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Development of biodegradable hyper-branched tissue adhesives for the repair of meniscus tears

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ABSTRACT

Meniscus tears are one of the most commonly occurring injuries of the knee joint. Current meniscus repair techniques are challenging and do not bring fully satisfactory results. Tissue adhesives are a promising alternative, since they are easy to apply and cause minimal tissue trauma.

In this study, a series of amphiphilic copolymers based on polyethylene glycol, trimethylene carbonate and citric acid were synthesized and subsequently end-functionalized with hexamethylene diisocyanate to form reactive adhesive materials.

The shear adhesive strength of the networks to bovine meniscus tissue measured in a lap-shear adhesion test ranged between 20 and 80 kPa, which was better than for fibrin glue (10 kPa). The elastic modulus of the networks depended on composition and was in the same range as that of human meniscus. Cell compatibility was assessed using Alamar Blue staining after incubation of the bovine meniscus cells with different concentrations of the glues for 7 days. Cell viability was not affected after adding up to 3 mg of the adhesive/mL of medium.

The proposed materials are suitable candidates to be used as resorbable tissue adhesives for meniscus repair. They have excellent mechanical and adhesive properties that can be adjusted by varying the composition of the copolymers.

Statement of Significance

Meniscal tears often occur and current treatment strategies do not bring fully satisfactory results. Use of biodegradable tissue adhesives would be an interesting option, but currently available adhesives are not suited due to toxicity or poor mechanical properties.

Here, we describe the development of novel biodegradable, hyper-branched, adhesive copolymers. These adhesives cure upon contact with water forming flexible networks. Their adhesion to bovine meniscus tissue was significantly better than that of clinically used fibrin glue. The tensile properties of the cured networks were in the same range of values of the human meniscus. When physiologically relevant amounts were added to cells in culture, not toxic effects were observed. Therefore, the proposed materials are interesting resorbable tissue adhesives for meniscus repair.

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1. Introduction

Menisci are fibro-cartilaginous tissues present in duplicate in the knee joint. They play a crucial role in shock absorption and distribution of forces in the joint, as well as in lubrication and

nutrition of articular cartilage [1]. Most injuries of the knee are associated with meniscus trauma; the meniscus tears which lead to pain, swelling and locking of the joint. Since menisci are only well-vascularized in the outer, peripheral zone, they have very limited capacity to self-repair [2,3].

The preferred treatment strategy is to repair the meniscus using sutures or staples to restore the integrity of the tissue [4], or in case of tears in the avascular outer part, a partial meniscectomy is frequently performed. However, both solutions carry their drawbacks.

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Meniscectomy brings instant pain relief, but removal of only 15–34% of the meniscus will lead to a 350% increase in the contact stress in the joint and thus eventually will lead to development of degenerative changes and osteoarthritis [5]. Using sutures on the other hand, is mostly successful in the vascularized, peripheral zone of the meniscus, where cells have access to nutrients and growth factors [6,7]. The arthroscopic procedure using sutures is technically challenging, time-consuming, the sutures are expensive and the success rate very much depends on the location and type of tear [8].

An attractive alternative for suturing would be use of biodegradable tissue adhesives [9]. Ideally, these materials provide stability by holding the torn tissue together during the period of healing, and gradually degrade to biocompatible products [10]. The application procedure could be faster, easier and cheaper than in the case of sutures. Tissue adhesives are already successfully used in other surgical applications, such as Dermabond® (2-octyl cyanoacrylate) for skin lacerations [11] or fibrin glue in hemostasis or pulmonary air leaks [12,13]. However, none of them is suitable for gluing the damaged meniscus. Cyanoacrylates are rigid and brittle materials, their elastic modulus (E_{mod}) is approximately 500 MPa [14], while the E_{mod} of meniscus tissue (in circumferential direction) is only between 40 and 160 MPa [1,15]. Moreover, formaldehyde is a degradation product, which limits their application within the body [16]. Fibrin glue is a natural biocompatible compound, but has poor mechanical and adhesive properties and a rapid degradation profile [17,18]. Furthermore, it can be a source of disease transmission [19].

With these limitations in mind, we have been developing new polymeric tissue adhesives that are flexible and strong, and at the same time biocompatible and biodegradable. The adhesion process to the tissue consists of two steps: (1) wetting the surface of the tissue and (2) attachment to the tissue and curing of the material (network formation) [20]. Therefore, in order to provide optimal gluing of the meniscus, the glue must first spread well on the wet tissue surface. The material should therefore be sufficiently hydrophilic. At the same time, the polymeric network that is formed upon curing of the adhesive should be able to withstand the mechanical forces present at the site of application. For this, we envisaged the use of amphiphilic block-copolymers with hydrophilic blocks that ensure good spreading on the tissue surface and hydrophobic blocks that lead to networks with adequate mechanical properties.

Previously, we reported on the synthesis and characterization of 3-armed star-shaped isocyanate-terminated block copolymers based on trimethylene carbonate (TMC) and trimethylolpropane ethoxylate (TMPE) [21]. These materials are capable to react with primary amines present in the proteins at the surface of the tissue and form stable covalent urea bonds with them [22]. At the same time they react with surrounding water forming a solid polyester-polyurethane network.

We showed that these 3-armed copolymers had good adhesive potential and demonstrated better properties than analogous linear copolymers. Based on these results, we expect that by increasing degree of branching of the copolymers, and then the number of reactive groups which attach to the surface, it will be possible to enhance their adhesive properties.

In this paper, we report on the synthesis and characterization of novel hyper-branched amphiphilic, isocyanate-terminated copolymeric oligomers that vary in composition and in architecture and their possible application as a tissue adhesive for meniscus repair.

2. Materials and methods

2.1. Materials

Poly(ethylene glycol) with number average molar mass (M_n) of 200 g/mol (PEG₂₀₀) and 600 g/mol (PEG₆₀₀), citric acid (CA),

chloroform-d (CDCl_3), fibrinogen and thrombin (both isolated from bovine plasma), phosphate buffered saline (PBS), cholesterol esterase (from porcine pancreas, 35 U/mL) (CE) were purchased from Sigma Aldrich (the Netherlands). Trimethylene carbonate (TMC) was obtained from ForYou (China). Hexamethylene diisocyanate (HDI) was purchased from Merck Schuchardt (Germany). Diethyl ether was purchased from Biosolve (the Netherlands). PEG₂₀₀ and PEG₆₀₀ were dried at 120 °C under vacuum, diethyl ether was dried over molecular sieves prior to use. All other chemicals were used as received. Dermabond® was obtained from Ethicon (Johnson & Johnson, The Netherlands). Dulbecco's Modified Eagle's Medium (DMEM), fetal bovine serum (FBS) and Antibiotic-Antimycotic (PSF, contains 10,000 units/mL of penicillin, 10,000 µg/mL of streptomycin, and 25 µg/mL of Fungizone®) were purchased from Gibco® (UK). Collagenase type II was purchased from Worthington (USA). Bovine meniscus tissue was obtained from a local abattoir.

2.2. Synthesis of oligomers and isocyanate-terminated hyper-branched oligomers

A series of reactive isocyanate-terminated hyper-branched oligomers was prepared in a three step synthesis process, which is schematically depicted in the Fig. 1. Ring opening polymerization of TMC using PEG as initiator was performed as previously described [21] (Fig. 1a). TMC was reacted with PEG₂₀₀ or PEG₆₀₀ using $\text{Sn}(\text{Oct})_2$ (0.02 mmol/mol of monomer) as a catalyst. The polymerization was conducted at 130 °C for 3 days under argon atmosphere. Linear oligomers with TMC to PEG molar ratios of 2:1 and 4:1 were prepared. The used nomenclature for these block-copolymeric precursors is: $\text{PEG}_m\text{-(TMC}_n)_2$, where m is molar mass of PEG, n is the number of TMC units (in PTMC chain) per PEG chain end.

Then, the linear oligomers were reacted with CA in a polycondensation reaction at 120 °C for 1 day under vacuum (Fig. 1b). In this manner hyper-branched oligomers were obtained with $\text{PEG}_m\text{-(TMC}_n)_2$ to CA molar ratios of 4:1, 7:1 and 10:1, respectively. The used nomenclature of these hyper-branched oligomers is: $\text{CA-xPEG}_m\text{-(TMC}_n)_2$, where x is 4, 7 or 10. To obtain reactive isocyanate-terminated molecules, these hyper-branched oligomers were subsequently reacted with excess of HDI at 75 °C for 1 day under argon atmosphere (Fig. 1c). Drop-wise addition of the hyper-branched oligomer to HDI ensured that the molar excess of HDI was at least 1:3. Unreacted HDI was removed by washing in dry diethyl ether. The product was then dried under vacuum overnight. The resulting products were labelled: $[\text{CA-xPEG}_m\text{-(TMC}_n)_2\text{-HDI}]$.

An overview of prepared reactive isocyanate-terminated hyper-branched oligomers is given in Table 1.

The composition and chemical structure of the intermediate linear- and hyper-branched oligomers, and of the isocyanate functionalized end-products was evaluated using ¹H NMR spectroscopy (Bruker 400 MHz NMR spectrometer) using CDCl_3 as the solvent. The –NCO content of the reactive hyper-branched oligomers was determined by back-titration of the isocyanate groups according to the ASTM D2572 standard.

2.3. Characterization of the networks obtained after curing the isocyanate-terminated hyper-branched oligomers

Cross-linked polyurethane networks were obtained by casting 0.3 mm thick films of the isocyanate-terminated hyper-branched oligomers on glass plates, subsequent overnight immersion in water at room temperature (RT) allowed the curing reaction to take place.

In order to determine the physical characteristics of the obtained water-cured network films, they were dried in vacuum

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