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SYNTHESIS AND CHARACTERIZATION OF COPPER-LOADED HYDROXYAPATITE-ALGINATE MICROSPHERES

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Microspheres of hydroxyapatite (HA) in alginate (Alg) shell can be successfully used for controlled release of drugs, growth factors, and antibacterial compounds. Hydroxyapatite is a perfect material for biomaterials production due to its high sorption capacity to metal ions, low solubility in water, high stability to oxidisers and reducers, low cost and biocompatibility. Sodium alginate used for microspheres formation due to its cross-linking capability with divalent cations (Cu^{2+}, Ca^{2+} etc.). Microspheres HA/Alg-Cu were obtained by 2 variants of synthesis and showed more rough surface than that of microspheres HA/Alg-Ca what is better for cell proliferation. XRD results show that HA is the main crystalline phase in obtained microspheres. According to the results of adsorption kinetics study, HA has the main contribution in process of Cu^{2+} ions adsorption. The temperature, increasing the rate of the adsorption process, has negligible effect on the adsorption capacity of HA due to the saturation of energetically heterogeneous active sites on the microspheres surface with Cu^{2+} ions. Adsorption index of HA/Alg microspheres to Cu^{2+} ions was calculated to be above 60 mg/g. Adsorption of Cu^{2+} ions on HA/Alg microspheres has an ion-exchange character. Due to the Cu^{2+} ions release obtained microspheres showed antibacterial effect on S. aureus and E. coli in concentration 6 mg/mL.

Keywords: *hydroxyapatite, alginate, microspheres, composite, adsorption, antibacterial properties, biomaterials*

INTRODUCTION

Nowadays the design of new biomaterials is focused on mimicking functions of the extracellular matrices of body tissues and naturally derived materials recently regaining much attention due to their biocompatibility [1, 2]. Alginate (Alg)-based materials and composites have been studied in orthopaedic research for promoting osteogenesis, improving osteogenic differentiation, and delivering cells, drugs and growth factors to bone defect sites [3].

Sodium alginate (SA) is a naturally occurring linear anionic polymer containing blocks of (1,4)-linked β-*D*-mannuronate (M), α-*L*-guluronate (G) residues and alternating G-M residues (Fig. 1). It is derived from brown seaweed and widely used for biomaterial applications due to its biocompatibility, low cost, mild gelation, crosslinking capability by addition of divalent cations and structural similarity to extracellular matrices of living tissues [2]. Interaction with divalent cations and intermolecular cross-linking occur mostly due to the interaction with G-blocks, so G-block length, molecular weight and M/G ratio are strongly affecting the physical properties of alginates and their hydrogels [4, 5].

The most significant application of alginates is biomaterial production [3, 6]. They are used as stabilizers in pharmaceutical industry, for controlled drug release, scaffolds production, cells encapsulation [3, 5], wound dressings and haemostatic materials [3, 5]. Alginate based fibers are non-toxic, non-allergic, bacteriostatic, biocompatible with high absorptive properties [5, 8]. Nanocomposite beads (SA/HA) are used as drug-controlled release matrices [9]. Alg/HA nanocomposite beads loaded with sodium diclofenac as the model drug was prepared by the *in situ* generation of HA micro-particles in the beads during the sol–gel transition process of SA. The synergistic effect of biopolymer and

inorganic material as well as the strong interfacial interactions between them via electrostatic interaction and hydrogen bonding could improve the mechanical properties, swelling behavior, drug loading efficiency and controlled release behavior of the biopolymer matrices. HA is an ideal material for the preparation of drug scaffolds because of its excellent properties, such as the capability to adsorb a variety of chemical species and biocompatibility. The release of drugs from HA is very fast, owing to the weak interaction between the drugs and the HA particles [10]. The combination of biopolymer and HA seems to be a feasible way to prolong the release of drugs to make the biopolymer/HA composites applicable for long-term controlled release carriers. The HA micro-particles act as inorganic crosslinkers in the nanocomposites and restrict the movability of the SA polymer chains, and then change the surface morphology and decrease the swelling ratio. The reaction time, temperature and concentration of Ca^{2+} ions, influenced on the entrapment efficiency and release rate of drugs. The entrapment efficiency of sodium diclofenac was improved in sodium alginate/hydroxyapatite nanocomposite beads [11].

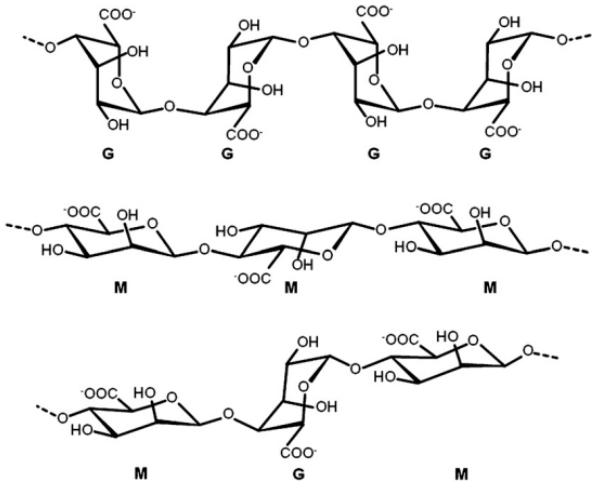


Fig. 1. Chemical structure of alginate: M-blocks, G-blocks and alternating M-G blocks

One critical drawback of ionically crosslinked alginate gels is the limited long-term stability in physiological conditions, because these gels can be dissolved due to release of divalent ions into the surrounding media, and exchange reactions with monovalent cations. In addition, the calcium ions released from the gel may promote hemostasis, while the gel serves as a matrix for aggregation of platelets and erythrocytes [3]. The affinity of alginates towards divalent ions decreases in the following order: Pb > Cu > Cd > Ba > Sr > Ca >Co, Ni, Zn > Mn [12]. Ionotropic gels and acid gels from alginate will behave differently in terms of swelling properties and physical and chemical features. The degradation of alginate ionotropic gels could arise from the breaking of the divalent crosslinking [5].

Metal ions in biopolymer-based matrix play an important role in the repair and regeneration of skin wounds due to the antibacterial properties. They prevent or control excessive proliferation of bacteria, which decreases inflammation of implanted material. Although metal ions are essential for wound healing, the toxicity of metal-incorporated materials should be controlled. Characterization of adsorption properties allows obtaining composite materials with required concentrations of metal ions.

HA and HA-Alg materials can be used as excellent natural adsorbents to remove Zn(II) from wastewaters with good efficiency and low cost. The amount of Zn^{2+} adsorption was found to increase with increase in initial metal ion concentration and contact time but found to decreases with an increase in amount of adsorbent and temperature. The maximum adsorption capacity of hydroxyapatite was found to 62.5 mg/g with an initial Zn^{2+} concentration range of 30 to 90 ppm, whereas for HA-Alg was 56.49 mg/g with the same Zn^{2+} ion concentration range [13]. Adsorption capacity for HA/Alg

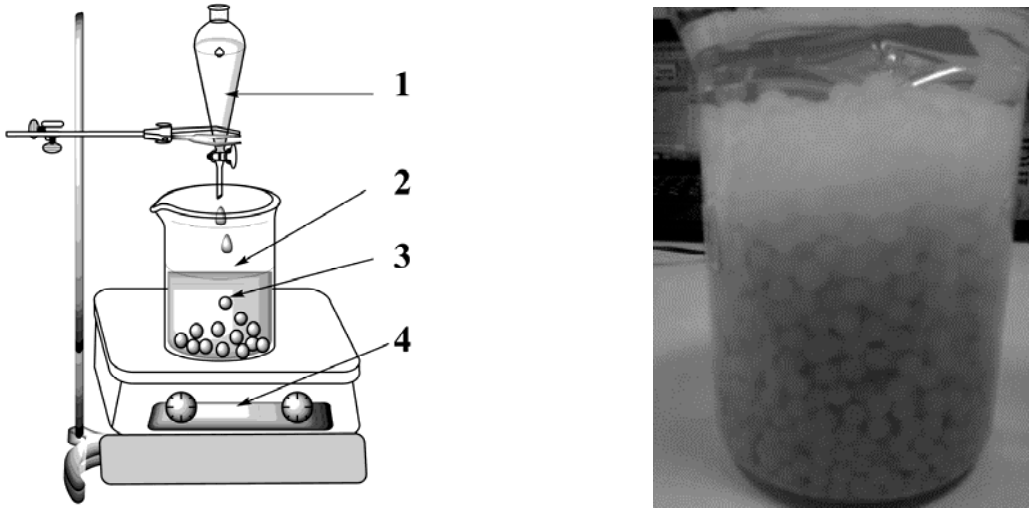
microspheres to Zn^{2+} ions was studied in our previous work [14]. In this article Cu^{2+} ions are used as active antibacterial components of obtained composite materials. Copper has been used as a medicine for thousands of years due to its antibacterial and anti-inflammatory action. More recently, research has indicated that copper helps prevent inflammation in arthritis and similar diseases. It is incorporated into proteins and metalloenzymes, which perform essential metabolic functions. Copper is necessary for growth, development and maintenance of bone and connective tissue so its application in materials for bone substitution is very promising. Besides, concentration of copper in obtained materials should be safe for human organism. The European Food Safety Authority sets Tolerable Upper Intake level for copper – 5 mg/day [15], so capability of HA/Alg microspheres to copper adsorption should be estimated for obtaining biomaterials with required properties. Adsorption properties of for HA/Alg microspheres to Cu^{2+} ions, morphology, phase composition and antibacterial properties are studied in this work.

MATERIALS AND METHODS

Synthesis of HA-Alg microspheres. Hydroxyapatite was synthesized by following reaction:

$$10\,Ca(NO_3)_2 \cdot 4H_2O + 6\,(NH_4)_2HPO_4 + 8\,NH_3{\cdot}H_2O \rightarrow$$
$$\rightarrow Ca_{10}(PO_4)_6(OH)_2 + 20\,NH_4NO_3 + 46\,H_2O.$$

Obtained HA was washed three times with distilled water and filtered. HA slurry was mixed with 1 and 3 % SA solutions in relation 1:1 (samples 1 and 2 respectively). Two ways of synthesis are proposed: 1) HA-Alg mixture was added dropwise into 0.1 M $CaCl_2$ solution, washed and immersed into 0.1 M $CuSO_4$ solution for 24 h (samples 1 *a*, 2 *a*) (Fig. 1 *a*); 2) HA-Alg mixture was added dropwise into 0.1 M $CuSO_4$ solution for 24 h (samples 1 *b*, 2 *b*). Microspheres HA/Alg without Cu^{2+} ions were obtained by the same way: HA-Alg mixture was added dropwise into 0.1 M $CaCl_2$ solution, washed, dried and used for comparison and following experiments (samples 1 *c* and 2 *c*). The experimental setup for microspheres production is shown in the Fig. 2.



a *b*

Fig. 2. *a* – Experimental setup for obtaining of HA/Alg microspheres: *1* – alginate solution mixed with as-prepared hydroxyapatite slurry; *2* – 0.1 M $CaCl_2$ solution; *3* – formation of microspheres HA/Alg; *4* – magnetic stirrer; *b* – general view of obtained microspheres (sample 1 *b*)

Adsorption of Cu^{2+} ions by microspheres. Adsorption index was calculated by using formula:

$$A = \frac{\left(C_{M\,Cu^{2+}} - t\right) \cdot V \cdot 32.7 \cdot 1000}{m}, \qquad (1)$$

where C_M Cu^{2+} – initial concentration of Cu^{2+} ions (mol/L), t – contact time (hours), V – volume of solution (L), m – mass of dried microspheres, g.

To characterize the adsorption rate, the graphical dependence of the adsorption index

(mass (mg) of adsorbed Cu^{2+} ions per 1 g of adsorbent capsules) on the temperature and contact time at a constant concentration of Cu^{2+} ions in solution was analyzed. Adsorption process was characterized at constant temperature and stirring. Samples of adsorbents were mixed with the initial 100 mmol/L $CuSO_4$ solution (with the relation of solid to liquid phase 1:10) at 22 and 50 °C. Contact time was changed from 5 min to 24 h.

Analysis techniques. The as dried products were characterized using an optical microscope (Karl Zeiss Primo Star, Karl Zeiss Microimaging, GMBH, Germany), a scanning electron microscope (SEM; REMMA-102, "Selmi" Ukraine) with integrated micro analytical system. The surface chemical composition was determined with an energy dispersive X-ray (EDX) detector. The analytical signal of the characteristic X-ray emission was integrated by scanning the 50×50 μm^2 area of the sample surface. The crystallinity and structure of precipitates were examined using an X-ray diffractometer XRD (DRON-4, "Burevestnik", Russia) connected to a computer-aided system for the experiment control and data processing. The Ni-filtered CuK_α radiation (wavelength 0.154 nm) with a conventional Bragg–Brentano θ-2θ geometry was used. The current and the voltage of the X-ray tube were 20 mA and 40 kV, respectively. The samples were measured in the continuous mode at the rate of 2.0 °/min, with 2θ-angle ranging from 10 to 60°. All experimental data were processed by means of the program package DIFWIN-1 ("Etalon PTC" Ltd, Russia). Identification of crystal phases was done using the JCPDS card catalog (Joint Committee on Powder Diffraction Standards). Concentrations of Cu^{2+} ions in solutions were determined by means of an atomic absorption spectrometer (AAS) CAS-120.1 ("Selmi", Ukraine). Calibration solutions were prepared by diluting the initial solution of $CuSO_4 \cdot 5H_2O$ with concentration 100 mmol/L up to 1000 times for obtaining concentrations: 0; 0.05; 0.1 (mmol/L $CuSO_4 \cdot 5H_2O$). The experimental conditions were: λ(Cu) = 327.5 nm and spectral slit width = 0.4 nm. Concentrations of Ca^{2+} ions were determined by complexometric titration with EDTA solution.

Bacteria studies. The study of antibacterial activity was carried out in 2 stages using a modified serial dilution method in nutrient broth and subsequent quantitative seeding on dense nutrient media. Experimental samples were immersed into four sterilized test-tubes, containing 1 mL of nutrient media in amount of 1.5, 3.0, 6.0 and 12 mg. Two test-tubes were used as control of the medium and control of culture respectively. Daily culture of *E. coli, P. aeruginosae and S. aureus*, isolated from patients with respiratory viral infections, from which microbial suspensions were prepared equivalent to 0.5 McFarland standard, and diluted 100 times in a nutrient broth, were used for inoculation. Thereafter 1 mL of the bacterial suspensions was added into the tubes containing experimental samples and nutrient broth ("culture control" to make the final concentration of the bacteria cells approximately 5.0×10^5 (CFU/mL). All test tubes, except the "culture control", were incubated for 24 h at 35 °C in an oven to simulate physiological solution conditions. A "culture control" test tube was placed in a refrigerator at 4 °C for comparison. In order to determine the presence of microorganisms, the test tubes with bacterial culture were examined in passing light by comparing with the reference "culture control" test tube containing the initial inoculum stored in the refrigerator. The minimal inhibitory concentration (MIC) was determined at the lowest concentration of the studied substances, which suppressed growth of microorganisms. Experiments were carried out in triplicate and results were expressed as mean values with standard deviations.

RESULTS AND DISCUSSION

Two ways of synthesis are proposed: 1) HA-Alg mixture was added dropwise into 0.1 M $CaCl_2$ solution, washed and immersed into 0.1 M $CuSO_4$ solution for 24 h (samples 1 *a*, 2 *a*); 2) HA-Alg mixture was added dropwise into 0.1 M $CuSO_4$ solution for 24 h (samples 1 *b*, 2 *b*) (Fig. 3). Microspheres obtained directly in 0.1 M $CaCl_2$ solution were taken for comparison.

Fig. 3 illustrates the morphologies and surface microstructures of the HA/Alg in 0.1 M $CaCl_2$ solution (sample 2 *c*) and copper loaded microspheres (samples 1 *a*, 2 *a*, 1 *b*, 2 *b*). HA has been incorporated into the alginate microspheres. Apparently, the HA/Alginate after Cu^{2+} adsorption has a relatively more rough surface than that of microspheres obtained in $CaCl_2$ solution. Relation of Ca/P was calculated

(1.67 at. %) that corresponded to HA. Peak of Cu indicated the presence of Cu in the obtained material (Fig. 3).

Phase composition of obtained materials was examined by XRD (Fig. 4). The main crystalline phase in obtained samples is HA. The presence of alginate is confirmed by the decreased crystallinity of samples 2 *a* (*a*) and 2 *b* (*b*) as compared to pure hydroxyapatite (*c*).

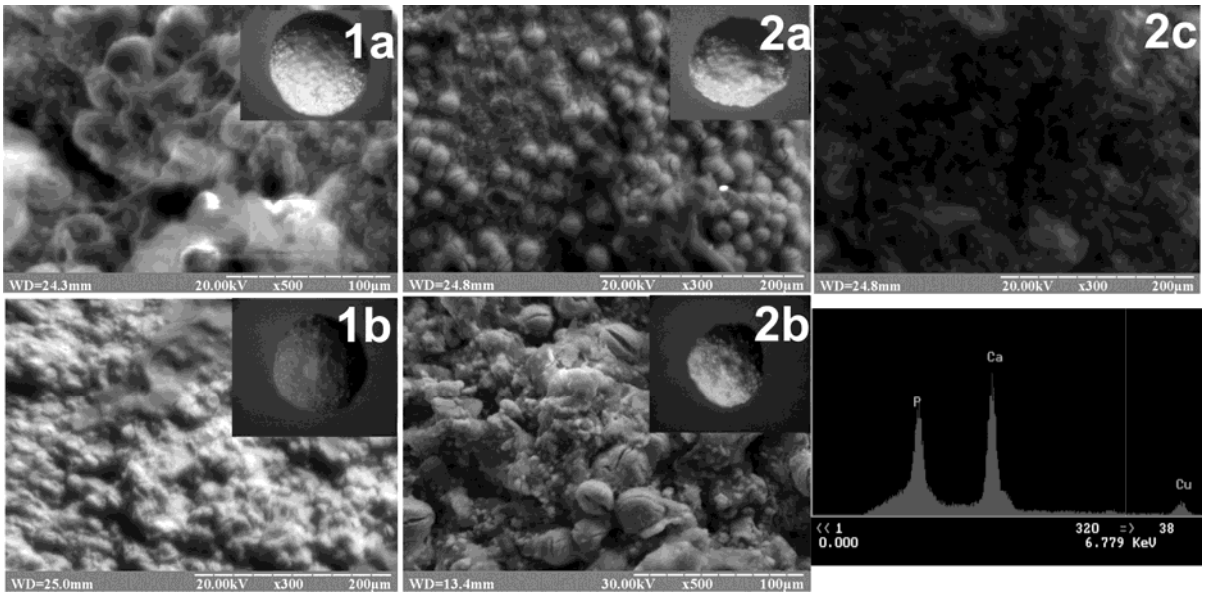


Fig. 3. SEM images of the surfaces of microspheres HA-Alg obtained in 0.1 M $CaCl_2$ solution (2 *c*); HA-Alg obtained in $CaCl_2$ solution and immersed into 0.1 M $CuSO_4$ solution (1 *a*, 2 *a*); HA-Alg obtained in 0.1 M $CuSO_4$ solution (1 *b*, 2 *b*); EDX spectra of the sample 2 *b*

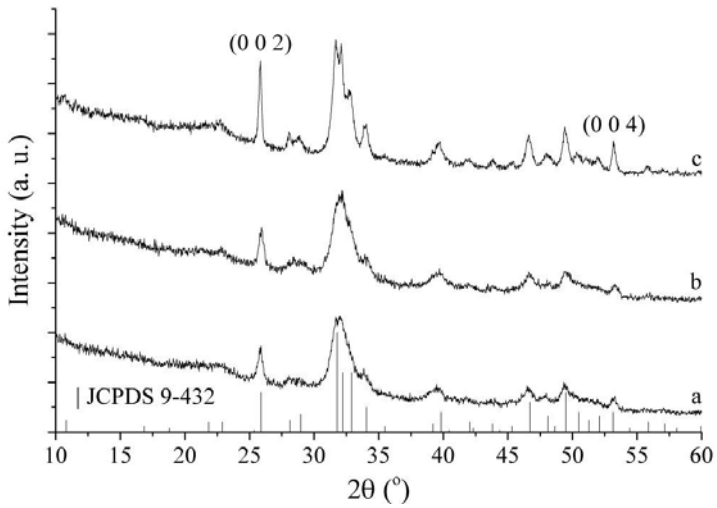


Fig. 4. XRD patterns of samples: *a* – HA/Alg (2 *a*), *b* – HA/Alg (2 *b*), *c* – pure HA

Adsorption kinetics. After 24 h of microspheres immersion the solution was filtered and concentrations of Cu^{2+} ions in the filtrate were determined by AAS method. For samples 1 *a* and 2 *a* filtrate concentrations were the same 24 mmol/L. In the case of samples 1 *b* and 2 *b* they were 19 and 21 mmol/L respectively. So Alg shell has no sufficient contribution to adsorption capacity of obtained microspheres.

Experimental results of the adsorption rate at constant concentration of Cu^{2+} ions in the solution are shown in the Table 1 and Fig. 5.

Table 1. Experimental results of Cu^{2+} ions adsorption by HA/Alg microspheres (sample 1 *c*)

Sample No	Mass of microspheres, (*m*) g	Temperature, (*T*) °C	Time, (*t*) min	C_M Cu^{2+} mmol/L	Adsorption index (*A*) mg/g
1	0.5015	50	5	95	3.2
2	0.5020	50	15	73	17.2
3	0.5000	50	40	67	21.1
4	0.5005	50	60	58	26.9
5	0.5015	50	720	23	49.1
6	0.5025	50	1440	16	53.5
7	0.5015	22	5	98	1.3
8	0.5020	22	15	86	8.9
9	0.5000	22	40	77	14.7
10	0.5005	22	60	78	14.1
11	0.5015	22	720	28	45.9
12	0.5025	22	1440	23	49.0

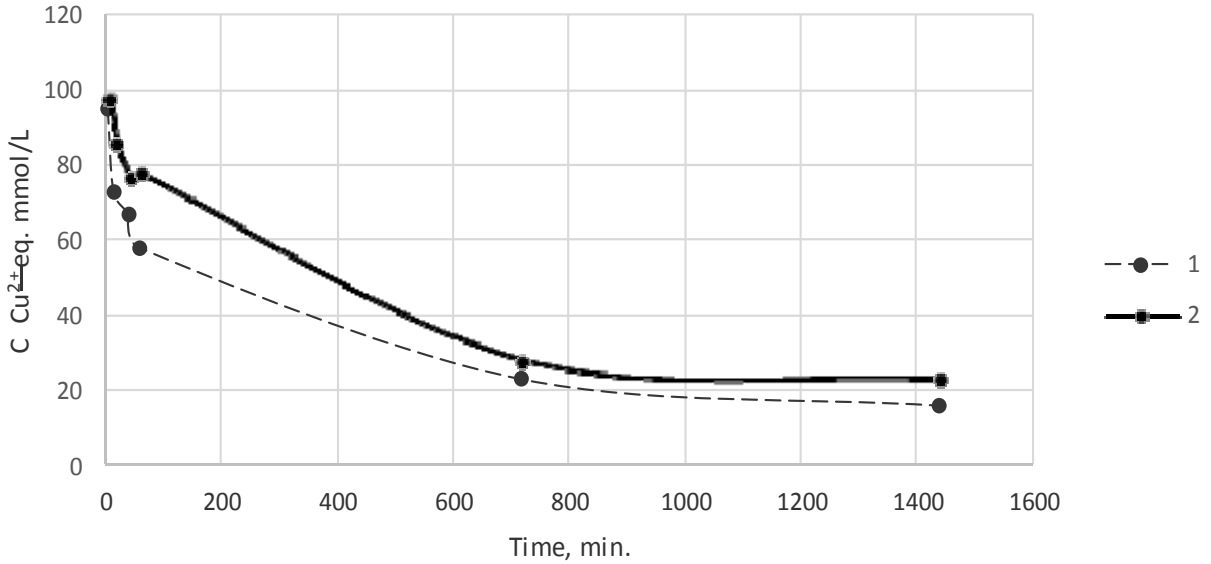


Fig. 5. The influence of temperature on the adsorption rate of copper ions by HA/Alg microspheres with C_0 – initial concentration of Cu^{2+} 100 mmol/L: *1* – adsorption rate of Cu^{2+} ions at 22 °C; *2* – adsorption rate of Cu^{2+} ions at 50 °C

The presented data (Table 1) prove the fact that the temperature has a significant effect on the adsorption rate. Adsorption capacity of the same adsorbent increased with increasing temperature at constant initial concentration of Cu^{2+} ions in the solution. It could be noticed mostly at the first stages of adsorption (Fig. 5).

As follows from the data given in Table 1, the decrease in the content of Cu^{2+} ions in the filtrate due to adsorption processes is more intense at the higher temperature (Fig. 5, Curve 2).

As it is shown in Fig. 6, increasing of temperature slightly increases adsorption index of copper ions by HA/Alg microspheres under prolonged contact of the solution with adsorbents. This indicates the saturation of the adsorbent surface with Cu^{2+} ions. In this case the temperature, increasing the rate of this process, has negligible effect on the adsorption capacity of hydroxyapatite due to the saturation of energetically heterogeneous active sites on the microspheres surface with Cu^{2+} ions. Adsorption index of HA/Alg microspheres to Cu^{2+} ions does not exceed 60 mg/g (Fig. 6). The low values of the adsorption index are associated with certain features of the process of Cu^{2+} ions incorporation on to the adsorbent surface.

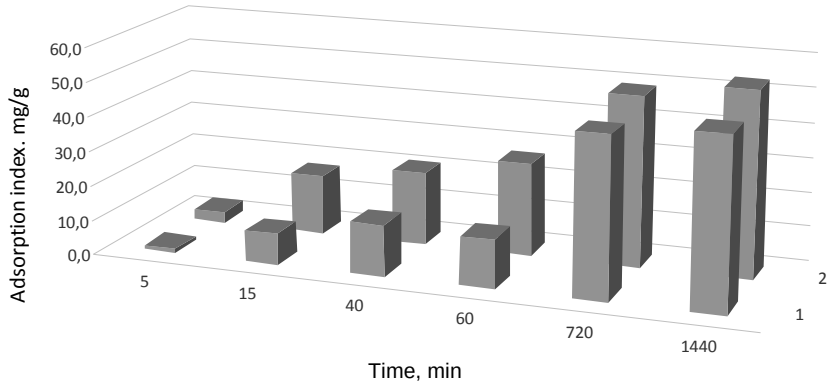


Fig. 6. Time dependence of Cu^{2+} ions adsorption index (mg/g) at various temperatures: 22 °C (line 1) and 50 °C (line 2)

The existence of white precipitate was observed in all experimental solutions after immersion of HA/Alg microspheres (sample 1 *c*) and finishing of the adsorption experiments. We assume that the formation of this precipitate is associated with the release of Ca^{2+} ions from the surface layers of the HA and their replacement by Cu^{2+} ions. On the solid surface will adsorb such kind of ions which can complete the crystal lattice, or form insoluble compounds with the ions as follows from the Fajans-Panetta rule. As it is known, the $Cu_3(PO_4)_2$ is practically insoluble in water (K_{sp} is $1.3 \cdot 10^{-37}$), and Ca^{2+} ions could be displaced by Cu^{2+} ions due to the formation of less soluble phases on the HA surface involving Cu^{2+} ions. The process can be schematically represented as follows:

$$Ca_{10}(PO_4)_6(OH)_2 + x\ Cu^{2+} \rightarrow$$
$$\rightarrow Ca_{10-x}Cu_x(PO_4)_6(OH)_2 + x\ Ca^{2+}.$$

Transition of Ca^{2+} ions from crystal lattice to adsorbate is accompanied by precipitation of these ions in the form of a low-soluble substance $CaSO_4$.

To confirm this assumption, filtrate samples were analyzed after adsorption. For comparison, samples were taken after 5 min of contact with 100 mmol/L $CuSO_4$ solution and after 24 h. The precipitates present in these samples were dissolved in the same filtrate by addition of few drops of HCl (density 1.19 g/cm³). Obtained transparent solutions were taken to determine the presence of divalent metal ions (Ca^{2+} and Cu^{2+}).

The concentration of these ions was determined by complexometric titration with EDTA in accordance with the standard procedure in the presence of murexide in an alkaline medium (Table 2).

Table 2. Concentration of Ca^{2+} and Cu^{2+} ions in the filtrate after adsorption

Number of sample	Temperature, °C	Time, min	Concentration of Ca^{2+} and Cu^{2+} ions in the filtrate after adsorption, mmol/L		
			$C_{м\ general}$ Me^{2+} in filtrate after dissolution of precipitate	$C_м$ Cu^{2+} in filtrate above precipitate	$C_м$ Ca^{2+} in filtrate after dissolution of precipitate
1	50	5	100	95	5
6	50	1440	50	16	34
7	22	5	100	98	2
12	22	1440	55	23	32

As follows from the data presented in Table 2, at the beginning of the adsorption process (contact time 5 min), the presence of Ca^{2+} ions in the filtrate is insignificant in comparison with Cu^{2+} ions. But after 24 h, concentration of Cu^{2+} ions decreased while

concentration of Ca^{2+} ions increased. Part of the Ca^{2+} ions form a slightly soluble $CaSO_4$ precipitate. At the same time, increasing of temperature promotes ion exchange on the HA surface. After 24 h, the concentration of Cu^{2+} ions in the filtrate above the precipitate is about 20 mmol/L. Nearly 30 mmol/L of Ca^{2+} ions are precipitated in the form of $CaSO_4$.

Thus, the interaction characteristics of Cu^{2+} ions adsorption on HA have an ion-exchange character and are associated with the capability to immobilize a significant amount of metal ions. It could be possible due to ion exchange reactions at the surface and to the co-precipitation of slightly soluble phases of metal phosphates [15].

Antibacterial properties. Antibacterial activity of the substances studied with respect to different types of microorganisms. None of the compositions inhibited growth of *P. aeruginosae*. Samples 1 *b* and 2 *b* in a quantity of 6 mg per 1 ml of medium caused the suppression of *S. aureus* and *E. coli* (MIC) growth (Table 3). In the Table 3 concentrations that suppressed bacterial activity are shown by using black colour. Samples 1 *c* and 2 *c* showed no antibacterial activity, as evidenced by the dynamic growth of microorganisms during incubation of samples from an initial volume of 10^5 CFU/mL to 5×10^6 and 10^8 CFU/mL at the end of the incubation.

Table 3. Antibacterial activity of HA/Alg microspheres loaded with Cu^{2+} ions

Sample	Type of bacteria		
	E. coli	***P. aeruginosae***	***S. aureus***
	mass of HA/Alg microspheres loaded with Cu, g/mL		
1 *b*	0.0066	0.0067	0.0060
2 *b*	0.0065	0.0072	0.0074
1 *c*	0.0069	0.0064	0.0067
2 *c*	0.0073	0.0066	0.0061

CONCLUSIONS

Microspheres HA/Alg-Cu were obtained via 2 variants of synthesis. Both of them are possible and could be used for obtaining bone substitutive materials. HA/Alg microspheres after Cu^{2+} adsorption have more rough surface than microspheres obtained in $CaCl_2$ solution. Hydroxyapatite is the main phase of obtained composite materials and has the main contribution in process of Cu^{2+} ions sorption in comparison with sodium alginate. The temperature, increasing the rate of the adsorption process, has negligible effect on the adsorption capacity of hydroxyapatite due to the saturation of energetically heterogeneous active sites on the microspheres surface with Cu^{2+} ions. Adsorption index of HA/Alg microspheres to Cu^{2+} ions does not exceed 60 mg/g.

Increasing of temperature promotes ion exchange at the HA surface and Ca^{2+} ions are precipitated in the form of $CaSO_4$. Thus, the mechanism of Cu^{2+} ions adsorption on HA/Alg microspheres has an ion-exchange character, co-precipitation of slightly soluble phases of metal phosphates is also possible. Due to the Cu^{2+} ions release, obtained microspheres showed antibacterial effect on *S. aureus* and *E. coli* in concentration 6 mg/mL that corresponded to the mass of Cu^{2+} − 0.36 mg.

Синтез та характеризація мікросфер гідроксиапатит-альгінат, збагачених міддю

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Мікросфери гідроксиапатиту (ГА) в альгінатній оболонці можуть бути успішно застосовані для контрольованого вивільнення лікарських засобів, факторів росту та антибактеріальних сполук. Гідроксиапатит є відмінним матеріалом для створення біоматеріалів завдяки своїй високій сорбційній ємності до йонів металів, низькій розчинності у воді, високій стабільності до окисників та відновників, низькій ціні та біосумісності. Альгінат натрію (Альг) використовується для утворення мікросфер завдяки його здатності до комплексоутворення з двохвалентними катіонами (Cu^{2+}, Ca^{2+} та ін.). Мікрогранули ГА/Альг-Си були отримані, використовуючи два варіанти синтезу, та мають більш шорсткувату поверхню ніж мікросфери ГА/Альг-Са, що покращує проліферацію клітин. Результати рентгенівської дифракції свідчать, що ГА є основною кристалічною фазою в отриманих мікросферах. Відповідно до результатів дослідження кінетики адсорбції, ГА вносить основний вклад в процес адсорбції йонів Cu^{2+}. Температура, збільшуючи швидкість процесу адсорбції, має незначний ефект на адсорбційну ємність ГА завдяки насиченню енергетично гетерогенних активних центрів на поверхні мікросфер йонами Cu^{2+}. Адсорбція йонів Cu^{2+} мікросферами ГА/Альг має іонообмінний характер і становить близько 60 мг/г. Завдяки виходу йонів Cu^{2+} отримані мікросфери мають антибактеріальний ефект на S. aureus та E. coli в концентрації 6 мг/мл.

Ключові слова: *гідроксиапатит, альгінат, мікросфери, композити, адсорбція, антибактеріальні властивості, біоматеріали*

Синтез и характеризация микросфер гидроксиапатит-альгинат, обогащенных медью

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Микросферы гидроксиапатита (ГА) в альгинатной оболочке могут быть успешно применены для контролируемого высвобождения лекарственных средств, факторов роста и антибактериальных соединений. Гидроксиапатит является отличным материалом для создания биоматериалов благодаря своей высокой сорбционной емкости к ионам металлов, низкой растворимости в воде, высокой стабильности к окислителям и восстановителям, низкой цене и биосовместимости. Альгинат натрия (Альг) используется для образования микросфер благодаря его способности к комплексообразованию с двухвалентными катионами (Cu^{2+}, Ca^{2+} и др.). Микрогранулы ГА/Альг-Си были получены с использованием двух вариантов синтеза и имеют более шероховатую поверхность, чем микросферы ГА/Альг-Са, что улучшает пролиферацию клеток. Результаты рентгеновской дифракции показывают, что ГА является основной кристаллической фазой в полученных микросферах. Согласно результатам исследования кинетики адсорбции, ГА вносит основной вклад в процесс адсорбции ионов

Cu^{2+}. Температура, увеличивая скорость процесса адсорбции, незначительно влияет на адсорбционную емкость ГА благодаря насыщению энергетически гетерогенных активных центров на поверхности микросфер ионами Cu^{2+}. Адсорбция ионов Cu^{2+} микросферами ГА/Альг имеет ионообменный характер и составляет около 60 мг/г. Благодаря выходу ионов Cu^{2+} полученные микросферы обладают антибактериальным эффектом на S. aureus и E. coli в концентрации 0.006 мг/мл.

Ключевые слова: *гидроксиапатит, альгинат, микросферы, композиты, адсорбция, антибактериальные свойства, биоматериалы*

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