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RADIATION TECHNOLOGY FOR THE MANUFACTURE OF MEDICAL PRODUCTS WITH NANOSILVER: FROM DEVELOPMENT TO COMMERCIALIZATION

Introduction. *The distance between the obtainment of a researchresult and the appearance on the market of a new product is large in the sense of time and efforts and has certain specific features, depending on industry.*

Problem Statement. *The search and implementation of advanced materials,in particular in the field of radiation technology for the manufacture of medical products from metal-water-polymer nanocomposite is an urgent task today.*

Purpose. *The purpose of this research is the popularization of the technology for the manufacture of medical products from metal-water-polymer nanocomposite and the dissemination of experience in bringing R&D product to commercialization.*

Material and Methods. *High molecular weight polymers, silver salts, and water have been used. The electron irradiation method, optical spectroscopy, electron microscopy, microbiological analysis, and the method for curing thermal injuries and purulent wounds.*

Results. *The regularities of the effect of radiation on the microstructure and properties of hydrogels based on the polyvinyl alcohol — polyethylene glycol system and on the formation and stability of silver nanoparticles in the composition of 3D polymer networkshave been established. A technology for manufacturing a metal-water-polymer nanocomposite with nanosilver has been developed;the bactericidal properties of the nanocomposite have been experimentally demonstrated. The technology formanufacturingmedical products from this nanocomposite under the HYDROBINT trademark has been developed and put into production. The organizational and technical procedures for the state certification of HYDROBINT medical products, asestablished by the legislation of Ukraine, have been described. The medical results of their use have been illustrated. A road map of developer'sactions for commercialization of innovation product has been proposed.*

Conclusions. *Electronic irradiation of polymer hydrogels makes it possible to create new composite materials with properties relevant for the treatment of wounds and inflammations. The products made of such composites are effective in medical practice and commercially attractive in the market.Practical recommendations for the commercialization of an R & D innovation in the form of a roadmap for the developer's actions have been offered.*

Keywords: innovation, medical product, nanosilver, technology, development, and roadmap of commercialization.

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Among the special properties of the matter structured within 1–100 nanometers, there is the ability of silver nanoparticles (SNP) to inhibit the development and even to destroy single-celled microorganisms. This ability has been relatively recently discovered to exceed 10—15 times that of ionic Ag+ or colloidal silver (particles larger than 100 nm) [1—5]. One of the most popular explanation for this phenomena is as follows.

As a result of certain dimensional effects,the particles of metallic silver with a size of ~10 nm have the property to denature peptidoglycans that are the proteins forming the basis of unicellular membranes and absent in higher organisms, including human being. When a silver nanoparticle comes into contact with the membrane of a microbe, the protein locally denatures, which leads to significant mechanical stresses and the formation of a hole in the membrane, through which the cytoplasm leaks out and the microbe dies. This happens much faster than the death of the microorganism due to the gradual accumulation and intoxication with Ag+ ions, in the case of conventional silver preparations. Ag+ ions form chemical compounds with constituent substances of the microorganism, which actually leads to its intoxication. Thus, these silver atoms remain bound in the body of the dead microbe and no longer affect others. In contrast, after the formation a hole in the microbe's membrane, silver from the SNPcomposition can move further to killother single-celled organisms in the same way. This way does not depend on the specificity microbespecies, so itis universal. It does not require the involvement of SNP or Ag+ in certain exchange processes of single-celled organisms, which excludes the possibility of their mutational adaptation. Therefore, nanosilver has the highest bactericidal efficiency among the known antiseptics against all infections and does not have negative side effects on the human body [1—2, 5—8]. That is why nanosilver is considered a promising alternative to antibiotics, with many world R&D institutions studying its properties and methods of production. Why do we still not usenanosilver to cure diseases?

The problems of practical implementation of the SNP potentialinclude not only the technological difficulties of producing SNPs, but also the fact that the nano-sized state of silver is unstable in the water environment (of which the human body consists and which is one of the means of drug transport to it). In water, SNPs quickly coagulate into larger ones, and the dimensional effect on microbes disappears. In addition, as compared with other industries, the implementation of innovations in medicine is a much more difficult task because of highly bureaucratized procedure of certification of new drugs and medical devices. After all, unless having obtained a state certificate of compliance with the requirements of the Technical Regulations of Ukraine forMedical Devices [9], one may not use new drugs and medical devices in medical practice. In particular, in our fairly typical case, it took more than a year and cost more than UAH 300 thousand to certify the innovation. This is a very important element of the transition of science into innovation, without which none R&D invention is of practical interest to an investor or an industrial manufacturer of medical products. Therefore, the purpose of this research is to familiarize the reader not only with the R&D aspects of the radiation technology developed and implemented by us for the production of antiseptic materials for medicine with silver nanoparticles, but also with the main stages of the certification procedure for innovation medical products in Ukraine.

RADIATION TECHNOLOGY FOR THE PRODUCTION OF MEDICAL PRODUCTS WITH NANOSILVER

The idea underlying our technology is to apply the electron-beam treatmentforthe creation of SNPs by radiation-chemical reduction of ionic silver; their stabilization in the state of a hydrocolloid solution by radiation cross-linking of polymers in the composition of the hydrocolloid; the formation of biologically compatible hydrocolloid bactericidal material in different aggregate sta-

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tes, from liquid through cream-gel to resin-like elastomer; the production of bactericidal medical products for the treatment of wounds and burns from hydrocolloid bactericidal material and their sterilization together with packaging. That is, we are talking about the combination of five physical processes of the effect of ionizing radiation on a substance in one technological process of electron beam treatment. The implementation of this idea has made it possible to create a highly profitable technology for the production of bactericidal medical bandages and aerosol antiseptic preparations for curing thermal, mechanical, purulent wounds and ulcers, which has significant advantages over the existing prototypes in terms of all medical indicators.

The purpose of the R&D project, the results of which are described below, is to develop an investment-attractive technology for the production of effective bactericidal medical products for the treatment of wounds and burns based on silver nanoparticles as an active substance. To this end, the following works have been carried out: 1) an effective and economical method for forming Ag nanoparticles with a size of 15—40 nm, which ensures their significant bactericidal efficiency has been developed; 2) a method to avoid the coagulation of nanoparticles (hydrocolloid stabilization) during the storage for, at least 2 years, has been proposed; 3) a biologically inert medium suitable for solving the first two problems, convenient for quick application to affected areas of the human body and effective infusion of Ag nanoparticles into it has been invented; 4) medicobiological studies of the bactericidal and toxic properties of the materials obtained from the SNP and their optimization for medical use have been carried out; 5) experimental samples of antiseptic (bactericidal) products made of SNP for medical use have been designed and manufactured; 6) a technology for small-scale manufacture of medical devices (MD) from SNP has been developed and implemented; 7) design and working drawings for two modifications of nanosilver- based medical products (non-stick antiseptic medical bandages for the treatment of burns and wounds and liquid for painless disinfection of wounds, nasopharynx and eye mucous membranes) have been developed and issued in accordance with European standards; 8) all procedures for verifying compliance of innovative medical products with the standards (certification) and their manufacture technology with the requirements of the Technical Regulations of Ukraine for medical deviceshave been carried out.

The physical principles of the technology. While dissolving in water, silver nitrate $AgNO_3$ dissociates into Ag+ and $(NO_3)^-$ ions. Electrostatic repulsion between the similarly charged silver ions prevents them from gathering in clusters. Irradiation of such a solution with relativistic electrons (having an energy of over 1 million eV) leads to the ionization and radiolysis of water and the formation of free radicals (H and OH), as well as solvated (dissolved) electrons. The electrons are captured by the silver ions that thereby restore their neutral atomic state Ag^0 (radiation-chemical reduction). Electrostatic repulsion disappears, withthe silver atoms being able to accumulate (coagulate) into nanoparticles. In order to limit the growth of silver nanoparticles and to avoid their coagulation during further storage, we add biologically inert high-molecular polymers such as polyvinyl alcohol and polyethylene glycol to the solution [8, 10—13]. The interaction of radicals formed by radiation (broken bonds) in the macromolecules of these polymers leads to the so-called radiation crosslinking of the hydrogel, i.e. the formation of strong radical bonds between different polymer chains and the creation of a 3D network filled with water [14], with liquid hydrogel turninginto a rubber-like elastomer [15, 16]. The size of the unit cell of such a grid may range from tens to hundreds nanometers. The grid is formed under irradiation simultaneously with the formation of the SNP by the radiation and chemical mechanisms. Therefore, at a certain stage of the growth of nanoparticles, they find themselves stuck in a polymer network, which does not allow them to coagulate into larger ones. At

Fig. 1. Medical products *HYDROBINT* No. 1 — packs with antiseptic dressing for the treatment of superficial wounds and burns and *HYDROBINT* No. 2 — spray bottles with liquid for painless disinfection. Manufactured by project partner *RADITECH* LLC, under the license of the Institute of Physics of the NAS of Ukraine

the same time, inside the cells, SNPs remain in the state of a colloidal solution in water, which is stable for more than 2 years [17]. This is how a soft substance that can be called a metal-water-polymer nanocomposite is formed. It contains at least 80% water, up to 15% polymers, and up to 0.1% metallic silver. By changing the stoichiometry of the components, thermal and radiation treatment conditions, it is possible to produce such a composite in various aggregate states: from liquid, to creamgel and rubber-like elastomer. This enables making functionally different medical products from it, in particular, sterile bactericidal medical dressing for the treatment of burns and purulent wounds, which do not stick to the wound [10, 18—21], as well as liquids and aerosols for disinfecting wounds and mucous membranes by washing or moistening. The samples of these products are shown in Fig. 1.

PRACTICAL RESULTS OF MEDICAL APPLICATION OFPRODUCTS OBTAINED WITH THE USE OF THE TECHNOLOGY

The results of the external application of *HYDROBINT* medical products are shown below, in photographs of the state of wounds of real patients at various stages of the treatment.

Figure 3 features a leg with impaired blood circulation. The patient describes hissituation, “I had been suffering from problems with my legsfor ma-

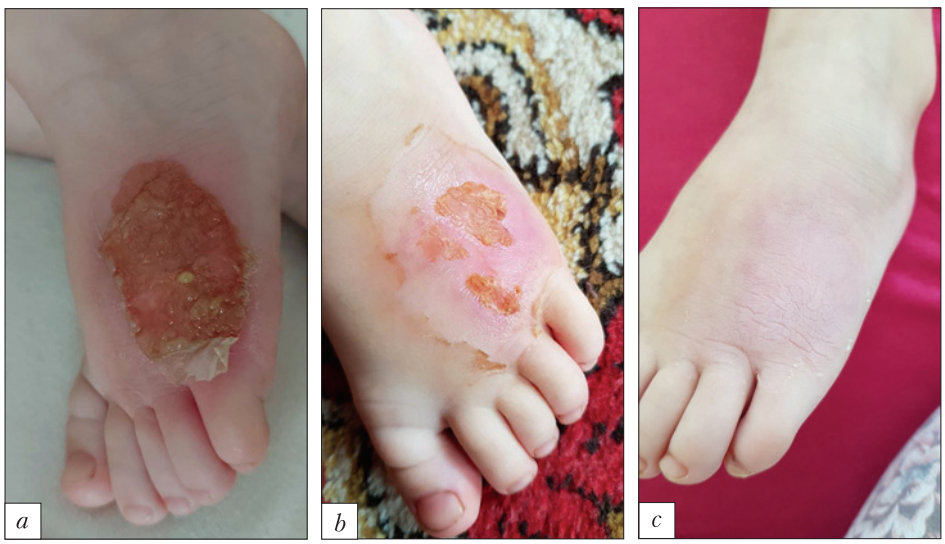

Fig. 2. Changes in the appearance of the burned part of the body of a 5-year-old child with the time of treatment with the *HYDROBINT* product: *a* — before the treatment; *b* — the 5th day of the treatment; *c* — the 10th day of the treatment

ny years. In this leg, a cava filter was installed to retain blood clots. The blood circulation in the leg was poor. I hadundergone a course of treatment with hirudotherapy (with medical leeches). After that, the wounds on the leg did not heal for three months. At the same time, I was suffering from a terrible itch. The legs swelled up, the wounds got cracked and enlarged. The cure (plates and spray) immediately relieved itching. The swelling has gone. After a week, the wounds started to be covered with a thick crust. In a month, everything has healed. At the places where the plates were applied, the leg has become lighter in color."

The result of the use of *HYDROBINT* medical products for the treatment of trophic ulcers is shown in Fig. 4. The patient could not heal these ulcers for 5 years. The complex application of *HYDROBINT No. 1* dressing and *HYDROBINT No. 2* aerosol disinfectant has led to complete healing of ulcers in 4.5 months.

It should be noted that clinical studies of the action of *HYDROBINT* medical products at the Kyiv Center of Burns Treatment have shown a significantly better therapeutic effect as compared with the hydrogel prototypes *BurnTec* (Poland) and *Armagel* (Ukraine). They havehigher hydrophilicity; better mechanical parameters that determine the ease of use; and are cheaper.

HYDROBINT No. 2 disinfection liquid is chemically similar to *HYDROBINT No. 1*, but has different aggregate state and different stoichiometry of components and microstructure. It is a double hydro-colloid. The first level is a colloidal solution of microscopic clusters (several microns in size) of *HYDROBINT No. 1* in water.Inside each its cell there is an aqueous solution of the second level — silvernanoparticles. When liquid *HYDROBINT No. 2* is applied with a drop pipette or an aerosol sprayer to the surface of a wound or mucous membrane of the nasopharynx, even hard-to-reach places are wetted and an island film is formed from microclusters of *HYDROBINT No.* 1 (the total area of the islands is approximately

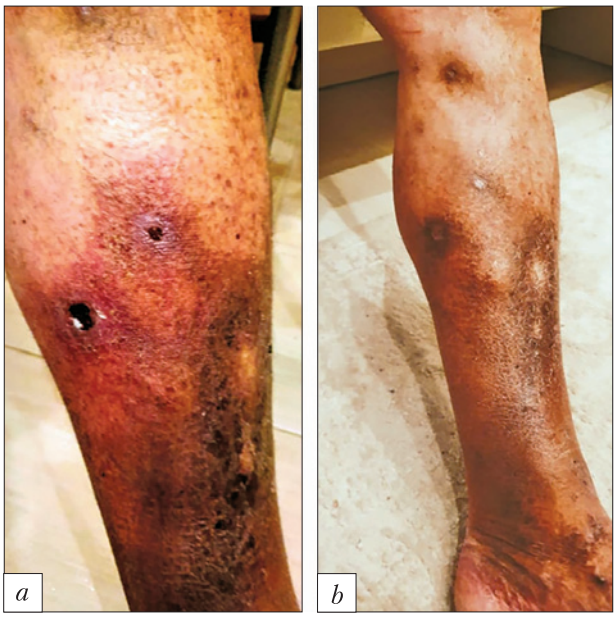

Fig. 3. The effect of the use of *HYDROBINT* medical products for the treatment of blood circulation disorders in the leg: *a* — before the treatment; *b* — afterthe treatment during a month

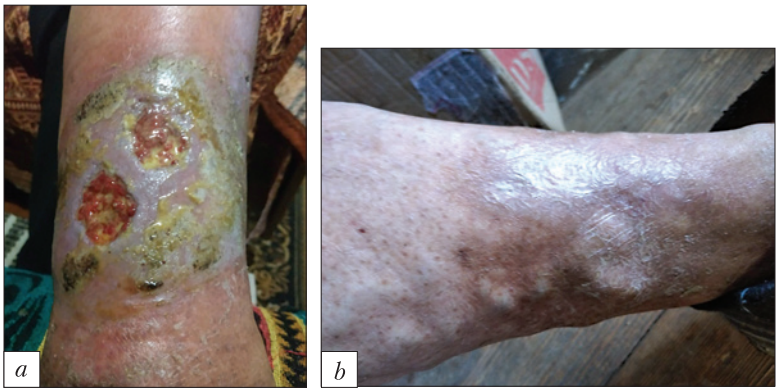

Fig. 4. Treatment oftrophic ulcers on the leg with *HYDROBINT* medical products: *a* — before the treatment; *b* — after 4.5 months of the treatment

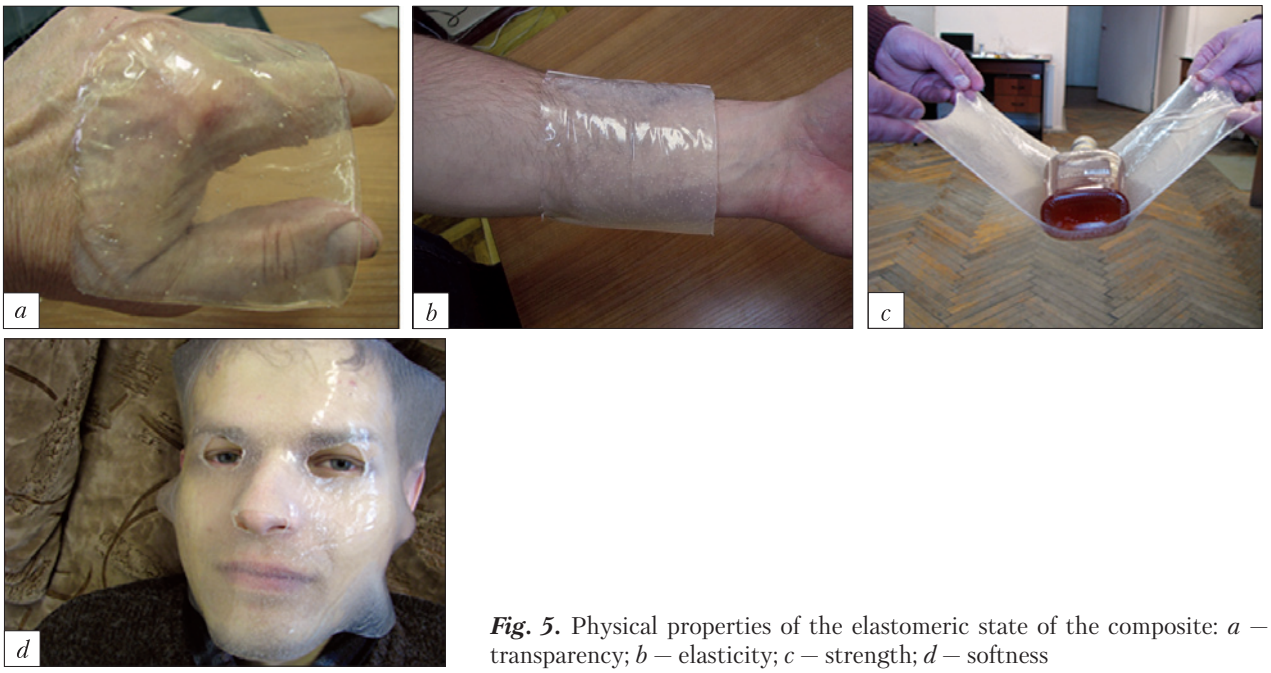

Fig. 5. Physical properties of the elastomeric state of the composite: *a* — transparency; *b* — elasticity; *c* — strength; *d* — softness

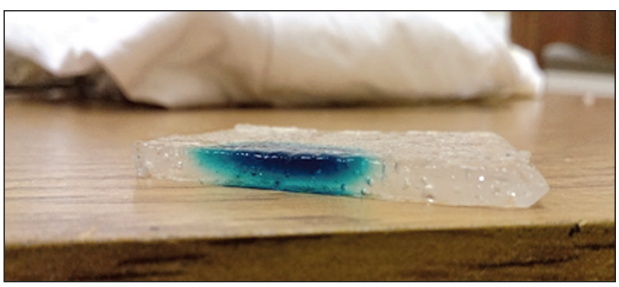

Fig. 7. A cross-section of an about 5 mm thick elastomer sample, on the upper surface of which a drop of "diamond green" solution was dripped 3 hours ago

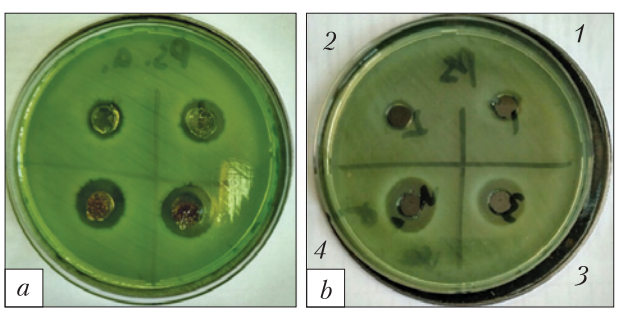

Fig. 8. Petri dishes with *Pseudomonas aeruginosa* bacteria seeded in agar and samples in the form of washers of the composite in the state of elastomer on its surface (*a*); in the state of liquid poured into wells in the agar (*b*)

equal to the total area of the spaces between them). This film is odorless; does not give any sensation when touched; does not interfere with the functioning of mucous membranes. However, it creates a kind of internal mask, a filter for infection on the surface of the nasopharynx. Sticky hydrogel islands not only contribute to the purification of inhaled air from dust and aerosols, but also serve as a depot supplying nanoparticles and silver ions that have a bactericidal effect on most types of single-celled microorganisms such as bacteria, some fungi, hepatitis B, herpes, and HIV. In 2020, the first data on the preventive effect of such an internal mask with nanosilver on the spread of COVID-19 were obtained [29].

Physical, medical, and biological properties of silver-water-polymer nanocomposite that serves as basis for the *HYDROBINT* medical products

Figure 5 illustrates the physical properties of the composite in the elastomer state, which serves as basis, in particular, for medical dressing *HYDROBINT* No. 1. This is a transparent material that is moist to the touch like jelly (and therefore does not stick to the wound) in the form of 3—5 mm thick plates, soft and elastic (is stretched

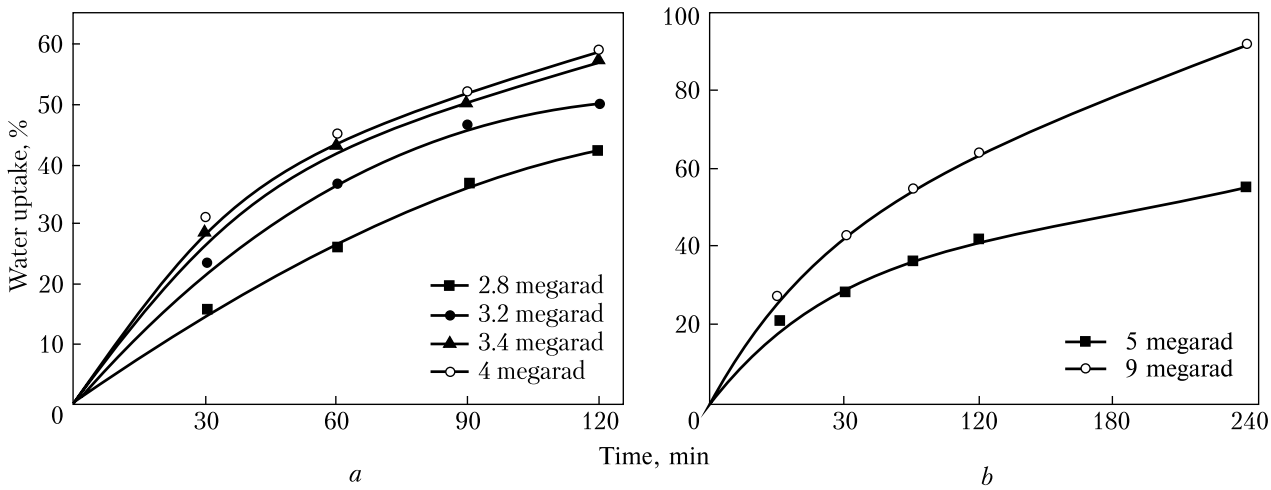

Fig. 6. Dependences of the weight-to-volume ratio of composite samples in the elastomeric state on the time spent in water at room temperature for different doses of electronic irradiation

to its double length before rupture), but strong enough to be applied in the field as medical and protective coatings for treating burns and wounds, like artificial skin.

The hydrophilicity, i.e. the ability to absorb water, of such a material is rather non-trivial. Figure 6 shows the dependence of the relative change in the weight and volume of composite samples on the time spent in water at room temperature. It can be seen that the material that initially consists of 85% of water, continues to absorb it from the outside. Due to the adsorption of water, its weight and volume increases by 1.5—2 times in 2—3 hours, depending on the dose of electron irradiation during the production. The ability to absorb moisture is one of the necessary requirements for dressing materials. After all, most types of wounds are characterized by liquid physiological secretions that need to be disposed of so as not to be a nutrient medium for bacteria and fungi.

Another important characteristic of dressing materials is the ability to diffuse gases and liquids. Figure 7 shows a photo of a cross-section of a composite sample with a thickness of about 5 mm, on the upper surface of which a drop of "diamond green" solution was dripped 3 hours ago. There is a visible characteristic diffusion profile of "green" spread from one surface of the sample to another. It should be noted that this in no way interferes with the adsorption of solutions (for example, wound exudate) from the opposite surface. After all, diffusion occurs along the concentration gradient, and opposing diffusants do not interfere with each other.

This is a clear illustration of the fact that diffusion through such a composite allows the transport of a drug solution to the wound from the outside, without removing the bandage and without violating its sterility. Below, we describe it in detail.

As already mentioned above, the size of the unit cell of the 3D network of polymer macromolecules, which forms the basis of the considered composite, ranges from tens to hundreds nanometers that is, at least, an order of magnitude smaller than the typical size of bacteria. Accordingly, such a material is a barrier for bacteria and at the same time is transparent for the diffusion of low-molecular-weight solutions. A bandage made of such material protects the wound not only from external mechanical irritations, but also from the penetration of microorganisms. A solution of drugs from an external source (for example, a wet wipe on the top of a bandage) due to diffusion enters the wound after a few hours without violating

sterility. That is, such a bandage is a unique coating-filter that protects the wound from mechanical influences and the penetration of microbes, but allows medicine and oxygen to penetrate into the wound from the outer surface.

The sterility of products made of our metal-water-polymer nanocomposite is automatically ensured by electronic irradiation during which it is formed. Doses above 30 kGy are used, although, according to the standard of radiation sterilization [22], the surgical level of sterility (10^{-6}) is provided by a dose of 25—30 kGy.

The bactericidal properties of this composite have been evaluated by the width of themicroorganism growth inhibition zone when they (microorganisms) are grown in agar [10, 11]. For example, Fig. 8a shows photographs of Petri dishes with bacteria sown in agar and round samples of the composite in the state of elastomer on its surface. Fig. 8b features a similar example for composite samples in a liquid state poured into round wells cut in agar. The concentric rings around the samples are zones of bacterial growth inhibition caused by the bactericidal effect. There is a correlation between the concentration of silver in the composite and the width of the growth inhibition zone: the more silver,thewider the growth inhibition zone. However, it has been established that the degree of sensitivity to the silver bactericidal effect at the same concentrations is different for different microorganisms.

A certain idea about this and the effect of the silver concentration in the composition of the composite on its bactericidal properties is given in Table 1. The experimental dependences of the width of the growth inhibition zone around the composite samples on the silver concentration in them are given here for seven types of microorganisms that most often interfere with wound healing in surgical practice and in the treatment of superficial wounds.

Table shows that different types of microorganisms are differently sensitive to the action of silver. However, for all of them, it is typical that the higher is the silver concentration, the stronger is the effect.

It should be noted that the bactericidal effectiveness of SNPs depends on their size and shape in addition to their concentration [6, 8, 11, 23]. We have controlled the size and concentration of the SNPs formed in the described way in the nanocomposite by measuring and analyzing the optical absorption spectra. Figure 9 shows the characteristic absorption spectra of the composite at different doses of electron irradiation or at different concentrations of ionic silver in the original hydrogel. The peak in the region of 400 nm is caused by the absorption of surface plasmons of SNPs. Its spectral position is determined by the size of nanoparticles, and its amplitude is determined by their concentration [10, 24—27].

We have used the experimentally determined in [27] dependence of the position of the band

Table 1. **Width of Bacteria Growth Inhibition Zone around the Composite Samples for Various Microorganisms**

Microorganism	Initial концентрація $AgNO_3$, mg/l							
	0	10	20	30	50	60	120	240
Pseudomonas aeruginosa	0	0	0	10	12	15	17	20
Proteus mirabilis	0	0	0	10	10	10	10	15
Klebsiella pneumoniae	0	14	15	17	20	20	20	20
Escherichia coli	0	0	10	15	15	15	15	15
Staphylococcus aureus	0	0	0	15	20	20	20	20
Enterococcus faecalis	0	0	0	0	0	25	25	25
Candida albicans	0	0	0	10	10	10	10	15

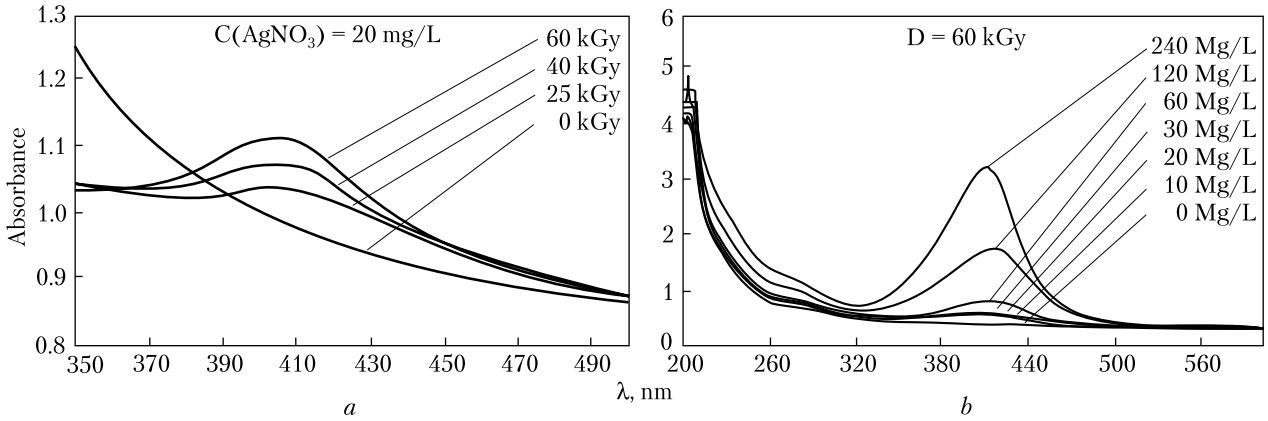

Fig. 9. Characteristic absorption spectra of the composite at different doses of electron irradiation (*a*) and at different concentrations of ionic silver in the initial hydrogel (*b*)

maximum on the SNP size. The quantitative results of the analysis of this group of spectra are summarized in Tables 2 and 3.

It can be seen that in a hydrogel with a fixed content of polymers, after electron irradiation with doses in the range of 25—60 kGy, SNPs with a size of 18—22 nm appear. Their concentration and size grow with an increase in the radiation dose, as well as with an increase in the initial content of silver in the ionic state.

These conclusions from the analysis of the optical measurements have been directly confirmed by the results of scanning electron microscopy (SEM) studies, which are shown in Fig. 10. This is aSEM image of the surface of a dried elastomer sample, from which water is removed by drying to provide the necessary vacuum in the electron microscope chamber. Since the composite in the elastomeric state contains about 85% of water, complete drying reduces its volume by almost an order of magnitude. As a result of this, SNPs approach each other and form cloud-like clusters that are visible in the photo as light spots. Their contrast corresponds to the metal in both modes (the secondary electrons and the inversely reflected electrons).

Thus, this technology makes it possible to produce a silver-water-polymer nanocomposite with properties that solve the main problems of the practical use of SNPs as an antiseptic for medical purposes. Namely: 1) the production of material that contains SNPsthat have sizes and concentrations sufficient to ensure a significant bactericidal effect and do not contain harmful substances; 2) stability of the size and concentration of SNPs, which ensures the preservation of the biological activity of the material for a long time; 3) medical products made of this composite do not cause ir-

Table 2. **Dependence of the Size of Silver Nanoparticles Formed by a Radiation Dose Φ = 50 kGy on Initial Concentration of Ionic Silver**

Concentration of $AgNO_3$, mg/l	λ, nm	Nanoparticle size, nm
10	406	23
20	411	30
30	417	38

Table 3. **Dependence of the Size of Silver Nanoparticles on Radiation Doze at Initial Concentration of Ionic Silver $N_{Ag}NO_3$ = 20 mg/l**

Dose, kGy	λ, nm	Nanoparticle size, nm
25	402	18
40	403	19
60	405	22

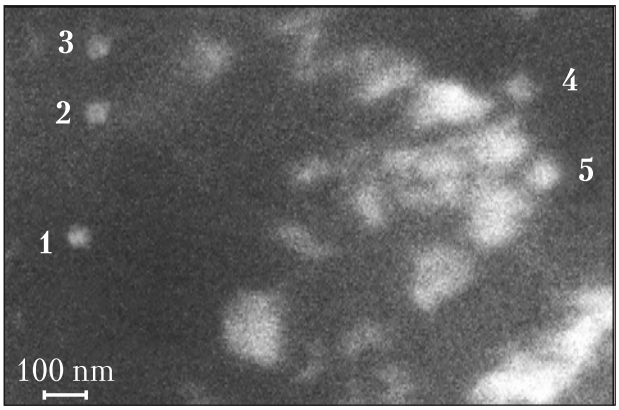

Fig. 10. SEM-image of the surface of a dried sample with an initial $AgNO_3$ content of 30 mg/l, irradiated with a dose of 50 kGy

ritation of the tissues of the human body even in open wounds.

However, the creation of an innovative material and the technology for manufacturing a marketable product from it is the first step on the way to the commercialization of R&D innovation. The next, second step is the registration of intellectual property related to the main ideas and principles of innovation, for example, patenting of a method for manufacturing a new material or products from it. The term of the standard patent examination procedure for an application for an invention in Ukrpatent is about 24 months or longer (not regulated by legislation), the quick procedure for an additional fee lasts 6—9 months [28]. A patent for an invention does not so much protect the rights of the developer and the future manufacturer as it serves as a sign for the investor about the reality and novelty of the R&D innovation, verified and certified by patent examination.

This sign is important at the third stage of search or creation of a subject of administrative and economic law, which assume the responsibility, costs, and risks of the MANUFACTURER with respect to the creation and introduction to the market of a product that is a result of this technology. Research institutions of the National Academy of Sciences are nonprofit organizations and do not have the right to perform such functions. However, the functions of the MANUFACTURER may be assumed by any business entity, for example, a limited liability company organized by the developers of the technology themselves (the so-called startup). In addition to the financial contribution to the statutory fund, the startup members usually make part-time labor contributions to its activities.

At the next 4th stage, such a MANUFACTURER company, for a certain interest in its future revenues, concludes a license agreement with the DEVELOPER institute on the right to use the patent for its development. In the course of the implementation of the license agreement, the DEVELOPER may lease production premises and equipment to the MANUFACTURER, involve the MANUFACTURER on partnership terms in projects aiming at the development and implementation of this technology. Thedevelopment and introduction into production of innovative products thanks to the capabilities of the transferred technology may be an outcome of the license agreement. In our case, it is a bactericidal medical product made of silver-water-polymer nanocomposite under the *HYDROBINT* trademark in two versions: medical dressing (*HYDROBINT* No. 1) and aerosol (*HYDROBINT* No. 2) for the treatment of burns and wounds.

The 5th step is the development of Specifications for a given type of the advanced products based on the transferred technology. This is a very important document that starts the state certification procedure, without which the use of most medical devices are not allowed. The specifications are data that enable identifyingthe product among other analogs and prototypes. The specifications shall contain the following information about the product: areas of application, description of appearance, basic parameters (weight, dimensions, color, etc.), chemical composition, list of raw and source materials, functional characteristics, completeness, labelling, packaging, acceptance rules (handover and acceptance tests, qualification tests, typical tests), description of measurement methods during tests, requirements for

transportation and storage, operating rules, guarantees and details of the manufacturer. Draft specifications of medical devices are subject to mandatory review and approval by authorized state bodies, in particular, by the State Service of Ukraine for Food Safety and Consumer Protection, on which the corresponding certificate of the state sanitary and epidemiological examination is issued. The certificate enables the next 6th step on the way to the commercialization of R&D innovation, namely, carrying out clinical trials of medical product samples. The purpose of the trials is to check the properties of a new medical product for toxicity, pyrogenicity, sterility, and the presence of an irritating and sensitizing effect. These studies use procedures and methods established by international standards, including tests on animals. Therefore, in Ukraine, there is a limited list of institutions authorized to carry out such activities. In particular, the clinical trials of samples of our product *HYDROBINT* were carried out at the Medved Research Center for Preventive Toxicology, Food and Chemical Safety of the Ministry of Healthcare of Ukraine. The results of clinical studies are reported in the form of a protocol (in our case, it has 12 pages) and a conclusion of the state sanitary and epidemiological examination of the medical product.

It should be noted that sterile medical products are not accepted for clinical studiesunless their sterilization processes are validated. That is, it is necessary to provide documentary evidence that the technological operations with the product ensure its sterility. Such evidence is the procedurefor the sterilization of this product and the report on its validation (i.e. inspection). The fact that our *HYDROBINT* product is inevitably and automatically sterilized by electronic irradiation during the production process is not taken into account. Only specialized enterprises are authorized to develop the procedure for radiation sterilization and to carry out its validation for an appropriate fee. In our case, this work has been done by specialists of the State Enterprise for Radiation Sterilization of Materials (RADMA). The total volume of the procedure for the radiation sterilization of the *HYDROBINT* medical product and the report on its validation is 23 pages. This activity should be considered as the 7th step towards commercialization.

An affirmative positive conclusion of the state sanitary and epidemiological examination gives the right to test the new product in medical practice on volunteer patients under the supervision of volunteer doctors who believe in the prospects of R&D innovation. The task is to practically check the efficiency of new product, to optimize its parameters, and to improve technology for its manufacture. However, this requires many laboratory samples of medical product of the same type. Therefore, it becomes necessary to create, adjust, and launch a pilot process line formanufacturing small batches of products and quickly adjusting technological operations. At this 8thstage, the legal responsibility of the startup company as a MANUFACTURER becomes very important. From this moment on, it is the MANUFACTURER who is responsible for the conformity of the products made with the use of new technology with the Specifications andapplicable standards for this type of goods, as well as for the quality of manufacture, the order of implementation and the consequences of the use of the products.

The *HYDROBINT* medical product in two versions (No. 1 — elastic dressing for the protection and treatment of wounds and burns; No. 2 — liquid for disinfection) has been tested both on individual volunteers and on groups of patients. Positive feedback has been received from the Military Clinical Medical Center of the Northern Region of the Ministry of Defense of Ukraine; from Kyiv City Clinical Hospital No. 2; from the Bogomolets National Medical University; and from the State Research Institution Center of Advanced Medical Technologies of the National Academy of Sciences of Ukraine. No negative effects of the use of *HYDROBINT* medical products have been reported.

The collected test materials, together with a general description of the medical product, instructions for use, copies of the conclusion of the state

sanitary and epidemiological examination of the product and the protocol of its preclinical studies are attached to the MANUFACTURER's notification letter to the State Service of Medicines and Narcotics Control of Ukraine about the intention to conduct official clinical studies of this product in a medical institution of the appropriate specialization and level. This is the 9th stage that lasts 60 days. Unless during this time the State Medical Service does not send reasoned objections, it is possible to make a contract with the relevant medical institution on clinical studies and to start preparations for them.

At this 10th stage, in addition to the manufacture and delivery of a sufficient number of studied products to the medical institution, it is necessary to develop a clinical study plan together with the specialists who conduct the studies, and their results shall be issued in the form of a researcher's brochure and a research protocol in accordance with the requirements of the DSTU EN ISO standard 14155:2015.

The 11th step towards the commercialization of innovation can be considered the preparation of the so-called "technical file" for the certification procedure of the newly created medical product for compliance with the requirements of the Regulations of Ukraine on medical products. Such certification is carried out on behalf of the state by a limited list of special enterprises by verifying the presence and compliance with the requirements of international standards of the following documents:

1. Document on the priority of the intellectual property underlying an innovation (invention patent) and on MANUFACTURER'stitles to it (license agreement with the DEVELOPER)

2. Specifications for medical product as approved by the relevant expert service.

3. Procedurefor radiation sterilization of a medical product and a report on its validation.

4. Quality management program for manufacturing processes at the MANUFACTURER of the medical product to be certified.

5. Conclusion of the State Sanitary and Epidemiological Examination on the sterility of the certified medical product.

6. Conclusion of the State Sanitary and Epidemiological Expertise on the bactericidal and nontoxicity of the certified medical product.

7. Protocol of clinical trials of the medical product to be certified.

8. Reviews of the results of practical testing of the product from medical institutions.

9. Plan of clinical studies of the medical product, brochure with results and protocol with conclusions of clinical studies.

In this list, a special place is occupied by point 4 "Quality management program (QMP) for manufacturing processes of the medical product to be certified at the MANUFACTURER enterprise". This is a detailed list of procedures and forms of organizational and technical control and regulation of all actions of the personnel of the MANUFACTURER company during the manufacture (DSTU ISO 9001:2015), starting with the periodic certificates of verification of aruler used for measuring the dimensions of the product package to the preparation of protocols for the return of defective products and the monthly plans for cleaning premises. The number of papers that shall be prepared in this part of the "technical file" significantly exceeds the number collected at all other stages. However, without QMP, nothing is accepted for consideration. However, companies that make certification of medical devices kindly offer the development of QMP for an additional fee.

About a month after the prepayment, the applicant receives QMP and starts preparing for the final 12thstage that is the arrival of auditors at MANUFACTURER enterprise. At this point, manythings depend on friendliness. And maybe, next month, after meeting all the comments left by the auditors, the applicant will be able to become the owner of the two certificates at once: compliance of your medical product with the requirements of the Technical Regulations of Ukraine on medical devices and compliance of the Quality Management Systemof the MANUFACTURER of theinnovative product with European quality standards.

Already at this stage, it is worth promoting the innovation to the appropriate segment of the investment market: submitting information about it to databases of proposals for international cooperation, participating in industry exhibitions and conferences, etc. Spreading positive information about the innovation through mass media, for example, through popular science TV and radio programs, articles in newspapers and on the Internet,plays an important role. Cooperation with the press service of the Presidium of the National Academy of Sciences is very useful and effective in this direction. Its employees always kindly help to professionally prepare the submission of information and contribute to its distribution in other mass media.

If the product is so new that it has not been yet on the market at all, then firstly it is necessary to promote it by oneself: to prepare business plans for attracting even small investors, to establish the production and sale of small signal batches of the product in iconic places, to invest in advertising, etc. However, such activity does not require scientific and technical qualification. It is much better performed by financial and economic specialists.

CONCLUSIONS

1. An electron-beam technology for radiation modification of hydrogels based on the polyvinyl alcohol — polyethylene glycol — silver system has been developed and patented.It allows for the production of a 3D nanostructured metal-water-polymer nanocomposite with antiseptic properties of a wide range of action.

2. The developed technology makes it possible to manufacture antiseptic nanocomposites in 3 aggregate states: liquid; creamgel; and elastic elastomer. This technology has been implemented in the production of bactericidal non-stick dressing for the treatment of burns and wounds, as well as aerosols for the disinfection of mucous membranes, wounds, and other surfaces.

3. A roadmap for commercializing innovations in the field of medical products in the modern conditions of Ukraine has been developed, tested, and prepared for distribution.

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РАДІАЦІЙНА ТЕХНОЛОГІЯ ВИРОБНИЦТВА МЕДИЧНИХ ВИРОБІВ
ІЗ НАНОСРІБЛОМ: ВІД РОЗРОБКИ ДО КОМЕРЦІАЛІЗАЦІЇ

Вступ. Різниця в часі між отриманням наукового результату та появою на ринку зумовленого ним нового продукту є суттєвою й має певну специфіку в різних галузях.

Проблематика. Пошук та впровадження інноваційних матеріалів на сьогодні є актуальним завданням, зокрема в галузі радіаційної технології виготовлення медичних виробів з металводополімерного нанокомпозиту.

Мета. Популяризація технології виробництва медичних виробів із металводополімерного нанокомпозиту та поширення досвіду доведення наукової розробки до комерціалізації.

Матеріали й методи. Використано високомолекулярні полімери, солі срібла та воду. Застосовано методи опромінення електронами, оптичної та електронної мікроскопії, мікробіологічного аналізу, медицини термічних уражень і гнійних ран.

Результати. Встановлено закономірності впливу радіації на мікроструктуру та властивості гідрогелів на основі системи «полівиниловий спирт — поліетиленглюколь», а також на формування і стабільність наночастинок срібла у складі тривимірних полімерних сіток. Розроблено технологію виготовлення металводополімерного нанокомпозиту з наносріблом та продемонстровано його бактерицидність. Розроблено й впроваджено у виробництво технологію виготовлення із розробленого нанокомпозиту медичних виробів під торговою маркою «ГІДРОБИНТ». Описано організаційно-технічні процедури державної сертифікації медичних виробів «ГІДРОБИНТ», передбачені законодавством України. Проілюстровано медичні результати їхнього застосування. Запропоновано дорожню карту дій розробника з доведення наукової розробки до її комерціалізації.

Висновки. Електронне опромінення полімерних гідрогелів дозволяє створити нові композитні матеріали з властивостями, актуальними для лікування ран і запалень. Вироби з таких композитів є ефективними у медичній практиці і комерційно привабливими на ринку. Практичні рекомендації з впровадження науково-технологічної розробки у виробництво запропоновано у формі дорожньої карти дій розробника.

Ключові слова: інновація, медицина, наносрібло, технологія, розробка, дорожня карта комерціалізації.