



New injectable elastomeric biomaterials for hernia repair and their biocompatibility



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ARTICLE INFO

Article history:

Received 31 May 2015

Received in revised form

11 October 2015

Accepted 14 October 2015

Available online 19 October 2015

Keywords:

Hernia repair

UV crosslinking

Methacrylates

Injectable polymers

Fatty acid

ABSTRACT

Complications associated with implantation of polymeric hernia meshes remain a difficult surgical challenge. We report here on our work, developing for the first time, an injectable viscous material that can be converted to a solid and elastic implant *in vivo*, thus successfully closing herniated tissue. In this study, long-chain fatty acids were used for the preparation of telechelic macromonomers end-capped with methacrylic functionalities to provide UV curable systems possessing high biocompatibility, good mechanical strength and flexibility. Two different systems, comprising urethane and ester bonds, were synthesized from non-toxic raw materials and then subjected to UV curing after injection of viscous material into the cavity at the abdominal wall during hernioplasty in a rabbit hernia model. No additional fixation or sutures were required. The control group of animals was treated with commercially available polypropylene hernia mesh. The observation period lasted for 28 days. We show here that artificially fabricated defect was healed and no reherniation was observed in the case of the fatty acid derived materials. Importantly, the number of inflammatory cells found in the surrounding tissue was comparable to these found around the standard polypropylene mesh. No inflammatory cells were detected in connective tissues and no sign of necrosis has been observed. Collectively, our results demonstrated that new injectable and photocurable systems can be used for minimally invasive surgical protocols in repair of small hernia defects.

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1. Introduction

An abdominal wall hernia is one of the most common health problems and is related to an outpouching of the parietal peritoneum through a preformed or secondarily established hiatus [1]. Around 10% of the Earth's population experiences some type of abdominal wall hernia during their lifetime [2], with a large majority being inguinal hernias [3]. In the USA, there were 920,000 hernia surgeries performed in 2006 which accounts for 1.8% of all surgical procedures [4]. Statistical nationwide data for USA (2006) [4], Poland (2007–2009) [5], and Denmark (2006–2010) [6] show there are respectively 1700, 1480 and 1650 inguinal hernia surgeries per million citizens carried out each year. To reinforce

weakened tissue and avoid its over-stretching, non-resorbable synthetic materials—usually polypropylene meshes (PPM)—are used during hernioplasty [7–12].

Currently, the most popular are heavyweight meshes that are often oversized in terms of mechanical stiffness and contribute to tissue damage and pain [13]. Examples of these type of meshes include Marlex®, Prolene® and Atrium®. Lightweight polypropylene meshes have larger pores and are more compatible with tissue. Surgipro®, Permilen® or 3DMax™ Light Mesh are examples of lightweight meshes. There is also a niche of meshes made of poly(ethylene terephthalate), Mersilene® being one of them.

These commonly used polymer meshes themselves are responsible for some complications. Surgical meshes are regarded as physically and chemically inert and stable, non-immunogenic and non-toxic. However, numerous experimental and clinical studies have revealed a typical foreign-body reaction at the interface of mesh devices, including inflammation, fibrosis, calcification, thrombosis or infection [14–17]. In many cases the mesh shrinks with time *in vivo*, which can cause rupture of the anchors

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resulting in tissue stresses, further causing pain and inflammation [18–20].

Due to the aforementioned mesh-related issues, new approaches are being developed. They include coatings on classical meshes providing them with antimicrobial [21–24] or anti-adhesive [25–27] properties. Other approach focuses on incorporating various materials into the mesh structure, including poly(vinylidene fluoride) [28,29], poly(tetrafluoroethylene) [30,31], cellulose [32], or chitosan [33]. About ten years ago the topic of resorbable meshes gained great attention. A resorbable mesh is composed of various types of polyester and polycarbonate fibers having different times of degradation [34,35]. Another example can be a mesh plug made of polyester and polycarbonate that degrades in about six months [36]. Resorbable meshes composed of poly(4-hydroxybutyric acid) [37], fibroin [38], poly(ϵ -caprolactone) [39], or polyurethanes [40,41] have also been described. Still, resorbable hernia meshes are a novelty and no comprehensive clinical data are available to confirm their reliability and safety. In the contrary, early *in vivo* studies suggest that some of them can cause complications [42,43].

Meticulous analysis of the state-of-the-art regarding hernia repair clearly shows that there is still a lot of space for improvement both in terms of biomaterials and protocols. In our opinion it is evident that an effective, safe and long-term degradable, suture-free material suitable for minimally invasive protocols would be a milestone in modern approach to hernia therapy. It would also facilitate the expansion of endoscopic techniques in this field.

Recognizing the importance of the problem, we fabricated for the first time injectable polymers capable to turn into flexible materials in defected tissue cavity. We report here on our investigation on the mechanical properties and biological response *in vitro* and *in vivo* of flexible materials formed upon UV-curing of telechelic methacrylic macromonomers comprising fatty acids [44]. In addition, we examined the potential of the injectable material for herniated tissue reinforcement and reconstruction.

2. Experimental

2.1. Materials

Two different telechelic macromonomers, containing dimerized fatty acid as a core molecule with urethane and ester groups, and terminal acrylic functionalities, were synthesized according the procedure described elsewhere [44]. Briefly, 5 ml of methylene chloride (MC, Sigma Aldrich), 15 mg of isophorone diisocyanate (98%) (IPDI, Sigma Aldrich) and 12 mmol dibutyltin dilaurate (95%) (DBTDL, Sigma Aldrich) were introduced to a 100 mL round bottom that was kept in an ice bath. After 30 min of stirring, dimer fatty acid ester, Priplast 1838 (kindly provided by Croda, The Netherlands) in 20 mL of MC was added dropwise over 30 min. When the addition was complete, the ice bath was removed and the reaction continued at room temperature until the isocyanate groups stopped decaying. This was determined by FTIR. We monitored the ratio of A 1534/A 2263, where A 1534 is the FTIR absorbance at 1534 cm^{-1} (bending N–H vibrations in forming urethane bond) and A 2263 is the absorbance at 2263 cm^{-1} (N=C=O vibrations in decaying isocyanate groups). When the isocyanate groups stopped decaying, a small amount of DABCO and 25.2 mmol of 2-hydroxyethylmethacrylate (97%) (HEMA, Sigma Aldrich) were introduced and the bath temperature was raised to 35 °C. The reaction continued until all isocyanate groups were converted, as confirmed by FTIR. Phenothiazine was then added to the reaction mixture, the product was precipitated into five-fold excess of ice-cold methanol, washed thoroughly with methanol, and the residual solvent was evaporated. The resulting

product, abbreviated as P1838-UR was a transparent, highly viscous, sticky, colorless liquid. The yield relative to Priplast 1838 was 80%.

A second macromer containing ester groups was obtained in a condensation reaction of Priplast 1838 with MC. Briefly, 33.6 mmol of Priplast 1838 was introduced to a 100 mL round-bottom flask. Then, MC was added, followed by 40 mmol of triethylamine (TEA, POCh, Poland). The reaction mixture was cooled down to 0 °C and stirred for 30 min. Afterward, 37 mmol of MC was added dropwise over 30 min. The reaction mixture was removed from the ice bath and allowed to warm to room temperature. Stirring was continued for another 24 h. Then, the reaction mixture was filtered to remove the trimethylammonium salt and subsequently extracted with saturated sodium bicarbonate solution (twice), deionized water (twice) and brine (once). The organic phase was dried over magnesium sulfate and filtered. After adding 100–200 μmol of phenothiazine for each mol of C=C double bond content, the organic phase was evaporated to dryness. The product, abbreviated as P1838-DMA, was viscous, sticky and colorless fluid. The yield relative to Priplast 1838 was 70%.

As a reference UV-curable material not containing fatty acid, an ester-urethane derived from poly[di(ethylene glycol) adipate] (PDEGA-UR) was synthesized according procedure analogous to procedure for P1838-UR using poly(diethyleneglycol adipate) (PDEGA), hexamethylene 1,6-diisocyanate (HDI), and 2-hydroxyethylene methacrylate (HEMA). This material served as reference in the hernia repair model.

Scheme 1 presents the chemical structure of urethane and ester macromonomers.

Selected properties of prepared macromonomers are summarized in Table 1.

2.2. Photocuring process

Synthesized telechelic macromonomers were photocured with a black light ($\lambda_{\text{peak}} = 365 \text{ nm}$) for 2–5 min in air. 1–2% of photoinitiator (IrgacureTM 819, Ciba) was used. A solution of Irgacure 819 in dichloromethane was added to a macromonomer, such that the macromonomer concentration was 50% (w/v) and the photoinitiator content with respect to the macromonomer was 1% (w/w). The clear solution of the macromonomer with photoinitiator was then poured into a Petri dish and the solvent was evaporated under reduced pressure. The composition was then irradiated using a UV-torch with emission peak at 365 nm (Labino, Sweden). The total irradiance was 12 mW/cm^2 . After 180 s of UV exposure under air atmosphere at room temperature flexible films of 0.5 mm thickness were obtained.

2.3. Characterization of chemical structure

To characterize chemical structure of photocured networks, infrared spectrophotometric measurements were performed with Bruker Alpha – Platinum ATR apparatus, with Beamsplitter KBr, in the range of 4000–400 cm^{-1} at 24 scans and the resolution of 4 cm^{-1} .

2.4. Water contact angle

Contact angle measurements were carried out on photocured 0.5 mm thick films by sessile drop shape analysis using Krüss DSA 100 Drop Shape Analyzer equipped with a camera and recording system. A 3 μL distilled water drop was applied and the contact angle was measured every second for a period of 60 s. This was repeated on 10 different areas of the sample.

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