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Recent applications of polymer materials in biomedical sciences

L. H. Yoanidu[1*], Y. I. Uzunova[1], I. D. Stefanova[2]

Medical University-Plovdiv, Bulgaria, Faculty of Pharmacy

[1]Department of Chemistry and Biochemistry,

[2]Department of Medical Physics and Biophysics,

15A V. Aprilov Blvd., 4002 Plovdiv, Bulgaria

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There has been a rapid development of novel polymer materials in the last decade, due to their versatile nature and the vast array of fields where these materials are utilized. Stimuli-responsive polymers have found their application in the construction of novel drug delivery systems. Self-healing polymers are useful in the creation of implant materials. Combinations of natural and conductive polymers could be beneficial in tissue regeneration. The objective of this mini review is to outline the achievements in the last decade, regarding polymer materials used in innovative pharmaceuticals, as well as in tissue engineering.

Key words: *polymers, nanocarriers, hydrogels, scaffolds, implants*

INTRODUCTION

Polymer materials have been an object of interest in the biomedical field, since they allow the construction and modernization of many devices ranging from novel drug delivery systems to various implants. There is a wide variety of polymers, which allows for choosing optimal properties for the purpose of use. Natural and synthetic polymers have found their application in biomedicine, either used separately, or in combination as co-block polymers or hybrid polymers. Biopolymers presently used in different areas of biomedicine are primarily polysaccharides-chitosan and its derivatives, dextran, cellulose, hyaluronic acid (HA), pullulan, alginates due to their biocompatibility, low cytotoxicity and diverse chemical properties have become the basis for development of novel drug delivery systems (DDS) as well as biomaterials in tissue engineering and wound healing [1]. Polypeptides [2] and proteins-collagen [3, 4] and gelatin [5] are also applicable materials. Synthetic polymers and copolymers have found their application in the production of extracorporeal devices, joint implants, as well as a variety of pharmaceutical formulations. Frequently used polymers are poly(ethylene glycol) (PEG), poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(N-isopropylacryl amide) (PNIPAAm), derivatives of methacrylic acid, poly(vinylalcohol) (PVA), poly(N-vinylpyrrolidone) (PVP), poly(glycolic acid) (PGA), poly(lactic-co-glycolide) (PLGA) copolymers, poly(glycerol sebacate), polyhydroxyalkanoate [6]. The tendency in the development of novel polymeric materials is to incorporate both types in the construction of the material as well as to conjugate synthetic polymers with growth factors or adhesion molecules in order to ensure better biocompatibility [7]. This article aims to present some of the recent applications of polymer materials, focusing on the opportunities these materials provide for creating innovative pharmaceutical formulations for cancer treatment, tissue regeneration and implant materials.

PHARMACEUTICAL APPLICATIONS

The need for constant introduction of novel drug delivery systems stems from the challenges current therapies pose as well as the development of modern therapies for a number of diseases, among which cancer being one of the leading causes of death.

Polymeric nanoparticles, micelles and hydrogels are presently created to meet the needs of oncology treatment. Various stimuli are used as triggers, which could lead to targeted and controlled drug release. pH-sensitive drug delivery systems have been fashioned by using different types of polymers that could initially possess functional moieties which make them react to changes in the pH or suitable acid-sensitive linkers are employed in their preparation [8]. A recent study reports the preparation a chitosan based DDS, which incorporates an appropriate pH-sensitive

* To whom all correspondence should be sent.
E-mail: lubka84@abv.bg

adjuvant [9]. Due to that the doxorubicin (DOX) loaded chitosan-tripolyphosphate nanoparticles (NPs), undergo membranolytic changes in the acidic medium, typical for endosomes and lysosomes. In another study poly(aspartamide) grafted with L-Lysine and hydrazine was used as a biocompatible polymer matrix. DOX was incorporated via formation of hydrazone bonds that allow for an acid-triggered drug release, but would be stable under physiological pH [2]. In a similar fashion Zang *et al*. [10] used a chemical reaction which led to the formation of a Schiff base between DOX and the methoxy-poly(ethylene glycol)-aldehyde (mPEG) chain. Hydrophobic agent curcumin could be encapsulated in formed NPs. After successful internalization of the NPs, Schiff base would disintegrate and simultaneous delivery of both substances would be obtained.

Polymer materials responsive to changes in the levels of gluthatione aim at destabilization of the carrier in a reduced environment and release of the incorporated drug. This could be achieved by the introduction of disulfide bonds cleavable in the presence of reducing agents. Several studies reported the preparation of such systems. Tang *et al*. [11] proposed novel redox-responsive star-shaped micelles and utilized a PEG-PCL copolymer, with disulfide bonds as redox-sensitive linkers. This polymer presented several advantages compared to linear polymers such as enhanced stability, presence of a greater number of functional groups for further modification and better loading capacity. HA was used for the preparation of a polymer-drug conjugate, for the delivery of paclitaxel (PTX). Disulfide bond was introduced via modification of paclitaxel with 3,3'-dithiodipropionic acid. HA shows specific affinity towards CD44 bearing cells, a fact used to achieve targetability [12]. Human serum albumin (HSA) crosslinked with dithiobis(succinimidyl propionate) was utilized in NPs which served as a vehicle for photosensitizer Chlorin e6. Due to the inclusion of the thiol-cleavable bonds in the structure of the cross-linker the developed system disintegrated in the intracellular reducing environment. Redox-sensitive HSA-NPs produced optimal cytotoxicity in comparison to the free photosensitizer and to NPs that incorporated glutaraldehyde, a non-redox responsive crosslinker [13].

Natural and synthetic thermo-responsive polymers are applicable materials in targeted and controlled drug release [14]. Hu *et al*. [15] proposed a novel drug delivery system, based on a triblock copolymer consisting of a poly(L-lactide) central block and two poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide) lateral blocks. The obtained micelles displayed thermo-responsive phase transition and in temperatures higher than their lower critical solution temperature (LCST) the lateral blocks experienced dehydration. This led to a much higher drug release and improved drug accumulation in tumor mass, which displays temperatures above the LCST. Rejinold and co-workers [16] prepared thermo-responsive fibrinogen-graft-PNIPAAm nanogels. Fibrinogen could target overexpressed $\alpha_1\beta_5$ integrin receptors on the surface of breast cancer cells. Through a series of in vitro studies the authors demonstrated improved drug release in temperatures above the LCST as well as specific toxicity to MCF-7 cells.

Polymers that could react to changes in glucose levels are currently investigated for the preparation of insulin delivering systems. Yao *et al*. [17] synthesized thermo- and glucose-responsive polymeric micelles, by including PNIPAAm into the structure of monomethoxy poly(ethyleneglycol)-block-poly(phenylboronate ester) acrylate. Glucose responsiveness was achieved by incorporating phenylboronic acid (PBA) in the polymer. Micelles obtained by random polymerization displayed different insulin release in normal and pathological glucose concentrations, which was attributed to polymer architecture. A microgel based on glucosyloxyethyl acrylated chitosan (GEA-chitosan) and immobilized concanavalin-A was designed by another group. GEA-chitosan offers the possibility of increased insulin loading, while concanavalin-A provides response to changes in glucose concentration. The microgel displayed pulsatile insulin release, in response to changes in the glucose level and could be utilized as an insulin delivery system, glucose sensor or an actuator after further investigation and optimization of its properties [18].

TISSUE ENGINEERING

Polymeric materials have found extensive application in the construction of scaffolds for the purposes of tissue engineering. Polymeric scaffolds are meant to ensure cell adhesion and proliferation, and should be fashioned in a way that fulfills requirements such as biocompatibility, biodegradability, suitable mechanical properties, porosity, and supply of oxygen and nutrients to the cells [19]. Electrical stimulation could be beneficial for neural and muscle tissue regeneration. A recent review names more than twenty five conductive polymers and emphasizes on their versatility and the possibilities for utilizing these polymers in a variety of devices in the biomedical field. Polypyrrole, polythiophene derivatives, polyaniline are commonly used conductive polymers, but due to constant development and modification of these

polymers novel and improved electro conductive materials are now emerging such as polypyrrole-thiophene oligomers, poly(3,4-alkylenedioxypyrrole), PLA and aniline pentamer copolymer etc [20]. Conductive polymers do not possess suitable mechanical or chemical properties to be used as biomaterials by themselves. Combinations of different polymers, as well as inclusion of inorganic materials in the matrices, allow for tailoring of the properties of biomaterials in accordance with the specific tissue requirements.

In a recent study a composite scaffold was produced by incorporating bioglass nanoparticles and collagen in a chitosan hydrogel, for the purposes of bone tissue repair. To overcome the low mechanical strength of collagen it was incorporated in a thermoresponsive modified chitosan matrix. This provided optimal mechanical properties as well as suitable porosity of the material, as well as an opportunity of in situ gelation, after injecting the composite [3]. Polymeric scaffolds for bone and cartilage repair were successfully synthesized by combining HA with dextran and hydroxyethyl methacrylate [21]. Collagen type 1 is reported as a suitable polymer for obtaining scaffolds in cases of neural damage serving as a medium which could improve the proliferation and differentiation of neural stem cells, and thus offer potential treatment in spinal cord injury [4]. Collagen combined with chitosan was used as a supporting structure for bone marrow mesenchymal stem cells, and the co-transplantation was shown to be favorable in terms of cell viability and retention of cells in treated areas [22]. A polypyrrole/ poly(D,L-lactic acid) conduit exerted a positive effect on the axon regeneration and myelination compared to those in poly(D,L-lactic acid) conduits, which demonstrates the beneficial effect of including a conductive polymer [23]. PLGA–poly(3-hexylthiophene) axially aligned nanofibers displayed improved conductivity compared to random ones and had a positive influence on the adhesion and proliferation of Scwann cells, indicating the potentials as scaffold for neural tissue engineering [24]. Natural polymers are suitable materials in treating damages to cardiac tissue. Chitosan/fibrin, chitosan/alginate/collagen scaffolds were investigated as patch materials, but lacked tensile strength. Pok *et al*. prepared a scaffold of chitosan and gelatin and synthetic polymer PCL which combines the soft gel structure and biodegradability of natural polymers and the additional mechanical strength of the PCL core [25]. A polypyrrole/chitosan injectable hydrogel was studied as a material for supporting injured heart as well as providing a connection between healthy myocardium and viable cardiomyocites. Through a series of in vitro and in vivo experiments the authors demonstrated that this novel biomaterial may lead to enhanced myocardial recovery [26]. Gelatin and aniline pentamer hydrogels were prepared where the inclusion of the natural polymer led to reduced cytotoxicity of the conductive polymer [5].

IMPLANT MATERIALS

In recent years advancements have been made in the development of implants to replace damaged organs and tissues. However with time the implanted material usually suffers from mechanical or chemical damage which creates a necessity for novel approaches in solving this issue. A class of self-healing materials is now under investigation as an emerging new strategy for overcoming the problem of implant longevity. Mimicking naturally occurring processes like DNA or protein repair, ideally those materials would be able to sense, halt and repair damages on a microscopic level. In a thorough review by A. Brochu [27] and co-workers several generations of self-healing materials have been described based on the ability of the material to repair when damaged. Some of the materials utilize the incorporation of a microencapsulated healing agent which upon contact with cracks or damages would be released and others rely on the formation of dynamic chemical bonds and interactions. A novel dental composite was constructed based on the strategy of encapsulating a healing agent into microcapsules intended to be released in case a propagating crack occurs. Successful crack healing was observed in the model composites when silica microcapsules that contained polyacrylic acid as a healing liquid were dispersed in a polymer resin network formed by monomers 2-bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)propane (Bis-GMA) and hydroxyethyl-methacrylate (HEMA). This healing liquid is intended to react with strontium fluoroaluminosilicate particles and form a glass ionomer cement to heal the defect. As a major advantage the authors of the study pointed the biocompatibility of all materials used and suggested further addition of active components such as antimicrobial agents and hydroxyapatite for improving the qualities of the composite [28]. This strategy was applied by Wu *et al*. [29] in the preparation of a dental composite with poly(urea-formaldehyde) microcapsule containing triethylene glycol dimethacrylate (TEGDMA) and N,N-dihydroxyethyl-p-toluidine as a healing liquid. In the composite two other components were included - dimethylaminohexadecyl methacrylate for its antibacterial properties and nanoparticles of amorphous calcium phosphate to achieve remineralization. The polymer matrix was prepared

by BisGMA and TEGDMA. The authors reported that this first of its kind dental composite offers a promising way of preventing bulk fracture and secondary caries.

Although the majority of research on self-healing materials so far has been done on cements, adhesives and composites this new strategy of obtaining novel biomaterials is now applied in the construction of hydrogels. These materials could potentially find applications in the biomedical field and lead to improved performance of the devices made out of them. As we already mentioned injectable hydrogels as biomaterilas have many advantages when applied as tissue scaffold materials or drug delivery systems. Recent studies have reported the preparation of stimuli-responsive and self-healing hydrogels. Miao *et al*. [30] designed a thermo-responsive, self – healing hydrogel based on alginate grafted with β-cyclodextrin. As a thermo-sensitive polymer Pluronic® F108 (poly(ethylene glycol)-*b*-poly(propylene glycol)-*b*-poly(ethylene glycol)) was included in the hydrogel on the basis of host-guest interactions. The physically dual-crosslinked hydrogel displayed thermo-resposive and self-healing properties when tested in vitro. Another study was conducted where a number of hydrogels were prepared using PEG macromonomers obtained by conjugation with either a derivative of phenylboronic acid or with a diol [31]. Self-healing hydrogels were formed due to the reversible interactions between phenylboronic acid moieties and diol moieties. Hydrogels prepared under pH 7 were subjected to shear-thinning and self-healing tests. PEG-4-carboxyphenylboronic acid (PEG-PBA) and PEG-4-carboxy-3-fluorophenylboronic acid (PEG-FPBA) gels were observed to completely recover their viscosity after network disruption, and additionally PEG-FPBA gel reformation from two pieces was observed. Glucose-responsive behavior of prepared hydrogels and cytocompatibility were also established. The prepared hydrogels could be a useful platform for drug delivery or tissue engineering.

CONLCUSION

A large variety of polymeric materials has been created for biomedical applications. Through combining synthetic and natural polymers the properties of resulting polymeric materials are upgraded or new properties of resulting materials are obtained. Novel techniques of producing polymeric materials have also played a crucial role in the construction of modern pharmaceuticals and implant materials. Even though significant improvements have been made so far, there are still challenges posed by the physical and chemical characteristic of polymer materials. Future endeavors should be directed at obtaining better biocompatibility, tunable mechanical and chemical properties and safe commercial use of these materials.

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СЪВРЕМЕННИ ПРИЛОЖЕНИЯ НА ПОЛИМЕРНИТЕ МАТЕРИАЛИ В БИОМЕДИЦИНСКИТЕ НАУКИ

Л. Х. Йоаниду[1], Й. И. Узунова[1], И. Д. Стефанова[2]

Медицински Университет-Пловдив, Фармацевтичен факултет,
[1] Катедра „Химия и биохимия",
[2] Катедра „Медицинска физика и биофизика",
бул. В. Априлов 15А, 4002, Пловдив, e-mail: lubka84@abv.bg

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(РЕЗЮМЕ)

Разнообразието на полимери и възможностите за приложението им в различни направления на биомедицината, доведе до усилено разработване и проучване на нови полимерни системи. Полимери реагиращи на разнообразни фактори на средата се използват за създаване на иновативни лекарство-доставящи системи. Проучват се самовъзстановяващи се полимери и възможностите за включването им в нови материали за импланти. Комбинация от биополимери и синтетични проводими полимери се очертава като подходяща стратегия за постигане на тъканна регенерация. Целта на този мини обзор е да представи последните постижения в разработването и приложението на полимерни материали в медицината.

Ключови думи: *полимери, полимерни наночастици, хидрогелове, полимерни подложки, импланти*