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Biodegradable non-aromatic adhesive polyurethanes based on disaccharides for medical applications

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ABSTRACT

This work addresses synthesis, characterization, adhesive properties, protein adsorption and *in vitro* biodegradation of non-aromatic polyurethanes (NPUs). The following reactants were used in the syntheses of polyurethanes (PUs): non-aromatic 4,4′-Methylenebis(cyclohexyl isocyanate) (MCI), disaccharides (maltose and sucrose) and polyethylene glycol 200 (PEG 200). The NPUs exhibited low glass transition temperature (T_g) and good thermal stability. The dynamic contact angles on NPUs were influenced by the ratios of PEG 200-disaccharide monomer and the hard segment of the NPUs. The highest adhesion strength in whole polyurethanes was found as 307.6 ± 50.1 kPa for 15% sucrose containing polyurethane. Protein adsorptions of polyurethane films were measured as average 10 μg Bovine Serum Albumin (BSA)/cm^2 and 5 μg fibrinogen/cm^2 for maltose, and 15 μg BSA/cm^2 and 5 μg fibrinogen/cm^2 for sucrose. Biodegradability ratios of NPUs were in the range of 15–35% for 8 weeks depending on the disaccharides containing NPUs.

1. Introduction

Surgical tissue adhesives continue to evolve as an important technology for the facial plastic and reconstructive surgery [1]. Twelve years ago there was little routine use of these substances; however, in the past 5 years there have been significant advances [1,2]. Today, as a tissue adhesive, many items are used from cyanoacrylates to fibrin tissue adhesives. But these adhesives do not provide the requirements of today′s medical applications. An ideal surgical tissue adhesive must meet the following criteria: strong binding strength, ease of application, tissue biocompatibility, biodegradable byproducts, minimal tissue reactivity, and reasonable cost [1].

Polyurethane is a unique material that offers the elasticity of rubber combined with the toughness and durability of the metal and proves to be very versatile with high-performance polymers having applications as diverse as coatings, adhesives, elastomers, fibers and foams [3]. Polyurethanes are also one of the most popular groups of biomaterials applied for medical applications because of their biocompatibility and excellent mechanical properties [4–6]. Their segmented block copolymeric character endows them a wide range of versatility in terms of tailoring their physical properties, blood and tissue compatibility. However, as most polyurethanes are non-degradable, they may cause long-term foreign body reaction, may fail to integrate or exhibit material fatigue and have found little use in the field of tissue engineering [7]. The biocompatibility and biodegradability of the polyurethanes can be improved by chemical modification of their structure by cross-linking with multi-functionalized natural compounds. Biodegradability of polyurethanes is generally achieved by hydrolysable moieties into the polymer backbone [8]. The most common method for fulfilling this goal is the application of polyols (soft segments) with hydrolysable bonds as starting materials for the preparation of polyurethanes. Polycaprolactone, polyalkylene adipate, polylactides, or polyglycolides were used for the synthesis of hydrolytically degradable polyurethanes [9–11]. Disaccharides and PEG units in polymeric structure may carry biodegradable properties for polyurethanes. In addition to, using non-aromatic diisocyanate can contribute to biocompatibility properties of polyurethanes.

In the previous study, Rao, et al. investigated the feasibility of PEG-containing PU hydrogel as coatings for neural electrodes in order to achieve a stable neural interface. They suggest that PU–PEG hydrogel coating is feasible and favorable for neural electrode applications [12]. PEG modified PU surfaces were also reported to prevent the bacterial adhesion [13]. PEG-containing novel PU was prepared for PU scaffold with improved mechanical and biomedical properties. These novel PU scaffolds are expected to potentially be employed in tissue engineering as temporary mechanical scaffolds [14].

Surprisingly there have been little works published on renewable sources polyurethanes and most of them were based on the

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combination of these polymers with other natural resource materials such as soy dreg, soy protein, starch, castor oils and cellulose triacetate [15–20]. Saccharide based aromatic polyurethanes reported in the literature are just rigid chemical structured polymers and do not show flexible property [21]. But in this study, by adding PEG group to non-aromatic polyurethane structure, these materials have more flexibility and stronger adhesive properties. Thus, prepared saccharide and PEG containing non-aromatic polyurethanes are good candidates for medical applications as a tissue adhesive material.

With this background, this paper reports on synthesis, characterization, adhesive properties, protein adsorption and *in vitro* biodegradation of non-aromatic polyurethane based on disaccharides (maltose and sucrose).

2. Materials and Methods

2.1. Materials

All chemicals, used for the synthesis of the polyurethane, were obtained from Sigma-Aldrich (Gillingham, U.K.). 4,4′-Methylenebis (cyclohexyl isocyanate) (MCI) (Aldrich, U.K.) was dried in 4 Å molecular sieves before the experiment. Polyethylene glycol (PEG 200, Mw=190–210 g/mol), BSA and fibrinogen were obtained from Sigma-Aldrich, St. Louis, MO, USA. H_3PO_3 and Toluene were obtained from Fisher Chemical (Loughborough, U.K.). Sodium dodecyl sulfate, o-phthaladehyde, Tetrahydrofuran (THF) and KBr were used as received from Merck (Darmstadt, Germany). Tetrahydrofuran (THF) was also dried by vacuum distillation. The other reagents were used as received.

2.2. Experimental techniques

Infrared spectra were recorded as KBr pellets in the range 4000–400 cm^{-1} on an ATI UNICAM systems 2000 Fourier transform spectrometer. Thermogravimetry (TG) curves of all the NPU samples were recorded using Shimadzu TGA-50 analyzers. The curves were obtained at a heating rate of 10 K min^{-1} in dry air atmosphere (30 ml min^{-1}). The sample weight was ca. 5 mg. The thermal degradation temperature (T_d of these materials) is defined as the temperature at the point of intersection of the tangents drawn from a point before the main decomposition step and from the point of inflection of the main step. Differential scanning calorimetry (DSC) was performed on all NPU samples using a Shimadzu DSC-60. The scanning rate was 10 K min^{-1} in dry air atmosphere (30 ml min^{-1}) and the sample weight was ca. 5 mg. The glass transition temperature (T_g) was defined as the temperature at the point of intersection between the tangents drawn at the point of inflection of the transition and at the flat part of the curve before the transition. Adhesion properties of the NPUs were recorded with a material strength testing machine (SYC-500, Sundoo, China) by the peel test-method [22].

2.3. Synthesis of NPUs containing disaccharides

4,4′-Methylenebis(cyclohexyl isocyanate) (MCI) (0.05 mol) was dissolved in tetrahydrofuran (THF). Then, poly-ethylene glycol (PEG) and various ratios of maltose (M) or sucrose (S) were added to the diisocyanate solution with rapid stirring at 30 °C for 10 min followed by more stirring at 90 °C for 5 h to complete the reaction. The NCO:OH ratio was kept constant at 1:1 and the saccharide content was varied. The NCO:OH ratio was controlled by a method as described in publication of Chivers et al. [23]. The ratios of PEG 200-disaccharide monomer units in the polyols were: 95:5, 90:10, and 85:15, respectively (Fig. 1). The final concentration of NPU in

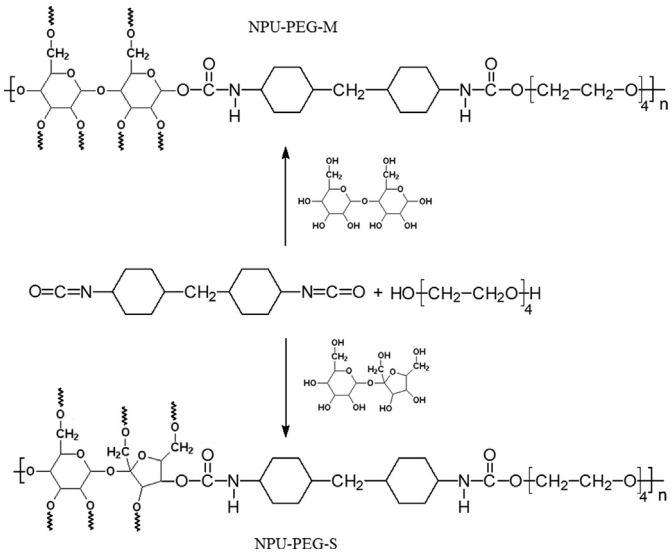

Fig. 1. Synthesis of disaccharide containing NPUs.

THF was 30% by weight. The NPU films were formed by casting the solution in a mold and then removing the solvent at 70 °C for 3 h. The polymer was dried at 60 °C under vacuum for 4 days. The infrared (IR) spectrum was recorded to determine the reaction extent and end of the reaction. The disappearance of –NCO groups was an indication of reaction completion [24].

2.4. Preparation of NPUs containing disaccharide films

One part of the polyurethane solution was degassed in vacuum and then quickly transferred to a glass plate using a doctor blade (e=2 mm). The solvent was evaporated at 100 °C for 3 h and treated at 150 °C for 2 h. The film was removed from the glass plate by soaking it in cold water.

2.5. Adhesive strength analysis

Strength tests were performed using aluminum adherends (20 mm width × 100 mm length). The adherends were polished by grinding well and were cleaned after polishing by soaking for 10 min each in ethanol and then water. The adherends were dried overnight in air at room temperature. A 20 mm × 20 mm (4 cm^2) overlap area for adhesive was used with 0.2 g samples. After overlap, samples were incubated for 1 h and 24 h cure in air at room temperature. After this cure, shear load–extension curves were obtained with material strength testing machine (SYC-500, Sundoo, China). The force applied to the fixture was measured with a 500 N load cell. Samples were held in place in the testing and extended in the shear direction at a speed of 20 mm/ min. Adhesion force, in Newtons, was determined by the maximum point of the distance versus force plot, just prior to failure, after which the force dropped substantially. Adhesion forces expressed in Pascals (Pa) were obtained by dividing the shear force (in Newtons) by the adherend overlap area (in m^2) [22]. Each adhesion measurement was repeated at least five times. Results were given as the mean ± standard deviation.

2.6. Protein adsorption assay

The assessments were performed on disaccharides-based on polyurethanes with Bovine serum albumin (BSA) and fibrinogen proteins according to a standard protocol [25]. For protein adsorption, samples were weighed 0.1 g and films were prepared with 1 cm diameter. Simply, after equilibrated in PBS buffer for 1 h, the