



Synthesis and characterization of cycloaliphatic hydrophilic polyurethanes, modified with L-ascorbic acid, as materials for soft tissue regeneration

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ABSTRACT

In this paper we described synthesis and characteristic of obtained hydrophilic polyurethanes (PURs) modified with ascorbic acid (commonly known as vitamin C). Such materials may find an application in the biomedical field, for example in the regenerative medicine of soft tissues, according to ascorbic acid wide influence on tissue regeneration Flora (2009), Szymańska-Pasternak et al. (2011), Taikarimi and Ibrahim (2011), Myrvik and Volk (1954), Li et al. (2001), Cursino et al. (2005). Hydrophilic PURs were obtained with the use of amorphous α,ω -dihydroxy(ethylene-butylene adipate) (dHEBA) polyol, 1,4-butanediol (BDO) chain extender and aliphatic 4,4'-methylenebis(cyclohexyl isocyanate) (HMDI). HMDI was chosen as a nontoxic diisocyanate, suitable for biomedical PUR synthesis. Modification with L-ascorbic acid (AA) was performed to improve obtained PUR materials biocompatibility. Chemical structure of obtained PURs was provided and confirmed by Fourier transform infrared spectroscopy (FTIR) and Proton nuclear magnetic resonance spectroscopy (¹HNMR). Differential scanning calorimetry (DSC) was used to indicate the influence of ascorbic acid modification on such parameters as glass transition temperature, melting temperature and melting enthalpies of obtained materials. To determine how these materials may potentially behave, after implementation in tissue, degradation behavior of obtained PURs in various chemical environments, which were represented by canola oil, saline solution, distilled water and phosphate buffered saline (PBS) was estimated. The influence of AA on hydrophilic-hydrophobic character of obtained PURs was established by contact angle study. This experiment revealed that ascorbic acid significantly improves hydrophilicity of obtained PUR materials and the same cause that they are more suitable candidates for biomedical applications. Good hemocompatibility characteristic of studied PUR materials was confirmed by the hemocompatibility test with human blood. Microbiological tests were carried out to indicate the microbiological sensitivity of obtained PURs. Results of performed studies showed that obtained AA-modified PUR materials may find an application in soft tissue regeneration.

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1. Introduction

PURs are one of the most extensively developed synthetic polymers for biomedical applications. The major advantage of PURs is the ease of their physicochemical and mechanical properties design, which may be performed by proper selection of raw materials used for their synthesis [7,8]. This is an important issue especially in the field of materials dedicated to regenerative medicine and tissue regeneration [9–11].

PURs consist of alternating soft (SS) and hard (HS) segments. Segmented structure of PURs led to the phase separation of these materials, which affect their physicochemical and thermomechanical properties. SS are formed by polyester, polyeter or polycarbonate polyol and HS

are derived from diisocyanate and low molecular chain extender. SS provide elastomeric character of the PUR and HS provide good mechanical strength due to the hydrogen bonds formed between urethane linkages. Changing in chemical composition, the molecular weight and the ratio of HS and SS led to synthesize PURs of different physicochemical characteristic as well as biocompatibility and biodegradability [12–14].

Constantly growing interest of PURs application in biomedical field is related to their suitable biocompatibility, hemocompatibility and biodegradability [15–19]. The biodegradation rate is mainly dependent on the SS structure related directly to the type of used polyol [20]. Many different polyols are engaged in the synthesis of biomedical PURs. To the most commonly used polyols belong poly(ϵ -caprolactone) (PCL), poly(propylene glycol) (PPG), poly(ethylene glycol) (PEG) and poly(glicolide) [21]. HS plays an important role in case of biocompatibility of PURs [22]. In the field of tissue engineering, where biodegradable

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scaffolds are produced, aliphatic diisocyanates are engaged to the synthesis of PURs. It is due to the reduced toxicity of PUR degradation products synthesized by using aliphatic diisocyanates (in comparison to aromatic diisocyanates) in vivo conditions [23]. To the most commonly applied diisocyanates for biomedical PUR synthesis belong 1,4-butanediisocyanate (BDI), isophorone diisocyanate (IPDI), 1,6-hexamethylene diisocyanate (HDI) [7,22,24].

One of the most important parameters, which evaluate the applicability of synthetic polymers in biomedical applications, is their hydrophilic character. Hydrolytic degradation plays a key role in the development of materials dedicated to biomedical applications [25]. Degradation of poly(ester urethane)s was divided into three steps. First step is the incubation, where absorption of water occurs. In the second step the induction happens during which the polymer chains are broken via ester bonds. Last step is the erosion where water-soluble entities (such as PEG blocks and oligomers) are dissolved in the buffer solution, with corresponding polymer mass loss [26,27]. The hydrophilicity concept of synthetic polymers reports that surface characteristic of polymer should include the degree of water absorption to the polymer surface, what is associated with blood response. The suitable hydrophilic characteristic of polymeric surface prevents macrophages adhesion to their surface and the same prevents formation of blood clots, which presence could cause a serious system response [28,29]. An optimization of the hydrophobic-hydrophilic ratio of polymeric surface improves blood compatibility by reducing platelet adhesion [30]. Hydrophilic character of PURs is directly related to their chemical composition [28].

PURs may exhibit the hydrophobic surface properties, what is related to their composition, and due to this fact in such situation they need to be modified at variable levels to improve their hydrophilicity and the same the degree of their biocompatibility [31]. Literature data report many examples of PUR modifications performed directly to improve their antithrombotic character and biocompatibility [12]. For example, surface of PURs designed for tissue scaffolds may be functionalized to induce the cascade of biological processes, which lead to rebuilding and regeneration of destroyed tissue. Bioactive factors, which are used for this type of functionalization, may be introduced into the polymer matrix during the polymer synthesis [32], may also form a compatible protective covers (e.g. heparin, silicone) or bioactive factors may be physically, chemically or biologically functionalized onto the polymeric surface as for example phospholipids [33], biological anticoagulants (heparin) [34,35], anti-platelet factors such (glycoprotein inhibitor IIb/IIIa) [36] and also antiproliferative agents (rapamycin) or proliferation agents that improve cells growth [37,38].

To achieve the suitable hydrophilic characteristic and the degree of biocompatibility AA may also be used according to the fact that it improves tissue regeneration [7,39], AA is a strong antioxidant which prevents proteins oxidation [1] and improves function of ECM cells by stabilization of tetrahydrobiopterin, which is the main and necessary cofactor of nitric oxide synthase [2] Some references reported also that AA reveals the antibacterial activity against some microorganisms like *Streptococcus pneumonia*, *Escherichia coli* or *Pseudomonas aeruginosa* [3–6].

In this paper we described the synthesis and characteristic of hydrophilic PURs for biomedical applications such as regenerative medicine of soft tissues, what is the development of previously undertaken studies of our team [7]. To achieve proper hydrophilic characteristic PURs were obtained with the use of selected raw materials: amorphous polyester α,ω -dihydroxy(ethylene-butylene adipate) (dHEBA), difunctional chain extender 1,4-butanediol (BDO) and cycloaliphatic diisocyanate (4,4'-methylene bis(cyclohexyl isocyanate) (HMDI)). HMDI was chosen as a nontoxic diisocyanate widely reported in references as a suitable raw material for biomedical PUR synthesis. Moreover, the degradation products of aliphatic isocyanate-based PURs are considered as nontoxic for living organisms and so they are removed in natural life cycles [22]. To improve biomedical character of obtained PURs the modification

with AA was performed, due to its wide influence on tissue regeneration [7,39]. Already described PUR-AA-based systems were designed for bones tissue regeneration and different raw materials were used in comparison to our study [40,41]. Due to our knowledge, there are no references yet describing AA influence on hydrophilic characteristic of PURs designed for biomedical applications. Chemical structure and composition was studied by FTIR and ^1H NMR spectroscopy. DSC analysis was performed to indicate the T_g , T_m and melting enthalpies of obtained PUR materials. To determine the degradation behavior of obtained PURs interactions with selected media (canola oil, saline solution, distilled water and phosphate buffered saline (PBS)) were studied. The characterization of materials' interactions with such media is commonly performed for medical-grade polymers [42]. Canola oil assay may be used to determine the in situ behavior of the biomaterials according to the lipids present in the living body [43]. The exposure of biomaterials to lipids may lead, in vivo conditions, to swelling and degradation in otherwise stable biomaterials [44]. Furthermore, drugs delivered to the body, encapsulated in a biodegradable polymer, are often introduced to the system as a lipid emulsion [45]. Contact angle was defined to estimate the degree of hydrophilic-hydrophobic characteristic of obtained PURs. Literature data require polymeric materials of contact angle in the range of 45–76° as most suitable for cells adhesion and proliferation [46]. Moreover, the ability of polymeric materials, of hydrophilic character, to form hydrogen bonds improves their biocompatibility by solvation water molecules, which form at their surface water film that is biologically neutral [46]. To study microbiological sensitivity of obtained PURs the microbiological test was performed against selected microorganisms: *Staphylococcus aureus*, *P. aeruginosa* and *E. coli*. These microorganisms are dominant amongst the bacterium, which cause inflammatory complications [47] and examples of the common post-implantation infections [48].

2. Experimental

2.1. Polyurethane synthesis (PURs)

PURs were synthesized by standard two step polymerization procedure [49,50]. In the first step a prepolymer was obtained with 8% of free isocyanate groups. It was derived from oligomeric α,ω -dihydroxy(ethylene-butylene adipate) (dHEBA) polyester (trade name Polios 55/20; Purinova, Poland) (65 wt%) and aliphatic 4,4'-methylenebis(cyclohexyl isocyanate) (HMDI) (Sigma Aldrich, Poland) (35 wt%). The prepolymer reaction was carried out in the glass, 4-neck, reactor at 80 °C for 6 h. In the second step the chain extender - 1,4-butanediol (BDO) (POCH, Poland) - was added to obtain unmodified PURs with molar ratio of free isocyanate groups (NCO) (in the prepolymer) to hydroxyl groups (OH) of chain extender BDO NCO/OH = 0,9:1. Dibutyltin dilaurate (DBTDL), at the amount of 1 wt%, was used as a catalyst, commonly used for the synthesis of biomedical PURs [51,52]. The reaction mixture was subjected to intensive stirring and then transferred into a mold, set at 80 °C overnight. Then, the samples were left in a drier at 80 °C for 48 h to complete the reaction.

The synthesis of modified PUR was as follows: to the obtained prepolymer 2 wt% of solid AA (Sigma Aldrich), calculated per mass of the prepolymer (prepolymer: AA = 1:0,25), was added at room temperature. This amount of AA was established as most suitable in preliminary studies. After addition of the AA to the prepolymer, the temperature was raised to 80 °C and the reaction was continued for 1 h. Then the chain extender BDO was added to obtain AA-modified PURs. Reaction mixture, after vigorous stirring was transferred to a mold of 80 °C overnight. After this time, the AA-modified PUR was left in the drier for 48 h at 80 °C to complete the reaction. Thus samples of 2 mm thickness were obtained. Reaction of unmodified and AA-modified PURs was presented at Scheme 1. Table 1 presents symbols used to mark the obtained PURs and a brief explanation of them.

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