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Y.M. Samchenko [1], A.P. Maletsky [2], L.O. Kernosenko [1], S.M. Dybkova [1], O.V. Artiomov [2], T.P. Poltoratska [1], L.S. Rieznichenko [1], N.O. Pasmurtceva [1], V.I. Podolska [1], T.G. Gruzina [1]

SPONGE-LIKE HYBRID HYDROGELS FOR ENDOPROSTHETICS IN OCULO-ORBITAL AREA

[1] F.D. Ovcharenko Institute of Biocolloid Chemistry of National Academy of Sciences of Ukraine
42 Akademika Vernadskogo Blvd., Kyiv, 03680, Ukraine, E-mail: kernosenko@ukr.net
[2] Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine
49/51 Francuzsky Blvd., Odessa, 65061, Ukraine, E-mail: maletskiy@filatov.com.ua

In recent years, significant progress has been made in both the synthesis of metal nanoparticles and the creation of hydrogel platforms. It is assumed that their synergistic combination will allow to create the advanced hydrogel nanocomposites for the repair of anatomical and functional disorders of the human body, as well as for the needs of reconstructive surgery. The aim of the study is to develop a porous polymeric material based on polyvinylformal with incorporated functional hydrogels and gold nanoparticles, the study of its physicochemical properties and biocompatibility in vitro and in vivo. The developed hybrid hydrogel material is intended for use in reconstructive surgery of the oculo-orbital area and for filling postoperative cavities with simultaneous prevention of recurrence. The morphology of the synthesized hybrid hydrogel composites with gold nanoparticles was investigated by means of electron microscopy (SEM), while their thermal stability was studied by TGA and DSC methods. It was proved that the synthesized hybrid hydrogel materials demonstrate thermal stability in a wide temperature range, which significantly exceeds the range of their application, and can withstand steam sterilization (121 °C) without significant changes. The synthesized hybrid hydrogels were characterized as biocompatible in vitro according to the parameters of cytotoxicity, genotoxicity and biochemical markers (ATPase and LDHase activity) using L929 cell line. The study of the soft tissue reaction to implantation in vivo demonstrated the formation of fibrous tissue on the periphery and inside the implant, and a marked decrease in macrophage-histiocyte reaction and inflammatory infiltration in favor of fibroblastic proliferation and the absence of resorption, which creates the prerequisites for a stable clinical result. Thus, the developed spongy hybrid hydrogel material can be used in reconstructive surgery of the maxillofacial and ophthalmic-orbital areas.

***Keywords**: pH-sensitive hydrogels, endoprosthesis, gold nanoparticles, polyviniformal, acrylic acid, hydrogel implants, biocompatibility*

INTRODUCTION

Over the past decades, the development of nanotechnology has provided new ways and opportunities to adapt nanomaterials in a controlled manner for effective targeted interaction with biological systems. Of particular interest are hybrid materials based on biocompatible polymers and metal nanoparticles (NPs), which have significant potential to improve the diagnosis, prevention and treatment of human diseases [1–5]. Considerable progress in the development of biomedical materials in recent years has been achieved on hydrogel platforms [6–10]. The combination of the advantages of technologies for the synthesis of "smart" hydrogels, which are able to respond to changes in pH or temperature of the environment, with nanotechnology (production and incorporation of bioactive NPs into the gel matrix) makes it possible to obtain innovative hybrid materials with a wide range of applications, including targeted drug delivery, immunomodulation, detoxification, and tissue engineering.

The global experience of using hydrogels for tissue engineering has proven their advantages and outlined areas for improving their properties. One of the undoubted advantages is the extremely high biocompatibility of gels with high equilibrium water content compared to solid polymers, primarily due to the similarity of their 3D structure to the extracellular matrix. Fundamentally new possibilities are offered by non-biological implants with a porous cellular structure, primarily based on spatially cross-linked hydrogels, which are capable of biointegration with the surrounding orbital tissues. Gold nanoparticles (AuNPs) have demonstrated regenerative effects on living

tissues [11–14] and have shown a potential to solve the problem of resistance to microorganisms, so their incorporation into hydrogels will allow to impart these additional properties to composites.

The loss of the organ of vision leads not only to functional disorders, but also to changes in the psycho-emotional status of patients [15]. Therefore, the development of new and improvement of existing methods of reconstructive surgery in the orbit and oculo-orbital area after trauma and tumors is not only of scientific and applied, but also of medical and social importance. The creation of hybrid hydrogel composites with incorporated functionalized AuNPs will allow to obtain materials that best meet the requirements for recovery from anatomical and functional disorders, reconstructive surgical interventions in the orbit and other parts of the facial skeleton, as well as functional materials with complex antitumor activity for filling postoperative cavities.

The study is devoted to the synthesis and characterization of the chemical composition, structure, and physicochemical properties of a polyvinylformal (PVF)-based sponges with incorporated functional hydrogels and AuNPs as an implant for filling postoperative cavities and endoprosthetics in the oculo-orbital area, as well as to the study of its biocompatibility under *in vitro* and *in vivo* conditions.

MATERIALS AND METHODS

Acrylic acid (AAc), (Merck, 99 %) was distilled under vacuum with the addition of 1 ml of concentrated sulfuric acid to remove the polymerization inhibitor (hydroquinone) and purified by fractional crystallization. Acrylamide (AAm), (Merck, 99 %); N,N′-methylenebisacrylamide (MBA); (Merck, 98 %); ammonium persulfate (PSA); $(NH_4)_2S_2O_8$, (Sigma, 98 %); linear polyvinyl alcohol (PVA), (AppliChem GmbH, 98 %; molecular weight 72 kDa); formaldehyde (LAB-SCAN, 37 %); concentrated sulfuric acid H_2SO_4; Triton X-100 (AppliChem GmbH) were used as received without additional purification. Distilled water was used as a solvent in all experiments.

Synthesis of gold nanoparticles. Spherical AuNPs with an average size of 30 nm were synthesized by the method of hydrothermal synthesis: the reduction of gold hydrochloric acid ($HAuCl_4 \cdot 3H_2O$) (≥ 99.9 % trace metals basis, Sigma-Aldrich) with sodium citrate in the presence of potassium carbonate was carried out at the temperature of 121 °C, pressure of 1.04 atm for 15 min. As a result, suspension with a concentration of C_{Au} = 38.6 μg/ml by metal was obtained.

Synthesis of PVF-based sponges. Acetalization of PVA was carried out by its condensation with formaldehyde in the presence of sulfhuric acid and Tryton X100, with addition of an appropriate amount of pre-synthesized AuNPs. The details of the synthesis of polyvinylformal (PVF) were discussed in our previous work [16]. To incorporate AuNPs, the calculated amount of suspension with a concentration of 12.06 μg/g by metal was added to the gel-forming composition with intensive stirring.

Hydrogels synthesis. Hydrogels based on AAc, as well as copolymers of AAm and AAc, were synthesized by radical polymerization in aqueous monomers solution using PSA as an initiator and covalently crosslinked by bifunctional monomer MBA. The synthesis of hydrogels was carried out as follows. Argon was bubbled through the reaction mixture (an aqueous solution of a mixture of monomer and crosslinker) before adding the initiator. After that, the composition was transferred to a mold consisting of two parallel glass plates separated by 1 mm thick spacers and kept in a thermostat for 4h at 60 °C. The details of the synthesis of functional hydrogels based on AAc and hydrogel copolymers based on AAm and AAc were discussed in our previous papers [17, 18]. After aging in a thermostat, the hydrogels were removed from the molds and intensively washed by distilled water at room temperature to remove unreacted residues. The water was changed 2 times per day, and the washing process was controlled using a UV spectrometer (SPECORD M40, Carl Zeiss, Germany). Gel samples in the form of disks were cut out using a punch (d = 10 mm) and dried to a constant weight at 25 °C. The composition of the synthesized hydrogels is shown in the Table 1.

Synthesis and squeezing of PVF-based sponges. Hybrid materials based on PVF and functional pH-sensitive hydrogels (AAc and AAm-AAc) were obtained by swelling the PVF-based matrix in the corresponding gel-forming composition for 5 min. After that, the

swollen matrix was placed in argon atmosphere at 20 °C for 10 min, after which it was kept for 24 h at 40 °C. At the same time, composites with partial pore filling were obtained by squeezing a certain part of the gel-forming composition from the swollen sponge. For this purpose, the swollen sponge was subjected to uniform mechanical compression, which led to the removal of the required amount of the composition from it. The appearance of unfilled PVF sponges, PVF sponges with AuNPs filled with pH-sensitive hydrogels based on AAm-AAc is shown in Fig. 1 (digital photo whithout magnification).

The scheme of the synthesis of PVF-based sponges with incorporated functional pH-sensitive hydrogels and AuNP is shown in Fig. 2.

Table 1. Components content in hydrogels

Component, weight %	Type of hydrogel	
	AAc	**AAm-AAc**
AAm	–	9.0
AAc	9.9	0.9
MBA	1	
PSA	5.0	
Water	84.1	
AuNPs, μg/g	12.06	

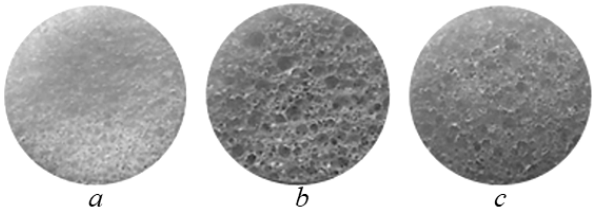

Fig. 1. Appearance of PVF-based sponges: without AuNPs and AAm-AAc hydrogel (*a*); C_{Au} = 12.06 μg/g (*b*); C_{Au} = 12.06 μg/g, filled with AAm-AAc hydrogel (*c*)

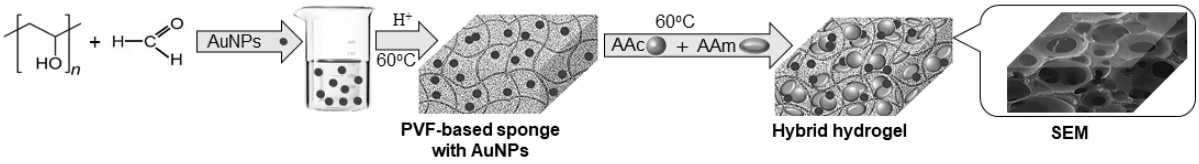

Fig. 2. The scheme of the synthesis

The morphology and pore structure of the hydrogel composites were obtained from micrographs taken on a Tescan Miga SEM with LMU equipped with an Oxford X-Max 80 energy dispersive spectrometer with a PECS Gatan 682 sample preparation system. The sample fragments were fixed on an adhesive conductive substrate (carbon tape SPI 05081-AB on a research table SPI 01506-MB). The sample, thus fixed, was covered with an ultra-thin (30 nm) layer of conductive material (Au/Pd mixture) using the PECS Gatan 682 device in order to avoid local charge accumulation during the scanning electron microscopy study.

Thermal analysis of hydrogels were studied using a thermogravimetric analyzer TA Instruments TGA Q50, a Derivatograph Q-1500 and aTA Instruments DSC Q2000. TGA were fulfilled in the temperature range from 25 to 800 °C in air atmosphere. DSC thermograms were obtained in the range of temperatures 35–700 °C.

The biocompatibility in vitro of the synthesized PVF-based hydrogels has been estimated by the parameters of cytotoxicity, genotoxicity and biochemical markers (ATPase and LDHase activity) using L929 cell line (ATCC: CCL-1™) from the collecton of

D.K. Zabolotny Institute of Microbiology and Virology named after of NAS of Ukraine according to the Guidelines "Safety assessment of medical nanopreparations" [19].

The biocompatibility in vivo of the hybrid hydrogels was studied on 12 chinchilla rabbits weighing 2–3 kg, aged for 5–6 months. The experiments were conducted at the vivarium of the State Institution "Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine". All animal experiments were performed in compliance with the Law of Ukraine on Protection of Animals from Cruel Treatment No. 3447-IV dated 21.02.2006 and European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes from the European Treaty Series (Strasbourg, 1986), and approved by a local Bioethics Committee of the Filatov Institute (Minutes No. 2 dated 25.06.2020). Prior to surgical procedure, animals were anesthetized with sodium thiopental 0.1 % (1.0 mL/kg body weight, intramuscularly). A hybrid hydrogel implant sized 10.0×5.0×2.5 mm was placed into the scleral sac and orbital tissue of each animal, and the wound margins were sutured with interrupted 6–0 silk sutures. At days 2, 5 and 10 after implantation surgery, important clinical signs, such as tissue edema, state of sutures, and discharge, if any, were noted. Animals were euthanized by air embolism immediately after removal of implants with adjacent tissues under anesthesia at days 10 and 30. A histological study to evaluate the effects of implantation of the examined hydrogel was conducted at the Pathomorphology and Electron Microscopy Laboratory, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" (Laboratory Competence Certificate No. PT-397/23 dated 31.10.2023). Tissue fragments in the area of implants were placed in a 10 % formalin solution for one day and then examined by standard histological methods with paraffin embedding. Histological tissue sections were colored by hematoxylin-eosin.

RESULTS AND DISCUSSION

SEM analysis. The microstructure (morphology) of the synthesized hydrogels was investigated using the SEM method after lyophilization of the samples swollen to equilibrium in water. The corresponding micrographs with different magnifications are shown in Fig. 3. The synthesized hydrogels are porous materials with a well-developed system of connected pores. The average pores with diameter approximately from 5–10 to 200–250 μm can be observed (Fig. 3 *a–d*). No nanopores were found in the synthesized systems. It can also be seen that in the case of hybrid hydrogel systems with partially filled pores with acrylic hydrogels, mainly the surface of the pores was modified. The micropores inside the walls were almost unaffected, while the micropores on the surface were filled with the hydrogel composition (Fig. 3 *c–d*). In general, the modification of PVAc with acrylic hydrogels reduces the size of the micropores inside the walls for all hydrogels systems, and also fills larger pores with a diameter of > 200 microns. The hydrogel based on PVF has a more pronounced cellular structure than other composites based on it and has pores of regular shape (Fig. 3 *a*, *b*) and a wall thickness of several micrometers, which are slightly thicker than those of composites based on functional hydrogels.

The presence of Au nanoparticles was confirmed by SEM elemental analysis, which was considered with of a sample of a hybrid composite based on PVA and AA_C (Fig. 4). At the sample preparation stage, the mentioned sample was coated with an ultra-thin (30 nm) Au layer using a Gatan PECS 682 device to prevent local charge accumulation during electron microscopy studies. The presence of such a metal layer leads to the presence of a peak in the spectra of characteristic X-rays. However, the image obtained using a backscattered electron detector indicates the presence of a phase-contrast inclusion. At the same time, in the region "Spectrum 1" corresponding to such an inclusion, a significantly higher Au content is noted, in the absence of other elements that can create a phase contrast. This indicates that such a phase contrast region is the localization of Au in the native sample (Fig. 4 (insert), Table 2).

Thermal analysis. The thermal characteristics (TG, DTG, DSC) of synthesized hybrid hydrogels were examined by air heating of the samples in a wide range of temperatures. The process of thermal decomposition for present organic molecules is very complicated and occurs in a few stages. As can be seen from the DSC and TG/DTG curves (Figs. 5 and 6),

four main stages of thermal destruction are observed for all the analyzed gels.

The stage of physicochemical transformations (dehydration, molecular conformation changes, primary fragmentation, *etc.*) occurs at relatively low temperatures (from 172 to 227 °C) and the weight loss at these stage do not exceed 7.5 %. These first minor mass losses also is associated with the endothermic removal of physically bound water (despite preliminary drying at 50 °C).

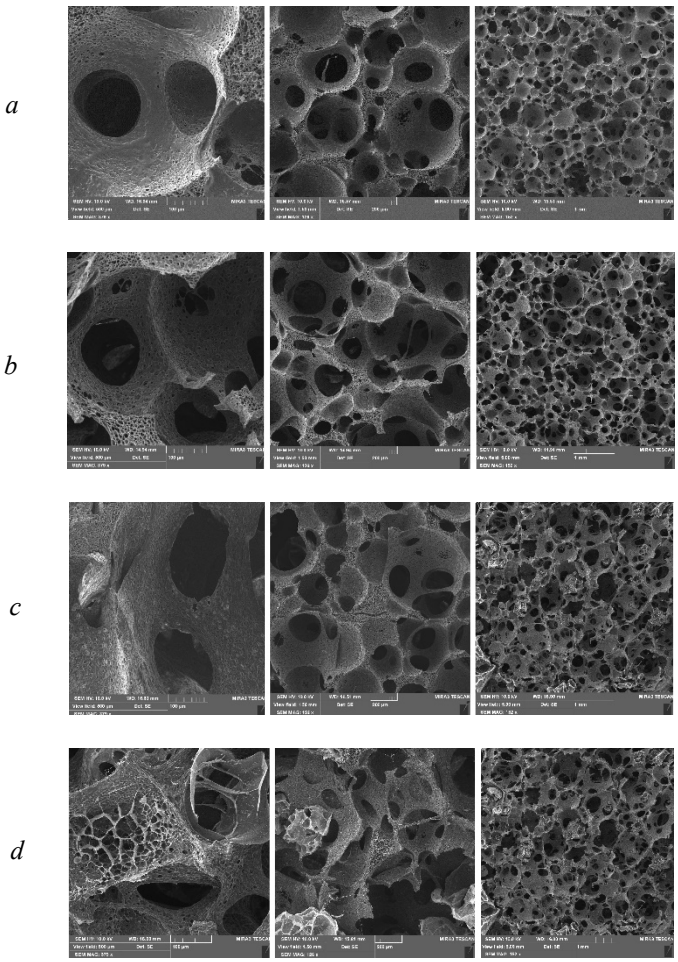

Fig. 3. SEM micrographs at different magnifications of: PVF-based sponges (*a*); PVF-based sponges filled by 12.06 μg/g Au (*b*); PVF-based sponges and AAm–AA_C + 12.06 μg/g Au (*c*); and PVF-based sponges and AA_C + 12.06 μg/g Au (*d*) (squeezing rate 75 %)

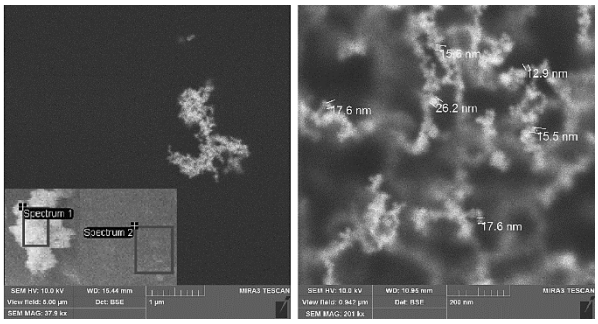

Fig. 4. SEM micrograph of AuNPs conglomerate on the example of PVF-based sponges and AA_C + 12.06 μg/g Au; (lower inserts – a phase contrast region with the localization of AuNPs)

Table 2. Elemental analysis (normalized) for PVF-based sponges and AA_C

Area	Weight, %			
	C	O	Au	Total
Spectrum 1	62.67	10.54	26.79	100.00
Spectrum 2	70.22	13.37	16.40	100.00

At higher temperatures, the next decomposition stages correspond to processes of partial defragmentation and organic decomposition. According to TGA data, three peaks of mass loss were recorded. Peaks at 329.8 and at 438.9 °C may be associated with the destruction of acrylamide and acrylic acid links, accompanied by the release of volatile molecules of ammonia, carbon dioxide and water. The process of decarboxylation of the carboxyl group of acrylic acid links also contributes to weight loss [20]. The 4th stage of thermal destruction (peak at 505.6 °C) corresponds to the complex organic decomposition of polymer molecules that make up hibride hydrogel structure, including PVF sponge. The data obtained correlate well with the results of DSC, according to which three peaks of mass loss of the hybrid hydrogel were observed at 325–370 °C, about 450 °C, and at 498 °C (Fig. 6). Stabilization of the sample mass was observed at 595 °C, and the total mass loss was 99.7 %.

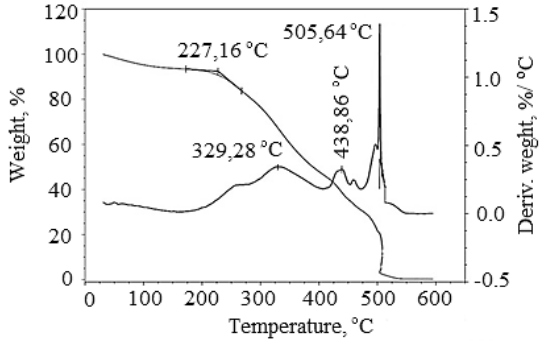

Fig. 5. TGA for a composite based on PVF and AAm-AAc (squeezing rate 75 %)

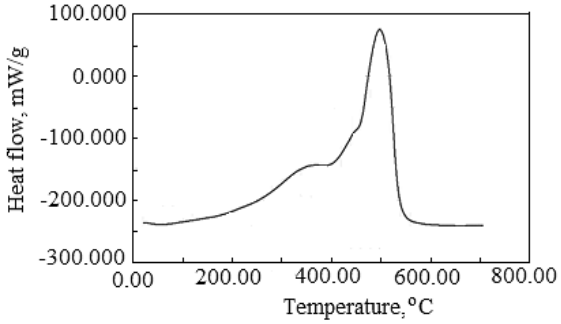

Fig. 6. DSC for a pH-sensitive hybrid composite based on PVF and AAm-AAc at a temperature of 35–700 °C (squeezing rate 75 %)

Thus, the synthesized hydrogel materials for medical purposes demonstrate thermal stability in a wide temperature range, which significantly exceeds the range of their application and processing. The obtained results prove that the synthesized hybrid hydrogels withstand steam sterilization (121 °C) without significant changes, which is extremely important for medical devices.

The biocompatibility in vitro of the PVF-based hydrogels. The data of the hydrogels' biocompatibility estimation *in vitro* show that all synthesized hydrogels were non toxic in tests of cytotoxicity (MTT assay, crystal violet staining

assay), genotoxicity (Comet assay) and biochemical markers (ATPase and LDHase activity tests).

In vivo evaluation* of *PVF-based hydrogels biocompatibility. As a result of experimental studies of the reaction of the soft tissues of the rabbit orbit to the implantation of a hybrid hydrogel into the scleral sac and the orbital tissue, we note the following. The first and most important requirement for implants is their biocompatibility. Our studies have shown that – all experimental rabbits had a moderate inflammatory reaction which disappeared by day 8–10. It is important to note that in all groups of experimental animals, wound healing occurred by primary tension, and therefore in no case was the implant denudation, which is extremely important for the successful use of implants. Pathohistological studies showed that by 10 days there were residual inflammatory phenomena in the immediate vicinity of the implant in the form of lymphocytic and leukocytic infiltration, while in more distant areas they were absent. Germination of surrounding tissues into the implant structure by the 10th day after implantation with the initial formation of a fibrous skeleton replacing part of the hydrogel structure, and by the 30th day – replacement of most of the implant with fibrous tissues. (Fig. 7, arrows).

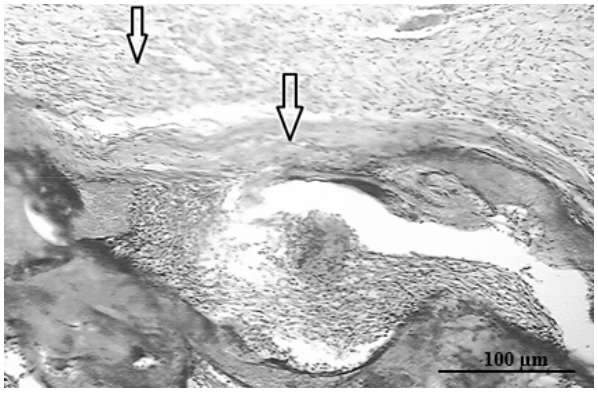

Fig. 7. Implantation of a hybrid hydrogel into the scleral sac, 30 days. Ingrowth of fibroblastic tissue from the side of the stroma without a capsule (arrows). Magnification: 100×

Another extremely important advantage of the implant is its lack of resorption, which creates the prerequisites for obtaining a stable clinical result.

CONCLUSION

Methods for the synthesis of porous polymeric material based on polyvinylformal with incorporated functional hydrogels and gold nanoparticles have been designed and physicochemical and biomedical studies have been carried out. The newly developed hybrid hydrogel material is intended for use in reconstructive surgery of the maxillofacial and ophthalmic-orbital areas, as well as for filling postoperative cavities with simultaneous prevention of repeated recurrences.

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Губчасті гібридні гідрогелі для ендопротезування щелепно-лицевої ділянки

Ю.М. Самченко, А.П. Малецький, Л.О. Керносенко, С.М. Дибкова, О.В. Артьомов, Т.П. Полторацька, Л.С. Рєзніченко, Н.О. Пасмурцева, В.І. Подольська, Т.Г. Грузіна

Інститут біоколоїдної хімії ім. Ф.Д. Овчаренка Національної Академії Наук України
бульв. Академіка Вернадського, 42, Київ, 03680, Україна, kernosenko@ukr.net
Інститут очних хвороб і тканинної терапії ім. В.П.Філатова Національної академії медичних наук України
бульв. Французький, 49/51, Одеса, 65061, Україна, maletskiy@filatov.com.ua

В останні роки досягнуто значного прогресу як у синтезі наночастинок металів, так і у створенні гідрогелевих платформ. Передбачається, що їхнє синергетичне поєднання дозволить створити новітні гідрогелеві нанокомпозити для відновлення анатомічних та функціональних порушень організму людини, а також для потреб реконструктивної хірургії. Мета роботи - розробка пористого полімерного матеріалу на основі полівінілформалю з інкорпорованими функціональними гідрогелями та наночастинками золота, дослідження його фізико-хімічних властивостей та біосумісності in vitro та in vivo. Розроблений гібридний гідрогелевий матеріал призначений для використання в реконструктивній хірургії щелепно-лицевої ділянки та очно-орбітальної зони, а також для заповнення післяопераційних порожнин з одночасною профілактикою повторних рецидивів. Морфологію синтезованих гібридних гідрогелевих композитів з наночастинками золота досліджено за допомогою електронної мікроскопії (СЕМ), а термічну стабільність – з використанням методів ТГА та ДСК. Доведено, що синтезовані гібридні гідрогелеві матеріали демонструють термічну стабільність у широкому температурному інтервалі, що значно перевищує діапазон їхнього застосування, та витримують стерилізацію парою (121 °С) без суттєвих змін. Синтезовані гібридні гідрогелі охарактеризовані як біосумісні in vitro за параметрами цитотоксичності, генотоксичності та біохімічними маркерами (АТФазна та ЛДГазна активність) з використанням культури клітин лінії L929. Дослідження реакції м'яких тканин на імплантацію in vivo продемонструвало формування фіброзної тканини по периферії і всередині імплантату, а також виражене зниження макрофагально-гістіоцитарної реакції і запальної інфільтрації на користь фібробластичної проліферації і відсутність резорбції, що створює передумови для стабільного клінічного результату. Таким чином, розроблений губчастий гібридний гідрогелевий матеріал може бути використаний у реконструктивній хірургії щелепно-лицевої та офтальмоорбітальної ділянок.

***Ключові слова**: pH-чутливі гідрогелі, ендопротезування, наночастинки золота, полівініформаль, акрилова кислота, гідрогелевий імплантат, біосумісність*

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