why, in order to obtain an overall picture of the additive effect of concentrations on the properties of the obtained nanoparticles, the work used the method of mathematical experimental design – the method of simplex Scheffé lattices, which has already been used to characterize nanoscale materials [19].

To optimize the composition of the three-component system by the Scheffe method, a fourth-degree polynomial can be used.

The range of investigated concentrations of initial solutions with compositions corresponding to the graphic representation in the area of the equilateral triangle ABC (Fig. 1, a) was selected on the basis of experimental data on the synthesis of colloidal solutions of Cu metal nanoparticles given in the literature [1, 9–10]. Fig. 1, b shows the results of an experimental study of the stability of colloidal solutions of copper nanoparticles.

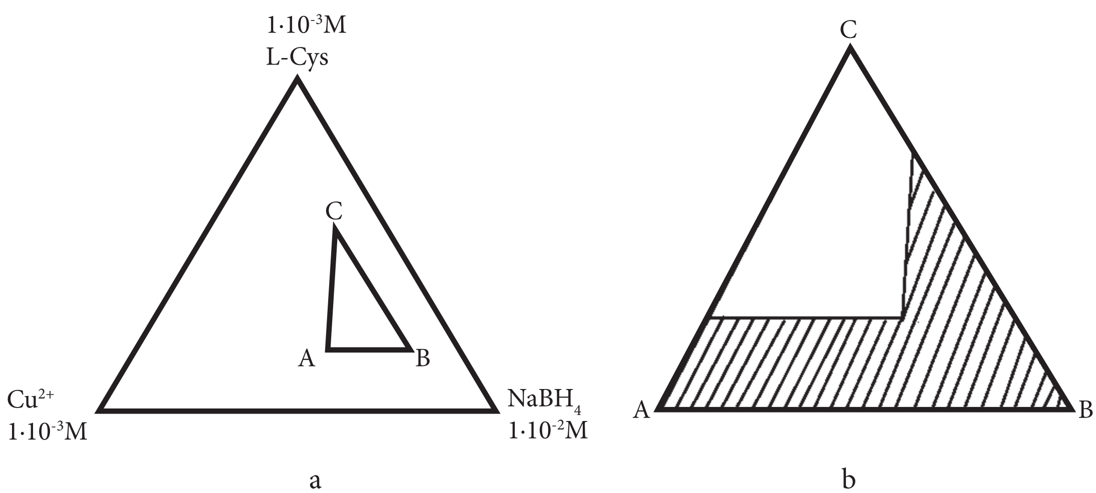

Fig. 1. a – Graphical representation of the studied region of the composition of the Cu^{2+}– L-Cys-$NaBH_4$ system during the mathematical planning of the experiment; b – graphical representation of the region of compositions of Cu NP solutions that remain stable during the studied time (120 days) (shaded area – unstable solutions, precipitation is observed).

The coded compositions of the studied solutions, the ratio between the precursors of the studied system and the result of the action of metallic copper nanoparticles on test cultures of microorganisms are given in Table 1.

Table 1.

Experimental planning matrix for obtaining a fourth-degree model in the Cu^{2+} – L-Cys – $NaBH_4$ system and the results of the study of Cu NPs on the example of test cultures of microorganisms P.aeruginosa, C.albicans, B.subtilis by serial dilution method.

№	Coded scale			Relationship between components	Test cultures of microorganisms					
	A	C	B	Cu^{2+}/L-Cys/$NaBH_4$	P.aeruginosa MBsC	P.aeruginosa MBcC	B.subtilis MBsC	B.subtilis MBcC	C.albicans MFsC	C.albicans MFcC
1	1,00	0	0	1:4,5:2,27	1:4	1:2	>1:2	>1:2	1:2	>1:2
2	0,75	0,25	0	1:6,57:2,63	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
3	0,50	0,50	0	1:9,37:3,125	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
4	0,25	0,75	0	1:13,46:3,846	1:2	>1:2	1:4	1:2	>1:2	>1:2
5	0	1,00	0	1:20:5	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
6	0	0,75	0,25	1:17,5:6,75	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
7	0	0,50	0,50	1:15:8,5	>1:2	>1:2	>1:2	>1:2	1:4	1:2
8	0	0,25	0,75	1:12,5:10,25	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
9	0	0	1,00	1:10:12	1:2	>1:2	>1:2	>1:2	1:4	1:2
10	0,25	0	0,75	1:7,69:7,88	>1:2	>1:2	>1:2	>1:2	>1:2	>1:2
11	0,50	0	0,50	1:6,25:5,31	1:2	>1:2	1:2	>1:2	1:2	>1:2
12	0,75	0	0,25	1:5,26:3,59	>1:2	>1:2	>1:2	>1:2	1:2	>1:2
13	0,50	0,25	0,25	1:7,81:4,218	1:2	>1:2	>1:2	>1:2	1:4	1:4
14	0,25	0,50	0,25	1:9,615:6,538	>1:2	>1:2	>1:2	>1:2	1:2	>1:2
15	0,25	0,25	0,50	1:11,538:5,192	>1:2	>1:2	>1:2	>1:2	1:2	>1:2
Cu^{2+}	–	–	–	$1\cdot10^{-3}$ моль/л	1:2	>1:2	>1:2	>1:2	1:2	>1:2
L-Cys	–	–	–	$5\cdot10^{-2}$ моль/л	1:2	>1:2	>1:2	>1:2	1:2	>1:2
$NaBH_4$	–	–	–	$3\cdot10^{-2}$ моль/л	1:2	>1:2	>1:2	>1:2	1:2	>1:2

Minimum bacteriostatic concentration (MBsC), minimum bactericidal concentration (MBcC), minimum fungistatic concentration (MFsC), minimum fungicidal concentration (MFcC).

Observations over time (120 days) of changes in optical parameters (surface plasmon resonance bands) of colloidal solutions of copper nanoparticles (Fig. 2, using the example of solution № 2) made it possible to limit and identify areas for further research.

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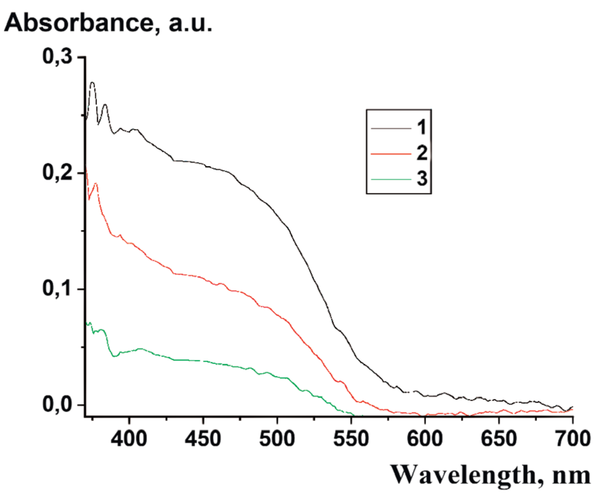

Fig. 2. Optical absorption spectra of colloidal solutions of metallic copper nanoparticles (№ 2) over time: 1 – 1 day; 2 – 10 days; 3 – 20 days after the synthesis of nanoparticles.

The optical indices of solutions № 3–5, 10, 11, 14 remain stable during the studied time, which makes it possible to determine the region of stable colloidal solutions of Cu nanoparticles within the studied concentration range of precursor solutions.

The optical absorption spectra for solutions № 6–9 are characterized by a shift of the optical absorption edge to the long-wavelength region and a decrease in the absorption maximum of solutions with partial coagulation of particles (first, turbidity appears with subsequent formation of a precipitate).

In solutions № 1, 2, 12, 13, 15, a blue precipitate appeared, which indicates an excessive concentration of cuprum ions in the studied medium and a lack of sodium tetrahydroborate content for the reduction of Cu^{2+} ions to Cu^0 particles.

The change in optical properties over time is shown using the example of solution № 1 (Fig. 3). Thus, during the studied time from 1 minute after synthesis to 60 minutes, a clear coagulation of particles is already observed, a precipitate appears, and the spectral curve becomes more deformed, the absorption intensity decreases.

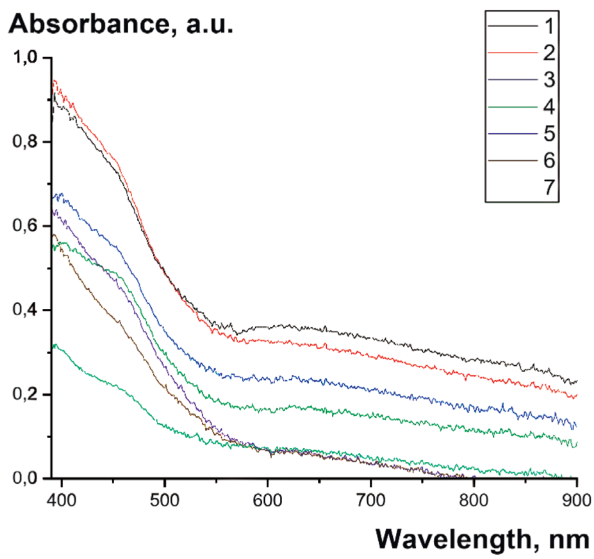

Fig. 3. Optical absorption spectra of a colloidal solution of metallic copper nanoparticles of composition №. 1 in time: 1–1 min, 2–15 min, 3–20 min, 4–30 min, 5–40 min, 6–50 min, 7–60 min after synthesis.

Coagulation for other solutions, for example solution № 2, does not occur as quickly as for solution №1, and begins to be observed on the second day after synthesis. The reason for this difference between solutions № 1 and № 2 can be explained by the ratio of components in the reaction medium. Under the condition of a lack of reducing agent and a large amount of L-Cysteine, the formation of not only Cu NPs, but also Cu^{2+}/L-Cys chelate complexes occurs, which are actually the centers of precipitate formation. The formation of such complex compounds is also facilitated by an excess of copper ions in the reaction medium and the fact that L-Cysteine has three functional groups – amino – NH_2, sulfhydryl – SH and carboxyl – COOH (sulfhydryl and carboxyl groups can interact with metal ions) [13]. Spectral curves for solutions № 1–4 (solutions with a lack of reducing agent), taken on the next day after synthesis, are shown in Figure 4.

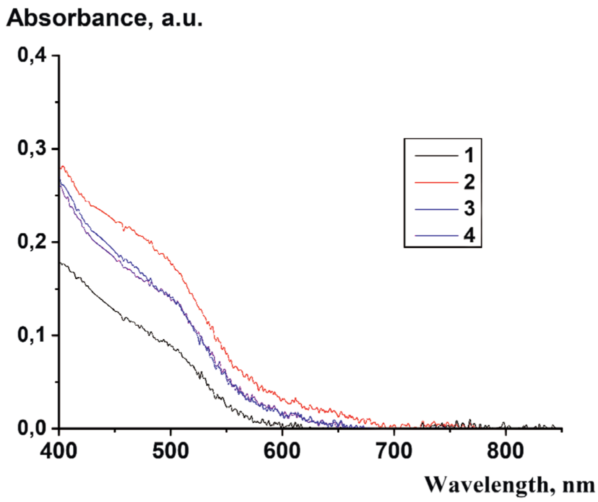

Fig. 4. Optical absorption spectra of colloidal solutions of metallic copper nanoparticles № 1–5 24 h after synthesis.

The generalized influence of the ratio between the components Cu^{2+}-L-Cys-$NaBH_4$ in the reaction medium on the optical properties of Cu/L-Cys solutions is shown in Figure 5. This is a projection onto the plane of the change in the optical absorption edge for a series of 15 solutions (solution composition according to Table 1.) from the ratio between all components of the studied system. The equation describing this dependence has the following form:

$$\boldsymbol{y} = 565\,x_1 + 565\,x_2 + 572\,x_3 + 20\,x_1x_2 + 16\,x_1x_3 + 40\,x_2x_3 + 101{,}3\,x_1x_2(x_1 - x_2) + 37{,}3\,x_1x_3(x_1 - x_3) - 26{,}7\,x_2x_3(x_2 - x_3) + 37{,}3\,(x_1 - x_2)^2x_1x_2 - 64\,(x_1 - x_3)^2x_1x_3 - 117{,}3\,(x_2 - x_3)^2x_2x_3 + 896\,x_1^2x_2x_3 - 992\,x_1x_2^2x_3 + 272\,x_1x_2x_3^2,$$

where y is the optical absorption edge, x_1, x_2 and x_3 are new independent variables that are a linear combination of the basic variables X1, X2 and X3 (the composition of the initial precursor solutions) - the coordinates of points A, B and C in the coded scale.

The equation describing the dependence of the absorption edge λ_{lim} on the composition of the three-component system with a fourth-degree approximation was derived for homogeneous solutions № 1–15. The value of the optical absorption edge corresponds to the spectra taken 15 min after synthesis, since later some of the solutions became inhomogeneous.

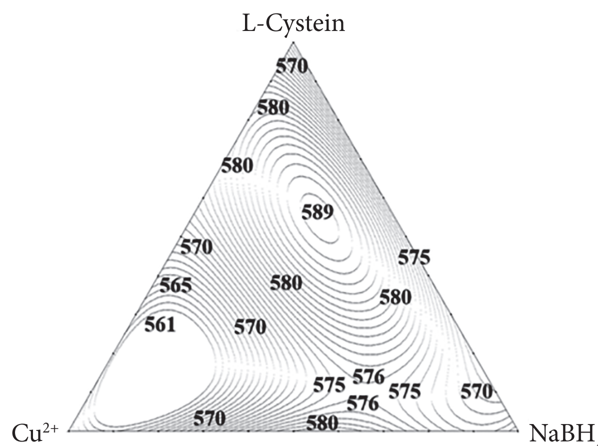

Fig. 5. Isolines of the absorption edge of the studied solutions № 1–15 (interpolation by the fourth degree approximation).

As an object of investigation of antimicrobial activity, we have 15 points from Table 1. from the Scheffe plan and the final doses of L-Cysteine, Sodium tetraborate and cuprum acetate salts. The test cultures included a strain of the spore culture Bacillus subtilis ATCC 6633, a strain of the gram-negative culture Pseudomonas aeruginosa ATCC 9027 and a standard strain of the fungus Candida albicans ATCC 885-653. The bacteriostatic properties of the studied objects were established based on the results of the growth of reference strains of microorganisms in solutions of a series of experiments (Table 1), which were performed by the method of successive double dilutions of 1:2 and 1:4 in meat-peptone broth. The evaluation was carried out according to the values of the zones of inhibition of growth of test cultures, as well as the values of the minimum bacteriostatic (MBsC), minimum bactericidal (MBcC), minimum fungistatic (MFsC) and minimum fungicidal (MFcC) concentrations of the studied substances of different composition of solutions (№ 1–15, Table 1.) for test cultures of microorganisms P.aeruginosa, C.albicans, B.subtilis.

The obtained results of the bioscreening showed that among the studied compositions of the Cu^{2+} – L-Cys – $NaBH_4$ system, the most effective antifungal indicators were demonstrated by solutions № 7, № 9 and № 13, which showed fungistatic and fungicidal properties against the yeast-like fungus C. albicans in a dilution of 1:2 and 1:4 (the areas with the responses of the test cultures are shown in Figure 6, according to the composition of the solutions.) Thus, solutions with an excess content of reducing agent inhibit the growth of C. albicans.

Fungistatic properties against C. albicans in a 1:2 dilution are also exhibited by solutions with an excess of copper ions № 1, № 12, № 14, solution № 11 (ratio between copper ions and reducing agent 1:1) and solution № 15 with an excess of reducing agent compared to copper ions.

Solution № 4 in dilutions of 1:2 and 1:4 exhibited bacteriostatic and bactericidal properties against the gram-positive bacterium B.subtilis. And solution № 11 exhibited bacteriostatic action against B.subtilis in dilutions of 1:2.

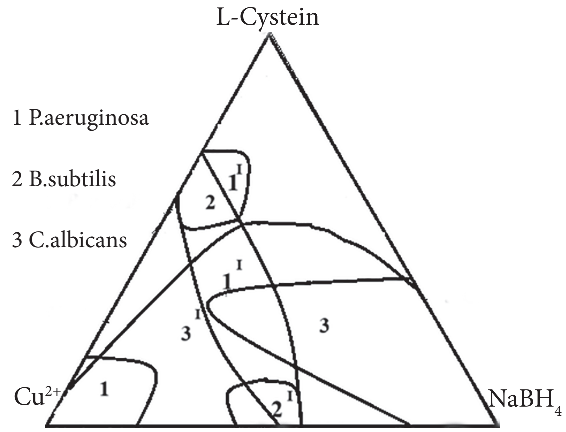

Fig. 6. Generalized map of the effect of test cultures of microorganisms on the tested solutions № 1–15 (area 1 – P.aeruginosa; 2 – B.subtilitis; 3 – C.albicans (MBsC) and 1^I – P.aeruginosa; 2^I – B.subtilitis; 3^I – C.albicans (MBsC).

The results of studies on the Gram-negative bacterium strain P.aeruginosa showed that solution № 1 exhibits a bacteriostatic effect at a 1:2 dilution and a bactericidal effect at a 1:4 dilution, solutions № 4, № 11, and № 13 exhibit bactericidal activity at a 1:2 dilution.

CONCLUSIONS. Based on the conducted experimental studies, the optimal ratio between the solutions of the precursors Cys, $NaBH_4$ and Cu^{2+} was determined, the colloidal solutions of which NPs remained stable for 120 days. The excess of copper ions in relation to Sodium tetraborate imposes additional effects on the overall picture of the change in the value of the optical absorption edge in the concentration limits of the starting components. This may be due to the fact that free, unbound in NPs, copper ions under such conditions easily interact with the stabilizer, forming complexes of different composition. Due to the fact that the selected stabilizer has several working groups, the formed complexes can serve as a bridge for connecting the formed Cu particles, which in turn causes additional optical effects.

From the side of high values of the reducing agent concentration, the nature of the change in isolines is simpler, but with increasing sodium tetraborate concentration, the value of the optical absorption edge of the solutions increases more intensively. Such a change may be associated with the destruction of the stabilizer, which in turn leads to coagulation of the resulting solutions of copper nanoparticles.

The compositions of solutions have been experimentally established, which, in comparison with other colloidal solutions, exhibit a higher effect on test cultures of microorganisms P.aeruginosa, C.albicans, B.subtilitis. However, it is the solutions of these compositions (№ 1, № 7, № 9, № 13, №. 15) that are not stable under storage conditions in an oxidizing environment for a long time.

Synthesized colloidal solutions of copper nanoparticles exhibit more pronounced antifungal activity against C. albicans.

The results obtained are an impetus for further research in the field of synthesis of stable and simultaneously active colloidal solutions of Cu nanoparticles in the fight against microorganisms.

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ОПТИМІЗАЦІЯ УМОВ СИНТЕЗУ БІОСУМІСНИХ КОЛОЇДНИХ РОЗЧИНІВ МЕТАЛІЧНИХ ЧАСТИНОК МІДІ

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У роботі проведено комплексний підбір умов синтезу нанорозмірних частинок Купруму у водному окиснювальному середовищі з використанням як стабілізатора біосумісної амінокислоти – L-Цистеїну, відновника – Натрій тетраборату та застосуванням методу математичного планування експерименту – методу Шеффе.

Використання методу математичного планування дало можливість спрогнозувати адитивний вплив співвідношення між прекурсорами у досліджуваному середовищі на значення краю оптичного поглинання отриманих колоїдних розчинів наночастинок купруму, їхню стабільність у часі та дію на тест-культури мікроорганізмів P.aeruginosa, C.albicans, B.subtilitis.

Встановлено співвідношення між вихідними реагентами, які призводять до утворення стабільних колоїдних розчинів наночастинок купруму за значення pH=6 та температури 20^0C в окиснювальному реакційному середовищі.

Побудовано математичну модель у вигляді проекції на площину рівностороннього трикутника залежності значення краю оптичного поглинання колоїдних

розчинів наночастинок металічної міді від співвідношення між прекурсорами. Отримано математичне рівняння – поліном четвертого ступеня, що описує залежність значення краю оптичного поглинання колоїдних розчинів наночастинок купруму залежно від співвідношення між трьома незалежними змінними – кристалоформуючими компонентами стійких у часі частинок у реакційному середовищі. Досліджено протибактеріальні активності серії досліджуваних розчинів мікрометодом серійних розведень відповідно до процедур Європейського комітету з тестування чутливості до референс-штамів бактерій (P.aeruginosa, C.albicans, B.subtilitis.). Із використанням математичної моделі Шеффе визначено концентраційні області та співвідношення між компонентами досліджуваної системи, які проявили найвищий вплив на дію тест-культур мікроорганізмів.

Ключові слова: наночастинки, оптичні показники, купрум, мікроорганізми P.aeruginosa, C.albicans, B.subtilitis.

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