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Researching of Biologically Active Polymeric Hydrogel Transdermal Nanomaterial’s Modification by Humic Acid

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***Abstract*—Biologically active polymer hydrogel transdermal nanomaterial’s based on gelatin, hydroxypropyl cellulose, sodium alginate, modified by humic acids, were designed and researched. It has been found that effective processes for receiving biologically active polymer hydrogel transdermal nanomaterial’s based on gelatin, hydroxypropyl cellulose and sodium alginate can be carried out in different humic acids concentration values while achieving an increase in hydrogel polymers structuring processes. In this article, effective 3D printing technology of biologically active polymeric hydrogel transdermal nanomaterial’s microneedles patches based on gelatin, hydroxypropyl methylcellulose and sodium alginate, modified by humic acids, were researched. Biologically active polymeric transdermal hydrogel nanomaterial’s microneedles patches were produced using a micromolding technique where an FDM 3D printer was used to print the master mold. Form modeling was done in Autodesk's Fusion 360. The resulting 3D model was processed by a slicer to receive a file with commands for a 3D printer. It is shown that the application of new biologically active polymeric hydrogel transdermal nanomaterial’s microneedles patches based gelatin, hydroxypropyl methylcellulose and sodium alginate modified by humic acids allows improving the skin moisture-lipid balance.**

Keywords*—*polymeric, hydrogel, transdermal, nanomaterial, 3D printing, mold, microneedle, patche

I. INTRODUCTION

The current trend in the development of bioactive polymer materials is their active use in transdermal delivery systems of drugs and active substances in the human body [1]. Transdermal delivery systems based on bioactive polymeric materials are of increasing interest due to their ability to introduce drugs through the skin in case of need for local therapeutic actions and for system local delivery of drugs to affected skin. They are also widely used in active cosmetology in the form of various types of patches. Polymers for transdermal delivery systems based on bioactive materials of biological origin can be extracted from natural raw materials using physical or chemical methods. These polymers are widely used in the effective smart hydrogels form for loading cells to form tissues, build vascular, nervous, lymphatic networks, as well as to implement multiple biological, biochemical, physiological, biomedical and other functions [2].

The biopolymer biologically active polymers and hydrogels use is one of the direction for sustainable design using 3D printing technology development [3].

For a long time, 3D printers were used exclusively for functional or aesthetic prototypes production, and the technology itself was called "rapid prototyping" [4]. Computer technology development has led to the various methods appearance of additive technologies implementation: from laser stereolithography (SLA) to widespread Fused Deposition Modeling (FDM) 3D printing [5].

Modern sustainable design (Smart engineering) with 3D printing technology help is a multifaceted modern direction of industrial materials science development, which requires hardware, software modeling and materials constant convergence [6]. The last decade of sustainable design using 3D printing technology development has been largely driven by advances in hardware and software modeling, at the same time, there is growing interest in the effective materials development specifically for such processes. An important aspect of sustainable design development with 3D printing technology helps is the circular economy principles implementation: hardware, software modeling and materials [7].

Sustainable design using 3D printing technology of biopolymer biologically active polymers and hydrogels is a modern technology for receiving such materials[8]:

- artificial biological organs with precise control of their location in the body [9];

- transdermal biologically active polymeric materials with cells of the desired type deposited in them, target biomaterials and desired biologically active substances or drugs [10].

Over the past decade, a number of sustainable design technologies have been developed using 3D printing technology [11]. In contrast to traditional biomedical materials production technologies, they allow individual or personalized tissue structures production. Natural polymers play a leading role in supporting cellular and biomolecular processes both before, during and after 3D bioprinting [12].

Our previous works proved that humic substances are one of the materials that improves not only the mechanical properties of polymer hydrogels [13], but also directly affects their transdermal properties [14]. That is why an acute direction in the development of hydrogel nanomaterial production is the biologically active transdermal hydrogels based on gelatin-alginate and hydroxypropylmethyl cellulose-alginate systems modified with humic acids.

II. MATERIALS AND METHODS

The study’s objects of biologically active polymeric hydrogel transdermal nanomaterial’s were:

- food gelatin brand R-11 (Ukraine);
- hydroxypropyl methylcellulose brand Walocel™, produced by Dow Corning (USA);
- sodium alginate (China);
- humic acid with nanodispersion in the range of 52 - 380 nm [15], were received by extraction from lignite [16].

First, a gelatin solution (7 % wt.), a defined amount of polymer was placed in 50 mL of distilled water (preheated at 90 ± 2ºC) and stirred on VEVOR 85-2 Magnetic Stirrer with Heating Plate to obtain a clear solution. Then, a hydroxypropyl methylcellulose solution (8 % wt.), a defined amount of polymer was placed in 50 mL of distilled water (preheated at 90 ± 2 ºC) and stirred on VEVOR 85-2 Magnetic Stirrer with Heating Plate to obtain a clear solution. For the co-mixture of gelatin and sodium alginate, sodium alginate (2,5 % wt.) was added in the previously prepared gelatin solution (7 % wt.) to mix homogeneously on a VEVOR 85-2 Magnetic Stirrer with Heating Plate. For the co-mixture of sodium alginate and hydroxypropyl methylcellulose, sodium alginate (2,5 % wt.) was added to solution hydroxypropyl methylcellulose (8 % wt.) to mix homogeneously on a VEVOR 85-2 Magnetic Stirrer with Heating Plate.·After that, to co-mixture solutions of gelatin, hydroxypropyl methylcellulose and sodium alginate, humic acids were added in concentration of 2,5, 5 and 7,5 % wt.

3D printing sustainable engineering technology included form modeling for smart biologically active polymeric transdermal hydrogel patches. Modeling of the mold modeling was carried out in Autodesk's Fusion 360 and Cura software package.

The smart biologically active polymeric transdermal hydrogel patches mold for the patches was prepared by the SLA method using the Gray SLA material.

Microscopic studies were carried out using the electron microscope Digital Microscope HDcolor CMOS Sensor (China).

The swelling degree of smart biologically active polymeric transdermal hydrogel was calculated according to formula (2) [17]:

$$Q = 100 \cdot \left(\frac{m_1 - m}{m} \right) \qquad (1)$$

where m_1 is the mass of the swollen sample, g.;

m is the mass of the sample before standing in an aqueous solution, g.

To determine the moisture-lipid skin balance a professional skin moisture and oiliness analyser SK-92 (China) was used. This device operates on the basis of the Bioelectric Impedance Analysis (BIA) method - measuring the skin resistance tissues under the electric current.

We measured the moisture-lipid balance in the area around the eyes before and after application of biologically active humic-polymer hydrogel transdermal materials for 15 minutes in control group of five women aged 23-35 years. 3 parallel experiments were carried out for each biologically active humic-polymer hydrogel transdermal material. Statistical treatment was expressed as the mean value with its standard deviation (mean ± standard deviation) for each sample. Statistical analysis was performed using Student's t-test, and differences were considered significant at p-values below 0.05. The data presented in the study are average values with the specified margin of error. These errors are given based on the deviation of the obtained values from the arithmetic mean and/or permissible errors according to the methods for determining certain indicators.

III. REAULTS AND DISCUSSION

First studies were carried out to determine the effect of modification of humic acids on the swelling degree and effect on the moisture-lipid balance of the skin of biologically active polymeric hydrogel transdermal nanomaterial’s. Table 1 shows the operational properties of biologically active polymeric hydrogel transdermal nanomaterial’s modified by humic acids.

TABLE I. OPERATIONAL PROPERTIES OF BIOLOGICALLY ACTIVE POLYMERIC HYDROGEL TRANSDERMAL NANOMATERIAL’S BASED ON GELATIN, HYDROXYPROPYL METHYLCELLULOSE AND SODIUM ALGINATE MODIFIED BY HUMIC ACIDS.

Sample	**Humic acid content (%wt.)**	**Swelling degree (% wt.)**	**Skin moisture-lipid balance, %**	
			Moisture	**Lipid**
Pure gelatin-sodium alginate composition		19.82	58-60	52-54
gelatin-sodium alginate, modified by humic acids	2.5	27.17	60-62	54-56
	5	26.83	62-64	56-58
	7.5	23.21	64-66	58-60
Pure hydroxypropyl methylcellulose-sodium alginate composition		29.82	56-58	50-52
hydroxypropyl methylcellulose - sodium alginate, modified by humic acids	2.5	36.23	58-60	52-54
	5	35.66	60-62	54-56
	7.5	34.44	62-64	58-60

Table 1 shows that the modification of smart biologically active polymeric hydrogel transdermal nanomaterial’s by humic acids makes it possible to obtain transdermal nanomaterial’s with an increased swelling degree. In hydrogel materials for transdermal delivery, it is very important to ensure prolonged bioavailability of target biologically active substances through the skin barrier in the presence of high adhesion to the skin, stability of their geometric dimensions and shape preservation in temperature conditions throughout the entire period of exposure to human skin [18].

Such complex of properties of hydrogel materials for transdermal delivery can be achieved by researching the optimized level of viscosity, electrical conductivity and structural formation of hydrogels [19]. For example, in [20] it was shown that by increasing the viscosity and structuring of polyacrylamide–polydopamine hydrogels with mesoporous silica nanoparticles, hydrogel patches with high adhesiveness for transdermal drug delivery were obtained. Therefore, the initial studies consisted in determining the dependence of the conditional viscosity and electrical conductivity of bioactive humic-polymer hydrogel transdermal materials based on gelatin and sodium alginate, as well as based on hydroxypropyl methylcellulose and sodium alginate, on the different content of humic acids in them [21].

According to [22], the electrical conductivity of bioactive humic polymer hydrogel transdermal materials, which is related to the content of ionogenic substances, can actually be used as a measure of the level of hydration using a high-density and rigid network in water-soluble polymer hydrogel materials. It is important to note that the using new smart biologically active polymeric hydrogel transdermal materials based on gelatin and sodium alginate modified by humic acids allows to improve the skin moisture-lipid balance [17]. So, from the initial values of 34-36% moisture and 8-10 skin fat, they increase to 58-66% and 52-60%.

Next, biologically active polymeric transdermal hydrogel nanomaterial’s microneedles patches were produced using a micromolding technique. FDM 3D printer was used to print the master mold. It is important to note that recently 3D printing has been used to print microstructures - microneedles patches [23]. At the same time, only some polymer materials can be made into microstructures in microneedles patches using the 3D printing technique [24].

In our study, the FDM 3D printing technique was used to manufacture polylactide master molds [25]. This micromolding technique is considered effective because the master mold and production mold can be reused to cast a large number of microneedles patches [26].

The form modeling was carried out in Autodesk's Fusion 360 program. First, a plate measuring 8.5 mm by 8.5 mm was created in Autodesk's Fusion 360 program. The microneedles of the needle are arranged in a 7 × 7 array on an area of 1 cm^2. The microneedle has a conical shape with an average base height and width of 975 ± 20 and 360 ± 20 μm (n = 10). The resulting 3D model was processed with a slicer to obtain a stl* file with commands for a 3D printer - fig. 1. The resulting 3D model of transdermal hydrogel nanomaterial’s microneedles patches form was processed by a slicer to obtain a file with sets of commands for a 3D printer. The resulting stl* file is added to the slicer - the Cura software package. In this program, such parameters as the thickness of the print layer (0.1 mm) and the filling factor are adjusted (about 80%) and whether auxiliary elements are needed [27].

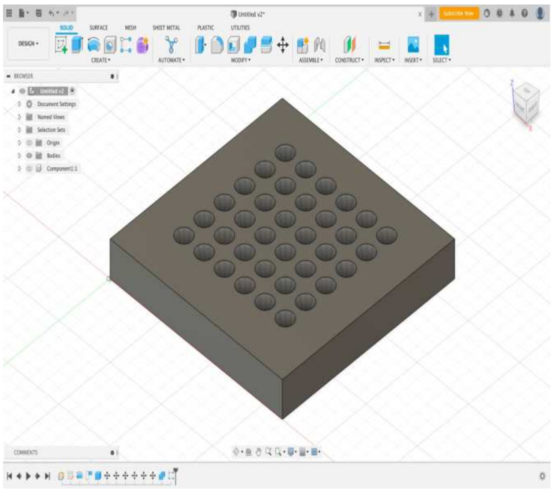

Fig. 1. The resulting 3D model of transdermal hydrogel patches form

The received file with a set of instructions for a 3D printer is ready for 3D printing. The 3D printed transdermal hydrogel nanomaterial’s microneedles patches mold photo and microscopy image of surface arrangement of recesses for microneedles in the mold are shown in fig. 2.

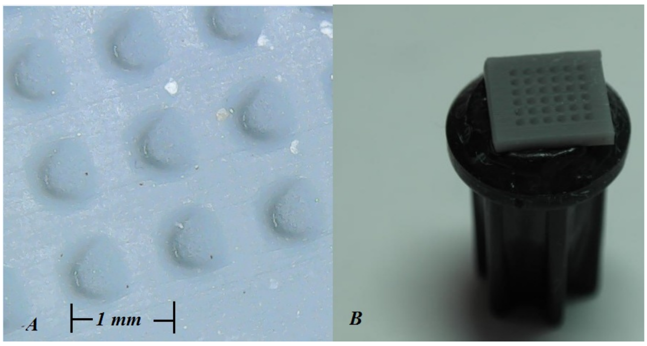

Fig. 2. 3D printed microscopy image of surface arrangement of recesses for microneedles (A) and transdermal hydrogel patches mold photo (B).

The biologically active polymeric hydrogel nanomaterial’s microneedles patches based on gelatin, hydroxypropyl methylcellulose and sodium alginate modified by humic acids photo and microscopy image of superficial arrangement of microneedles are shown in fig. 3.

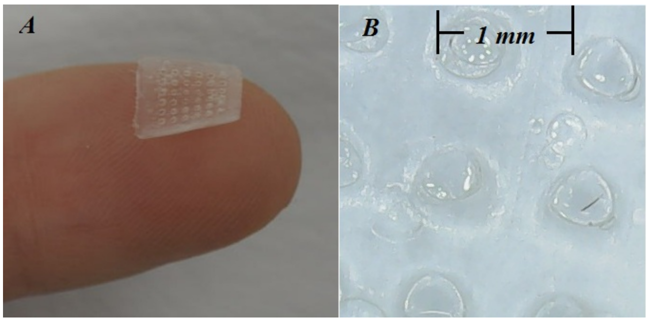

Fig. 3. The resulting 3D model of transdermal hydrogel patches mold.

In fact, thanks to designed biologically active polymeric transdermal hydrogel nanomaterial’s microneedles patches based on gelatin, hydroxypropyl methylcellulose and sodium alginate modified by humic acids using, it becomes possible to transfer the skin from slightly moist-fatty hard to highly moist-fatty elastic condition.

IV. CONCLUSIONS

In this work, modification of gelatin-sodium alginate and hydroxypropyl methylcellulose-sodium alginate biopolymer hydrogels by humic acids makes it possible to obtain biologically active polymeric hydrogel transdermal nanomaterial’s with an increased swelling degree and ability to improve the skin moisture-lipid balance. Biologically active polymeric transdermal hydrogel nanomaterial’s microneedles patches were produced using a micromolding technique where an FDM 3D printer was used to print the master mold. Form modeling was carried out in Autodesk's Fusion 360. The resulting 3D model was processed by a slicer to receive a file with commands for a 3D printer. In future researching is perspective to determine transdermal level of designed biologically active polymer transdermal hydrogels nanomaterial’s microneedles patches for most important medicine and cosmetic biologically active substances.

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