PHOTOPOLYMERIZABLE MATERIALS FOR BIOCOMPATIBLE IMPLANTABLE MATRICES

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The review considers photopolymerizable compositions based on biocompatible polymers for regenerative medicine. Assessment of the physical-mechanical and biological properties of photopolymerizable polymeric matrices, polyethyleneglycol, lactic acid, collagen, and hyaluronic acid, as well as of the effectiveness and toxicity of various photoinitiator supplements has been performed. Mechanical properties and degradation rate of the photopolymerizable matrices are ensured by selection of proportions of methacrylated mono-, oligo-, and polymers these consist of, while their toxicity largely depends on the photoinitiator systems used. It has been concluded that it is necessary to search for and develop the methods to obtain photopolymerizable polymeric matrices by using the compounds capable of initiating radical polymerization with lower toxic effect.

Keywords: biocompatible polymers, photoinitiators, matrices

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ФОТОПОЛИМЕРИЗУЕМЫЕ МАТЕРИАЛЫ ДЛЯ БИОСОВМЕСТИМЫХ ИМПЛАНТИРУЕМЫХ МАТРИКСОВ

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В обзоре рассмотрены фотополимеризуемые композиции на основе биосовместимых полимеров для регенеративной медицины. Проведена оценка физико-механических и биологических свойств фотополимеризуемых полимерных матриксов полиэтиленгликоля, молочной кислоты, коллагена и гиалуроновой кислоты, а также эффективности и токсичности различных фотоинициирующих добавок. Механические свойства и скорость деградации фотополимеризуемых матриксов обеспечиваются подбором пропорций метакрилированных моно-, олиго- и полимеров в его составе, тогда как их токсичность в большей степени зависит от используемых фотоинициирующих систем. Сделан вывод о необходимости поиска и развития способов получения фотополимеризуемых полимерных матриксов с применением соединений способных инициировать радикальную полимеризацию при меньшем токсическом эффекте.

Ключевые слова: биосовместимые полимеры, фотоинициаторы, матриксы

Вклад авторов: И. С. Рудик — сбор, анализ, систематизация литературных данных, планирование и написание обзора; А. В. Миронов — сбор литературных данных, редактирование, написание заключения; В. С. Кузнецова — рецензирование; А. В. Васильев — планирование, структурирование обзора, рецензирование.

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The set of unique properties, specifically moisture resistance and resistance to biological media, fast transition between liquid and solid states, the possibility of adjusting physical and mechanical properties without altering chemical composition allow biocompatible photopolymerizable compositions to become popular materials not only in dentistry and orthopedics, but also in regenerative medicine and tissue engineering [1]. Thus, with development of additive manufacturing, biocompatible photopolymerizable compositions have become widely used as the stereolithography materials when manufacturing implantable devices [2, 3]. According to the Google Scholar statistics, more than 10,000 research papers focused on photopolymerizable polymer matrices for biomedical applications have been published since 2020, and the number of such paper increases by an average of 15% every year (Fig. 1).

Despite the large number of new studies, modification of polymers with acrylate groups is still the main method to produce biocompatible photocurable materials. Today, the number of photopolymerizable systems suitable for biomedical applications is limited, since ions or radicals formed when photopolymerization is initiated make a considerable number of such materials toxic [4, 5]. Furthermore, the living tissues can be exposed to toxic effects of the components that have not fully reacted during the polymerization process [6, 7].

In terms of effects on the living tissues, radical transfer and intermolecular crosslinking at the functional acrylate groups represent the most secure photopolymerization method. Furthermore, it is important to select appropriate initiator or initiator–co-initiator pair, the main requirement for which is low toxicity in both inactive and radical form. Currently, no more than 10 various biocompatible photoinitiators are used in practice, among which camphorquinone (CQ) and diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO) are the most common [8].

The review was aimed to systematize the literature data describing the types of photopolymerizable materials and certain components of such materials for biomedical applications. Keyword search in the PubMed, Google Scholar,

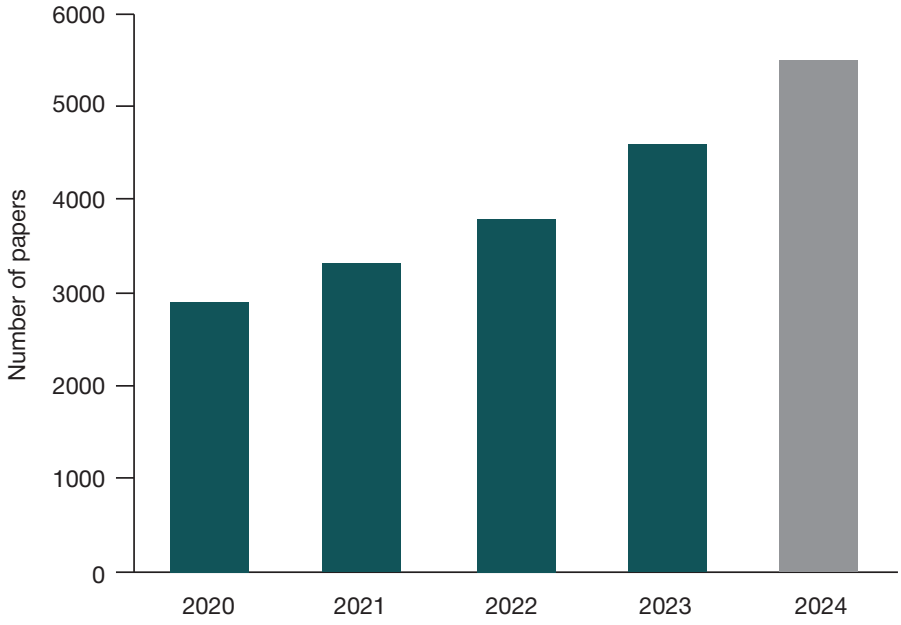


Fig. 1. Number of papers focused on photopolymerizable compositions in biomedical research published between 2020 and 2024 according to Google Scholar

and Elibrary databases was performed. The number of studies published in 2020–2024 was assessed based on the following requests: photopolymerization, photocurable biomaterials, photo-crosslinkable hydrogels, tissue engineering, degradable biomaterials, 3D-printing, photoinitiator.

PHOTOCURABLE MATERIALS FOR PRODUCTION OF MATRICES

Polymer matrices are produced by crosslinking of modified oligomeric or polymeric chains containing two or more active groups. Each active group can be chemically integrated either in the growing polymer chain, or in the crosslink between two chains due to radical formation. Transfer of radicals from initiators to the polymerized compound results in macroradical formation. Further attachment of the parent substance molecules to the growing macroradical ensures molecular weight increase, while interaction of two macroradicals results in the polymerization reaction termination (Fig. 2) [9]. The presence of competing mechanisms makes it possible to control supramolecular structure and molecular weight of the compound produced, which, in turn, helps control its physical and mechanical properties [10].

The use of photocurable materials as polymer matrices is of great interest in terms of solving the problems of biomedical materials science due to their capability of crosslinking at physiological temperatures in the absence of aggressive chemicals and good biocompatibility [3].

Photocurable polymer systems can be conditionally divided into synthetic and natural (biopolymers) based on their components. Among synthetic systems, polymer matrices based on polyethylene glycol, polylactide and their derivatives are actively studied, while the actively studied natural polymers are collagen and hyaluronic acid.

Polyethylene glycol

Polyethylene glycol is a water-soluble, biocompatible ether that is widely used in tissue engineering and for drug delivery [11]. Polyethylene glycol-acetal-dimethylacrylate was used to produce biodegradable polymers potentially applicable for bone tissue regeneration. Nanoparticles made of calcium carbonate possessing enough reactivity for conversion to hydroxyapatite were used as an additive [12]. The resulting matrices were implanted in the subcutaneous pockets of mice for 15 and 30 days. Histological examination showed comparable moderate tissue response involving primarily macrophages, which showed biocompatibility of the photocurable polymer system. To solve the problem of infections following prosthetics, a specific technology of covering implants with a photocurable polymer based on polyethylene glycol and polyallyl-mercaptan was developed [13]. The technology demonstrates the possibility of mixing various antibiotics with the photopolymer solutions ensuring the necessary antimicrobial compatibility.

Polyester-based polymers

Such polymers are widely used in medicine as surgical threads, orthopedic implants, as well as for production of personalized scaffolds in tissue engineering. The personalized tissue scaffolds, 3D printed of the polycaprolactone-polyurethane photopolymers, are characterized by high cytocompatibility and survival rate of murine fibroblasts (above 85%), as well as by rapid biodegradation (2–6 h) [14]. Of interest is the example of producing the polylactide and polyethylene glycol-based polymer matrices for cartilage tissue restoration. Thus, the poly-D,L-lactic acid–poly(ethylene glycol)–poly-D,L-lactic acid co-polymer was developed [15]. The chondrocyte culture-based *in vivo* tests showed that the composition showed the capability

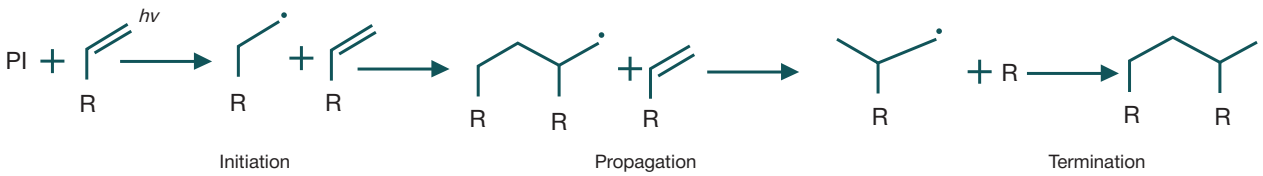


Fig. 2. Free radical polymerization reaction mechanism

Table 1. Photocurable polymer matrix composition and production conditions

Composition	Photoinitiator	Photocuring conditions	Area of application	Literature
Methacrylated polyethylene glycol-acetal	Lithium phenyl(2,4,6-trimethylbenzoyl) phosphinate (LAP) 0.1% w/v	UV radiation 365 nm 30 s	Connective and soft tissue regeneration	[11]
Methacrylated polyethylene glycol-acetal	2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone 0.2% w/v	UV radiation 365 nm 15 min	Injectable bone substitutes	[12]
Acrylated derivatives of polyethylene glycol and polyallyl mercaptan	2,2-dimethoxy-2-phenylacetophenone	UV radiation 365 nm 20 mW/cm^2 5 min	Antimicrobial coating for implants	[13]
Acrylated polycaprolactone Polyethylene glycol diacrylate	TPO 3% w/v	LED light 405 nm 30 s	3D printing for personalized tissue engineering	[14]
Acrylated derivatives of poly-D,L-lactic acid and polyethylene glycol	LAP	UV radiation 395 nm	Implant fixation	[15]
Methacrylated type I collagen Genipin	VA-086 1% w/v	UV radiation 365 nm 17 mW/cm^2 1 min	3D printing of tissue scaffolds	[17]
Methacrylated type I collagen	LAP	UV radiation 365 nm 5 mW/cm^2 30 min	Circulatory system repair	[18]
Chitosan-azide Keratin	–	UV radiation 365 nm 100 mW/cm^2 15 min	Connective and soft tissue regeneration	[20]
Methacrylated chitosan Oxidized hyaluronic acid	LAP 0.1% w/v	UV radiation 405 nm 10 mW/cm^2 120 s	Drug delivery	[21]
Methacrylated chitosan Methacrylated gelatin Polyethylene glycol diacrylate	2-hydroxy-2-methylpropiophenone 0.5% w/v	UV radiation 320 nm 180 mW/cm^2 120 s	Drug delivery	[22]
Methacrylated hyaluronic acid Methacrylated gelatin	LAP 0.1% w/v	UV radiation 405 nm 25 mW/cm^2 60 s	Tissue engineering	[23]
Oxolated hyaluronic acid Polyethylene glycol dimaleimide	LAP	UV radiation 365 nm 30 mW/cm^2	Injectable cartilage substitutes	[24]
Hyaluronic acid Methacrylated chitosan	LAP 0.01–0.05% w/v	UV radiation 385 nm 19 mW/cm^2	Extracellular matrix for tissue regeneration or drug delivery	[25]

of forming high-strength bonds with the host cartilage tissue under conditions of photopolymerization without affecting cell viability and tissue phenotype.

Collagen

This is one of the basic biopolymers used in tissue engineering and regenerative medicine, since it accounts for about 33% of all body's proteins and forms the skin, tendons, cartilage and bone tissues, blood vessel walls [16]. Low mechanical resistance represents one collagen's disadvantage, however, polymer constructs with improved properties can be produced due to dual crosslinking. The study results have shown that dual crosslinking positively affects the elastic modulus and degradation degree, increasing them 2-fold relative to the non-crosslinked hydrogels [17]. The methacrylamide-modified collagen hydrogel developed for vascular tissue engineering compared to modified gelatin was characterized by high degree of polymerization (83–88% vs. 74–84%), adjustable mechanical properties (elastic modulus 4.8–9.4 kPa vs. 3.9–8.4 kPa), and higher cytocompatibility [18].

Chitosan

Chitosan is a linear aminopolysaccharide consisting of glicosamine elements with free amino groups ensuring high reactivity and solubility. It differs from other biopolymers with good cell adhesion [19]. The process of chitosan chemical modification by the photopolymerizable 4-azidobenzoic acid groups is described in detail [20]. The study was aimed to produce a photocurable polymer membrane based on chitosan-azide and keratin. It is noteworthy that photopolymerization of the keratin-chitosan membranes occurred without adding a photoinitiator. The results of in vitro tests have shown that the keratin concentration increase positively affects the cell survival rate and adhesion. In the similar study, methacrylic anhydride-modified chitosan was used to produce a novel photopolymerizable composition characterized by rapid polymerization and high injectability [21]. It was reported that survival rate of mesenchymal stem cells exceeded 92%. The method to produce the chitosan and gelatin-based photopolymerizable hydrogel containing the albumin particles was reported [22]. Incubation tests in the model physiological

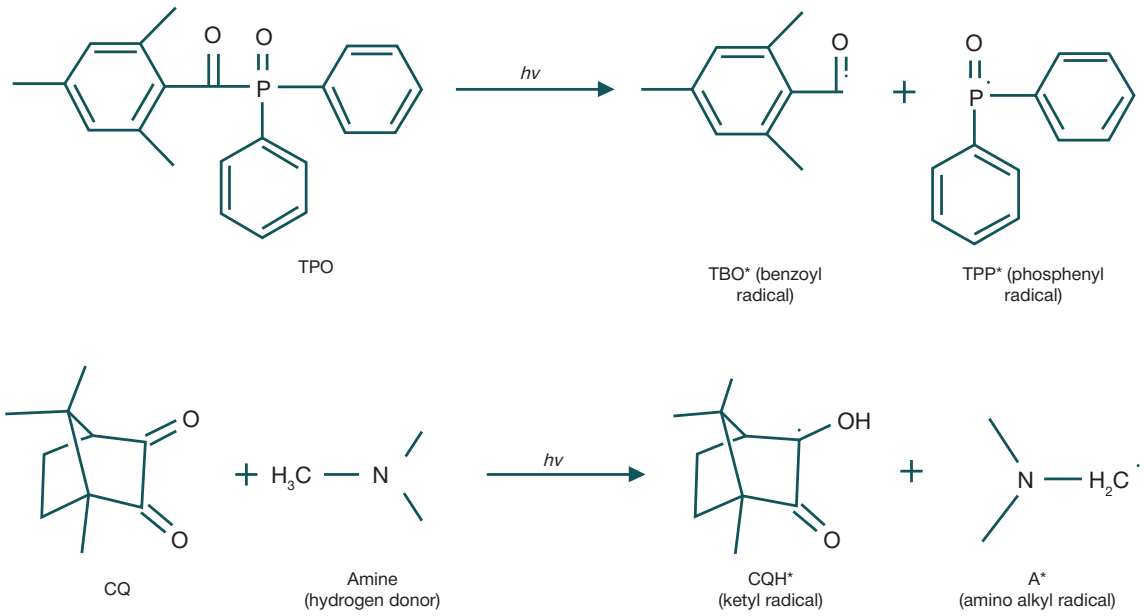


Fig. 3. Free radical production by type I and II photoinitiators under exposure of radiation on the example of TPO and CQ

fluids showed stability and no degradation of hydrogel. The murine fibroblast viability was 92.73%.

Hyaluronic acid

This natural polysaccharide contained primarily in the animal tissue extracellular matrix is highly hydrophilic and biodegradable [23]. The possibility of producing photocurable matrices based on hyaluronic acid and polyethylene glycol through dual crosslinking has been reported [24]. The cell survival rate and strength characteristics of the resulting polymer suggested the prospects of its use for the connective tissue repair. The combination of chitosan and hyaluronic acid is of special interest. Polymerization degree and rate, mechanical and rheological properties of the photo-crosslinkable polymers based on methacrylated chitosan and hyaluronic acid depending on their ratio were studied [25]. When the photoinitiator content was 0.04% w/v, the polymerization degree exceeded 90% within 3 s. All the polymer compositions were completely degraded within the first 20–24 days in hydrolytic environment and 5–10 days in enzymatic environment, which makes the use of such compositions for prolonged drug delivery or tissue engineering promising. The decrease in cell viability with increasing concentrations of photoinitiator and hyaluronic acid in the original mixture were demonstrated in the embryonic fibroblast culture. The cell survival rate reported for all the studied compositions was within the range of 85–96%.

The photocurable polymer matrix composition and production conditions are provided in Table 1.

The data provided suggest that synthesis of the biocompatible polymer methacrylated derivatives represents the main approach to production of biomedical photopolymerizable compositions.

PHOTOINITIATORS

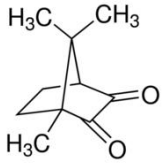
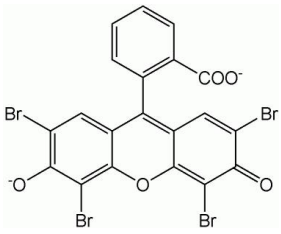
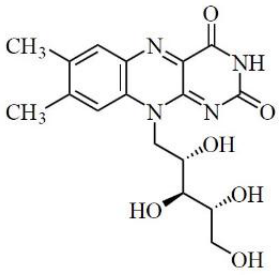
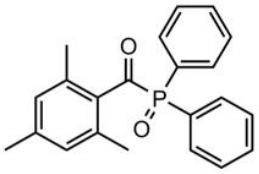
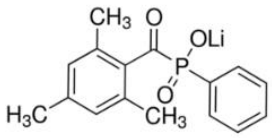
Photoinitiators are essential to initiate the free radical polymerization reaction. These are divided into two types. Type I photoinitiators undergo their own breakdown yielding free radicals after the light excitation. Type II photoinitiators produce radicals through hydrogen atom abstraction or electron/proton transfer from the co-initiator (Fig. 3) [26].

Camphorquinone is one of the first and still most commonly used photoinitiators. It belongs to the group of type II photoinitiators being less toxic compared to type I. However, the CQ lower chemical activity demands involvement of the tertiary amine as a photopolymerization reaction co-initiator. Polymerization rate is the main factor limiting the use of camphorquinone [7]. Special additives, representing the pyrrole derivatives that competitively absorb the initiating radiation, thereby preventing undesired formation of the initiator active form, have been proposed in order to increase resistance of the camphorquinone-based photocurable materials to sunlight [27]. Special attention is also paid to the camphorquinone toxicity. By the example of fibroblast lines it has been shown that the camphorquinone concentration increase from 50 mg/L to 100 mg/L in the photoinitiator system results in the cell viability decrease from 80% to 60% [28]. It has been proposed to use the compounds increasing the content of active groups (tetramethacrylate and tetraacrylate monomers) as co-initiators in photopolymerizable materials in order to ensure effective polymerization at the biologically acceptable camphorquinone concentrations [29].

Camphorquinone is poorly soluble in water, which considerably limits its use. In a number of studies, riboflavin and eosin were suggested as alternative water-soluble photoinitiators ensuring comparable photo-crosslinking characteristics. Eosin is non-toxic, cell viability exceeds 96% even when its concentration in the photopolymerizable material is 69 mg/L, and the survival rate exceeded 90% at the riboflavin concentration of 188 mg/L [30–32].

Type I photoinitiators include the aromatic ketone compounds, along with the phosphine and phosphine oxide derivatives (Table 2). TPO is one of the best studied and most commonly used in practice photoinitiators. The study focused on comparing the efficacy of type I and II photoinitiators showed that the monomer polymerization degree observed when using TPO was 13% higher, than that observed when using the camphorquinone–amine system. Furthermore, the radiation dose necessary for polymerization of the composition with CQ 4-fold exceeded the dose necessary for the same composition with TPO [33]. However, according to the TPO cytotoxicity assessment results, viability of various cell lines did not exceed 75% at the photoinitiator concentration of

Table 2. Photoinitiator efficacy and toxicity

Photoinitiator name	Type	Structural formula	Polymerization efficiency*	Cell viability*	Literature
Camphorquinone	II		★★★☆☆	★★★☆☆	[7, 28]
Eosin Y	II		★★★★½	★★★★★	[30]
Riboflavin	II		★★★★☆	★★★★☆	[31, 32]
TPO	I		★★★★☆	★★★½☆	[26, 33]
LAP	I		★★★★☆	★★★★★	[34, 35]

Note: * ★★★ — no more than 70%; ★★★★ — 70%–90%; ★★★★★ — more than 90%.

17.4 mg/L [26]. Significantly lower toxicity was demonstrated by the water-soluble lithium ion-modified LAP photoinitiator: the murine renal collecting duct cell viability was 95%. Thus, despite the fact that lithium is nephrotoxic, the lithium ions have not been identified as an important cytotoxic component [34].

The literature data analysis suggests that photoinitiators have a significant impact on cytotoxicity of the material produced. That is why photoinitiator selection becomes one of the defining challenges when designing the photopolymerizable composition. In terms of biocompatibility, it is preferable to use type II photoinitiators. Assessment of the efficacy and toxicity of the discussed photoinitiators is provided in Table 2.

CONCLUSION

The growing body of research on photopolymerizable compositions that are promising for tissue engineering suggests the increased need for such materials. The approaches to production of novel photopolymerizable materials are conservative, and there is still a trend towards predominant use of the method to produce such materials by methacrylation of various biocompatible oligo- and polymers. Thus, the main areas of material development are selecting and combining the proportions of methacrylated mono-, oligo- and polymers aimed to obtain the required physical and mechanical properties of the material with preserved biocompatibility.

In recent years, water-insoluble camphorquinone and diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide showing considerable cytotoxicity are still most commonly used as photoinitiator additives for radical polymerization. Currently, the compounds retaining the ability to effectively initiate radical polymerization with the relatively lower toxic effects, such as endogenic photoinitiator riboflavin, synthetic photoinitiators eosin and lithium phenyl(2,4,6-trimethylbenzoyl)phosphinate, have been found and tested.

The vast majority of the studies of photopolymerizable compositions for biomedical applications reported in modern scientific papers are not complex; these describe a limited range of properties of the material produced and involve a small number of cell types (usually only one type). That is why the studies focused on the development, assessment of physical and mechanical properties, biological and clinical testing of such materials are relevant.

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