ISSN : 0974 - 7494 Volume 10 Issue 2

Nano Science and Nano Technology
An Indian Journal

Review

NSNTAIJ, 10(2), 2016 [083-097]

Problems and prospects application of silver nanoparticles in medical practice

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At the end of 80-years of the last century into scientific terminology introduce a family of new terms with prefix «nano» as: nanotechnology, nanostructure, nanocompocite material, nanocluster, nanochemistry, nanophysics, nanobiotechnology and etc. In all over countries there were editions, journals where published results devoted exclusively to nanomaterials[1-3].

Great number of articles, reviews, monographies devoted to nanotechnology, nanostructures and nanomaterials has been written. Scientific centers, institutes, chairs and scientific schools which solved problems of nanotechnology have been created[4-6]. Frequently new knowledge with prefix «nano» were appropriated for long time to known objects or phenomena. However, exist, have taken root into use and have taken worthy place and such concepts which were not in an arsenal of researchers still 25-30 years ago and without which it is already impossible to present development of modern science to which it is possible to carry nanoparticles (NP) in all their diversification[1-7].

In this review possibilities obtaining, investigation of physico-chemical, medico - biological properties and structure of bactericidal preparations contained nanoparticles of silver are considered. Also results of investigation of authors at direction of formation nanoparticles of silver in the structure of cellulose and its simple aether Na - carboxymethylcellulose (Na-CMC) are presented. The choice of the given objects depend on by easy of restoration of silver ions till nanoparticles, their high bactericidal activity and possibility of regulation in wide range of the sizes and forms nanoparticle of silver at process of restoration.

The increasing an interest to silver nanoparticles it is connected, on the one hand by their high biological activity, and with another - occurrence of resistance of an organism to an existent antibiotics and many medical products an organic derivation.

Methods of obtaining of silver nanoparticles nowadays continue to develop intensively. At the present it is known two ways of obtaining of nanoparticles of silver[3,7,8];

The first - physical, under the influence of thermal or power factors;

Dispersion or mechanical crushing of massive substance concern physical methods[9].

Essence of these ways of obtaining NP of silver consist in intensive thermal or power influence on metallic silver and its compounds by such agents, as plasma, laser radiation, stream of electrons, γ -, IR - and UV - irradiation, etc. Physical ways of obtaining of NP it is the most perspective as far as predetermine obtaining of NP with increases level of free energy and allow obtaining the most pure on chemi-

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cal content of products.

The second – it is chemical method, consists in restoration of compounds of silver under the influence of chemical reducers.

Chemical methods of synthesis of NP of silver represent approaches inorganic, metalorganic and organic synthesis with processes heterogeneous phase formation in colloidal or other systems. The basic disadvantage of chemical ways, is complexity of obtaining of pure NP doesn't contain an impurity of reducer[10].

However, the specified methods are enough difficult in technological aspect, and they doesn't allow to keep the form and the sizes formed nanoparticle of silver. In process of decreasing in values of sizes formed nanoparticles, their superficial energy increased simultaneously which promote their agglomeration.

Careful control of parameters of process of restoration such as temperature, speed of mixing, concentration of reagents and stabilizing agent allow to obtain of NP, with narrow distribution in sizes but not always till necessary sizes and required stability[11].

Synthesis and studying of metal nanoparticles, stabilized in polymeric matrixes, today represents perspective direction in chemical science. Metals in an ultradisperse condition find out the unusual properties opening new possibilities of their practical application[1-8]. Therefore methods of reception of NP cannot be separated from methods of their stabilization. One of the most perspective methods of stabilization of silver NP with stable properties is formation their in the polymeric matrixes containing iongenic functional groups.

Scientists of the world are engage in creation of new materials from nanoparticles such metals, as silver, copper, silicon, zirconium, aluminum, magnesium, zinc, titan, etc. The particular interest is represented by workings out of preparations based on the nanoparticles of silver[12].

Pure silver - rather soft and plastic metal. At specific density (10,5 g/sm^3) concedes only to lead[13].

One of the impotent properties of silver - its bactericidal and anti- virus, disinfection activity which considerably increases at using nanoparticles in consequence of increase in the area of its surface. Silver and its compounds in form nanoparticles are used successfully in medicine, agriculture and other field of industries[10].

The main method - of chemical restoration ions of silver in the water medium at the conditions advantage to formation of small nanoparticles of metals. From chemical methods the most distribution has obtained by restoration ions of silver from water solutions of salts of silver at the presence of different reducers[14].

In point of fact is that the chemical methods consists in restoration of compounds of metals, as rule, from solutions by using of strong reducers. As reducers for preparation metal colloids are used formaldehyde, phosphorus, hydrazine and its derivatives, borane alkaline metals, hydroxylamine, hydrogen, hypophosphite sodium, connections of the titan (III), etc[15]. All used reducers have the characteristics and operate variously depending on conditions of carrying out of process. Among obligatory requirements to reducer - high restoration potential (exceeding potential of restoration of corresponding metal) and high speed of restoration. To the greatest degree these requirements is satisfy with tetragidroborat-ions (E_0 =1,23)[8,13].

In 1951 y. Turkevich with co-authors[16] are studied methods of obtaining hydrophilic NP of silver which consisted in restoration of nitrate silver ($AgNO_3$) by citrate sodium at boiling in water solution. According to data of transmission electron microscopy (TEM), the obtained NP of silver had the spherical form, narrow distribution in the sizes and average diameter 20 ± 1.5 nm.

It is natural that, for the obtaining stable during long time NP of silver with required properties it is impotent to carry out the process of restoration in the environment of this or that stabilizer. Some aspects of coordination interaction of NP with molecules of stabilizer are in detail considered in review[17].

One of the most knowing today's examples of obtaining of stable of NP silver with positively charged surface is described in work[18] where as the stabilizer it was used dibromide bis (11-

threemethyl- ammoniumundecanoilaminethyl) disulfide.

$[Me_3N^+(CH_2)_{10}C(O)NH(CH_2)_2S_2(CH_2)_2$
$NHC(O)(CH_2)_{10}NMe_3](Br^-)_2$.

At restoration with borhydride sodium in water phase of disulfide it is restored to tiola which possesses the increased reaction ability in relation to surface of metal NP. The obtained NP were stable in solutions at Hp from 5 to 9, but completely aggregated at Hp 1 and 14.

Significant disadvantage of the majority methods synthesis nanoparticle in water environments is the impossibility of achievement of high concentration of NP of silver in final solutions (only $<10^{-4}$ mol^{-1}) that is connected with their aggregate unstability. In this respect it has shown approach interest at work[19] which consists in restoration the concentrated solutions of nitrate of silver borhydride sodium in the attendance of synthetic inorganic material laponite. The mechanism of stabilization consists in adsorption clusters on surface laponite, that make impossible their aggregation. Unique method of increase in sizes of particles is growth at the expense of restoration of ions of silver on surface adsorbed cluster. By this method it is possible to obtain sol with the high content of silver ($7.35 \cdot 10^{-2}$ $mol \cdot l^{-1}$) with the average size of particles 7-10 nm.

Disadvantages of chemical methods of restoration of ions till nanoparticle attitude to existence of residue a reducer and a products as part of an final product of its oxidation that bring to determined difficulties at purification of nanoparticles.

At the present time widely used methods of photochemical restoration for the obtaining nanoparticles of noble metals[20]. On the base of this given method stay the generation of strong highly active reducers of type electrons, radicals and activated particles. For the photolysis typical energy make less than 60 EV. Advantage of method before chemical restoration consists in formation nanoparticle, discriminate large number purity, in the absence of the impurity accompanying processes with using chemical reducers[21]. For the obtaining of similar particles from corresponding water solutions of salts under the influence of light are formed active particles:

$$H_2O + h\nu \longrightarrow e^- + H_2O^+ \longrightarrow e^-_{(solv)} + H^+ + {}^{\bullet}OH$$

Solvated electron interacts with an ions of silver and reduced it untill metal.

$$Ag^+ + e^-_{(solv)} \longrightarrow Ag^0, nAg^0 + e^-_{(solv)} \longrightarrow Ag^0_n,$$

Photostimulated aggregations of particles of silver were investigate in many works. The aggregation mechanism is connected with occurrence under the influence of light of the particles having charges of different signs. Appearance of such particles to bring on an exchange of electric charges occur at the results of photoemission. At result of an exchange come into a remote-control the electric forces promoting approaching of particles till distances when appear forces of van-der-Vaalce moving to aggregation[22].

Successes in scientific investigation and using nanoparticle of metals at considerable step depended on possibilities of methods of synthesis – from that, allows chosen method to obtain the particles satisfying the requirements of the given scientific or practical goal. Thus, one of the significant problems is synthesis enough stable of nanoparticle specified size, for long time keeping high chemical or biological activity[23].

Possibly, any of using processes of restoration of metals in solutions passes stage formation of colloidal phases. The problem consists in preventing spontaneous coagulation of particles and formation of crystal structure of metals. Therefore obtaining of colloidals in liquid environments demands attendance of stabilizers. As the last used three basic groups of substances: natural or synthetic polymers, for example gelatin, an agar-agar, starch, polyvinyl spirit, polyethyleneglucol, cellulose, polyvinylpyrrolidone, high-molecular organic acids or surface-active substances, mainly cation type, or ligands π - acceptor type[24].

Stabilizers don‘t only increase aggregate stability of systems, but gives a high reactionary ability colloidal particles, in particular, in attitude to oxygen and other potential oxidizers. Cationic surface-active substances and π - acceptor ligands, adsorbed on surface коллоидных particles, reduce their high regenerative potential (≤-1).

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particles at the last time are used method of growing metal colloids directly inside synthetic micelle or cavities of zeolites[24]. Disadvantage of all listed method of stabilization is that, obtained colloidal step-by-step considerable degree lost his the catalystic unique and biological activity.

Researches in this area shows that, macromolecules don't only stabilize disperse systems, but also participate in their formation, control size and form of growing nanoparticle[25]. A special place among polymers occupy polyelectrolyte, in particular, polycarboxilic acids acrylic family. Carboxylic groups of polyacids are capable to form complexes with cation metals, for example silver[26], to restore them under the influence of light[27], and also to cooperate with positively charged cluster and atoms of surface nanoparticles, providing their stabilization[28]. It means that, the one of the factors defining disperse compound sol formed during photochemical synthesis of nanoparticle could be containing of carboxylic groups and their relative positioning on polymeric chain[29].

In the report[30] has written methods of obtaining and some properties a high dispersed hydrogelic microgranules on the basis acrylamid and acrylic acids which may be used as "nanoreactors" for the synthesis of nanoparticles at various chemical substances which shows interest, first of all, from the point of view of using in medicine. This, in particular, nanodimensional of noble metals, possessing a high bactericidal activity (for example, silver), magnetite, allowing to carry out purposeful transport of the microgranules filled with it to target organ, hydroxyapatite, perspective from the point of view of formation of bone tissues, and number of others[30].

Polycarboxilic acids acrylic family due to occurrence ionized carboxylic of groups interact with cations of metals, in particular silver, connecting them in strong complex restore them under the influence of light directly in it complex and stabilize consistently formed during synthesis small charged cluster and nanoparticles of metal[31].

At using heterochain of polyanions, in particular water-soluble of Na-CMC as agent at photochemical restoration of ions of silver till nanoparticle appear on the one hand, possibility of obtaining nanoparticle silver which don't contain chemical reducers and products of their oxidation and with another - chosen polyanion of Na-CMC may act as polymeric matrix at creation biodegradable bactericidal preparations and products[32].

Thus, all process of formation nanoparticle from initial cations till final nanoparticle proceeds immediate contact with polymeric matrix. One of the main factors defining given process, is contain in polymer ionised carboxylic groups which can be varied, changing molecular weight (M) polycarbonic acids, degree of their ionisation or using copolymers. Influence of these factors on the basic stages of process of formation nanoparticle silver is considered in work[33].

By method of potentiometric analysis, it has been shown that connected cations of silver polyacrylic - anions (PA) with molecular weight 450000 (PA_{450000}) and 1 250000 ($PA_{1250000}$) at degree of their ionisation à=1,0 occurs cooperative, i.e. with increasing content of silver in solution, increased concentration of chains in limiting degree filled with ions of Ag^+. The irradiation of water solution of complex Ag^+ • PA, obtained in these conditions, full light of mercury lamp of high pressure to bring on photorestoration of cations Ag^+. Thus, in the beginning in spectrum appear absorption band with maximum at λ_{max}-700 nm and shoulder in the field of λ_{max}-300 nm which can be carried to absorption small charged clusters of silver belong to Ag_8^{2+}. For absence of UV-light clusters of Ag_8^{2+} are stable during keeping two weeks. Further irradiation is accompany by disappearance of strips of absorption clusters of Ag_8^{2+} and formation of larger clusters of Ag_{14}^{2+} and nanoparticle of silver, characterised by absorption strips at λ_{max}-370 nm and λ_{max}-460 nm, accordingly[34].

Obtained colloidal solution is stable during keeping several weeks. Increasing total content of silver in all region cooperative connecting causes proportional growth of concentration clusters and nanoparticles, but dynamics their formation don't changed. Methods of TEM investigations shows that the obtained of nanoparticals of silver is spherical form but their average size don't depend on content of silver in all area of cooperative connecting and

makes 1-2 nm in case of PA_{450000} and 4-5 nm in case of $PA_{1250000}$[34].

The more huge attention of researchers is attract composites based on polymeric hydrogels, functionality which considerably broaden at an immobilization NP of metals of transitive group. Nanoparticles on his sizes to take up intermediate position between materials in volume and atomno-molecular structures that causes essential difference of some their physic-chemical parameters from properties of total material[35].

It is established that at changing of concentration of stabilising polymeric substrate of its degree of substitution on functional groups and average molecular weight, parametres and temperature of physical factors of influence, as reducer, it is possible regulation the form and size of formed NP of silver.

On the basis of results of our researches[36] it is established that at introduction cations of silver in water solutions of polysaccharides, containing carboxylic and carboxyl anion occur reaction of replacement with hydrogel formation polysaccharide.

Crossing solution of polysaccharide into hydrogel condition could be explained by formation of three-dimensional structure at the expense of replacement cations of silver at carboxyl- and carboxylat anion of functional groups with simultaneous formation intermolecular an ion-coordination bond at the expense of unpaired d-electrons of silver ions.

At the consequent UV-irradiation of hydrogel contained ions of silver optic generated electron goes to positively charged ions of silver connected with carboxylic group and being round it, on following equation, in conformity of the theory Gurney - Mott[33, 37].

$$R\text{-}COO^- + Ag^+ \xrightarrow{h\nu} R\text{-}COO^{\bullet} : Ag^0, \quad (1)$$

$$\mathbf{R\text{-}COO^{\bullet} : Ag^0 + \rightarrow R\text{-}COO^- : Ag^0,} \quad (2)$$

$$R\text{-}COO^- : Ag^0 + Ag^+ \xrightarrow{h\nu} R\text{-}COO^{\bullet} : Ag_2{}^0. \quad (3)$$

$$R\text{-}COO^- : Ag_2{}^0 \xrightarrow{h\nu} R\text{-}COO^- : (Ag^0)n,$$

Thus, in conformity of the approach of the theory Gurney - Mott photostimulated formation nanoparticle of silver it is possible to consider as electron-stimulated atomic process.

Till present time it is established that the NP consists of nuclei and capsule. The membrane of NP always contains easy atoms as O.C.B.S and etc. It is calculated[20] that NP of metals in diameter of 10 nm contains 103-130 atoms of metals. It is established that in range of 1-30 nm on surface of separately taken NP always are available products of interaction with the agent, making essential influence on properties NP of silver. It is experimentally established that for increasing stability of formed nanoparticle of silver it is necessary to use water liberate from dissolved oxygen during preparation of solution Na-carboxymethylcellulose.

Structure forming of nanoparticle silver at greater degree will be defined by methods of obtain. On spatial structure 3 classes nanoparticle in polymers are known: three-dimensional - crystal structures, two-dimensional - films obtained by method molecular layering, one-dimensional objects - whiskers, nanotube and nanofiber. These objects obtained by method of molecular layering, introduction of substances during cylindrical micropore[38].

At the present time the majority of methods allow to obtain nanoparticles with wide distribution in sizes and forms. Careful control of parameters of reaction at certain degree allows to narrow distribution in sizes forming of nanoparticle, but not always till desirable sizes. Only at correct choose of methods of formation and stabilization nanoparticle in pure environment probably monitoring of the size and distribution in the sizes turning out nanoparticle silver.

We are considered peculiarity of formation of silver nanoparticle in water solutions of Na- carboxymethylcellulose (Na-CMC), and also possibilities of formation of hydrogels[39], films[40] of Na-CMC and cellulosic fabrics[41] contained nanoparticles of silver, possessing disinfection, bactericidal, bacteriostatic and antifungal actions.

Photochemical restoration of silver cations and formation nanoparticle metal was preceded by formation polymer - metalcomplex of $[CMC]^-\bullet Ag^+$. Influence of degree of ionisation Na-CMC_{57000} and Na-CMC_{38000} on degree of replacement of ions of silver were investigated. Interaction of solutions Na-CMC by various molecular weight with cations of silver investigated potentiometric titration. It is established

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that degree of ionization of Na-CMC practically doesn't depend on its molecular weight and decreases in process of reduction pH solution[42].

Investigated specificity of formation nanoparticle in the conditions replay to high efficiency of linkage cations of Ag^+ with CMC^-, that is, in before-threshold region of the relative content carboxylic groups.

On the basis of experimental investigation it is established that by addition of ions Ag^+ in solutions of CMC^-, independently, its degree of ionisation, that is at various values of Hp environments, there is full replacement of ions Na^+ to H^+ in carboxymethylic groups on ions Ag^+ that confirmed to changing formed Ag-CMC to insoluble gel formation condition[42].

It has shown the obtained hydrogels contained clusters of silver are stable within three months to what absence of changes of band of absorption in UV - specter. It is established that the increasing in the content of silver at system in range $0,05 \leq Q_{Ag} \leq 0,5$, that is in all area of co-operative linkage, occurs linear growth intensity strips of absorption UV-spectra at λ_{max}-340 nm and λ_{max}-750 nm that specifies in simultaneous increase of concentration both cluster and nanoparticles[42]. Formation of nanorods with sizes 230-700 nm in length, with thickness of 60-70 nm could be explained by aggregation nanoparticles of silver in solution Ag-CMC, in the sub acid environment that is caused by concentration decrease carboxylate anions, containing connecting ion of silver, carrying out function «nanoreactors» where occur restoration and clusterization of silver (Ag^0)[42].

Probably, restoration of ions of silver outside of "nanoreactors" promotes formation nanoparticle which at increase in time of an exposition formed of nanorod particles.

For confirmation of the given assumption, further we conducted researches of reaction of replacement ions of sodium to silver ions under ultrasonic dispersion of solution Na-CMC in the alkalescent environment promoting full ionisation carboxymethyl groups with subsequent UV - an irradiation. Thus were obtained nanoparticles of silver approximate in form to spherical form, with sizes 10-30 nm[43].

On the basis of results of experimental investigation made a conclusion that depending on proportion, concentration of CMC and $AgNO_3$ are changes size and form of silver nanoparticle, formed in water solutions, during photochemical restoration of ions Ag^+[33].

X-ray diffraction investigation have shown that, CMC has amorphous structure and gives amorphous halo at $2\theta = 21,6$. CMC, contained silver ions also has amorphous structure with the least intensity amorphous halo in the same area. From X-ray diffraction results of polymeric composite of CMC with restored of silver nanoparticles two phases are revealed: (at corners of diffraction $2\theta=21,6$) corresponding to phase CMC which is in X-ray areas, and presence of phase of metal silver. Silver with the cubic crystal lattice having a=4.086 Å gives crystal reflexes in corners $2\theta = 38^0, 44^0, 65^0$ and 78^0 reflexions concerning planes (n.o.) (111), (200) and (220)[44].

The size crystallites of silver has been calculated on broadening peaks. Results of calculations have shown that the effective sizes crystallites of silver, being in matrix CMC and makes 15 nm[44].

Morphological investigation have shown that CMC is more favorable matrix for the obtain of silver nanoparticle with the smaller sizes and high uniformity in the sizes. The size and the form of nanoparticles metals depends on several factors, such as the polymer nature, degree of polymerization, degree of substitution, degree of purity and etc. Than low degree of polymerization and high degree of substitution, than a lot of probability of obtaining of nanoparticle with the spherical form and the least size of particles metal.

One of the most perspective methods of obtaining nanomaterials with stable properties is formation of silver nanoparticle in matrixes various types. The greatest interest is represented by heterochain natural polymers with carboxylic groups as Na-CMC which at introduction in an organism is subject biodegradation and resorption.

It is known that nanostructured biocomposites of silver possess high antimicrobic activity. It is proved that nanoparticle of silver disinfected more than 650 kinds of dangerous bacteria, viruses and fungus[45,46].

About bactericidal properties of metal silver and its compounds it is known from time immemorial. At few concentration it is safe for human cells, but

is pernicious for the majority of bacteria and viruses, therefore it was widely adopted for water and food disinfecting in life and in struggle against infections at treatment of people[46]. At the present time unique antimicrobic and anti-virus properties of compounds of silver are studied comprehensively[47] and to this question to some exhaustive reviews[48] were devoted.

It is represented improbable that microorganisms in the course of mutations are capable to develop resistance to silver (except those cases when it exists a priori) as its ions attack considerable quantity of various proteins entity to cell. At the present time this valuable property became especially actual with the appearance all of the grate quantity of strains the pathogenic bacteria resistant against antibiotics of narrow action and present serious threat for life and health of people[49].

At the Institute of colloids chemistry and chemistry of water ASc of Ukraine under the direction of Kulskogo researches on specification of the mechanism of action of silver on microbic cell have been extensive. It is known that absorption of metal by cell can occur three different ways:

1. Adsorption of metal by cellular surface;
2. Active carrying over of metal to cell;
3. Two-phase process: the first phase-adsorption which is quickly replaced by the second phase - «active transport» metal in cell, at determined values of their dimension.

The experiments conducted by employees of this Institute, it has been shown that absorption of silver by cages of microorganisms irrespective of their specific structure goes on the third way.

It is established that, various kinds of microorganisms have occur the high adsorption of silver by microbic cell therefore the cell stopped to breathe, and to die (shrink). Silver ions, adsorbed capsomere (proteins) viruses campsites (covers) deprive an ability virus to get into cages as the virus "become heavy" from silver, its activity decreased and at the end - the ends it died[49].

Bactericidal properties of metallic silver are connected with its slow oxidation and liberation of ions of Ag^+ in environment, therefore is represented perspective use of preparations nanosilver as special class biocides agents. Nanoparticles possess high antibacterial efficiency due to the developed of surface providing the maximum contact with environment. Besides, they are small enough and capable to get through cellular membranes, to influence endocellular processes from within[50].

For ascertainment antimicrobial properties of the ionised silver it is established that its bactericidal effect considerably above, than at carbolic acids, corrosive sublimate and chloric to exhaust. The spectrum antimicrobial action of silver is much wider than many antibiotics and sulfanilamide. The bactericidal effect exhibit at the minimum doses[47].

Silver possesses more expressed antimicrobic effect, than penicillin and other antibiotics, and also causes similar action to antibiotic resistant strain bacteria. On goldish staphylococcus, vulgar proteus, bluesuppurative and intestinal sticks silver ions render various antimicrobial action - from bactericidal till bacteriostatical[47].

Historically silver used as metal, and in an ionic kind. The most widespread preparation of ionic silver - silver nitrate ($AgNO_3$, lyapis). Protorgol - this silver contents albuminous connection, brown-yellow or brown powder hasn't odors, well solubled in water. Content of silver therein - 7,8-8,3 %. Are used to the same purposes, as collorgol. The liquid mix consisting from 0,2 g protorgol, 5 ml of glycerine and 15 ml of water, are used for an irrigation of vocal chords, and 1-3 % solution successfully are treated by cold and conjunctivitis[51].

With appearance of nanotechnology scientists have become to conclusion about possibility of application in medical practice preparations of nanosilver. Obtaining nanoparticle at the end of XX centuries has allowed to make preparations on basis nanosilver relatively safe for the person, and advanced nanotechnoogical workings out have neutralized barrier of high cost of such medicines and have made their accessible to treatment of various diseases. Nanoparticles of silver due to the small size are extremely active and could generate death of bacteria, viruses, fungi on the large surfaces. They have the large specific surface that increases area of contact of silver with bacteria or viruses, considerably raising its bactericidal properties[52].

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Thus, application silver as nanoparticle allows to lower in hundreds times concentration of metal at keeping of all its bactericidal properties[53].

Nanosilver reacts with cellular membrane of activators of the infectious diseases, representing structure from special fibers (peptidoglycanes), blocking their property to give oxygen into bacterium cell that bring to death of microorganism. Thus the action of silver is specific don't on an infection (as at an antibiotic), and on cellular structure. It is connected by that cell of higher organisms have membranes of absolutely other type (not contained peptidoglycanes). Therefore particles of nanosilver haven't point of the appendix of the action on cell of such organisms, including cell of the person[54].

By method of electronic microscopy it has been established that NP of silver don't only are anchor on cellular membrane, but are capable to get also through it and to be distributed into bacterium. Such capacity possessed only individual of NP, but not their agglomerates. Besides, the sizes of NP connected with membrane, as rule, didn't exceed the sizes of the particles which are in cell. On this basis the conclusion has been drawn that only clusters, capable to interaction with cellular cover, can introduce into cytoplasmatic space.

The mechanism on which NP gets into cells, up to the end isn't clear. It was informed[40] on strong changes in membrane to structure of bacterium *Å. coli*, increase in its permeability and destruction of microorganism at interaction from NP of silver. The bacterial wall contains considerable quantity sulfur - and phosphorous-containing the macromolecules co-operating from NP and losing the activity. Inside bacterium, the NP can co-operate with DNA which thus loses ability to replication,[44] that also causes its death.

According result of electronic microscopy have been made two main conclusions. First, it has appeared that all of NP fixed on virus capsule, in all experiments had the sizes from 1 till 10 nm. It confirms the conclusion about strongly pronounced dimensional dependence of biological activity clusters, made in work[56]. Secondly, it is detected the ordered spatial distribution of NP which are connected with virus cover and being on distance ~ 28 nm from each other is revealed.

At the last time wide distribution has obtained ready-made bandaging material contained colloidal (ultradisperse, nanocrystalline) silver[57]; numerous investigation confirm high antimicrobic and wound healing properties of current products[58], however different in ways of manufacturing, concentration, the sizes of particles, the material-carrier and so make difficult correct comparison of products[59]. Canadian investigation[60] has shown the improved clinical parameters and decreasing of surface bioloading of wound, at the same time flora of deeper fabrics stay invariable. Authors[61] also confirm that modern materials for bandage of wounds it is not enough to have only antibacterial efficiency, required the additional properties, accelerating healing of wound; for example, the description material which deletes products of metabolism of bacteria from zone of processing and connects endotoxin, formed at death of cell[62].

Compounds of colloidal (metal) silver with protein – trademarks "Argirol", "Protargol", "Kollargol" and so on. Some of them (for example, Argirol), obtained interaction silver oxide with gelatin or albumen (the maintenance of silver of 19-25 %). Kollargol and Protargol are used external at form of 1-2 % of solutions, as binding agent, antiseptic, anti-inflammatory agent at clinic of an ear, throat and nose; has shown possibility of application of these compounds in as antihypoxic[63].

There are the polymeric preparations of silver, occur salts polycarboxilic acids. So, scientists of Irkutsk institute of chemistry named A.E. Favorskogo of SO RASci have developed preparation of "Argakril",[28] which represents silver salt polycarboxilic acids. It rejoin the general formula $(\text{-CH}_2\text{-CHCOOH})_n$ - $(\text{CH}_2\text{CHCOO}^{>}\ \text{Ag}^{+}\text{-})_m$, where n=9000-40000; m=100-3000, molecular weight (MM) = 800000-3000000. It is shown that 1 % of solution of "Argakrila" contained 4 % of silver, completely suppresses growth of such microorganisms, as *Pseudomonas aeryginosa*, *E. coli 25922*, *Bacillus cereus*, *Proteus mirabilis*, *Staphylococcus epidermidis*. At increase in the content of silver its antimicrobic activity increases - at 10 % the content of silver it completely suppresses growth of all

known microorganisms. This composition has an essential disadvantage - silver ions easily oxidise polyacrylate and silver drops out in sediment in the form of metal (oxide). Similar process of formation of nanoparticle silver in water solutions of polyacrilic acids investigated in work[34]. However, up to the end aren`t studied toxicity preparation of "Argakril" at the more concentration of silver in preparation.

In the majority authors agree in opinion that, difference salts of other heavy metals, silver is not dangerous at external and medical internal application. Many scientists warn about risk of unlimited use of the various products advanced on the market in the form of biologically-active additives: «silver proteins», colloidal solutions and other commercial (nonmedical) preparations of silver[64]. Besides insufficient efficiency, authors point in risk of formation argyros at peroral application (argyria, argyrosis or argyrism, from Greek «argyros» - silver; brown or black-grey pigmentation of skin, mucous membranes, fabrics of an internal and the eyes, caused by adjournment in them of silver).

One of the last (2004 y.) researches in the field of toxicity of compounds of silver at external application is summarised by authors[65]. It is shown that at using of silver at burns, chronic and diabetic ulcers can conduct to absorption of silver by system of blood circulation and allocation on wound sites, in liver, kidneys and other bodies. Despite it, the risk of damage of fabric or functional infringements practically is absent.

Silver in general practically «has no unfavorable effects for people; argyria it is rare also an occasion mainly for cosmetic anxiety». In one of articles[66] it is unequivocally shown that *«... interest to silver as to preparation for processing and treatment of wounds tests the Renaissance».*

The analysis of literary data shows that silver compounds, especially nanoparticles of silver with narrow distribution on the size stabilized by polymeric systems represent huge interest at creation of new generation of medical preparations and products with unique new properties. Especially more interest represents creation bactericidal wound coverings, contained nanoparticles of silver in structure of biodecomposed water-soluble polymers. Such polymers in the form of powders, hydrogels and especially films in appointed degree simultaneously carrying out functions of skin, protect wound surface and do not injure it, possess bactericidal wound healing effect and are subject biodegradable[67].

Preparations on the basis of silver ion are widely used in medicine ("Kollargol", "Protargol", "Poviargol", etc.), working out of new methods of synthesis highly stable nanoclusters of silver with narrow distribution in the sizes for the purpose of creation on their basis of new preparations antimicrobic, fungus, anti-inflammatory, immunomodulatory action are actual.

We are generated nanoparticle of silver in polymeric matrix - Na-CMC in the size of 10-30 nm which content of silver make 0,01-0,006 %. It is established that, the obtained hydrogels[68] "Bacsergel", films[69] "Nanoderm" and cellulosic fiber[70] showed high bactericidal activity against wide range of bacteria and fungi by their small toxicity.

On the basis of results of researches following conditions of formation homogeneous in the sizes nanoparticle of silver are chosen. Time of the UV-irradiation of 30 minutes, content of CMC in hydrogel 0,08 mol, content of $AgNO_3$ in hydrogel $3 \cdot 10^{-5}$ mol. In the chosen conditions are formed spherical nanoparticle of silver with sizes 2-30 nm. The content of silver nanoparticles in hydrogel "Bacsergel" - 0,0066 %[68].

For the purpose of determination of biological activity nanoparticle of silver generated into ctructure hydrogels of CMC (Bacsergel), have been investigated their microbiological properties on strains *Staphylococcus epidermidis* and fungus *Candida albicans*. As objects of examination have been chosen 2 % - solution of CMC as control, water solution of nitrate silver, 2 % - hydrogel of Ag^+CMC^- and hydrogel of CMC contained nanoparticles of silver (Bacsergel).

At the investigation of water solutions of $AgNO_3$ it has been established that, they show bactericidal activity against fungus *Staphylococcus epidermidis*, but don't show activity against fungus *Candida*

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albicans to what testified to their growth in nutrient medium. The hydrogels contained ions of silver show bactericidal activity against *Staphylococcus epidermidis* of up to 30 %, than in case of nitrate silver of similar concentration, and in case of fungus *Candida albicans* don't show bactericidal activity.

The hydrogels contained ions of silver show bactericidal activity against *Staphylococcus epidermidis* of up to 30 %, than in case of nitrate silver of similar concentration, and in case of fungus *Candida albicans* don't show bactericidal activity. Comparatively high activity of ions of silver in structure CMC to respect with ions of nitrate silver could be explained that ions of nitrate silver because of high mobility quickly incorporate to functional groups of surface strains and the protein composition inside bacterial cells as *Staphylococcus epidermidis* and fungus *Candida albicans*. In case of silver ions in structure of CMC their mobility is limited also they keep biological activity.

At investigation of hydrogels CMC contained nanoparticles of silver (Bacsergel) it is established that, they show activity against strains of *Staphylococcus epidermidis* three times above than in case of water solution of nitrate silver and showed high activity against fungus *Candida albicans* to what absence in nutrient medium of growth of fungus.

Relatively high activity of silver nanoparticles against to silver ions it is visible, it is connected with that[56,68]:

- nanoparticle of silver cannot form chemical bond with functional groups of surface strains *Staphylococcus epidermidis* and fungus *Candida albicans* and the protein composition inside bacterial cells and nanoparticles are capable to get into kernels of their cell and to inhibit their growth and activity;
- decreasing in the sizes nanoparticles of silver promotes increase of the total area of their surface and acceleration of their ability to get into kernels of cell above-stated strains;
- increase in the sizes nanoparticles and changing of their forms from spherical to nanorods, on the one hand, bring to sharp decrease in their total superficial area and, on the other hand, bring to restriction of their possibility of penetration into kernels of cell of strains *Staphylococcus epidermidis* and fungus *Candida albicans*.

The most active against strain *Staphylococcus epidermidis* and fungus *Candida albicans* is hydrogels of CMC contained nanoparticles of silver with spherical structure and dimension of 2-30 nm (Bacsergel) that, explain the high values of area of surface and ability of their penetration into kernels of bacterium[68].

Hydrogels CMC contained rods like of nanoparticle with dimension 230-700 nm in length and 60-70 nm in width are less active in relation to the hydrogels (Bacsergel) contained nanoparticles of silver with spherical structure and the high area of surface, but they are more active then hydrogels, contained connected silver ions. Low values of activity of ions of silver connected with CMC probably explained that, at contact CMC, contained the connected ions of silver with surface stated strain by means of formation of coordination bonds with functional groups which are on surface strains occurs to surface inactivation of silver ions. On the basis of results medical - biological tests: acute intragastric toxicity, toxicity at application on skin, skin - resorptive action on skin and mucous membrane of eyes, sensibilize and sensitizing action, condition of mink reflex, the haemoglobin maintenance, red blood cell, leukocytes and bilirubin in peripheral blood at repeated skin influence by preparation of "Bacsergel" is made conclusion that the preparation nontoxic substance do not possessing skin - resorptive, local irritation action, at repeated chronic influence on skin it does not possess cumulative effect, does not irritate integuments both does not cause sensitization and does not possess sensitizing activity.

By estimation wound healing effect of preparation of "Bacsergel" at modelling of erosive -ulcer inflammatory process in uterus neck on white rats and rabbits it is established that as well as in early researches of preparation of "Bacsergel" has show resorptive antiulcer and anti-inflammatory action at its triple application on surface of an operational wound. It is established, that speed of healing erosion -ulcer on surface of neck of uterus more effective than in control group. On the basis of results of

medico-biological tests preparation of "Baksergel" could be recommended in surgical, obstetrics-gynecologic practice and combustiology at treatment of wounds and burns, after carrying out of clinical tests, can be used as treatment drug.

Bactericidal activity of samples films of CMC (Nanoderm)[69], containing ions and nanoparticles silver, studied on conditionally pathogenic test cultures *Staphylococcus epidermidis* and *Candida albicans*.

For the determination of antimicrobic action samples put in test tubes with thioglycolic (*for Staphylococcus epidermidis*) and Saburo (*for Candida albicans*) mediums in following systems: 1. Film of CMC•Ag^0 (C_{Ag}-0,0003 mol); 2. Film of CMC•Ag^0 (C_{Ag}-0,00003 mol); 3. Film of CMC•Ag^0 (C_{Ag}-0,000003 mol).

At the result of microbiological investigation it has been shown, that all samples possess to some extent antimicrobic activity due to conditionally pathogenic microorganisms of the human. Samples, films of CMC, contained nanoparticle of silver, are most active against strains *Staphylococcus epidermidis* and completely inhibited the growing of fungus *Candida albicans*.

The bactericidal effect of the sample films of CMC, contained ions of silver was shown, first of all, inhibit the growing of fungus *Candida albicans* but after 18-20 hours they continuous growing. At strain *Staphylococcus epidermidis* samples No 2 and No 3 inhibit growth of bacteria on 88,0 %, 99,9 % respectively.

The high bactericidal activity film of CMC, contained 0,000003 mol Ag^0, possibly, it is connected by that, nanoparticle of silver with dimension of 5-25 nm in films of CMC (Nanoderm) possess high bactericidal activity at the expense of the large area of their surface. Films of CMC, contained nanoparticles of silver with dimension of 5-25 nm, completely inhibit growth of strains *Staphylococcus epidermidis* and fungus *Candida albicans* and are the most bactericidal active. High bactericidal activity of these films can be explained by the assumed mechanism of action of hydrogels of CMC, contained nanoparticles of silver which has been presented in the previous section. The samples film of CMC, contained rod like nanoparticle with in length (l_1=40-80 nm, in diameter l_2=5-10 nm), are less active, than spherical structure of nanoparticles with dimension of 5-25 nm that could be explained with low values of their area of surface[69].

Films of CMC, contained nanoparticle of silver with the small dimension (2-28 nm) have appeared also less active in respect of films of CMC, contained nanoparticle of silver with dimension of 5-25 nm[69]. This fact can be explained by that, the total content of silver nanoparticle in this samples film of CMC has appeared almost 10 times less than in samples of films contained nanoparticle of silver with dimension of 5-25 nm.

This fact can be explained by that, at concentration of ions of silver in hydrogels of CMC which used for formation films of CMC is 0,031 % they almost completely are connected with carboxylate anions of CMC and because of restriction of speed of their mobility formation nanoparticle of silver occur with slow speed, it seems only in structure «nanoreactors»[69]. Thus, it is established that, bactericidal activity films of CMC against strains *Staphylococcus epidermidis* and fungus *Candida albicans* is determine both the form and dimension of silver nanoparticle, and their total content in structure films of CMC.

At department of Combustiology Republican Centre of science of Emergency Medical Aid of MH RUz for local treatment of burn wounds at group of patients at the age from 2 till 75 years have been used polymeric films on the basis of water-soluble polysaccharide of Na-CMC contained silver nanoparticle. Obtained the results of the limited clinical application wound coverings on the basis of CMC, contained nanoparticles of silver show their beneficial effect on current wound process, acceleration of time epithelization superficial burn wounds and preparation of area of deep burns for plastic closing[71].

On the basis of results of medico-biological investigations obtained films of CMC, contained silver nanoparticle (Nanoderm) can be used in medical practice as bactericidal wound covering agent for treatment of wounds and burns, after completing of their clinical tests[71].

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Bactericidal activity of the obtained samples of cotton fabrics (c/f), processed by solutions of CMC, containing ions and nanoparticles of silver are studied on conditionally pathogenic test cultures *Staphylococcus epidermidis* and *Candida albicans* at the laboratory of Institute of Microbiology of ASci of RUz.

At investigation on determination of bactericidal activity of cotton fabrics processed by solution of Na-CMC, contained silver nanoparticles it is established that, they show bactericidal activity against *Staphylococcus epidermidis* on 80 % and more active against control and in case of fungus *Candida albicans* show bactericidal activity on 98 %.

The most active against strains *Staphylococcus epidermidis* and fungus *Candida albicans* is cotton fabrics processed by solution of Na-CMC, contained silver nanoparticle with spherical structure in the sizes of 5-35 nm that could be explained, by high values of the area of surface silver nanoparticle[70].

Cellulosic fabrics processed by solution of Na-CMC, contained rod like structure nanoparticle of silver with sizes 130-420 nm in length and 15-40 nm in width, are less active in comparison with cotton fabrics processed with solutions contained nanoparticle of silver with spherical structure, but they are more active in comparison with cotton fabrics which processed with solutions contained silver ions at the same concentration. At washing of c/f contained nanoparticle of silver more than thirty times, despite insignificant decreasing of content in it silver nanoparticle, all of them still show bacteriostatic activity against mentioned strains.

Thus, it is established that introduction in structure of cotton fabrics and products on their bases stabilised silver nanoparticle promotes giving to them bactericidal and bacteriostatic properties. Bactericidal activity of cotton fabrics and products on their basis is defined by content, form and dimension of silver nanopartcle. Stabilization of silver nanoparticles in structure of polymeric substrate promotes preservation bactericidal and bacteriostatic activity at repeated washing of cotton fabrics and products on their basis.

Keeping of bactericidal activity of cotton fabrics subjected to washings, probably could by explained CMC•Ag^0 in structure of fabrics become an insoluble condition and formation of coordination bond between substrate and silver nanoparticles.

It is established high bactericidal activity and optimum conditions of synthesis of preparations contained silver nanoparticle like solution (Polyardez), hydrogels (Baksergel), films (Nanoderm) and cellulosic materials.

Based on results of investigation it is possible to conclude that, the polymeric systems contained silver nanoparticles could be used as biodecomposed and not decomposed nanostructured biopolymeric materials – solution (Polyardez), hydrogels (Baksergel), films (Nanoderm) and cotton materials - pharmaceutical preparations for the treatment of wounds and burns of various etiology with the high disinfectant, bactericidal and antifungal activity.

In addition to that with advantages of nanomaterials, contained nanoparticle of silver them could be inherent and some assume deficiency which should be eliminated or experimentally confirmed. Such as estimated limitation concern:

- Very high relative surface of silver nanoparticle which increases them adsorptive capacity, chemical reaction capacity. It can bring to increase in production of free radicals and active forms of oxygen leading to damage of biological structures (lipids, protein, nucleinic acids in particular DNA);
- Nanoparticle of silver in consideration of their small sizes can contact nucleinic acids, proteins, inter to cellular organella that can to lead to change of function of biostructures;
- High adsorptive activity nanoparticle of silver promotes absorption different contaminants that can facilitate their transport to cell, raise ability of their penetration through organism barriers resulting probabilities of increase in toxicity of the last;
- Because of the small sizes of nanoparticle silver protective systems of an organism can them don‘t recognize. They couldn‘t biotransformation and don‘t to become extinct from an organism. It probably can bring to accumulation nanoparticle in an organism.

CONCLUSIONS

The described method of synthesis dispersed nanosilver without using of toxic reagents, high biological activity of their compositions with the low content of metal allow to make preparations with high bactericidal, antiseptic and disinfectant activity preparations of new generation for applied medicine, epidemiology and sanitary.

The exception of negative influence silver nanoparticles in an organism can be reached correct choice of its concentration entered into an organism, by regulation of frequency rate of its introduction for full treatment of disease and choice of the size of silver nanoparticle.

Despite the most possibilities of practical application of silver nanoparticle in the pharmaceutical and medical industry it is necessary carrying out of advanced medical - biological tests providing their harmlessness for living organism.

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