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Synthesis and characterization of biodegradable polyurethane films based on HDI with hydrolyzable crosslinked bonds and a homogeneous structure for biomedical applications

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ABSTRACT

Synthetic biodegradable polymers are considered strategic in the biomaterials field and are used in various applications. Among the polymers used as biomaterials, polyurethanes (PUs) feature prominently due to their versatility and the ability to obtain products with a wide range of physical and mechanical properties. In this work, new biodegradable polyurethane films were developed based on hexamethylene diisocyanate (HDI) and glycerol as the hard segment (HS), and poly(caprolactone) triol (PCL triol) and low-molecular-weight poly(ethylene glycol) PEG as the soft segment (SS) without the use of a catalyst. The films obtained were characterized by structural, mechanical and biological testing. A highly connected network with a homogeneous PU structure was obtained due to crosslinked bonds. The films showed amorphous structures, high water uptake, hydrogel behavior, and susceptibility to hydrolytic degradation. Mechanical tests indicated that the films reached a high deformation at break of up to 425.4%, an elastic modulus of 1.6 MPa and a tensile strength of 3.6 MPa. The materials presented a moderate toxic effect on MTT assay and can be considered potential materials for biomedical applications.

1. Introduction

Polymers are suitable materials for different biomedical applications [1–6]. Several biodegradable polymers, both synthetic and natural, have been used in this field, such as collagen, chitosan, polyester, and polyamide, among others. Many of these polymers, however, do not have mechanical and physical properties comparable to natural tissues [7,8].

Polyurethanes (PUs) are a very important group of polymers because of their good mechanical properties and versatility [9]. PUs are composed of alternating hard and soft blocks that can lead to separate microphases under appropriate conditions to form hard and soft domains [10]. The soft segments are generally composed of polyester, polyether, or polycarbonate polyols, whereas the hard segments are produced by reactions between a diisocyanate and low-molecular weight diol or diamine chain extender [1,10]. The soft segment provides the elastomeric character to the polymer backbone, while the hard segment usually provides extra strength due to the hydrogen bonding involving urethane linkages [11]. Changing the chemical composition, the molecular weight and the ratio of hard and soft segments can lead to polymers with different physical and physicochemical properties and, subsequently, different biodegradability properties, to suit the intended application [11,12].

Biodegradable PUs applied as biomaterials are reported by several researchers [1,2,9–13], and their properties can be tailored by the proper choice of raw materials. The rate of polyurethane degradation is extremely dependent on the soft segment structure [14] composed of the polyols. The common polyols employed in biodegradable PUs include poly(propylene glycol) (PPG), poly(ethylene glycol) (PEG), poly(caprolactone) (PCL), and glycolic acid, among others. PEG exhibits attractive properties, including non-toxic degradation products, the absence of antigenicity and immunogenicity, solubility in water and organic solvents, and hydrophilicity [15]. PCL is frequently used as the soft segment in degradable polyurethanes because it can be hydrolyzed and its degradation products are non-toxic and can be metabolized [12]; however, it is rather hydrophobic and has a low degradation rate [15]. The use of polyols with higher functionality can lead to polyurethanes with crosslinked bonds. In general, a crosslinked structure prevents water from easily reaching the ester/ether groups, reducing the hydrolytic degradation capacity. Nevertheless, in some cases the presence of a triol crosslinker can prevent the aggregation of segments through hydrogen bonding of the hard segment, and increase the aggregation

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through covalent bonds, with the formation of a homogeneous structure with no phase separation. The disordering of the polymer matrix and the reduced movement freedom of the molecular chain caused by the chemical crosslinking allow the ester/ether groups to be exposed to water, improving hydrolytic degradation [16].

In the hard segment, the polyfunctional isocyanate can be aromatic, aliphatic, cycloaliphatic or polycyclic. Aliphatic diisocyanates yield PUs that are less rigid but have better oxidative and ultraviolet stabilities [17]. Some commonly used reagents to prepare biodegradable PU are 1,4-butanediisocyanate (BDI) and isophorone diisocyanate (IPDI), among others. 1,6-Hexamethylene diisocyanate (HDI) is an aliphatic diisocyanate often used in the preparation of biomedical PU [11,18–20], with a relatively non-toxic degradation by-product, diamine 1,6-hexanediamine, and that also provides good mechanical properties to the final product. Degradation products of polyurethanes based on aromatic diisocyanates like 4,4′-methylenediphenyl diisocyanate (MDI) and toluene diisocyanates (TDI) are toxic. Accordingly, aliphatic diisocyanates such as HDI, IPDI and BDI, are replacing aromatic ones in designing biodegradable polyurethanes as they have been reported to degrade into nontoxic decomposition products [18,21–23]. By introducing hydrolysable chain extenders into the hard segment, it is possible to increase the degradation rate of polyurethanes [12]. Conventional chain extenders used in PU formulations are 1,4-butanediol (BDO), 1,2-ethanediol and 1,2-ethanediamine. Diamines are usually more reactive than diols or triols. Glycerol is a non-toxic polyol that is soluble in water and contains hydroxyl groups. When used as a chain extender, it provides a crosslinked structure in the polyurethane and can also increase the thermal stability [24]. Modified crosslinked PUs can behave as hydrogels, absorbing large amounts of water without dissolving, which is an important quality for several biomedical applications [25].

The aim of this study is to develop new compositions of polyurethane based on HDI diisocyanates and biodegradable polyols with high functionality, forming a crosslinked network that can behave as a hydrogel polymer capable of hydrolytic degradation, for possible application in the biomedical field. This work obtains polyurethane films based on HDI and glycerol as the hard segment and PCL triol and PEG as the soft segment. PEG hydrophilicity can be an important mechanism for improving the PU′s affinity for water. The glycerol and PCL triol can crosslink, creating an interconnected network structure with a mixture of soft and hard segments, thus providing hydrogel characteristics and good mechanical properties to the material. Additionally, glycerol is a hydrolysable chain extender, increasing the hydrolytic degradation rate. The promising results demonstrated by this new material indicate that it is a candidate for applications in the biomaterial field.

2. Materials and methods

2.1. Synthesis of biodegradable polyurethanes films

HDI, PCL triol 900 $g \cdot mol^{-1}$ and PEG 600 $g \cdot mol^{-1}$ were obtained from *Sigma-Aldrich*. Glycerol and ethyl acetate were obtained from *Synth Brazil*. Polyurethane films were prepared by the pre-polymer process. First, PCL triol 900 and PEG 600 were added to the reactor, without any catalyst. The temperature was kept at 55 °C. After the melting of PCL and homogenization, HDI was slowly added to the reactor. The temperature and mixing were maintained for 2 h. 15 mL of the ethyl acetate (solvent) was then added. After mixing, glycerol was added to the reactor. The temperature was reduced to 40 °C, and the system was mixed for another 30 min. All processes were performed under a nitrogen atmosphere. Films were produced by casting the product into polypropylene molds and allowing them to dry at room temperature for 24 h and then for 72 h at 60 °C.

In the hard segment, HDI was kept at 34% and glycerol at 5% (mass composition). The mass composition of the polyols was varied in the samples PU3 (3% PCL Triol 900 and 58% PEG 600) and PU12 (12% PCL Triol 900 and 49% PEG 600).

2.2. Material characterization

The structure of the films was analyzed using a Thermo Scientific Nicolet 6700-OMNI Smart Accessory Spectrum Fourier transform infrared (FTIR) spectrometer. Spectra were collected in the mid-infrared range from 600 to 4000 cm^{-1} in the ATR mode, with 64 scans per spectrum at 4 cm^{-1} resolution. X-ray Diffraction (XRD) spectra of the films were collected on a Philips PW1700 series automated powder diffractometer using Cu Kα radiation at 40 kV/40 mA. Data were collected between 4.05 and 89.95° with a step of 0.06° and a dwell time of 1.5 s.

The measurements of synchrotron small angle X-ray scattering (SAXS) were performed using the beam line of the National Synchrotron Light Laboratory (LNLS, Campinas, Brazil). The photon beam used in the LNLS SAXS beam line comes from one of the 12 bending magnets of the electron storage ring. The white photo beam is extracted from the ring through a high-vacuum path. After passing through a thin beryllium window, the beam is monochromatized ($\lambda = 1.608$ Å) and horizontally focused by a cylindrically bent monochromater at the detection plane. The X-ray scattering intensity, I(q), was experimentally determined as a function of the scattering vector "q" whose modulus is given by $q = (4\pi/\lambda)\sin(\ )$, where λ is the X-ray wavelength and is half the scattering angle. Each SAXS pattern corresponds to a data collection time of 900 s. The parasitic scattering intensity produced by the collimating slits was subtracted from the experimental scattering intensity of each sample. All SAXS patterns were corrected for the non-constant sensitivity of the PSD, for the time varying intensity of the direct synchrotron beam and for differences in the sample thicknesses. Because of the normalization procedure, the SAXS intensities for all samples are expressed in the same arbitrary units so that they can be directly compared.

An Exstar 7200 from Seiko — SII Nanotechnology Inc. was utilized for the thermal analyses. Thermogravimetric analysis (TG) was carried out in the range of 25–700 °C in Nitrogen (flow = 20 mL min^{-1}) at a heating rate of 10 °C min^{-1}. Samples with masses of approximately 8 mg were used in a platinum can. Differential scanning calorimetry (DSC) was performed in the range of −50 to 150 °C. Samples were first cooled to −50 °C. Then, the samples were heated from −50 to 100 °C. After they had been cooled from 100 °C to −50 °C, a second heating was carried out from −50 to 150 °C. The scans were performed at the heating/cooling rate of 10 °C min^{-1} in a nitrogen atmosphere (flow = 40 mL min^{-1}).

Mechanical tests of the materials were performed on an EMIC-DL300 universal testing machine at ambient temperature. A 50 N load cell and a minimum of 5 test pieces were used in each test. The tensile tests of the films were based on ASTM D 882-12, using a crosshead speed of 20 mm/min.

The contact angle analysis was performed on a Goniometer Pixelink model DGD Int DI with the application of 6 μL of deionized water to the PU film surface at room temperature. Ten scans were performed on each sample.

For the water absorption test, PU films were dried at 60 °C for 4 h and then weighed and immersed in deionized water at room temperature. Samples were removed after predetermined periods of immersion, placed on a filter paper to remove surface water and weighed again. Assays were performed in triplicate. The content of water absorption from each sample was calculated according to Eq. (1), where M_t is the mass after immersion in deionized water, and M_s is the dry mass of the samples. The results presented are the average of three samples for each experiment, with standard deviation lower than 5%.

$$\text{Water Absorption}\ (\%) = \frac{(M_t - M_s)}{M_s} \times 100 \quad (1)$$