ABSTRACT

Dissertation for the degree of Doctor of Philosophy (PhD) in the educational program «8D05301 – Chemistry»

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«Synthesis and properties of double-network polymer hydrogels for biomedical applications»

General description of the dissertation research

The dissertation is devoted to the development and synthesis of novel biocompatible double-network polymer hydrogels suitable for high-precision 3D printing and intended for applications in personalized implantology.

Relevance of the research topic

Polymer hydrogels have attracted considerable research interest owing to their unique combination of elasticity and ability to mimic the physicomechanical properties of biological tissues. These materials are widely used in biomedicine, including tissue engineering, regenerative medicine, implantable systems, and functional biomaterials. However, conventional single-network hydrogels often exhibit insufficient mechanical strength, poor resistance to cyclic loading, and limited durability, which substantially restrict their practical applications.

One of the most promising strategies for improving the performance of hydrogels is the development of double-network materials that combine high strength, wear resistance, and fracture resistance while retaining biocompatibility and hydrophilicity. In this context, hydrogels based on poly(vinyl alcohol), which is highly biocompatible, chemically stable, and capable of both physical and chemical cross-linking, are of particular interest when combined with polyester resins that form a rigid network structure and enhance the mechanical properties of the material.

Despite substantial advances in the field of double-network hydrogels, the rational selection of components, optimization of synthesis conditions, and control of the structural and mechanical properties of hydrogels based on poly(vinyl alcohol) and polyester resins remain insufficiently investigated. In particular, the effects of the network ratio, the nature of inter-network interactions, and cross-linking parameters on the biocompatibility, mechanical strength, and stability of the resulting materials require further systematic investigation.

Given the growing demand for personalized and functionally adapted implantable materials, the development of novel double-network hydrogels based on poly(vinyl alcohol) and polyester resins represents a relevant scientific and applied challenge. Comprehensive investigation of structure-property relationships in these systems provides a basis for the rational design of next-generation hydrogels with tailored characteristics and expands their potential biomedical applications.

Research objective: to develop and synthesize double-network polymer hydrogels based on poly(vinyl alcohol) and polyester resins with tailored structural, mechanical, and physicochemical properties, and to establish relationships between

their formation conditions, structure, and performance characteristics for biomedical and implantological applications.

Research aim

1. To develop a method for synthesizing polyethylene glycol fumarate via the direct polycondensation of polyethylene glycol with fumaric acid, determine the effect of reaction duration on its molecular weight characteristics and unsaturated bond content, and confirm the chemical structure of the resulting macromonomer.
2. To develop methods for preparing PVA/PEGF–PEGDA- and PVA/PEGMA–PEGDA-based double-network hydrogels through the photochemical crosslinking of polyethylene glycol macromonomers and the physical crosslinking of PVA using cyclic freeze–thaw treatment.
3. To determine the effects of hydrogel composition and fabrication conditions—including the molecular weight and concentration of PVA; the contents of PEGMA, PEGDA, and tannic acid; UV irradiation time; and freeze–thaw parameters—on the structure and rheological, physicomechanical, and adhesive properties of the materials.
4. To investigate the phase state, morphology, and nature of intermolecular interactions within the hydrogels and determine the roles of PVA microcrystalline domains and hydrogen bonding with tannic acid in the formation of the double polymer network.
5. To establish the patterns of hydrogel thermal degradation and dehydration and determine the kinetic parameters of thermal degradation and the effective diffusion coefficients of water.
6. To optimize the fabrication conditions for three-dimensional hydrogel constructs using volumetric photopolymerization, extrusion-based 3D printing, and stereolithography; compare their structural and mechanical characteristics; and evaluate the cytocompatibility of the resulting materials with dermal fibroblasts.

Objects of research. Polymer hydrogels based on PVA and polyester resins.

Subject of research. The effects of synthesis and processing parameters, including component ratio, cryogenic treatment conditions, and printing method, on the structural, morphological, and mechanical properties of the hydrogels and their in vitro biocompatibility.

Research methods. The study employed direct polycondensation, photopolymerization, freeze-thaw cycling, gel permeation chromatography, FTIR and ^{1}H NMR spectroscopy, ATR-FTIR spectroscopy, optical microscopy, scanning and transmission electron microscopy, X-ray diffraction, rheometry, mechanical testing, swelling and dehydration studies, thermogravimetric and differential thermogravimetric analyses, kinetic modeling, bulk photopolymerization, extrusion-based 3D printing, stereolithography, adhesion testing, the MTT assay, and morphological analysis of dermal fibroblasts.

Main provisions submitted for defense:

1. An effective and scientifically substantiated method was developed for synthesizing water-soluble polyester macromonomers based on poly(ethylene glycol) fumarate with specified molecular-weight characteristics: a number-average molecular weight (M_n) of 3505 Da and a weight-average molecular weight (M_v) of

5834 Da. FTIR and ^{1}H NMR spectroscopy demonstrated that approximately 11% of the theoretically calculated unsaturated double-bond content was retained in the macromonomer structure, enabling subsequent chemical cross-linking and the formation of three-dimensional hydrogel networks with tunable physicochemical properties.

2. A method was developed for preparing double-network hydrogels based on poly(ethylene glycol) macromonomers (PEGF or PEGMA) and poly(vinyl alcohol). The first, chemically cross-linked polymer network is formed by photopolymerization at a wavelength of 365 nm using TPO-Li at a concentration of 0.25 wt.% as the photoinitiator. Subsequent freeze-thaw treatment (-50 °C; 2 h freezing and 2 h thawing) produces the second, physically cross-linked PVA network through the formation of microcrystalline domains, thereby enhancing the structural stability and mechanical properties of the hydrogels.

3. A novel type of biocompatible interpenetrating polymer-network hydrogel was developed based on a photocrosslinked PEGMA/PEGDA network and a physically cross-linked PVA network. The incorporation of PVA was found to increase the elastic modulus through topological entanglements between PVA chains and the PEGMA/PEGDA network. Sequential dual cross-linking of PVA by microcrystallites formed during freeze-thaw cycling and by cooperative hydrogen bonds with tannic acid increased the elastic modulus of the hydrogels by factors of 2 and 6, respectively. The formation of microcrystalline domains and hydrogen bonds was confirmed by X-ray diffraction and ATR-FTIR spectroscopy. Microphase separation was shown to promote the formation of PVA-rich microdomains and strengthen PVA-PVA intermolecular contacts. The resulting hydrogels exhibit mechanical properties comparable to those of human muscle and tendon tissues and biocompatibility confirmed using a dermal fibroblast model, supporting their potential application in regenerative medicine.

4. The developed hydrogels exhibited high biocompatibility, as confirmed by the MTT assay and direct-contact studies with dermal fibroblasts. After one week of incubation in phosphate-buffered saline, cell viability remained comparable to that of the control. Under direct contact between the hydrogels and cell cultures, cell viability exceeded 70%, satisfying the requirements of ISO 10993-5 for the in vitro assessment of cytotoxicity. These findings indicate the absence of pronounced cytotoxic effects and confirm the potential of the developed hydrogels for biomedical applications.

Characteristics of the main research results. A direct polycondensation procedure was developed for PEGF synthesis. The resulting macromonomer had Mn = 3505 Da, Mw = 5834 Da, and a polydispersity index of 1.665. Increasing the polycondensation time reduced the degree of unsaturation; after 8 h, the double-bond content was approximately 11% of the theoretical value and remained sufficient for photocrosslinking.

PVA/PEGF-PEGDA and PVA/PEGMA-PEGDA double networks were developed. The effects of PVA molecular weight and concentration, PEGMA and PEGDA contents, UV irradiation time, and cryogenic treatment on the phase state and rheological behavior were determined. Lower-molecular-weight PVA favored

the formation of more transparent and homogeneous systems, whereas increasing the UV irradiation time to 5 min produced a stable chemically cross-linked network with a pronounced storage-modulus plateau.

The incorporation of PVA into the PEGMA-PEGDA network increased the elastic modulus owing to topological entanglements. The maximum modulus was achieved at a PVA content of 2 wt.%; the decrease observed at higher concentrations was attributed to microphase separation. Increasing the density of physical cross-links reduced the swelling degree and enhanced structural stability. Replacing PEGF with PEGMA promoted a denser, more homogeneous, and more stable morphology. X-ray diffraction confirmed the formation of PVA microcrystalline domains, whereas ATR-FTIR spectroscopy confirmed hydrogen bonding between PVA and tannic acid.

Thermal analysis demonstrated that the network composition and cross-link density determine thermal stability and the multistage nature of decomposition. Increasing the PEGDA content raised the energy barrier to decomposition owing to the formation of a denser covalent network. Effective water diffusion coefficients were calculated using Fick's model; the decrease in these coefficients as dehydration slowed was associated with increased network density and greater resistance to moisture transport.

Hydrogel constructs were successfully fabricated by bulk photopolymerization, extrusion-based 3D printing, and stereolithography. Samples produced by bulk photopolymerization exhibited the highest mechanical properties, whereas additive-manufacturing techniques enabled the reproducible fabrication of three-dimensional objects with predefined geometries. The incorporation of 20 wt.% tannic acid increased the adhesive strength to approximately 9-10 kPa. The MTT assay and direct-contact tests with dermal fibroblasts confirmed the absence of a pronounced cytotoxic effect under the experimental conditions: relative cell viability exceeded 70%, and the cells retained their characteristic morphology.

Scientific novelty of the research:

1. For the first time, double-network hydrogels based on PVA and poly(ethylene glycol) macromonomers were obtained using PEGF, PEGMA, and PEGDA, enabling the formation of single-phase homogeneous systems over a broad compositional range. PEGMA was found to reduce the threshold PEGDA content required for gelation owing to its participation in copolymerization and incorporation into the network.

2. An independently physically cross-linked PVA network was formed within a photocrosslinked poly(ethylene glycol)-based network, producing stable double networks with high structural homogeneity. A combination of microscopic, spectroscopic, and thermal methods established relationships between the morphology and porosity of the hydrogels and the molecular structure and durability of the material.

3. The rheological characteristics of single and double networks were determined, and the conditions required to achieve optimal mechanical strength and partial structural recovery after deformation for extrusion-based 3D printing were established.

4. The effects of the PEGF/PEGMA, PEGDA, and PVA ratios and additional cross-linking with tannic acid on yield stress, viscosity, elastic modulus, swelling, the rate and extent of mechanical recovery, adhesion, and hydrogel cytocompatibility were established.

Significance of the research findings. The theoretical significance lies in establishing the regularities governing the formation and structural integration of components in PVA/PEGF-PEGDA and PVA/PEGMA-PEGDA double networks. The roles of topological entanglements, PVA microcrystalline domains, microphase separation, and cooperative hydrogen bonding with tannic acid in determining morphology, strength, viscoelasticity, swelling, and adhesion were clarified. The findings expand the current understanding of interpenetrating polymer networks and enable their behavior during deformation, heating, and dehydration to be predicted.

The practical significance lies in the development of hydrogel compositions and processing conditions that provide tunable mechanical and rheological properties suitable for bulk and additive manufacturing. The established photopolymerization and cryogenic-treatment conditions, together with the use of tannic acid, enable the targeted regulation of strength, stability, self-recovery, and adhesion. The confirmed in vitro cytocompatibility supports the further development of these materials for personalized implants and soft-tissue regeneration.

Relationship of the research to research projects and government-funded scientific programs. The dissertation research was conducted at the Karaganda Buketov National Research University within project AP19677568, 'Biocompatible Double-Network Polymer Hydrogels for Personalized Tissue Regeneration', implemented in 2023-2025.

Personal contribution of the author. The author independently planned the research and formulated its objectives, performed the experimental and computational work, processed, interpreted, and synthesized the results, and prepared scientific articles and conference abstracts based on the dissertation materials.

The doctoral candidate's contribution to each scientific publication included conducting the literature review, selecting an appropriate scientific journal, preparing and formatting the manuscript, interpreting the results, and corresponding with journal editors and reviewers. The research findings were published in the following scientific articles:

1. «Biocompatible Interpenetrating Network Hydrogels with Dually Cross-Linked Polyol» https://doi.org/10.3390/polym17202737 - the article focuses on the preparation of biocompatible interpenetrating polymer-network hydrogels based on PEGMA/PEGDA and PVA, with additional PVA cross-linking through microcrystalline domains and hydrogen bonding with tannic acid, and on establishing relationships among the structure, physicomechanical properties, and biocompatibility of the developed materials.

2. «Thermal Stability and Decomposition Mechanisms of PVA/PEGDA-PEGMA IPN-Hydrogels: A Multimethod Kinetic Approach» https://doi.org/10.3390/polym17202805 - the article presents a comprehensive investigation of the thermal stability and multistage decomposition mechanisms of

PVA/PEGDA-PEGMA interpenetrating-network hydrogels and determines their decomposition kinetics using isoconversional, model-fitting, and model-free methods.

3. «Synthesis of Water-Soluble Polyethylene Glycol Fumarates for Biomedical Applications» https://doi.org/10.31489/2959-0663/2-24-7 - the article focuses on developing a method for synthesizing water-soluble poly(ethylene glycol) fumarate, determining the effect of polycondensation time on its molecular-weight characteristics and chemical structure, and evaluating the suitability of the resulting macromonomer for the preparation of hydrogels for biomedical applications.

4. «Comparative Analysis of Thermal Decomposition Kinetics of Copolymers Based on Polyethylene Glycol Fumarate with Methacrylic Acid» https://doi.org/10.31489/2959-0663/2-23-6 - the article presents a comparative analysis of the thermal stability of poly(ethylene glycol) fumarate-methacrylic acid copolymers with different compositions, establishes the regularities of their thermal decomposition, and determines the kinetic and thermodynamic parameters of the decomposition process.

5. «Investigation of the Destruction of Copolymers of Poly(ethylene glycol) Fumarate with Methacrylic Acid Using Differential Equations» https://doi.org/10.31489/2021Ch3/47-52 - the article investigates the regularities of thermal decomposition of poly(ethylene glycol) fumarate-methacrylic acid copolymers and determines the kinetic parameters of decomposition using differential calculation methods.

6. «Study of Thermal Decomposition of the Copolymer Based on Polyethylene Glycol Fumarate with Methacrylic Acid» https://doi.org/10.51580/2022-3/2710-1185.99 - the article examines the thermal behavior of a poly(ethylene glycol) fumarate-methacrylic acid copolymer in an inert atmosphere, identifies the temperature ranges and stages of decomposition, and determines the kinetic and thermodynamic characteristics of the thermal decomposition process.

Validity and reliability. The experimental investigations were performed using modern certified equipment and analytical instruments, ensuring the reliability, reproducibility, and objectivity of the results.

Dissemination of the research findings. The main provisions, conclusions, and scientific results of the dissertation were presented and discussed at the international conferences 'MacroFrontiers 2025: 3rd International Conference on Macromolecular Compounds', dedicated to the 105th anniversary of Azerbaijan State Oil and Industry University (24-25 April 2025), and 'Polymeric Materials: from Nanoparticles to Tissue Implants. 16th Polymer Meeting 2025' (Prague, Czech Republic, 1-4 September 2025).

Publications. The principal results of the dissertation were reported in the following publications: four articles in scientific journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan, and two articles in international journals indexed in Scopus and Web of Science.

Structure and scope of the dissertation. The dissertation comprises an introduction, three chapters, conclusions, a list of references, and appendices. The

dissertation contains 114 pages of typescript, including 56 figures and 6 tables. The reference list comprises 137 sources.