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Synthesis of Biodegradable Medical Materials Based on Grafted Acrylate Copolymers on Collagen Obtained under Photocatalysis Conditions

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Abstract—The review summarizes studies on modification of fish collagen and pectin to obtain the branched and three-dimensional structures. They are biodegradable and biocompatible sealants prepared via radical graft copolymerization under photocatalysis in the presence of a $RbTe_{1.5}W_{0.5}O_6$ complex oxide of a β-pyrochlore structure, including the variation of composition of a initial reaction mixture, and via the isolation stage by introduction of known modification additives.

Keywords: medical sealants, biopolymer, synthetic monomer, photocatalysis, modification, fibrillar gel

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INTRODUCTION

Biodegradable and biocompatible sealants for medical purposes occupy a special place in practice. They are materials to cover wound and burn surfaces, disposable absorbent products, fasteners in the treatment of fractures, scaffolds for cell technologies, etc. The natural polymer materials are widely used for these purposes: proteins and polysaccharides or synthetic biocompatible polymers. Currently, the development of biodegradable and biocompatible composite structured materials based on natural polymers, among which collagen or its denatured analogue (gelatin) and polysaccharides occupy the leading positions, is preferred [1–10]. An environmental advantage of a starting material (natural renewable raw materials, most often industrial waste, and the prospects for widespread use in various fields) is added to those of new materials. This is also typical of collagen, which is obtained from waste of processed integumentary tissues of animals and fish, and of many polysaccharides [2, 11]. Pectin, a polysaccharide discussed in this review, is extracted from waste of processed vegetables and fruits [12, 13].

The aim to develop the structured composite materials based on natural fibrillar polymers is to create a three-dimensional architecture of macromolecules while maintaining biocompatibility/biodegradability and controllable degradation time to acquire new mechanical properties [1–11]. The preparation of three-dimensional structures in the case of collagen and pectin is possible only via modification of a starting natural polymer. A branched and three-dimensional architecture of macromolecules is created by various chemical agents or under physical action [2, 7, 14, 15]. Moreover, the “cross linking” to form covalent and ionic bonds is possible. One interesting technique for this purpose is the synthesis of copolymers. A variety of approaches are used, but it is more practical to use radical block and graft copolymerization processes of natural polymers with synthetic fragments with the addition of cross-linking agents [1, 2, 16–22]. The priority areas in this case are studies consistent with the principles of a “green chemistry,” in particular, photocatalysis in the presence of complex metal oxides. They are assigned to an environmentally friendly alternative to chemical sources of active particles in reagent transformations. The compounds with a perovskite structure and their derivatives were described initially in review papers [23]. Later, the structure and properties of pyrochlore compounds were studied actively [24, 25].

Despite the fact that titanium dioxide was previously used most often in water- and air-purification devices [25, 26], it is assigned to wide-gap semiconductors, whose bandgap is within 3.0–3.4 eV depending on formation method. This leads to its intense absorption of light only in the ultraviolet region of optical spectrum. Ultraviolet radiation in the solar spectrum, however, accounts for about 5% of the energy [27]. The development of new active photocatalysts capable of absorbing visible radiation is an important direction in the theory and practice of heterogeneous photocatalysis from the point of view of efficient use of solar energy. These include β-pyrochlore type complex oxides. Photocatalytic oxidation with their participation in visible light is known for the decomposition of various pollutants in water and air [28, 29]. The use of photocatalysis to produce polymer materials has been less studied [30–34], although it seems to be promising and interesting.

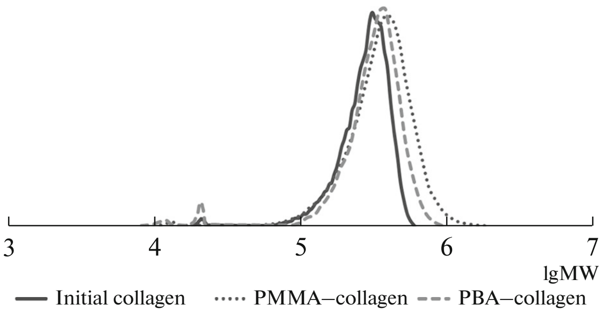


Fig. 1. MMD curves of initial collagen and grafted PMMA/PBA–collagen copolymers.

When an aqueous dispersion of complex β-pyrochlore structural type oxides is irradiated with visible light, the reaction volume contains various active particles—charged particles, radicals, singlet oxygen, and hydrogen peroxide—which are capable of destroying organic and any other compounds [35].

The aim of this review is to summarize the studies on modification of fish collagen and pectin to obtain the branched and three-dimensional structures via radical graft copolymerization using photocatalysis in the presence of a $RbTe_{1.5}W_{0.5}O_6$ complex oxide with a pyrochlore structure. This also included the variation of a composition of a initial reaction mixture and the isolation stage via introduction of known modification additives.

1. THEORETICAL BACKGROUND OF CONCEPT OF OBTAINING THREE-DIMENSIONAL POLYMER STRUCTURES UNDER PHOTOCATALYSIS CONDITIONS

The irradiation of a complex β-pyrochlore structural type oxide upon contact with water leads to the formation of electron–hole pairs, which can lead to some transformations including the formation of radical particles [35]. The $HO_2^{\bullet}$, $O_2^{\bullet}$, and $HO^{\bullet}$ particles are radicals. Nevertheless, only a hydroxyl radical has a tendency to radically interact with organic substrates [36, 37]. Its characteristic reaction is the elimination of a hydrogen atom from an organic substrate to form water and the corresponding radical [38]. If the process proceeds in water in contact with air, the addition of an oxygen molecule to form a peroxide radical and the subsequent oxidation of an organic substrate are quite possible. If the process is performed in an inert gas atmosphere, a radical of an organic substrate, much more stable than hydroxyl one, is capable of radical transformations: the recombination, addition to a multiple bond, etc. [39]. The structural units of collagen and pectin are fragments with hydrocarbon sections and ones containing a hydroxyl group. Collagen and pectin macroradicals are formed after the elimination of a hydrogen atom from these fragments.

The addition of synthetic polymer fragments to natural polymer macroradicals or the grafting of synthetic fragments onto a natural polymer macromolecule is quite possible during the dispersion of water and vinyl monomer in inert gas atmosphere. A branched copolymer will be obviously formed during grafting if chain termination proceeds through a disproportionation reaction (a reaction characteristic of methyl methacrylate [39]) or chain transfer to polymer. Cross links can be formed between macromolecules of a natural polymer due to the termination reaction of polymer chains of synthetic fragments via recombination. This reaction is typical for butyl acrylate [39]. Section 2 describes experimental data to realize such grafting.

2. SYNTHESIS OF GRAFTED ALKYL METHACRYLATE COPOLYMERS ON FISH COLLAGEN AND APPLE PECTIN UNDER PHOTOCATALYSIS CONDITIONS

Polymethyl methacrylate (PMMA) and polybutyl acrylate (PBA) copolymers grafted onto fish collagen were prepared under photocatalysis in the presence of $RbTe_{1.5}W_{0.5}O_6$ and characterized. These monomers were chosen due to the fact that alkyl methacrylate (AMA) copolymers are widely used in medical practice. Composite materials containing AMA are already widely used in medicine, in particular, in dentistry for artificial jaws and teeth, for fillings, and in manufacture of prostheses, contact lenses, and artificial lenses [40]. Natural polymer copolymers with AMA (hyaluronic acid [41, 42] and collagen [43, 44]) are used as fillers in cosmetology for decades. The materials based on copolymers of various synthetic monomers and natural polymers were prepared for regenerative medicine in recent years [31, 32].

The graft copolymerization process was performed in aqueous dispersion of a mixture of natural polymers, dissolved in aqueous phase, together with methyl methacrylate (MMA) and butyl acrylate (BA) organic monomers at temperatures of 20–25°C. Natural polymers dissolved in water are also nonionic emulsifiers [45–50]. Cod collagen isolated according to the method of [51] and Pudov commercial apple pectin (used without additional purification) were used as natural polymers.

The analysis of a polymer product isolated from the aqueous phase indicates that the grafted copolymers are formed. The fact that synthetic fragments are grafted onto a natural polymer is provided by the following data.

(1) An increase in total mass of a polymer product in comparison with native natural polymer by 13–30%.

(2) An increase in molecular weight of the grafted copolymer compared to native natural polymer. Figure 1 shows such changes (collagen as example): MMD curves of initial collagen and the copolymers

grafted with PMMA and PBA. This shift appears due to the grafting of synthetic fragments onto collagen.

(3) In the case of grafted collagen copolymers, the amount of nitrogen decreases compared to that of initial natural polymer (Table 1). It is worth noting that the amount of copolymer grafted with PMMA and PBA remains almost unchanged.

(4) The microstructure of copolymers was studied with a scanning electron microscopy (SEM) (Fig. 2). Comparison of photographs of collagen sponges (Fig. 2a) and its copolymers grafted with PMMA (Fig. 2b) and with PBA (Fig. 2c), as well as pectin sponges (Fig. 2d) and its copolymer grafted with PMMA (Fig. 2e), shows a noticeable difference in morphology, which is seen clearly in the compaction of fibers of structural matrices in the grafted copolymers. They appear as films in SEM photographs, because the surface of synthetic fragments has no spatial shape. In addition, the cellular structure of the copolymers with interpenetrating pores of different sizes is clearly visible. Moreover, if a clear fibrous structure is visible on collagen films dried in vacuum (Fig. 2h), the PMMA–collagen graft copolymer film has a more complex surface (Fig. 2i): the formation of bulky three-dimensional structures is due to cross+ linking. IR spectroscopy data showed that collagen film has the absorption bands characteristic of proteins: 1600–1700 cm^{-1} (NH and C=O bonds), 1510–1570 cm^{-1} (in-plane deformation vibrations of an NH bond), 1200–1350 cm^{-1} (deformation vibrations of C–N and NH bonds), and 1720–1730 cm^{-1} (valence vibrations of a carboxyl group C=O). The IR spectrum of PMMA also has an absorption band at 1720–1730 cm^{-1} assigned to valence vibrations of a carboxyl group C=O. A comparison of the IR spectra of the

Table 1. Properties of polymer products

No.	Starting substrate	Mass fraction of nitrogen, %	Amount of collagen in sample, %
1	Collagen	16.2 ± 1.6	100
2	PBA–collagen	11.8 ± 1.2	66.3 ± 7
3	PMMA–collagen	12.1 ± 1.2	68 ± 7

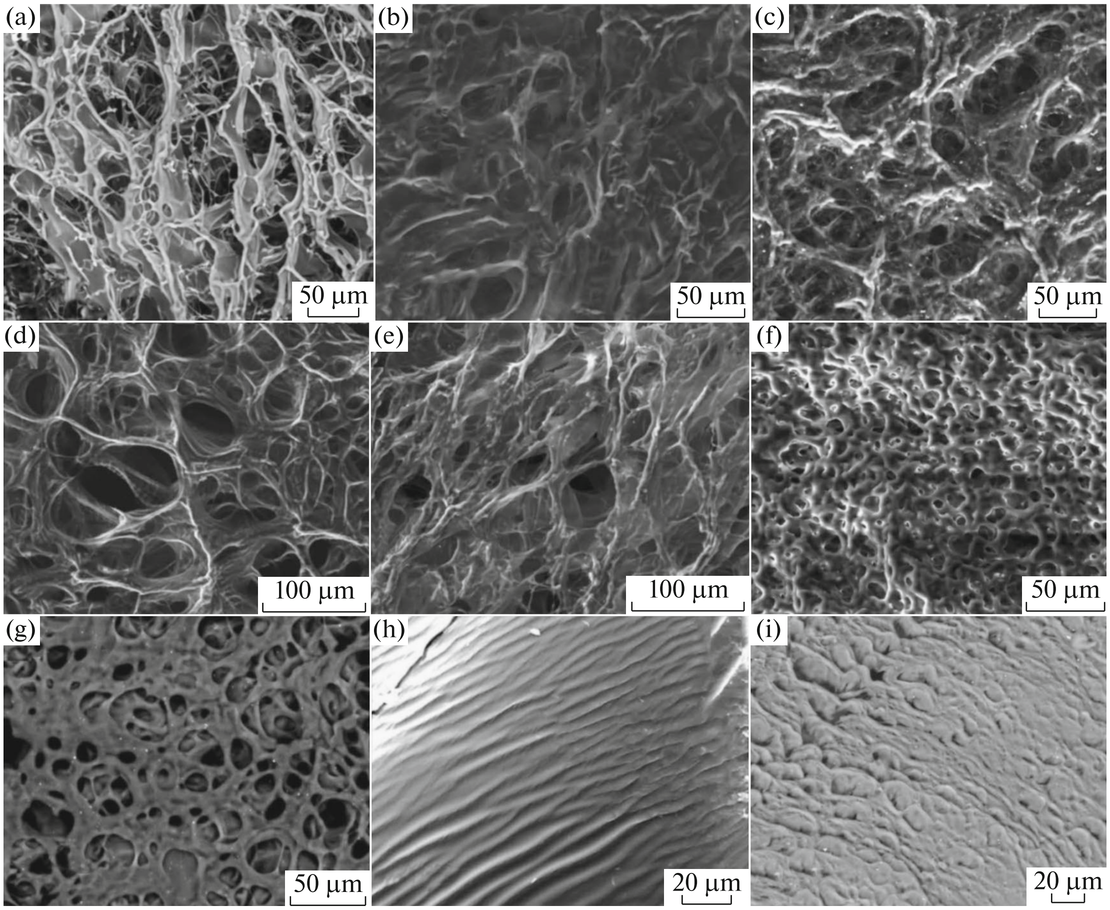


Fig. 2. SEM images of lyophilically samples: (a) initial cod collagen (CC), (b) graft copolymer of collagen with PMMA, (c) graft copolymer of collagen with PBA, (d) initial pectin, (e) graft copolymer of pectin with PMMA, (f) CCC-1, (g) CCC-2, (h) collagen films, and (i) films of graft copolymer of collagen with PMMA.

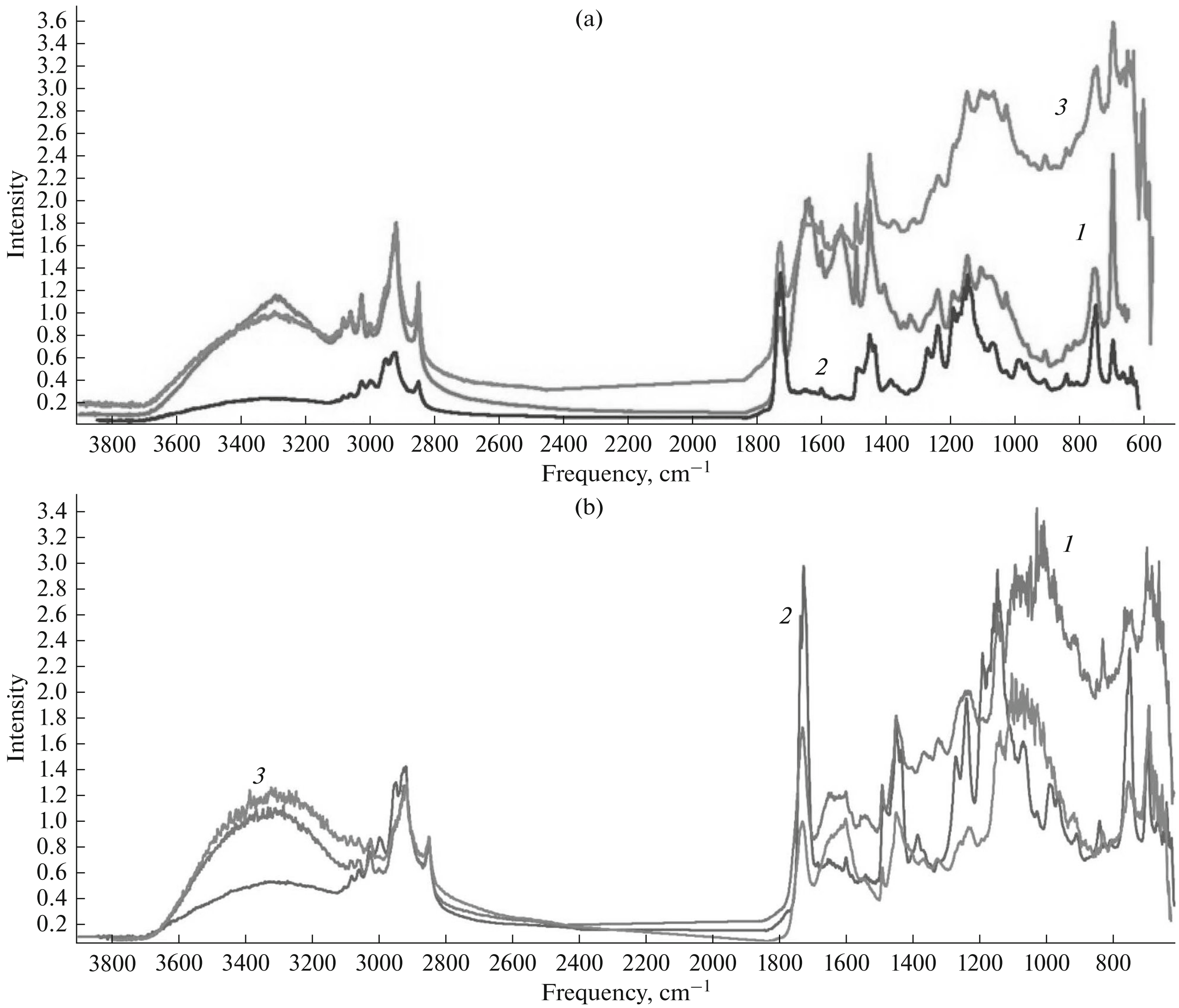


Fig. 3. IR spectra of (a) (*1*) collagen, (*2*) PMMA–collagen graft copolymer, (*3*) PMMA obtained using azoisobutyric acid dinitrile as initiator; (b) (*1*) pectin, (*2*) PMMA obtained using azoisobutyric acid dinitrile as initiator, (*3*) PMMA–pectin graft copolymer.

PMMA–collagen and PBA–collagen grafted copolymers with those of collagen and polyalkyl methacrylates indicates that the grafted copolymers exhibit all the bands characteristic of collagen and synthetic polymers. Figure 3a shows such comparative data (collagen and its copolymer grafted with PMMA as an example). Similarly, the IR spectrum of the PMMA–pectin graft copolymer (Fig. 3b) shows a characteristic absorption band at 1720–1730 cm^{-1} assigned to valence vibrations of a carboxyl group C=O. This also confirms the structure of PMMA observed there.

The grafting of synthetic fragments of PMMA and PBA onto natural polymeric macromolecules (collagen and pectin), therefore, leads to the formation of branched natural macromolecules and cross links between them. At the same time, it should be noted that the cross linking formed between the natural polymer macromolecules, which distinguishes the copolymer from starting substrate, does not lead to the coagulation of the copolymer. The results presented in this chapter indicate that AMA copolymers grafted on natural polymers can only be considered as a basis to obtain three-dimensional structures, the constituent components of gels.

3. MODIFICATION OF GRAFT COPOLYMERS UNDER SYNTHESIS CONDITIONS

The formation of gels via introduction of additional components with certain properties is the most common method. The most widespread modifier of the properties of protein substrates in medical and pharmaceutical practice is a polyethylene glycol (PEG) [52, 53]. The US Food and Drug Administration

(FDA) approved PEG as a substance for use in medicine (production of drugs), food, cosmetology, and as an E1521 food additive in the EU countries and in the Russian Federation [54]. The modification with PEG (pegylation) changes the properties of a peptide substrate primarily due to hydrogen bonds of hydrogen atoms of a PEG main chain, which significantly increases its hydrodynamic radius. Considering low natural chemical and mechanical stabilities of collagen (gelatin), it is "cross linked" with various chemical agents to improve these characteristics or its strength, firmness, and elasticity are increased by physical impact. A change in properties of a PMMA copolymer grafted on collagen was studied under photocatalysis in the presence of a $RbTe_{1.5}W_{0.5}O_6$ complex oxide during the modification of a composition of a initial reaction mixture and during the isolation stage through the introduction of known modification additives. The following techniques were used.

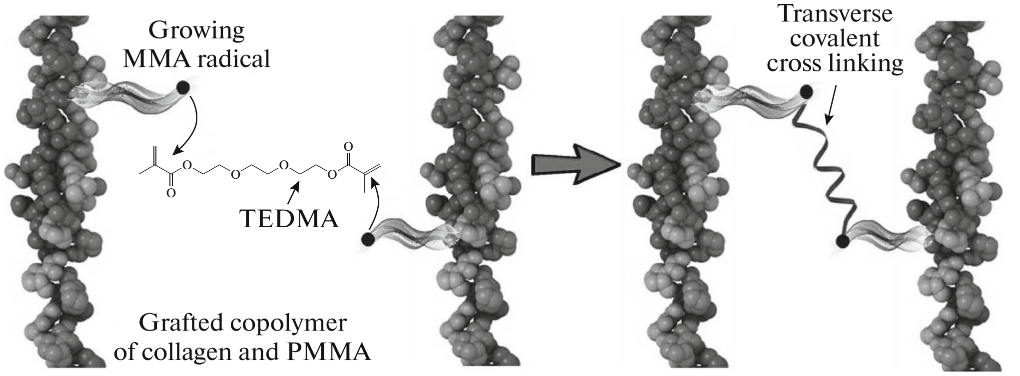
(1) A modifier of properties of protein substrates (PEG) was introduced into starting reaction mixture, and its influence on the composition and properties of a resulting composite was monitored in comparison with a PMMA–collagen copolymer.

(2) The composition of a starting reaction mixture was supplemented with a cross-linking agent for acrylate compositions (triethylene glycol dimethacrylate (TEDMA) and acrylic acid (AA)) to form an ionic "cross link" besides the natural one for proteins in the composite after neutralization of a final product. Their influence on the composition and properties of the resulting composite was assessed in comparison with a PMMA–collagen copolymer.

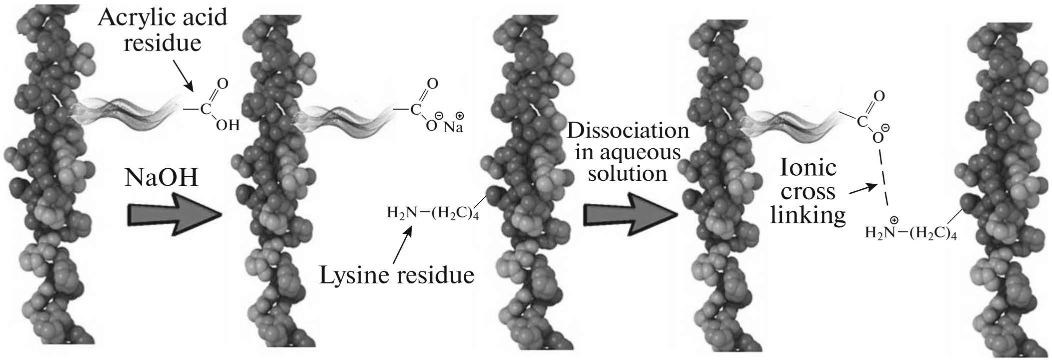
(3) The solution of a final product was neutralized to obtain a coagulate in the mixture.

The changes in structure and properties of PMMA–collagen grafted copolymers due to the action of modification additives were controlled by physicochemical properties.

Cross-linking agents for acrylate fragments (TEDMA and acrylic acid) were added to a starting reaction mixture to obtain cross links between collagen fibers. Cross links are formed in accordance with the introduced additives: TEDMA forms a transverse fragment (Scheme 1), and an additional ionic "cross link" in the composite containing acrylic acid fragments is formed after neutralization of the aqueous dispersion of the final product (Scheme 2) [49].



Scheme 1.



Scheme 2.

The aqueous phase is a stable homogeneous solution of a white polymer product color after synthesis with a ratio of CC : acrylic monomers : TEDMA = 1 : 2 : 0.007 (CCC-1) and a twofold increase of collagen in starting reaction mixture in comparison with CCC-1 (CCC-2). It remains in this state after neutralization with sodium hydroxide (Fig. 4a) [49]. An amount of nitrogen in the CCC-1 and CCC-2 samples is comparable to that in the PMMA–collagen graft copolymer (Fig. 4c). The comparison of SEM images

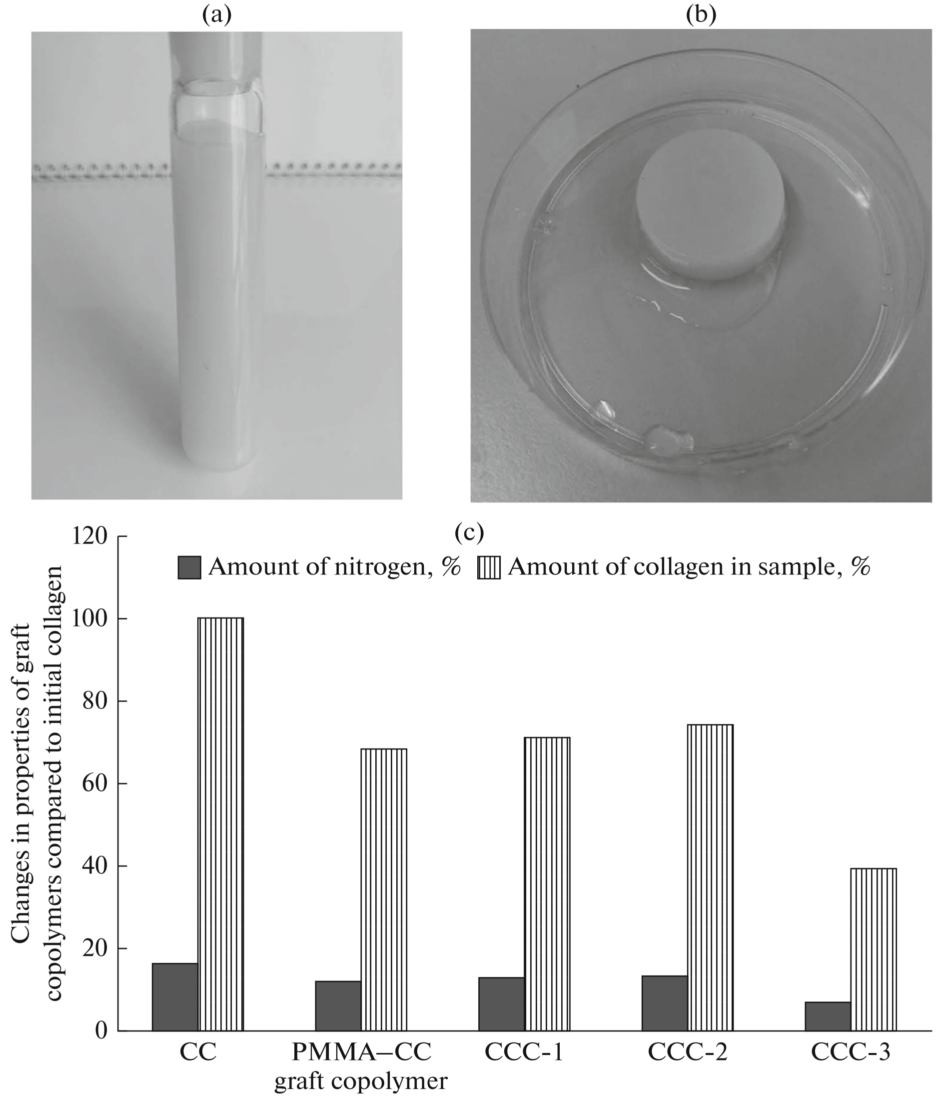


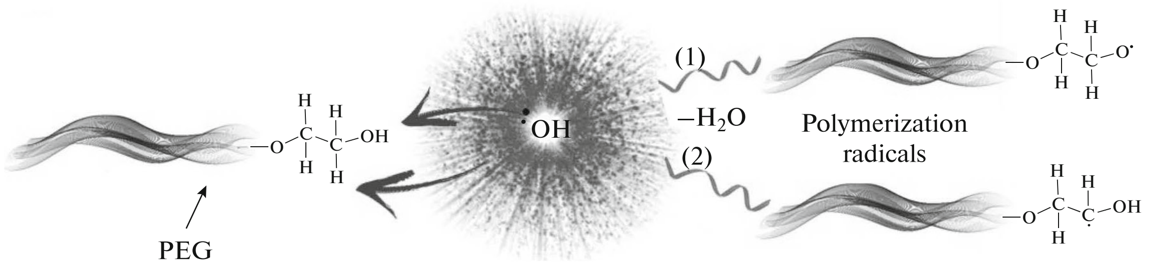
Fig. 4. Images: (a) CCC-1 solution and (b) CCC-3 gel. (c) Amount of nitrogen and collagen in samples according to elemental analysis data.

(Fig. 3) of the CC, CCC-1, and CCC-2 samples (Figs. 3a, 3f, 3g) indicates that a matrix with a fine cellular structure was formed in the sample due to additional cross linking. It is clearly visible that the collagen fibers are compacted with a grafted synthetic fragment [49].

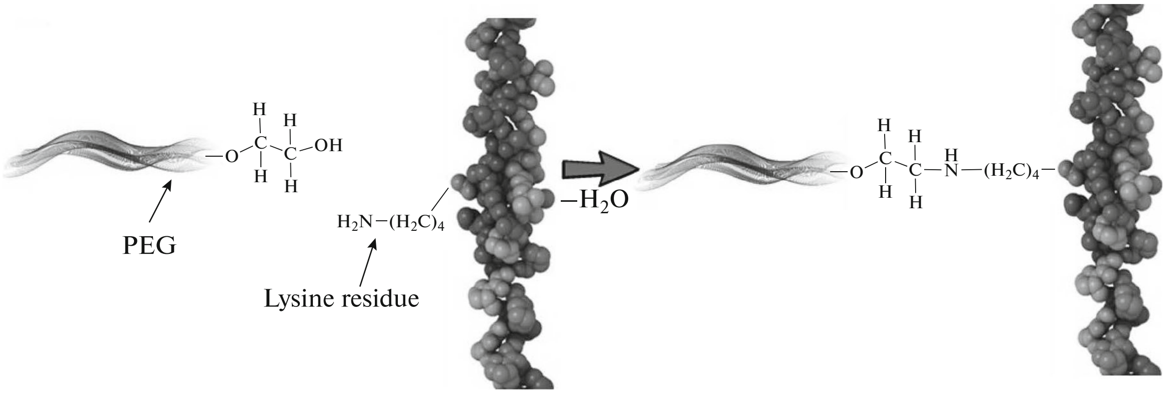
It was impossible to assess the molecular weight parameters of the resulting CCC-1 and CCC-2 copolymers: they remained on a filter with a pore size of 0.45 μm after preparation of the polymer solution for GPC analysis. The starting CCC-1 not incorporated into the matrix (its proportion in the solution after filtration was ~98%) and low-molecular-weight collagen with a molecular weight (MW) ~10 and ~20 kDa remained in the filtered aqueous phase.

When the composition of the starting reaction mixture was supplemented with a PEG modifier (CCC-3) in an amount that multiple of the collagen in the CCC-2 mixture, the aqueous phase after synthesis before adding sodium hydroxide solution was a stable homogeneous solution of the polymer white product without delamination as in previous cases. The coagulation of the polymer product, however, is observed after addition of alkali solution to pH ~7 to form a gel (Fig. 4b). The resulting gel easily releases water during drying in vacuum and forms a film of a polymer composite. Such a fibrillar gel is in demand as a base in the medical, pharmaceutical, and food industries.

When PEG is added to the composition, the gelation is due to additional radical processes with its participation. First, this is due to its interaction during the synthesis process with a hydroxyl radical, as in the case of collagen, owing to the elimination of a hydrogen atom from hydroxyl group of PEG (Scheme 3 (1)) or from a hydrogen atom of a hydrocarbon part of a PEG molecule (Scheme 3 (2)) to form radicals in the PEG macromolecule. These new radicals formed on the PEG surface are active in all radical transformations in the reaction mixture. They interact with the monomer and form a grafted synthetic fragment or participate in the chain transfer reaction or disproportionate with another active radical. In other words, they form additional covalent bonds in the material. Second, as noted earlier [55], PEG forms the covalent bonds with fragments of lysine and arginine amino acids (Scheme 4).



Scheme 3.



Scheme 4.

The prospect of using the structured collagen materials in various fields is, as already noted, due to their biocompatibility and biodegradability. The biodegradability plays an important role for various reasons. It is important from environmental point of view that any materials of this type will be destroyed under the action of biological substrates in nature: enzymes, bacteria, etc. When they are used in scaffold technologies, the destruction of a scaffold under the action of body enzymes is important during their operation. Collagen is destroyed much more rapidly: within a few minutes, to low molecular weight and oligomeric macromolecules [56–58]. It was important to find whether fragments of synthetic polymers decrease the rate of enzymatic hydrolysis in this regard.

Enzymatic hydrolysis was studied in the presence of proteolytic enzymes for PMMA copolymer samples grafted onto collagen [46]. PMMA–collagen was hydrolyzed with pancreatin in neutral medium, monitoring the change in molecular mass characteristics of the protein for 3 days. The data obtained allow one to conclude that synthetic fragments grafted onto a collagen macromolecule do not prevent the hydrolysis of peptide macromolecules, but change the destruction rate of polymers: the destruction proceeds much more slowly (Fig. 5). The hydrolysis proceeds much more slowly in the case of grafted copolymers in comparison with collagen, which decomposes much rapidly and predominantly to peptides with a molecular weight of ~10 kDa (Figs. 5a, 5b). In addition, the ratio of fractions with MWs of ~10 and 20 kDa differ significantly less, and they are changed symbatically (Figs. 5c, 5d). An amount of the polymer with MW of more than 20 kDa is ~70% an hour after the start of the process. Monitoring the process of enzymatic hydrolysis for three days indicates a gradual decrease in an amount of the polymer with MW of more than 20 kDa to almost zero values and a decrease in MW to 20 and 10 kDa.

The time of enzymatic hydrolysis of material can be obviously varied when initial collagen graft copolymer is modified through the introduction of modification additives. This allows one to consider the obtained materials to be promising for medical sealants for closing wound and burn surfaces and for disposable absorbent products, as well as for creating scaffolds in tissue engineering.

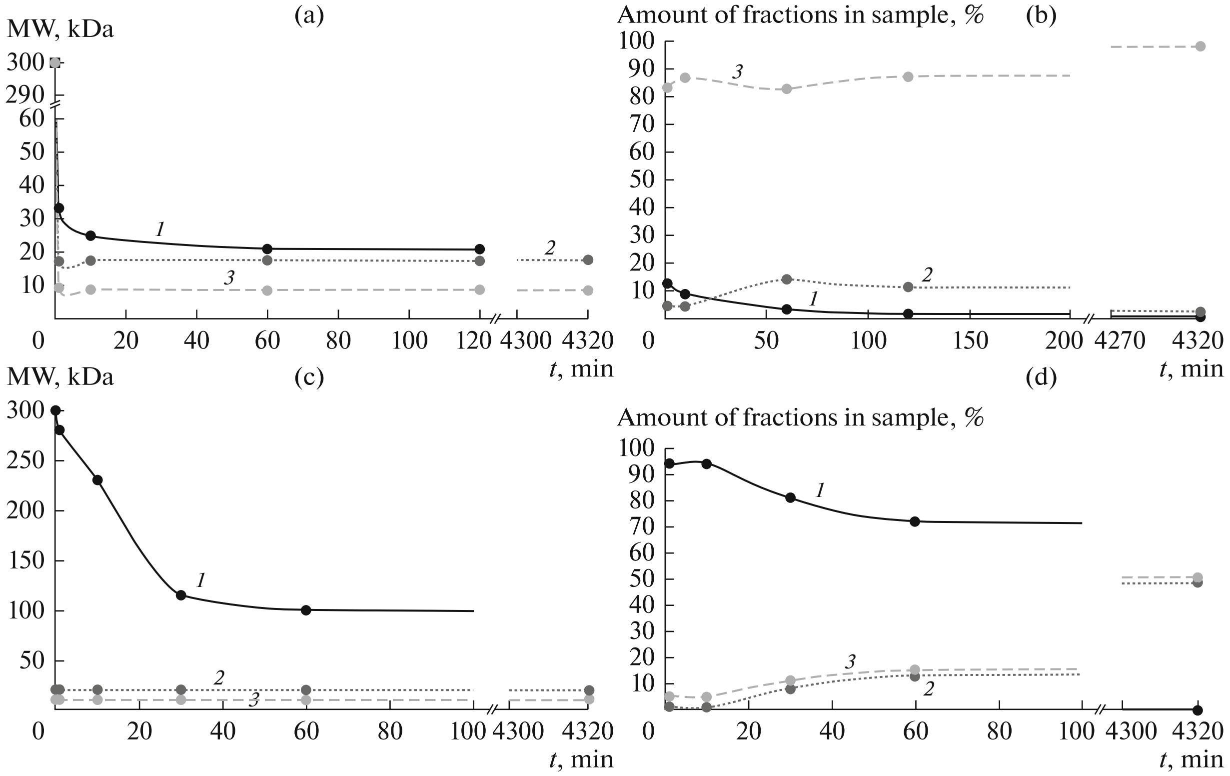


Fig. 5. Change in molecular weight and amount of various fractions during hydrolysis with pancreatin: (a, b) initial collagen and (c, d) PMMA–collagen graft copolymer.

CONCLUSIONS

A series of studies to modify fish collagen and pectin to obtain branched and three-dimensional structures via radical graft copolymerization under photocatalysis in the presence of a $RbTe_{1.5}W_{0.5}O_6$ complex oxide with a pyrochlore structure showed the possibility of grafting synthetic fragments onto natural polymers under mild conditions and irradiation with visible light. The variation of the composition and the introduction of known modification additives into the starting reaction mixture in the case of collagen as a initial material made it possible to obtain a fibrillar gel. Such a material is as a base in demand in the medical industry and can be widely used to obtain various forms—films, wound coverings, and components—in scaffold technologies, and in targeted drug delivery.

Extensive future studies will be required to fully characterize fibrillar gels to gain a thorough understanding of their potential in practical applications. Their physical, mechanical, and thermodynamic properties, as well as the study of their biocompatibility with human tissues, are important.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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