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ASCORBIC ACID IN POLYURETHANE SYSTEMS FOR TISSUE ENGINEERING

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Abstract. The introduction of the paper was devoted to the main items of Tissue Engineering (TE) and the way of porous structure obtaining as scaffolds. Furthermore, the significant role of the scaffold design in TE was described. It was shown, that properly designed polyurethanes (PURs) find application in TE due to the proper physicochemical, mechanical and biological properties. Then the use of L-ascorbic acid (L-AA) in PUR systems for TE was described. L-AA has been applied in this area due to its suitable biological characteristics and antioxidative properties. Moreover, L-AA influences tissue regeneration due to improving collagen synthesis, which is a primary component of the extracellular matrix (ECM). Modification of PUR with L-AA leads to the materials with higher biocompatibility and such system is promising for TE applications.

Keywords: modified polyurethane, ascorbic acid, polyurethane scaffolds, TE.

1. Introduction

In recent years a growing interest in TE is observed owing to its success in tissue regeneration for therapeutic purposes. It is an interdisciplinary field which applies the principles of engineering and life sciences to the development of biological substitutes that restore, maintain or improve tissue function [1]. TE aims to produce specific biological substitutes in an attempt to skip the limitations of existing clinical treatments for damaged tissue or organs [2]. The main regenerative TE approaches include injection of cells alone, development of encapsulated systems and highly biocompatible scaffolds fabrication [3]. Such scaffolds need to mimic the function of the natural extracellular matrix (ECM). The main goal of the scaffold is to serve as an adhesion substrate for the cell (facilitating the localization and delivery of cells when they are implanted), provide temporary mechanical support to the newly grown tissue by defining and maintaining a 3D structure and to guide the development of new tissue of appropriate function [4]. Properly engineered scaffolds should ideally reflect properties of tissues that are intended to be replaced. Biomaterials, used for tissues regeneration, should exhibit complex, mechanically anisotropic behavior optimized for their physiological function [5]. TE requires not only suitable biomaterials for scaffold design but also a suitable technique of scaffold fabrication.

Scaffolds designed for regeneration have been fabricated in a wide range of forms, such as sponges, meshes or films [5]. All of mentioned shapes have to possess interconnected open-cell micropores to enhance the compliance and increase transmural tissue ingrowths from the surrounding tissues [6]. The micropore-directed fabrication techniques include: electrospinning [7], thermally induced phase separation (TIPS) [8] and solvent casting-particulate leaching (SC/PL) [9, 10]. Electrospinning is a unique and versatile process to produce polymeric fibres suitable for vascular graft prostheses [5]. Fibres with a variety of cross sectional shapes and sizes may be produced from different polymers. Electrospun fibres, from polymer solutions and melts, can be obtained in the average diameter range of few nanometers to several micrometres (usually between 50 nm and 5 μm) [11, 12]. The weakness of this technique is the difficulty to preserve suitable pore sizes for cellular ingrowth caused by inadequate reproduction of extracellular matrix (ECM), poor reproducibility of the scaffolds and preservation of their restricted architecture [5]. TIPS is based on quenching the polymer solution below the solvent's freezing point and inducing liquid–liquid separation. Two phases are formed: a polymer-rich phase and a polymer-poor phase. The polymer-rich phase solidifies, whilst the polymer-poor phase crystallizes. The formed crystals are

removed, leaving a highly porous structure (more than 90 %) [13, 14].The structure of the scaffold obtained in this way depends on the polymer solution concentration, the quenching temperature and the quenching rate [15]. Solvents application was recognized as the main disadvantage of this technique. SC/PL involves leaching out of solid particles from the polymer solution. To the polymer solution, which is usually prepared at a concentration from 5 to 20 % [16], specified diameter particles are added. After solvent evaporation by air-drying, vacuum-drying or freeze-drying, salt particles remain embedded throughout the polymer matrix. After immersion in water, salt particles are leached out, leaving a porous structure. According to Zhu *et al.* [10], highly porous scaffolds with porosity up to 93 % and average pore sizes of up to 500 μm can be obtained with the use of SC/PL technique. The structure of the formed scaffold depends on many factors. The shape and size of pores are directly determined by the shape and dimensions of the leachable particles used [17-19]. Salt particles are mainly used, but the use of sugar, ammoniumchloride, sucrose, starch particles and gelatine, paraffin microspheres is also known [20, 9]. The main advantage of this method is the ease of fabrication without the need of specialized equipment. The disadvantage of this method is, according to Mikos *et al.* [21], the impossibility to produce thin porous materials below 3 mm thick.

2. Tissue Engineering Scaffolds

TE is a field, which has expanded noticeably due to the increasing demands for artificial tissues and organs. Interest in designing cellular scaffolds for tissue repair is continuously growing. Such scaffolds, used alone, should induce regeneration of functional tissues and internal organs. This process rarely happens and the TE is frequently applied to treat tissue defects. In this approach, scaffolds are seeded initially with autogenous cells, and subsequently the cell-scaffold construct is used as an implant. Synthetic scaffold implanted in the damaged area, after fulfilling its task (the cell growth), should slowly degrade to natural ECM (native extracellular matrix). There is no one “universal” scaffold to be used to treat defects of various hard and soft tissues [22-25] and different chemical compositions are being tested.

Scaffolds for TE should be biocompatible, promote attachment, proliferation, and activity of the specific cells, have pores (to allow cellular and tissue ingrowth), be preferably bioresorbable or biodegradable. The important factor of tissues regeneration is scaffold surface hydrophilic-hydrophobic characteristic. It is due to the fact that hydrophilic polymer surfaces enhance biocompatibility of polymeric materials. The suitable hydrophilic profile of the scaffold surface enables cells adhesion, migration and proliferation [26]. A number of cellular scaffolds for all types of tissues was developed from natural (chitosan, elastin, alginate, collagen) and/or synthetic (polyglycolide (PGA), polylactide (PLA), PUR) polymers or even from ceramic materials (hydrokxyapatite, bioglass) [27]. They have different chemical and physical characteristics. The presence of chemical groups at the scaffold’s surface is controlling the surface free energy, hydrophilicity, and the ability to form ionic bonds with cells. The physical properties comprises texture of surfaces that have contact with cells, presence of pores, their structure, size and distribution, and also mechanical properties of scaffold, that optimally might match those tissues, which have to be replaced. All these characteristics are strongly influenced by both the quality of the material and the technique used for scaffold preparation [24].

Mikos *et al.* [21] obtained highly porous biodegradable polymer scaffolds from poly(l-lactic acid) material by particulate-leaching method. To prepare porous membranes of controlled porosity they used sodium chloride, sodium tartrate or sodium citrate sieved particles. Different salt weight fractions were used. In case of using 50 and 60 wt % of salt fractions, asymmetric membranes were formed, independent of salt particle size. When 70–90 wt % salt was used, the membranes were homogeneous with interconnected pores. The porosity increased with the salt weight fraction, and the medium pore diameter increased as the salt particle size increased. The polymer/salt composite membranes could be quenched or annealed to yield amorphous or semicrystalline foams with desired crystallinity. All foams were 99.9 wt % salt free and had porosities as high as 0.93 and medium pore diameters up to 150 μm.

Rogers *et al.* [28] obtained three-dimensional PUR vascular scaffolds by solvent casting/ particulate leaching (SCPL) and by electrospinning for comparative studies. For SCPL, two different porogens, namely, alginate beads and D-fructose particles were used. Fabricated scaffolds with a regular geometry of pores and enhanced microporosity were developed by partially solubilising D-fructose porogens in situ using a solvent mixture of *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO). Micro-computed tomography (micro-CT) and mercury intrusion porosimetry characterizations combined with scanning electron microscopy (SEM) imaging revealed that scaffolds with 80–90 % porosity, were fabricated using the two porogens. Electrospun fibrous scaffolds having an average fiber diameter of ~200 nm were obtained as well. Scaffolds obtained by those methods were included in the studies of fibrous scaffold morphology effect on cell behavior. Human coronary

artery smooth muscle cells (HCASMC) culture studies indicated that scaffolds fabricated both by SCPL using alginate beads and D-fructose and by electrospinning, all have provided a favorable environment for cell growth.

3. Polyurethanes in TE

Properly designed PUR can be biocompatible and biodegradable (or bioresorable) materials, which possess desirable properties to serve as hard and soft tissues substitutes. They can be used as films or membranes, as well as they can be foamed or cast. That is why the variety of their utility is so wide in medical applications. PUR have been used in a variety of medical devices such as intravenous catheters (US 5752941; US20110178507, US20100256546), vascular grafts (US20080306181, US 8187319, US20120271200 A1), cartilage replacements (US20110105635, US20080262618), artificial hearts (EP0914834 A2, US5393858, US5500016), and pacemaker lead insulation [29-31]. PUR chains contain hard and soft segments, which allow for subtle control of their structure and properties. The hard, rigid segments are produced by the reaction between the diisocyanate and the chain extender, whereas polyether, polyester, or polycarbonate diol comprise the soft segments. The amount of hard segments influences the degree of phase separation, which in turn affects physical and mechanical properties [30], degradation rate and biocompatibility [32-33]. By varying the molecular weight of polyol and the composition of the different segments, properties of PUR can be tuned up for use in many areas of TE [34-38]. In this respect, the range of mechanical and morphological properties that can be obtained with PUR is significantly larger than with commonly used medical grade biodegradable polymers for example: PLA, PGA, poly(DL-lactide) (PDLLA) [39-42]. Many applications of segmented PUR in TE field, such as cardiovascular TE [34, 43, 44] musculoskeletal applications (anterior cruciate ligament) [42], knee joint meniscus [45], bone TE [46], smooth muscle cell constructs for contractile muscle [47, 48], and nerve regeneration[49-51], have been recently evaluated. For polyurethanes containing aromatic isocyanate moieties like methane-4,4'-diphenyl-diisocyanate (MDI) and 2,4-toluenediisocyanate (TDI) toxic aromatic diamines were indicated after degradation. To overcome this limitations attention was drawn towards the aliphatic isocyanates like lysine diisocyanate (LDI), lysine triisocyanate (LTI), isophorone diisocyanate (IPDI), 1,4-butanediisocyanate (BDI) and 1,6-hexa-methylene diisocyanate (HDI) or 4,4'-methylene bis(cyclohexyl isocyanate) (HMDI).

It was found that PUR based on BDI degrades into substances that occur naturally in the body [52]. The material may therefore be totally bioresorbable, which implies that the material will degrade and will be entirely eliminated from the body through natural pathways, without side effects [53].

Biodegradable, porous polyurethane (PUR) scaffolds prepared from LDI or lysine-derived components [51-61] and aliphatic isocyanates [62-67] have been reported to non-toxic degradation products, what was proven in a number of patented PUR materials (US Pat. No. 6221997 B1, US Pat. No. 2007/0299151 A1, 2008/0067720 A1, US Pat. No. 2009/0130174 A1, US Pat. No. 2009/0221784 A1, US Pat. No. 2010/0068171 A1, US Pat. No. 2010/0247672 A1, US Pat. No. 2010/0897082 A1, US Pat. No. 2011/0038946 A1) [46, 68-71]. From chemical point of view, by careful selection of diisocyanate, chain extender and macrodiol components, a broad range of polyurethane physical properties can be achieved [46].

4. Ascorbic Acid Based Polyurethane Systems for TE

Ascorbic acid (L-AA) is commonly known as vitamin C. It has found the application as a pharmaceutical agent, cosmetic ingredient and dietary supplement [72, 73]. L-AA is important antioxidant that can reduce superoxide, hydroxyl radical, hypochlorous acid and other radicals. L-AA as antioxidative agent is also tested in tissue regeneration [74-78].

L-AA is an appropriate molecule for the regulation of the homeostasis because of functional [79-81], regulatory and economic reasons. It allows to collagen formation and stability, it also has other various physiological and therapeutic effects [80, 82-88] including the stimulation of human fibroblasts [82]. Interestingly, systemic application of high dose of L-AA inhibited tumor growth *via* reduction of angiogenesis [87, 88]. L-AA added to wound dressings improved wound healing [79].

Zhang *et al*. in 2003 received nontoxic, biodegradable, model sponge-like PUR scaffolds from LDI, glycerol and L-AA. During the studies they showed that obtained LDI-glycerol-L-AA matrix degrade in aqueous solution to the nontoxic products of lysine, glycerol, and L-AA. The degradation products did not significantly affect the pH solution and physical properties [37]. Mouse osteoblastic precursor cells (OPCs), which they used to attach to the polymer matrix, remained viable. OPCs produced multilayered confluent cultures typical of bone cells. Furthermore, L-AA release stimulated cell proliferation, type I collagen, and alkaline phosphatase synthesis. Cells grown on the LDI-glycerol-L-AA matrix also showed an enhancement of mRNA

expression for pro-α1 (I) collagen and transforming growth factor-α1 after 1 week. The observations suggest that L-AA-containing polyurethane may be useful in bone TE applications [37]. In another paper Zhang *et al.* [57] proposed another L-AA containing scaffolds for bone tissue-engineering. They were synthesized also with LDI, L-AA and glycerol, but modified by adding polyethylene glycol (PEG). LDI-glycerol-PEG-L-AA matrix degraded in aqueous solution and yielded lysine, glycerol, PEG, and L-AA as breakdown products. The degradation products did not significantly affect the pH solution. The LDI-glycerol-PEG-L-AA matrix can support *in vitro* cell growth and can be fabricated into diverse scaffold dimensions. Green fluorescent protein-transgenic mouse bone marrow cells (GFP-MBMCs) attached to the polymer matrix and remained viable, and the cells became confluent cultures. Furthermore, L-AA released from LDI-glycerol-PEG-L-AA matrix stimulated cell proliferation, type I collagen, and alkaline phosphatase synthesis *in vitro*. Cells grown on LDI-glycerol-PEG-L-AA matrix did not differ phenotypically from cells grown on tissue culture polystyrene plates as assessed by cell growth, expression of mRNA for collagen type 1, and transforming growth factor beta [1]. These observations suggest that L-AA-containing polyurethane may be also proposed as a material useful in TE [57].

Stumpf *et al.* in 2011 [89, 90], proposed a novel drug-eluting platform for the potential use in wound dressings with the use of L-AA derivatives. The drug-eluting platform device (DEPD) consisted of biocompatible polymeric layers comprising polyethylene terephtalate (PET), polyvinyl alcohol (PVA), and polyurethane with PVA as the solvent for ascorbic acid-2-phosphate (ASC-2P), which is highly stable variant of L-AA. Their studies showed that ASC-2P significantly induced angiogenesis in five independent TFA and CAM assays and induced collagen synthesis in two different fibroblast cell lines.

In 2015 Kucinska-Lipka *et al.* [91] obtained the novel poly(ester urethane) (PEUs) from oligomeric α, ω-dihydroxy(ethylene-butylene adipate) (dHEBA), 1,4-butandiol (BDO) and aliphatic 1,6-hexamethylene diisocyanate (HDI) and modified them with L-AA. They created novel PEUs material designed for TE with a tensile strength in the range of 4–9 MPa, elongation at break from 27 to 351 % and hardness of 85–91°ShA. These properties, from a mechanical point of view are suitable for materials dedicated to soft TE. Modification with L-AA did not influence the mechanical properties of the PEUs. In addition PEUs were stable in variety of tested environments (oil, saline, and aqueous) for three months. The MTT assay revealed that the application of L-AA during the synthesis of PEUs was reasonable and in fact improved biocompatibility in comparison to unmodified PEUs. Good mechanical properties of obtained PEUs, their suitable stability in typical physiological environments, and improved hemocompatibility and biocompatibility, proved that L-AA modified PEUs might find an application in the field of soft TE.

In another research paper, Kucińska-Lipka *et al.* [92] studied unmodified and modified with L-AA (1 or 2 wt %) PURs with the use of FT-IR and NMR spectroscopy and revealed that only part of L-AA was incorporated into the PUR chains. The DMA analysis showed slight shift of loss modulus and tangent of an angle δ to lower temperature range after addition of L-AA to the PUR matrix. The observed glass transition temperature was 244 K for unmodified PESU, 242 K for PEUs modified with 1 wt % L-AA and 238 K for PEUs modified with 2 wt % L-AA. Both unmodified and L-AA modified PEUs were thermally stable up to approx. 523 K. The tensile strength and elongation at break was slightly higher for unmodified PEUs (tensile strength for the unmodified PEUs was equal to 7.2 ± 0.2 MPa while for modified PEUs it was 5.8 ± 0.2 MPa; elongation at break for unmodified samples was 172 ± 2 % and for modified it was 169 ± 1 %). The hardness of obtained PEUs was higher (90.1 ± 0.3°Sh A) for unmodified samples than for L-AA-modified PEUs (87 ± 0.2 °Sh A). It was concluded that L-AA, which was enclosed in PUR matrix, acted as an inactive filler, what caused slight decrease of mechanical properties of obtained modified PEUs. However the mechanical and thermomechanical properties of L-AA modified PEUs are comparable with literature data concerning biomedical PUR materials and may be suitable for applications in soft TE.

Kucinska-Lipka *et al.* [93] used a novel L-AA-modified PEU (L-AA-PU) system to prepare bone tissue scaffolds by phase separation/particle leaching (PS/PL) and solvent casting/particulate leaching (SC/PL) methods. The calculated porosity demonstrated that porosity value depended on both the PUR concentration and the type of solvent. The increase in polymer concentration caused the increase in the viscosity of the solution, which promoted the formation of closed pores. For DMF/THF solvent mixture, the highest porosity of 86 and 84 % was observed for 10 and 15 wt % of PUR concentration, while 84 % porosity was found for 20 wt % of PUR concentration in DMF, prepared by the SC/PL method. A higher porosity was obtained (76–86 %) using the PS/PL method. The SEM and OM analysis suggested that regular structure was observed for PUR prepared by SC/PL from DMF solution and PS/PL from DMF/THF solution. Thus prepared scaffolds had suitable swelling

(the tests for distilled water and saline water swelling) and mechanical properties for some types of bone TE.

5. Conclusions

TE is an interdisciplinary approach to design the proper chemical systems, from which one can obtain the scaffolds for tissue regeneration. The suitable choice of materials for the scaffolds takes into account their biocompatibility and/or biodegradability. Moreover very important is biologic activity. One of the polymer material broadly studied is PUR. Properly designed PUR can be applied as scaffolds for TE. Very often the particular PUR system is modified to enhance its properties. One of the modifier described in the literature is L-AA. It has antioxidative properties and influences tissue regeneration due to improving collagen synthesis, which is a component of the primary extracellular matrix (ECM). It was shown that it can be incorporated into the polyurethane structure to improve their biocompatibility and biodegradability. From L-AA modified PUR the scaffolds can be obtained by electrospinning or PS/PL and SC/PL.

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АСКОРБІНОВА КИСЛОТА В ПОЛІУРЕТАНОВИХ СИСТЕМАХ ДЛЯ ТКАНИННОЇ ІНЖЕНЕРІЇ

Анотація. *Розглянуті головні положення тканинної інженерії (ТІ) та спосіб отримання пористої структури, як поліуретанових каркасів. Обгрунтовано важливу роль таких каркасів в ТІ. Показано, що належним чином синтезовані поліуретани (ПУ) знаходять широке застосування в ТІ завдяки певним фізико-хімічним, механічним і біологічним властивостям. Описано застосування L-аскорбінової кислоти (L-АА) в ПУ системах для ТІ. Аскорбінову кислоту застосовують в цій області через її специфічні характеристики і антиоксидаційні властивості. Крім того, вона впливає на регенерацію тканин внаслідок покращення синтезу колагену, який є головним компонентом позаклітинної матриці. Модифікація ПУ аскорбіновою кислотою дає можливість отримувати матеріали з покращеною біосумісністю і тому така система є перспективною для застосування у ТІ.*

Ключові слова: *модифікований поліуретан, аскорбінова кислота, поліуретанові каркаси, тканинна інженерія.*