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Polyurethanes modified with natural polymers for medical application. Part II. Polyurethane/gelatin, polyurethane/starch, polyurethane/cellulose

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Abstract: This paper is a literature overview of biomedical PUR modifications with natural polymers such as starch, cellulose and gelatin. Properties like biodegradability and biocompatibility of modified PUR cause that these materials may be used as wound dressings, tissue scaffolds, tissue implants and also vascular grafts.

Keywords: biomedical polyurethanes, gelatine, starch, cellulose, wound dressings, tissue scaffolds, tissue implants, vascular grafts.

Poliuretany modyfikowane polimerami naturalnymi do zastosowań medycznych. Cz. II. Poliuretan/żelatyna, poliuretan/skrobia, poliuretan/celuloza

Streszczenie: Artykuł stanowi kontynuację przeglądu literaturowego dotyczącego modyfikacji poliuretanu (PUR) za pomocą polimerów naturalnych, takich jak: skrobia, celuloza i żelatyna, w celu nadania mu właściwości predestynujących do zastosowań medycznych. Dzięki właściwościom tych naturalnych polimerów, modyfikowane nimi poliuretany mogą znaleźć zastosowanie jako opatrunki, rusztowania w inżynierii tkankowej, implanty tkanek twardych i miękkich a także naczyń krwionośnych.

Słowa kluczowe: poliuretany biomedyczne, żelatyna, skrobia, celuloza, opatrunki, rusztowania w inżynierii tkankowej, implanty tkanek twardych i miękkich.

In biomedical field it is easier to use synthetic polymers than natural ones. Natural polymers are appropriate due to their biocompatibility and biodegradability, but their properties are not so good, when they are used alone [1]. Natural polymers are usually biocompatible, whereas synthetic polymers can contain a residue of initiators and other compounds/impurities that do not allow cell growth, which is undesirable in the biomedical field [2, 3]. One of methods to prepare polymeric materials for biomedical applications is to blend synthetic polymers with natural ones. Blends of synthetic and natural polymers can form a new class of materials with improved mechanical properties and biocompatibility compared to those of single components. They have been called bioartificial or biosynthetic polymeric materials [4—7].

Synthetic polymers have good mechanical properties and thermal stability, much better than several naturally occurring polymers. There is also a limitation in the performance of several natural polymers in comparison to

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synthetic polymers. Synthetic polymers can be processed into a wide range of shapes, whereas for natural polymers several shapes are not easily obtained; for example, high processing temperatures can destroy their native structure [1].

Polyurethanes (PURs or PUs) are recently intensively investigated synthetic polymers for biomedical applications. They contain urethane (or carbamate) bonds (–NH–COO–) in their main chains. They were described for the first time in work of Otto Bayer [8]. The great variety of building blocks can be incorporated into the PUR chain, their material properties can be tailored to a wide range of purposes. Over the past 40 years, PURs have been used in biomedical devices thanks to their biocompatibility and mechanical flexibility [9—12]. Both biocompatible and biodegradable PURs can be designed through a proper selection of building blocks. Bio-inert PURs are characterized by their excellent chemical stability, abrasion resistance and mechanical properties, and are often used in medical devices and artificial organs [10, 13]. Biodegradable PURs (e.g., containing degradable poly-ε-caprolactone segments), are often used as implants for tissue repair and as drug delivery systems [14]. PURs are also widely modified with natural polymers to impart properties required in biomedical applications, such as biocompatibility and biodegradability. In the first part of our paper we focused on polyurethanes modified with chitosan and collagen [15], but there are more natural polymers that are developed towards blending with PURs. These natural polymer modifiers, used in PUR modifications, are collagen derivatives such as gelatin and plant derivatives such as starch and cellulose [16—20].

The paper is an overview of the progress in working out new medical grade PURs using the above mentioned idea of blending natural polymers with synthetic once to prepare new polymeric compositions with improved properties, like biocompatibility or biodegradability. Newly developed polymeric materials based on the blends of natural polymers and synthetic ones should be biocompatible while, at the same time, possess good thermal and mechanical properties for use in biomedical applications.

GELATIN MODIFIED POLYURETHANES (PUR-GEL)

Gelatin is a protein substance derived from collagen, a natural protein present in tendons, ligaments and tissues of mammals. It is produced by boiling the connective tissues, bones and skins of animals, usually cows and pigs. Gelatin's ability to form strong, transparent gels and flexible films that are easily digested, soluble in hot water, and capable of forming chemical and physical interactions with other substances (including body fluids), have made it a valuable commodity inpharmaceuticals [21]. There are two types of gelatin. Gelatin derived from an acid-treated precursor is known as Type A. Gelatin derived from an alkali-treated precursor is known as Type B. Gelatin is obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals. In the medicine gelatin Type B is used primarily for making hard and soft gel capsules. Other pharmaceutical application for gelatin includes its use in tablets, surgical sponges, salves, suppositories, plasma substitute for medicines, etc. There are several papers, in which the application of gelatin as a modifier of polyurethanes for medicine is described. The thus-obtained materials were used as wound dressings [22, 23, 24], scaffolds or tissue culture cells, blood vessels and bones [16, 25, 26].

In 2001 Kezban Ulubayram et al. used gelatin to obtain a novel polymeric bi-layer wound dressing containing epidermal growth factor (EGF) — loaded microspheres. For this purpose, gelatin was chosen as a natural, nontoxic and biocompatible material, for the underlying layer. Various porous matrices in the sponge form were prepared from gelatin solution by freeze-drying technique. As the external layer, elastomeric PUR membranes were used. Bi-layer wound dressing was constructed in situ, at the wound site, by initially applying the sponges and then covering with commercially available PUR (OpSite). In this way a new type of wound dressing was created to cover the wound area, protect the damaged tissue, activate the cell proliferation and stimulate the healing process [22].

Another technological approach to incorporate gelatin into wound dressing material was taken by Sung Eun Kim and coworkers (2009). Gelatin of type B for a new type of wound dressing material was used in the form of nanofibers. The electrospinning solutions were prepared at different percentages in hexafluoro-2-propanol. The mixed solution was loaded into a glass syringe to fabricate nanofibrous scaffolds with uniform thickness. The electrospun nanofibers were dried overnight at the room temperature on the foil [23]. In the mechanical tests, the blended nanofibrous scaffolds were elastic and their elasticity increased with the total amount of PUR. Moreover, as the total amount of gelatin increased, the cell proliferation increased with the same amount of culture time. Therefore, this gelatin/PUR blended nanofiber scaffold has potential application as a wound dressing [23].

Nicola Detta et al. in 2010 also obtained wound dressing materials by electrospinning. Commercial elastomeric PUR Tecoflex®EG-80A and a Type B gelatin were used. Tecoflex®EG-80A was dissolved in a mixture of THF and DMF while gelatin solutions were prepared by dissolving the polymer in a mixture of distilled water, acetic acid and ethyl acetate. Coelectrospinning was successfully applied. Composite micro-nanostructure meshes benefiting from the mechanical characteristics of PUR and the natural biopolymer cytocompatibility were obtained with the potential application as blood vessels substitute, especially for small diameter vascular prosthesis [24].

In 2008 teams of Sartori found another way to introduce gelatin to polyurethane. In their experiments gelatin

of Type A was used. PUR was synthesized from PCL diol, 1,6-hexamethylene diisocyanate and 1,4-cyclohexane dimethanol as chain extender. In the next stage they prepared polyurethane films by solution casting from chloroform. PUR films were grafted with acrylic acid using argon plasma. The carboxyl groups formed were used to covalently bind gelatin and poly(L-lysine). Thus obtained material was used in the fabrication of scaffolds for tissue engineering [25].

Another interesting PUR-Gel combination is obtaining of polymer networks. Raju Adhikari and coworkers in 2010 developed and investigated PUR networks obtained with the use of gelatin as crosslinking and a foaming agent. Gelatin was used in the form of hydrated beads. Three types of PUR were prepared from different prepolymers. All polymers were prepared in reaction of prepolymer A with one of the three prepolymer B mixtures in equimolar amounts of isocyanate and hydroxyl functional groups from polycaprolactone triol alone or polycaprolactone triol mixed with 10 mol % dihydroxypolycaprolactone phosphorylcholine or polycaprolactone triol mixed with 10 mol % 1,2-dihydroxy-*N*,*N*-dimethylammonio-propane sulfonate. Then prepolymers were mixed with 10 wt % hydrated gelatin beads. The cured by gelatin PUR (cPUR-Gel) are suitable for use in articular cartilage repair. The use of thus introduced gelatin to PUR results in an increase of porosity and hydrophility of a product for medical applications [26].

STARCH MODIFIED POLYURETHANES (PUR-ST)

Starch belongs to polysaccharides. It consists of tens to hundreds or several thousand monosaccharide repeating units connected by alpha acetal linkages. It can be separated into amylose (makes colloidal dispersion in hot water) and amylopectin (insoluble in water). Starch can come from plants. Depending on starch origin, the ratio of amylose to amylopectin changes and its generally in the range of 10—20 wt % and 80—90 wt %, respectively.

Its application is very broad in the food industry but it is also often used as polymer modifier in polymer industry especially in packaging application. Its pharmaceutical application is well known as well.

There are only few papers [17, 18] describing its application for modification of PUR as biomedical materials. One example is a breathable multilayer PUR membrane (2007). It was found that starch was a suitable anti-blocking agent outperforming mineral fillers. At the same time starch incorporation decreases the membrane permeability for moisture in the consistent way with the Maxwell prediction [17]. In this model randomly dispersed fillers of nearly spherical shape inhibit permeability [17].

In 2013 Liu et al. reported preparation of PUR-based asymmetric membranes as wound dressing with the use of acetic starch. These resultant PUR-based asymmetric membranes consisted of an integral and dense skin layer supported by a porous sub-layer. The dense skin layer was sought to prevent bacterial penetration and dehydratation of the wound bed but allowed the drainage of wound exudates. The porous sub-layer exhibited high adsorption capability for fluids and performed drainage of the wound by capillary and tissue regeneration. The porosity and internal substructure of asymmetric membranes could be controlled by adjusting the ratio of the components (PUR species and amount of fillers). In vitro biodegradation assay indicated that the PUR/ASt composite membrane exhibited faster degradation behavior comparing to neat PUR. The authors pointed out that the PUR/ASt-based asymmetric membranes prepared in this study have potential for application as an ideal wound dressing [18].

CELLULOSE MODIFIED POLYURETHANES (PUR-CEL)

Cellulose is a naturally occurring material found in wood, cotton, hemp and other plant-based materials. It consists of repeating anhydroglucose units joined by β(1-4) linkages, forming the basic repeating unit. Cellulose is the structural component of the primary cell wall of green plants and many forms of algae. Cellulose is biocompatible and non-toxic, what makes it a good material candidate for medical applications e.g.: wound dressings, scaffolds for tissue engineering, soft tissue replacement and artificial blood vessels [27].

Cellulose membranes are widely used as hemodialysis biomaterials due to their good permeability of water and solutes and mechanical strength. Nevertheless, their blood compatibility is still not adequate for blood purification. Surface modification is an effective way to improve the blood compatibility. Yuan J. et al. (2003) synthesized a novel nonthrombogenic biomaterial by modifying the surface of cellulose with polyurethane in a three-step procedure. The platelet adhesion test showed that PUR-Cel membranes-grafted betaines have excellent blood compatibility [19].

Another example of cellulose chemical modification with polyurethanes is adding hydroxypropylcellulose (HPC) to the poly(esterurethane)s or poly(etherurethane)s. Macocinschi D. et al. obtained in this way materials with better hemocompatibility, biocompatibility and amphiphilic microphase-separated domain structures [20].

Platelet adhesion test has also been carried out in vitro and it appeared that the use of HPC in PUR reduces the platelet adhesion and therefore PUR–Cel is recommended as candidate for biocompatible materials [28].

Nanocrystalline cellulose (nCel) was also used to modify medical grade PUR. Floros et al. [29] added different amount of nCel to a completely bio-based TPUR derived from oleic acid. The physical properties of the TPUR nanocomposites were assessed by FT-IR, TGA, DSC, X-Ray XRD and DMA. The obtained PUR-nCel nanocomposites demonstrated enhanced stress and elongation at break and improved thermal stability compared to the neat bio-based TPUR. The best results were obtained

with 0.5 % of nCel in the TPUR. The glass transition temperature, melting temperature and crystallization behavior were essentially unaffected. This finding suggests a potential method to increase the strength and elongation at break of typically brittle and weak lipid-based TPURs without alteration of the other physico-chemical properties of the polymer [29]. Another physical modification of PUR was suggested by Raschip I.E. et al. who blended polyurethanes with hydroxypropylcellulose (HPC). It is one of the most useful methods of polymer modification. They obtained, from the polymer solution, new materials with possible medical applications.

It was observed that most of the films were homogeneous and transparent, while those with higher amount of HPC were brittle [30]. The biological analysis showed that the new blends present a good biocompatibility, and fibroblast cells cultured in the presence of polymers maintaining their normal cellular phenotype. The obtained blends are not cytotoxic and exhibit good surface properties and could be candidates for medical and pharmaceutical applications [31].

Khan et al. presented work showing the potential application of biocellulose-nanofiber reinforced PUR nanocomposites as bone scaffold implants. They used biocellulose nanofibers formed from bacterial cellulose (BCel) that possess very good mechanical properties and are highly biocompatible. Thus obtained nanostructured PUR — biocomposites have mechanical properties comparable to those of carbon nanotube composites in regards to bone scaffold applications [32].

SUMMARY

There is an increasing need for new materials that could be applied in medical devices. Due to the mechanical, physicochemical and biological properties of natural polymers and PURs multi-functional PUR-natural polymer biomaterials can be designed. The described blends of PUR and natural polymers have the potential for vast number of applications from wound healing membranes and tissue engineering to drug delivery systems. Papers published in the area of PUR blends may suggest that in the near future developing of production of new products based on the blends of natural and synthetic polymers will be growing.

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