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Research Paper

Elastic sealants for surgical applications

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ABSTRACT

Sealants have emerged as promising candidates for replacing sutures and staples to prevent air and liquid leakages during and after the surgeries. Their physical properties and adhesion strength to seal the wound area without limiting the tissue movement and function are key factors in their successful implementation in clinical practice. In this contribution, the advances in the development of elastic sealants formed from synthetic and natural materials are critically reviewed and their shortcomings are pointed out. In addition, we highlight the applications in which elasticity of the sealant is critical and outline the limitations of the currently available sealants. This review will provide insights for the development of novel bioadhesives with advanced functionality for surgical applications.

1. Introduction

Current technologies for reconnecting and sealing tissues after surgical procedures such as sutures, wires, and staples have several limitations, particularly in minimally invasive procedures. For example, the use of suture for wound closure is time-consuming, may cause further tissue damage, result in infection, and do not provide immediate sealing to stop body fluid and air leakages. The application of surgical adhesives is a convenient alternative method for wound closure because of their characteristics, such as simple implementation procedure, shorter time, less painful to patients, and no need for removal. Toward this goal, various types of surgical materials have been used for sealing, reconnecting tissues, or attaching devices to the tissues [1].

Surgical sealants are commonly used to prevent leakage of fluid and/or gas from a incision. Sealants can be formed by using natural or synthetic polymers, or a combination of both. The market for surgical sealants and hemostats is growing rapidly from $4 billion in 2012 to $7 billion in 2017, worldwide [2]. Although several tissue adhesives are commercially available, none of them are ideal surgical sealants for repairing elastic and soft tissues such as wounded lungs, heart, and blood vessels. It is extremely challenging to achieve significant adhesion to soft tissues while minimizing toxicity, tissue damage and other side effects of the sealing materials. Another limitation is the low adhesion strength of the most commercially available sealants in wet and highly dynamic environments in the body at the presence of blood. Most of the clinically available glues and sealants do not offer both elasticity and good adhesion. For example, cyanoacrylates have high stiffness and adhesion strength but are not elastic. On the other hand, fibrin-based sealants are more flexible with low stiffness and adhesion. There is a unmet need for surgical sealants, which can provide flexibility without compromising strength and can stop body fluid and air leakages in different procedures such as lung and cardiovascular surgeries.

Recently, extensive research efforts have been made to engineer biocompatible, biodegradable, and flexible sealants for the formation of leak-free closures in soft tissues [3–5]. The sealant materials are required to be elastic and compliant to allow normal function and movement of elastic native tissues such as lungs, skin, blood vessel, and heart tissues. In this review, various types of elastic surgical sealants made of natural and synthetic polymer are discussed. These include flexible synthetic sealants based on polyurethane (PU), polyethylene glycol (PEG), polyester, and naturally occurring or composite sealants made of proteins or polysaccharides

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(see Table 1). In addition, recent developments in the synthesis of mussel inspired elastic sealants with high adhesive properties are reviewed. Finally, some clinical applications for the elastic sealants in various surgical procedures are highlighted.

2. Synthetic polymer derived elastic sealants

Synthetic-based elastic tissue adhesives have attracted significant attention as suitable wound closure techniques for clinical applications due to their strong adhesive strength and tunable mechanical properties. In particular, elastic sealants based on synthetic polymers can be used for sutureless wound closure in elastic and soft tissues such as lungs, heart, and blood vessels. Some examples of this class of adhesives include PU-based, PEG-based, and polyester-based adhesives.

2.1. PU-based tissue adhesives

PU-based biomaterials have been used as sealants due to their high elasticity and strong adhesion to the tissues. In the prepolymer form, urethane can react with the amino groups of proteins of the tissues to create urea linkages and subsequently promote adhesion strength to the tissues [6]. PU-based biomaterials can be synthesized in biodegradable forms through modification with natural molecules. For example, Ferreira et al. synthesized a biodegradable PU-based adhesives through modification of castor oil with isophorone diisocyanate (IPDI) [7]. They also formed PU-based adhesives through reaction between polycaprolactone (PCL) diol and IPDI or hexamethylene diisocyanate (HDI) [6]. The engineered PU-based adhesives promoted adhesion to the tissue but induced thrombosis as shown by hemolysis tests, which can limit its clinical applications [6]. To overcome this limitation, the group later developed a photocrosslinkable PU-based adhesive through the modification of PCL with 2-isocyanatoerhylmethacrylate (IEMA) [8]. Their experimental data showed that the synthesized material was slightly hemolytic (within the acceptable limit) after directly applying with existence of blood. Moreover, hemolysis was stopped when the material was extracted with PBS solution [8].

Previous studies have shown that the use of PU-based tissue adhesives had no toxic degradation products after surgical procedures such as orthopedic and renal surgery, and pancreatic occlusion. PU-based adhesives have been also used in cosmetic surgery. For example, a sprayable PU adhesives (TissuGlu, Cohera Medical Inc., Pittsburgh, PA) was used for abdominoplasty surgery to avoid seroma formation in a canine abdominoplasty model [9]. It was shown that TissuGlu created strong bonding between tissue layers and supported natural healing process without any toxic effects [9]. Despite significant improvements in the formation of nontoxic and biodegradable PU-based surgical materials, safety concerns still exist for their utilization in surgical procedures.

2.2. PEG-based sealant

PEG-based biomaterials have been widely used as fluid barriers and hemostatic adhesives. There are several commercially available PEG-based surgical materials including Duraseal (Covidien Inc., Mansfield, MA), Coseal (Cohesion Technologies, Inc., Palo Alto, CA), FocalSeal (used to be produced by Genzyme Biosurgery, Inc., Cambridge, MA but it is currently discontinued), and AdvaSeal (Ethicon Inc., Johnson & Johnson Medical KK). Duraseal is made of PEG ester and trilysine amine solutions and has been used for neurosurgeries to prevent cerebrospinal fluid leakage after cranial and spinal operations [10–13]. For example, Preul et al. applied Duraseal on an incision of a cranial dura and arachnoid created in dogs to seal the dural gaps. It was shown that animals treated by the sealant had normal dural healing process with no adverse effects on the brain. In addition, the sealant reduced cerebrospinal fluid leakage and consequently facilitated surgical reexploration [13]. Kim et al. also performed a clinical study to use Duraseal as an adjunct spinal sealant to sutured dural repair. Their study confirmed that the sealant provided watertight closure during spinal surgeries, which was better than the standard care technologies (suture only) for dural closure in spine surgeries [10]. In another clinical study, the suitability of Duraseal for reducing scar tissue and post-operative pain after lumbar microdiscectomy was evaluated [11]. The results on 21 patients showed that Duraseal was safe and reduced post-operation pain as compared to the control group. In addition, the patients treated with the sealant had normal wound healing process with no post-operative complications [11].

FocalSeal is another PEG-based sealant, which was developed to stop air leaks after lung surgeries. It is made from a primer and an acrylated PEG-based sealant [14–16]. The primer layer should be first applied to provide good adhesion to the tissue, followed by the sealant layer to provide adequate mechanical properties and maintain the sealing during the tissue movement. Finally, the sealant is crosslinked by photopolymerization using visible blue light. It was shown that the engineered sealant had elastic modulus of 28 kPa, which was close to human lung tissue (29.4 kPa) and extensibility up to 700% [14]. The results of clinical studies demonstrated that FocalSeal functions as an adjunct to the traditional closure techniques to seal intra-operative pulmonary leaks [17]. In addition, the use of this sealant significantly reduced post-operative air leaks leading to the shorter hospitalization [17]. The production of FocalSeal was discontinued due to its poor adaption by surgeons. Coseal is also a commercially available PEG-based sealant, which is made of two 4-arm PEG with glutaryl-succinimidyl ester and thiol terminal groups [18]. The reaction between thiol groups and the carbonyl groups of the succinimidylester can form covalent bonds between PEG molecules after mixing [18]. Coseal has been employed in vascular surgeries to seal suture lines and stop bleeding [19]. PEG-based sealants have several advantages including biocompatibility, controlled degradability, flexibility, and relatively high adhesion strength. However, high swelling ratio of PEG-based sealants may cause pressure build up on the surrounding tissues when applied in closed cavities [20].

2.3. Other synthetic polymer-based sealant

Different types of polyester-based sealants with elastic properties have been developed for surgical applications to reduce the incidence of fluidic or air leaks. For example, Chen et al. developed a surgical sealant based on poly(glycerol sebacate) (PGS) and lactic acid (LA) [3]. The use of LA improved the cytocompatibility of the engineered sealant compared to PGS alone. The sealant could be applied at 45 °C and solidified at 37 °C to form an elastic gel by exposing to a cold gas. It was shown that the fabricated sealant had higher adhesion strength to the tissues compared to both fibrin glues and synthetic sealants such as Pleuraseal [3]. Photocurable elastomers based on PGS with ultimate strain between 42% and 189% and Young Modulus of 0.05–1.38 MPa were also developed through acrylation of PGS [21]. The engineered synthetic elastomer had been recently used for cardiovascular surgeries to close defects in heart and arteries and stop bleeding [22].

Sealants based on other synthetic polymers have been also developed to close wounds in different surgical procedures. For example, in a recent study, a polyvinyl alcohol (PVA)-based tissue adhesive for wound closure was prepared via sequential enzymatic reactions that were activated by glucose in the wound exudate [23]. The hydrogel was formed *in situ* after applying a mixed