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Modeling of Smart Bio-Medical Active Polymeric Hydrogel Transdermal Materials

Lebedeva K. O.[1][0000-0002-0851-5012], Cherkashina A. M.[1][0000-0002-5239-6364], Masikevych Y. G.[2][0000-0002-0324-1171], Masikevych A. Y.[2][0000-0003-2862-9671], Voronkin A. A.[1], Lebedev V. V.[1*][0000-0001-6934-2349]

[1] National Technical University "Kharkiv Polytechnic Institute", 2, Kyrpychova St., 61002 Kharkiv, Ukraine;
[2] Bucovinian State Medical University, 2, Theater Square, 58002, Chernivtsi, Ukraine

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***Corresponding email:**
vladimirlebedev1980@ukr.net

Abstract. In this article, effective 3D printing modeling technology of smart bio-medical polymeric hydrogel transdermal materials based on gelatin and sodium alginate, modified by humic acids, was researched. Such smart biologically active polymeric hydrogel materials showed interesting applicability in tissue engineering fields due to their intrinsic biological compatibility, adaptability, and capacity to replicate the extracellular matrix environment. A literature review was carried out and proved that 3D printing modeling technology is a perspective for the functional effect on the smart bio-medical polymer hydrogel transdermal properties. Smart biomedical polymeric transdermal hydrogel patches were produced using a micromolding technique. A stereolithography (SLA) 3D printer was used to print the master mold. The three-stage technology of lignite humic acids modification of smart biologically active polymeric hydrogel transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate was designed. It was shown that modification of gelatin-sodium alginate and hydroxypropyl methylcellulose-sodium alginate biopolymer hydrogels by humic acids makes it possible to obtain smart biologically active polymeric hydrogel transdermal materials with an increased swelling degree and ability to improve the skin moisture-lipid balance (from the initial moisture 34–36 % and fatness 8–10, they increase to 58–66 % and 52–60 %). Finally, the developed 3D printing modeling technology of smart bio-medical polymeric hydrogel transdermal materials hydrogel based on gelatin sodium alginate, modified by humic acids, is a transdermal material with required properties.

Keywords: smart material, 3D printing technology, sodium alginate, humic acid.

1 Introduction

For a long time, 3D printers were used exclusively for functional or aesthetic prototype production, and the technology was called "rapid prototyping" [1]. Computer technology development has led to various methods of additive technology implementation, from laser stereolithography (SLA) to widespread fused deposition modeling (FDM) and 3D printing [2].

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 constant materials convergence [3]. Advances in hardware and software modeling have mainly driven the last decade of sustainable design using 3D printing technology development. Simultaneously, there is growing interest in effective materials development specifically for such processes.

An essential aspect of sustainable design development with 3D printing technology is the implementation of circular economy principles: hardware, software modeling, and materials [4].

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 [5]. Transdermal delivery systems based on bioactive polymeric materials are of increasing interest due to their ability to introduce substances through the skin in case of need for local therapeutic actions and system local delivery of substances. They are also widely used in active cosmetology in the form of various types of patches.

The use of skin to transport active substances in transdermal delivery systems has significant advantages compared to many other routes of active substances, such as oral, sublingual, rectal and infusion deliveries, as well as intravenous and intramuscular injections [6]. Thanks to the use of bioactive polymer materials in transdermal delivery systems, the risk of systemic side effects is reduced due to the minimization of concentrations in the blood plasma compared to oral therapy, and prolonged release of the active substance at the site of application is ensured. It becomes possible to stop therapy quickly by removing the material, reducing fluctuations in the level of drugs in the blood plasma, and preventing injection-related pain.

Biopolymers, biologically active smart polymers, and hydrogels are one of the directions for sustainable design using the development of 3D printing technology. Sustainable design using 3D printing technology of biopolymer biologically active smart polymers and hydrogels is a modern technology for receiving such materials [7]:

– artificial biological organs with precise control of their location in the body;

– transdermal biologically active polymeric materials with cells of the desired type deposited in them, target biomaterials, and desired biologically active substances.

Considering the above, the development of the technology of transdermal bioactive hydrogels based on alginates, gelatin, nanocellulose, and cellulose ethers for the complex treatment and rehabilitation of military and civilians in the war and post-war periods is a very urgent task for the recovery of Ukraine.

This issue will be solved by functional modification of polymer and inorganic hydrogels with humic acids. It will allow the creation of new bioactive materials for military field and stationary medicine with the aim of their further use in the production of medicinal forms for pain relief, hemostasis, speeding up the healing of damaged skin, bone replacement in the body, cartilage, or other types of tissue. Modified biologically active hydrogels with improved transdermal, antibacterial, and restorative properties will be used to produce plasters, patches, implants, and artificial substitutes for bone, cartilage, or other tissue. Such materials will become a material basis for solving urgent social issues, which are related both to overcoming health disorders caused by injuries and to the need for complex rehabilitation of various population groups in the war and post-war periods.

2 Literature Review

Recent years have been characterized by great attention to innovative directions in developing biopolymers, biologically active smart polymers, and hydrogels [3]. External factors such as pH, temperature, electric and magnetic fields, light, and the concentration of biomolecules can be used to induce the release of biologically active substances from biomaterials such as polymer hydrogels [8].

Besides unmodified biopolymers, biologically active smart polymers, and hydrogels that make up hydrogel systems, additives are also used to increase their effectiveness. Such additives are inactive ingredients designed to structurally improve and enhance the hydrogel's characteristics and influence the degradation profile and cell-matrix interactions. Additives include materials from natural (e.g., collagen, pectin), synthetic (e.g., polyvinyl alcohol, poloxamers), and semi-synthetic sources (e.g., cellulose derivatives).

Additionally, nanocellulose promoted bioadhesion and cell growth in the smart hydrogel medium. In addition, in our previous work, it was proved that humic substances, due to their ability to cross-link some polysaccharides and proteins, are materials that improve not only the mechanical properties of polymer hydrogels but also directly affect such hydrogel properties as transdermal ability [9, 10].

By analogy, effective transdermal hydrogels based on cellulose ethers were used in [11], in which, due to the increased viscosity and degree of cross-linking of the hydrogel, it was convenient to apply hydrogels to the skin with sufficient penetration of active substances.

Therefore, it is essential to study non-cytotoxic alginate-gelatin and hydroxypropyl methylcellulose-alginate biopolymer biologically active smart polymers and hydrogels modified with humic acids as biomaterials with good mechanical strength and biocompatibility, which are advisable to use in transdermal patches, microcapsules for bioactive compounds, cells and preparations, as well as in regenerative medicine (for example, for bone tissue regeneration) or as a soft tissue patch for wound healing.

Over the past decade, several sustainable design technologies have been developed using 3D printing technology [12]. In contrast to traditional biomedical materials production technologies, they allow individual or personalized tissue structure production. Natural polymers play a leading role in supporting cellular and biomolecular processes before, during, and after 3D bioprinting [13].

3D printing technology, in association with biocompatible hydrogels, has emerged as a promising platform for developing smart wound dressings, overcoming several challenges [14, 15].

Today, different biologically active polymers are widely used in the effective smart hydrogel form for loading cells to form tissues [16–18]. In modern sustainable design using 3D printing technology, natural polymers with a sol-gel phase transition (i.e., gel point) can be used [19].

Natural smart polymers using 3D printing technology for sustainable design typically contain cells or biologically active substances with non-toxic toxicity, biodegradability, biostability, high mechanical strength, and manufacturability (machinability) [8].

Our previous works proved that humic substances are one of the materials that improve the mechanical properties of polymer hydrogels [10] and directly affect their transdermal properties [10].

That is why an acute direction in developing smart hydrogel biomaterials production is the biologically active transdermal smart hydrogels based on gelatin-alginate and hydroxypropylmethylcellulose-alginate systems modified with humic acids. In this part of the research, manufacturing techniques for alginate–gelatin and hydroxypropyl methylcellulose-alginate hydrogels modified with humic acids have been developed. As an example of the practical use of the obtained bioactive humic-polymer hydrogel transdermal materials for their use in cosmetic hydrogel patches for wrinkles under the eyes, the influence of the content of humic acids on the swelling degree and the moisture-lipid balance of the skin was studied.

This work aimed to design 3D printing, a sustainable engineering technology for smart, biologically active polymeric hydrogel transdermal materials.

The main objectives of the work are as follows:

– to model and design a smart biologically active polymeric hydrogel transdermal microneedles patch mold;

– to develop a technology of lignite humic acids modification of smart biologically active polymeric hydrogel transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate;

– to explore basic properties of technology of lignite humic acids modification of smart biologically active polymeric hydrogel transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate.

3 Research Methodology

The study's objects of 3D printing sustainable engineering technology for smart biologically active polymeric transdermal hydrogel designing were food gelatin brand R-11 (Ukraine), sodium alginate (China), hydroxypropyl methylcellulose (Walocel™, Dow Corning, USA), and humic acid received by extraction from lignite.

First, a gelatin solution (7.0 % wt.), a defined amount of polymer was placed in 50 ml of distilled water (preheated at 90±2 ºC) and stirred on a VEVOR 85-2 magnetic stirrer with a heating plate to obtain a clear solution. This equipment has a maximum temperature of 100 ºC and a maximum stirring speed of 2000 rpm.

Then, a hydroxypropyl methylcellulose solution (8.0 % wt.), a defined amount of polymer was placed in 50 ml of distilled water (preheated at 90 ± 2 ºC) and stirred on a VEVOR 85-2 magnetic stirrer with a heating plate to obtain a clear solution.

For the co-mixture of gelatine and sodium alginate, sodium alginate (2.5 % wt.) was added in the previously prepared gelatine solution (7.0 % 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 a solution of hydroxypropyl methylcellulose (8.0 % 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 concentrations of 2.5, 5.0, and 7.5 % wt.

3D printing sustainable engineering technology included form modeling for smart biologically active polymeric transdermal hydrogel patches. The mold was modeled using Autodesk Fusion 360 and the Cura software package.

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

Microscopic studies were carried out using the electron digital microscope HD color CMOS Sensor (China) with 5x digital zoom and 1000x magnification effect.

The swelling degree of smart biologically active polymeric transdermal hydrogel was calculated according to the following formula [10]:

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

where m_1 – the mass of the swollen sample, g; m – the mass of the sample before standing in an aqueous solution, g.

A professional skin moisture and oiliness analyzer SK-92 (China) was used to determine the moisture-lipid skin balance. This device operates based on the Bioelectric Impedance Analysis (BIA) method – measuring the skin resistance tissues under the electric current with the following characteristics: moisture-lipid – from 0 to 99.9 %; measurement step – 0.1 %; tolerance – 1.0 %.

We measured the moisture-lipid balance in the area around the eyes before and after applying biologically active humic-polymer hydrogel transdermal materials for 15 minutes in the control group of five women aged 23–35 years. Three 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 a 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 specific indicators.

4 Results

Smart biologically active polymeric transdermal hydrogel patches were produced using a micromolding technique. An SLA 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 [20].

Simultaneously, only some polymer materials can be made into microstructures in microneedle patches using 3D printing. The study used the SLA 3D printing technique to manufacture a polylactide master mold.

This micromolding technique is considered effective because the master mold and production mold can be reused to cast many microneedles patches [21]. The mold modeling was carried out in Autodesk Fusion 360 [22].

First, a plate measuring 8.5 mm was created in Autodesk Fusion 360. 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 (the total number n = 10).

The resulting 3D model was processed with a slicer to obtain *.stl file with commands for a 3D printer (Figure 1).

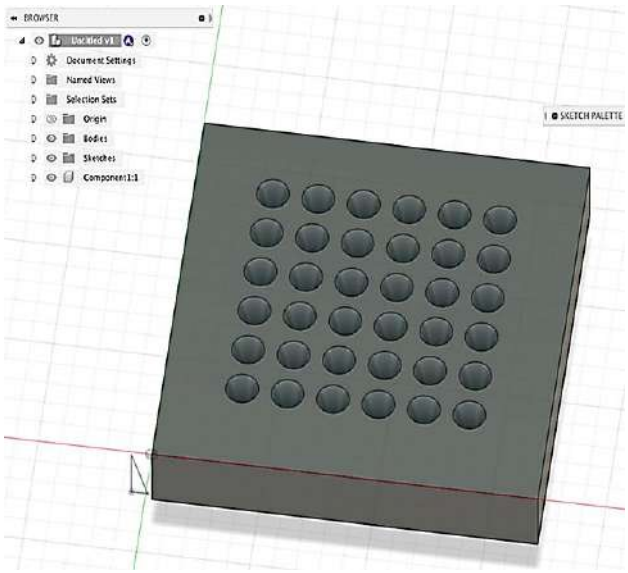


Figure 1 – The resulting 3D model of transdermal hydrogel patches mold

A slicer processed the resulting 3D model of the transdermal hydrogel patch mold to obtain a file with sets of commands for a 3D printer.

The resulting *.stl file is added to the Cura software package's slicer. In this program, parameters such as the thickness of the print layer (0.1 mm) and the filling factor are adjusted (about 80 %) and whether auxiliary elements are needed.

The received file with instructions for a 3D printer ready for 3D printing is presented in Figure 2.

The 3D printed transdermal hydrogel patches mild photo and microscopy images of the surface arrangement of recesses for microneedles in the mold are shown in Figure 3.

The smart biologically active polymeric hydrogel transdermal patch based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified by humic acids photo and microscopy image of the superficial arrangement of microneedles are shown in Figure 4.

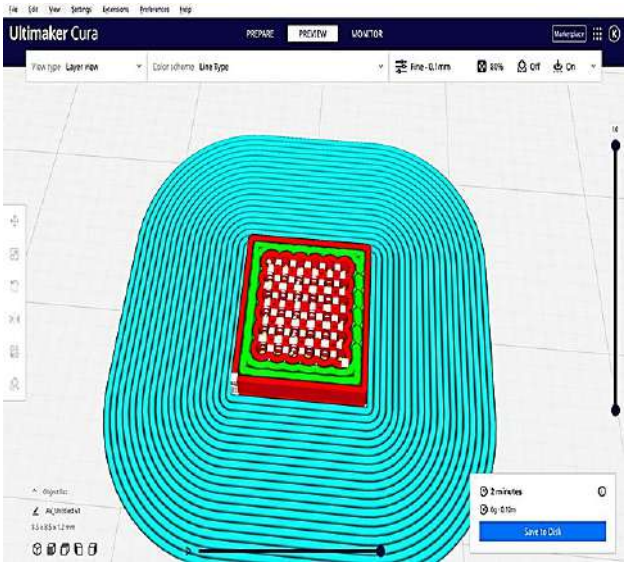
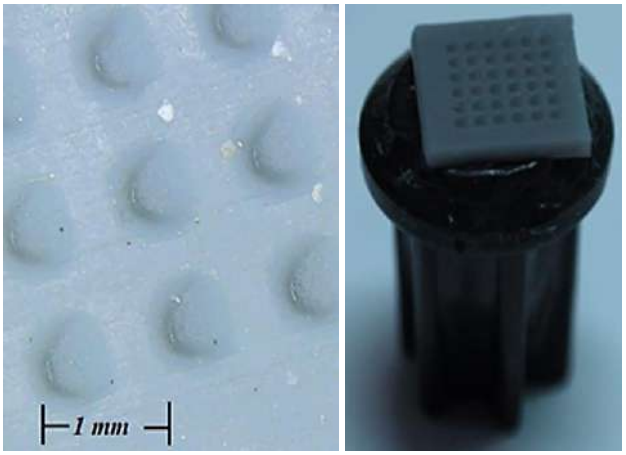
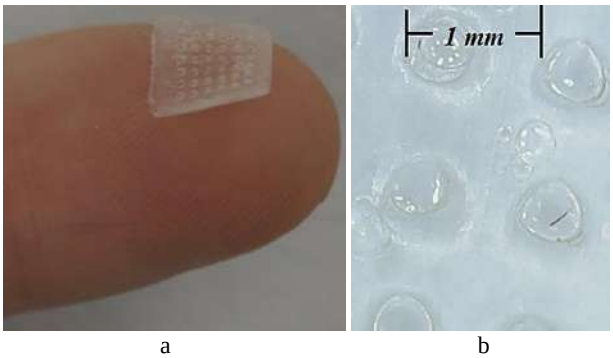


Figure 2 – Visualization of the work of a 3D printer when printing a part



a b

Figure 3 – 3D printed microscopy image of surface arrangement of recesses for microneedles (a) and transdermal hydrogel patches mold photo (b)



a b

Figure 4 – The resulting 3D model (a) of transdermal hydrogel patches mold (b)

Based on studies, the three-stage technology of lignite humic acids modification of smart biologically active polymeric hydrogel transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate was formalized (Figure 5).

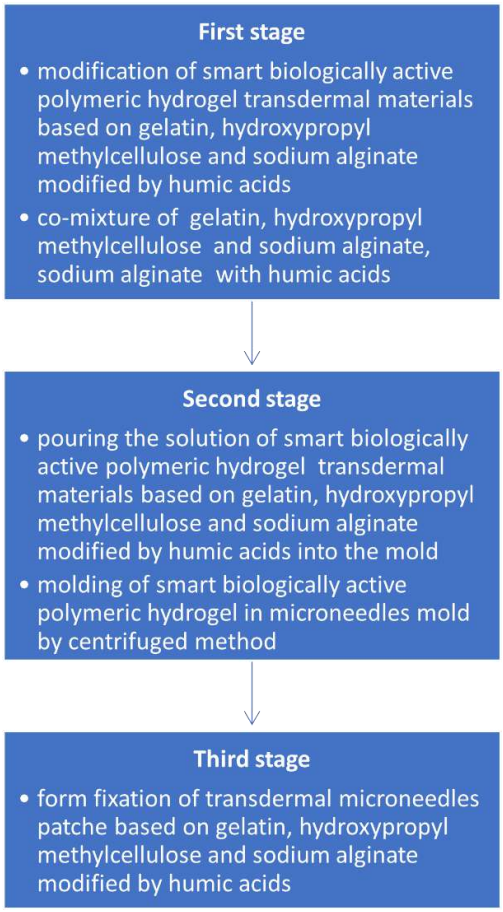


Figure 5 – A three-stage technology of lignite humic acids modification of smart biologically active polymeric hydrogel transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate

At the first stage, smart biologically active polymeric hydrogel transdermal materials are modified based on gelatin, hydroxypropyl methylcellulose, and sodium alginate by humic acids, which are received in a water solution form. At the second stage, the molding of smart biologically active polymeric hydrogel in microneedles mold by centrifuged method takes place. The third stage occurs from fixation of transdermal microneedles patches based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified by humic acids.

Next, studies were carried out to determine the effect of modification of humic acids on the swelling degree and the effect on the moisture-lipid balance of the skin of smart biologically active polymeric hydrogel transdermal materials.

Table 1 shows the operational properties of smart biologically active polymeric hydrogel transdermal materials modified by humic acids.

Table 1 – Operational properties of smart biologically active polymeric hydrogel transdermal materials based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified by humic acids

Sample	Humic acid content, % wt.	Operational properties		
		Swelling degree, % wt.	Skin moisture-lipid balance, %	
			Moisture	Lipid
Pure gelatin-sodium alginate composition		19.8	58–60	52–54
Gelatin-sodium alginate, modified by humic acids	2.5	27.2	60–62	54–56
	5.0	26.8	62–64	56–58
	7.5	23.2	64–66	58–60
Pure hydroxypropyl methylcellulose-sodium alginate composition		29.8	56–58	50–52
Hydroxypropyl methylcellulose-sodium alginate, modified by humic acids	2.5	36.2	58–60	52–54
	5.0	35.7	60–62	54–56
	7.5	34.4	62–64	58–60

Table 1 shows that the modification of smart biologically active polymeric hydrogel transdermal materials smart biologically active polymeric hydrogel transdermal materials by humic acids makes it possible to obtain biologically active polymeric hydrogel transdermal materials with an increased swelling degree. It is important to note that using new smart biologically active polymeric hydrogel transdermal materials based on gelatin and sodium alginate modified by humic acids improves the skin moisture-lipid balance. So, from the initial values of 34–36 % moisture and 8–10 skin fat, they increase to 58–66 % and 52–60%.

Thanks to the smart biologically active polymeric hydrogel transdermal materials based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified by humic acids, it becomes possible to transfer the skin from slightly moist-fatty hard to highly moist-fatty elastic condition.

5 Discussion

In fact, due to a scientific novelty, the developed 3D printing sustainable engineering technology for smart biologically active polymeric transdermal hydrogel design has clear advantages over the currently existing methods of 3D printing of biologically active hydrogels, widely described in recent works worldwide.

Thus, it does not require the use of specific equipment, which is used in the method of using particular hydrogel compositions as ink for 3D photoprinting of biologically active hydrogel materials [23] and does not include the stage of post-processing of annual products [24].

Also, the biologically active transdermal patches obtained using the developed 3D printing sustainable engineering technology are not inferior in dimensional accuracy to more expensive and multi-stage 3D printing methods: powder- and inkjet-based systems, materials extrusion, and vat photopolymerization [25, 26].

Thanks to the design of smart biologically active polymeric hydrogel transdermal microneedle patches based on gelatin and sodium alginate modified by humic acids, it becomes possible to transfer the skin from slightly moist-fatty hard to highly moist-fatty elastic condition.

In hydrogel materials for transdermal delivery, it is essential 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.

Such complex properties of hydrogel materials for transdermal delivery can be achieved by researching the optimized viscosity level, electrical conductivity, and structure formation of hydrogels. E.g., in [27], hydrogel patches with high adhesiveness for transdermal drug delivery were obtained by increasing the viscosity and structuring of polyacrylamide-polydopamine hydrogels with mesoporous silica nanoparticles.

Therefore, the initial studies consisted of 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.

The electrical conductivity of bioactive humic polymer hydrogel transdermal materials, related to the content of ionogenic substances, can be used as a measure of the level of hydration using a high-density network in water-soluble polymer hydrogel materials [28].

The moisture-lipid balance of skin improvement increases with increasing the humic substance content. Increasing the degree of swelling when modified with humic acids due to the formation of a more rigid network of hydrogels makes it possible to achieve long-term prolonged transdermal release of drugs, stability of their geometric dimensions and shape in temperature conditions throughout the entire period of exposure to human skin, and easier separation from the skin after application [29].

Notably, using new bioactive humic-polymer hydrogel transdermal materials based on gelatin and sodium alginate modified with humic acids improves the water-lipid balance of the skin. From Table 1, the improvement in the moisture-lipid balance of the skin increases with an increase in the content of humic substances.

Modification with humic acids makes it possible to obtain hydrogel transdermal materials, which, according to [30], when applied to the human body, will allow the regulation of the moisture-lipid balance of the skin uniformly for a long time.

Thus, thanks to the use of biologically active humic-polymer hydrogel transdermal materials based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified with humic acids, it becomes possible to transfer the skin from a relatively dry and rough state to an elastic-soft state.

6 Conclusions

Smart material is used in various engineering areas such as automotive, industrial, civil engineering, aerospace, and biomedical. Smart biologically active polymeric hydrogel materials have shown interesting applicability in tissue engineering fields due to their intrinsic biological compatibility, adaptability, and capacity to replicate the extracellular matrix environment.

In this work, effective 3D printing sustainable engineering technology of smart biologically active polymeric hydrogel transdermal materials based on gelatin, hydroxypropyl methylcellulose, and sodium alginate modified by different humic acid content were researched. Smart biologically active polymeric transdermal hydrogel patches were produced using a micromolding technique where an SLA 3D printer was used to print the master mold. Mold modeling was carried out in Autodesk Fusion 360.

A slicer processed the resulting 3D model to receive a file with commands for a 3D printer. The smart biologically active polymeric transdermal hydrogel patch mold for the patches was prepared by the SLA method using the gray SLA material. Modification of gelatin-sodium alginate and hydroxypropyl methylcellulose-sodium alginate biopolymer hydrogels by humic acids makes it possible to obtain smart biologically active polymeric hydrogel transdermal materials with an increased swelling degree and ability to improve the skin moisture-lipid balance: from the initial moisture 34–36 % and fatness 8–10, they increase to 58–66 % and 52–60 %.

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