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Review Article

Adhesive and sealant interfaces for general surgery applications

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Abstract: The main functions of biological adhesives and sealants are to repair injured tissues, reinforce surgical wounds, or even replace common suturing techniques. In general surgery, adhesives must match several requirements taking into account clinical needs, biological effects, and material features; these requirements can be fulfilled by specific polymers. Natural or synthetic polymeric materials can be employed to generate three-dimensional networks that physically or chemically bind to the target tissues and act as hemostats, sealants, or adhesives. Among them, fibrin, gelatin, dextran, chitosan, cyanoacrylates, polyethylene glycol, and polyurethanes are the most important components of these interfaces; various aspects regarding their adhesion mechanisms, mechanical performance, and resistance to body fluids should be taken into account to choose the most suitable formulation for the target application. This review aims to describe the main adhesives and sealant materials for general surgery applications developed in the past decades and to highlight the most important aspects for the development of future formulations. © 2015 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 104B: 626–639, 2016.

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INTRODUCTION

Despite sutures are considered a mainstay for several treatments and procedures in general surgery, they also have some drawbacks mainly associated with high infection rate, extensive handling, risk of blood-borne disease transmission and tissue reactivity.[1,2] Moreover, the presence of sutures or staple materials in surgical wounds is considered to increase the risk of infections, which may retard wound healing, cause wound chronicity, and also threaten the patient's life.[3,4] For these reasons, a general trend toward simpler, quicker, and minimally invasive surgical procedures has encouraged the development of sutureless techniques like the use of adhesive and sealant interfaces to restore soft tissue integrity and functionality. These interfaces can be successfully employed in the treatment of emergency hemostasis,[2,5] in sealing leaks of gas or fluids,[6] and in the reinforcement of sutures.[7] Hemostats work by causing blood to clot and are indicated to stop nonsuturable or noncauterizable bleeding particularly in anticoagulated or coagulopathic patients; several surgical operations require a perfect hemostasis, so that the principal aim is the reduction of post-operative bleeding and leakage, especially when parenchymal resections or vascular anastomoses are performed. The use of sealants has been widely described in liver surgery to reduce postoperative blood loss and bile leak, impacting both short and long-term prognosis as they are the most detrimental complications in liver surgery.[8] Spleen traumas represent another field for the application of sealant interfaces. Laparoscopic spleen-preserving procedures have been used for patients with hemodinamically stable splenic injuries; in these patients the topical application of sealants like fibrin glues has shown to enable good bleeding control, even in patients lacking clotting factors or platelets or taking anticlotting medications.[9] Sealants can also be used to prevent the leakage of organic fluids, including lymph cerebrospinal fluid and gastrointestinal contents. Anastomotic leakage can occur at all levels of gastrointestinal surgery; recent studies have shown that this risk appears to be reduced by the use of sealants.[10–12] Tissue approximation of wounds with no tension represents another field in which adhesives can be very useful[13]; in these cases the adhesives need to be strong, water resistant

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and able to function as antibacterial barrier. Another common procedure in general surgery is the use of implantable biomaterials that should be maintained *in situ* in close contact with the target tissue; for instance, implanted devices like meshes, gauzes, webs or catheters need to be kept in place to properly fulfill their functions. Also in these cases, sutureless techniques offer considerable advantages.[14,15]

Overall, general surgery requires an increasing use of adhesive and sealant interfaces for a wide range of operations and treatments. All these strategies are based on the concept of bioadhesion, defined as the process whereby synthetic and/or natural macromolecules adhere to a biological tissue for an extended period of time in the body.[16] To create stable and safe interfaces, an ideal bioadhesive should possess several properties. Provided the biocompatibility of the formulation, which must not be locally irritating, inflammatory, toxic or antigenic, the adhesive should be easily applied or injected in a form of liquid or hydrogel on the target surface. Then, the reticulation process should take place in the presence of body fluids in a conveniently short time, according to the requirements of the specific operation. After reticulation, the adhesive should be as pliable as the tissue, in order to follow its physiologic expansion/contraction, while at the same time ensuring strong binding efficacy; for this reason adequate mechanical properties are required for a proper elasticity/compliance of the interface. In some cases, the adhesive should progressively undergo biodegradation after having exerted its function. Finally, one of the main challenges of bioadhesion is bonding in a wet physiological environment.[16,17]

This wide range of functions is pursued by employing polymers capable of generating a three-dimensional network that binds to the target tissue. Current surgical adhesive and sealants are either based on natural compounds or on synthetic materials; the former are generally well accepted by tissues but often exhibit low adhesive strength while the latter typically display higher strength but lower biocompatibility. Depending on the nature of the polymers, the main classes of adhesives for general surgery include fibrin,[18–20] gelatin,[21] and formulations based on proteins and polysaccharides,[3,22] cyanoacrylates,[23,24] polyurethanes,[25,26] and polyethylene glycol (PEG).[27,28] Beside polymers, novel adhesive strategies considering the topography of gecko-foot[29] as well as the use of silica nanoparticle solutions for gluing gels and tissues are being investigated.[30] The reticulation step can follow different routes: it can be triggered by the chemical reactivity of the adhesive compounds or by the interaction with biological molecules. Chemical approaches include polymerization by contact with physiological fluids (for example, cyanoacrylates) and reticulation triggered by crosslinkers (for example, glutaraldehyde or carbodiimide) or by reactive substituents on the polymer backbone. Biological approaches to initiate network formation include the enzymatic crosslinking as in the case of fibrin-based adhesives in which occur the exploitation of transglutaminase-catalyzed reactions that occur during blood coagulation.[21,31] In general, biochemical crosslinking approaches are preferred, because they provide a more biocompatible adhesion strategy.

The effectiveness of a given formulation stems from a compromise between cohesive and adhesive forces,[32] the former being due to molecular forces within the interface (bulk-bulk bonding), the latter being due to attractive forces between the adhesive and the target surface. Cohesive interactions are required only to a certain extent since too much cohesion may result in a hardened material without significant affinity for a surface. However, adhesive interactions with the target tissue are a fundamental aspect that must be considered for each specific organ of the body.

This review is aimed at considering the most important adhesive and sealant materials for general surgery applications, thus highlighting the scientific progress over recent years and suggesting the importance of continuous research in this field.

ADHESIVES BASED ON NATURAL PRODUCTS

Adhesives based on natural products refer to a class of substances formulated from bio-based raw materials, which are employed as adhesives in man-made technology[33]; some of these bioadhesives work in wet environment,[21,34] which is one of the most important properties for a surgical adhesive, and they typically show good biocompatibility.[35] However, batch-to-batch variation may be a serious concern and sometimes it is difficult to establish reliable large scale production processes. Most bioadhesives proposed for general surgery are based on a variety of substances like proteins (for example, collagen, fibrin, gelatin, and albumin)[36,37] and polysaccharides (for example, chitosan, starch, and dextran).[38,39] Protein-based materials are more commonly used, although polysaccharide-based systems are gaining increasing attention.

Protein-based adhesives

Proteins such as gelatin, fibrin, and albumin have been used in general surgery for many years; the main advantage of protein based formulations is related to their haemostatic properties that can assist the coagulation process.[40,41] They can also be combined with traditional wound closure methods such as stitches, grafts or sutures.[42,43] The main disadvantages of employing proteins as adhesives are their source, the enzymatic degradability, and the high sensibility to fluids, as well as the relatively high price. The major components of these bioadhesives are directly extracted from human biological sources, such as blood, or are based on proteins isolated from animals, such as porcine gelatin or bovine albumin. Fibrin-based haemostatic adhesives carry a risk of disease transmission due to the presence of plasma derived components.[44] These adhesives can be used without the involvement of any other chemical reagents or in combination with active agents (chemical, enzymatic, or photochemical crosslinkers) that trigger crosslinking reactions of the glue while simultaneously forming covalent bonds with the tissue surface.[2] The main protein-based adhesives and sealants are described hereafter.

Fibrin glue. Fibrin-based formulations are currently one of the main biological sealant systems in general surgery applications; they are designed to mimic the last stage of blood

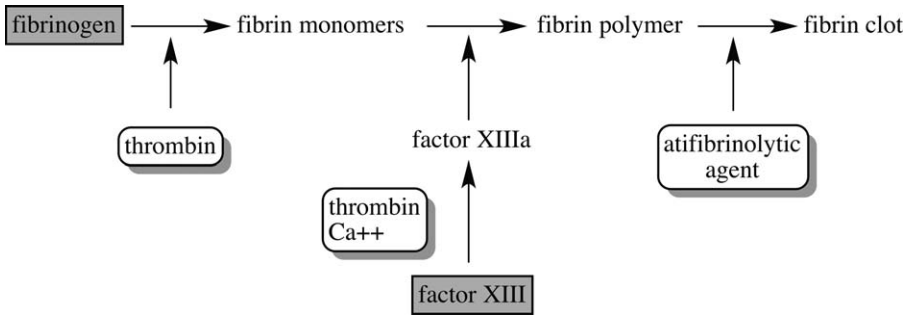

FIGURE 1. Formation of clot based on fibrin crosslinking.

clotting, during which fibrinogen is converted into fibrin clot through a complex coagulation cascade (Figure 1).[45] The process requires the catalysis by thrombin and factor XIIIa, enzymes belonging to the family of transglutaminases. Factor XIIIa catalyzes the formation of covalent bonds between the side chains of different fibrin molecules, contributing to stable crosslinking and resistance to dissolution. Crosslinking occur through the formation of amide bonds between glutamine (Gln) and lysine (Lys) residues in proteins. The transglutaminases have, for this reason, been classified as natural biological adhesives.[46]

Commercial formulations of fibrin glue are typically supplied as a two-component system, in which thrombin (in combination with a calcium chloride solution) and a concentrated solution of human-derived fibrinogen (together with factor XIII) are placed in separate syringe tubes; the two components are mixed together prior to the application on the wounded tissue. In some preparations of fibrin glue, an antifibrinolytic agent is included, in order to prevent premature lysis of the clot and to control gelling kinetics.[44] The Vivostat® system (Vivolution A/S Alleroed, Denmark) is an automated medical device that allows the preparation of an autologous fibrin sealant starting from patient's blood.[47] This approach enables to eliminate the risk of transmitting blood-borne diseases, which is one of the major concerns related to the clinical use of fibrin glues. However, the time required to produce fibrin this way is approximately two days; for this reason, the use of autologous fibrinogen is not compatible with trauma and emergency surgery. All commercial fibrin glues are biodegradable and bioresorbable and the degradation of the fibrin clots occurs through thrombolysis in a time that ranges from few days to weeks. The properties of commercial fibrin glues can be modulated by varying their composition[48]: in a typical formulation the fibrinogen concentration is higher than the one in human plasma, which positively contributes to the strength of the fibrin glue, while thrombin concentration determines the curing time to achieve maximum adhesive strength.[49] The use of fibrin glue hastened when the ability of producing highly concentrated fibrinogen was developed, accounting for stronger adhesion properties.[50] The main physical and chemical processes used for obtaining the fibrinogen necessary to prepare fibrin glues and sealants are based on cryoprecipitation and precipitation with ammonium sulfate, ethanol or PEG. Cryoprecipitation involves several cycles of freezing/thawing and although being a time consuming process, it presents the advantage of avoiding the addition of exogenous chemicals[51,52]; however, this method enables to obtain low concentrations of fibrinogen, which reduces the effectiveness of the adhesive formulation. Conversely, chemical precipitation is considered a fast and efficient method to obtain high fibrinogen concentrations, but with insufficient purity.[53] Fibrin-based adhesives are clinically used in general surgery mainly as hemostats, primary wound closure agents, and as adjuncts to sutures and staples. The majority of reported applications are in surgical procedures, to control bleeding and leaking during and after surgery.[18–20] Fibrin glue is also used as hemostatic agent and sealant in vascular surgeries, particularly to prevent bleeding from suture line and graft area, which is a common issue in this type of operations.[54–56] The application of fibrin glues in the treatment of gastrointestinal diseases, such as in patients suffering from bleeding peptic ulcers, has also been investigated with the aim of replacing surgical procedures by noninvasive endoscopic injections.[57] The main disadvantages of these adhesives are the poor mechanical strength and adhesion in wet environment and the concerns related to the safety of the products. The main concern regards viral transmission (such as HIV, parvovirus B19, hepatitis B, or hepatitis C) from formulations prepared using pooled blood.[2] Only in 1998, the FDA approved the product Tisseel® (Baxter Healthcare, Deerfield, IL), the first generation of commercial fibrin glues. However, some adverse responses can be associated to the use of fibrin-based adhesives. For instance, allergic skin responses[58] or anaphylactic reactions[59] were reported in patients who have been exposed to the bovine aprotinin contained in fibrin sealant. Recently, the efficacy of fibrin sealants was tested in a clinical trial: patients undergoing laparoscopic Roux-en-Y gastric bypass were treated with human fibrin sealant and a reduction of the postoperative bleeding was observed.[37]

Gelatin based adhesives. Gelatin is an irreversibly hydrolyzed form of collagen with many industrial, pharmaceutical, and biomedical applications. Gelatin has been used for centuries as an adhesive for technical applications and was among the first polymeric components to be adapted for medical adhesives. Gelatins are cheap, biocompatible and

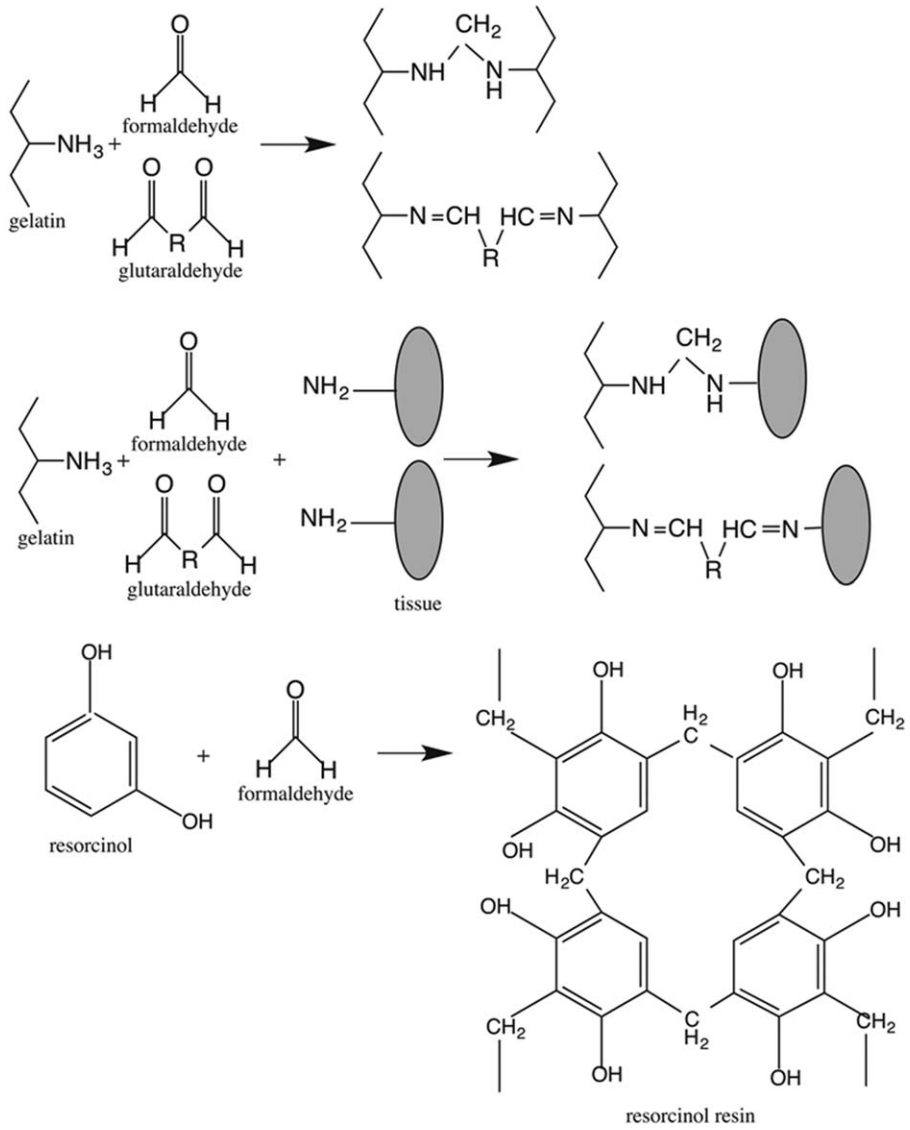

FIGURE 2. Crosslinking of gelatin with aldehydes and resorcinol (Reproduced from Ref. 2).

bioresorbable materials that can form strong, transparent, and flexible gels and films, granting them suitable properties for internal surgery. Gelatin-based tissue adhesives have been recently proposed in clinical field for the treatment of aortic dissection: the amino groups of gelatin were modified with cholesteryl residues conferring improved properties to the adhesive in terms of bonding strength and tissue penetration.[60] Because gelatin hydrogels are relatively unstable in aqueous solutions (they swell and typically dissolve above 35 °C), various chemical crosslinking methods have been used to confer stability under biological conditions to meet bioadhesive properties. The primary purpose of the chemical modification of gelatin with a crosslinker is to increase its adhesion strength and control its degradation rate; crosslinking can be achieved through chemical, photochemical, and enzymatic approaches, as described in the next sections.

Chemically crosslinked gelatin (gelatin-resorcinol-formaldehyde, GRF glue). In these formulations, gelatin chains are crosslinked by aldehydes through a polycondensation reaction. Simultaneously, gelatin amine groups react with amine groups of tissue proteins to form a covalent bond with it (Figure 2); in addition, resorcinol molecules are reticulated by means of formaldehyde to yield a three-dimensional network.[2]

The curing profile of GRF adhesives can be altered by adjusting the ratio of the components; these adhesives are capable to bind to wet tissues and form covalent linkages with functional groups on the tissue surface. Bonding strength is ensured by the penetration of the components into the tissue. Nevertheless, its performance is limited by the cytotoxicity associated with formaldehyde.[61] Resorcinol is less toxic than other phenols because it is less oxidized and produces lower levels of oxygen radicals.[62] Some researchers

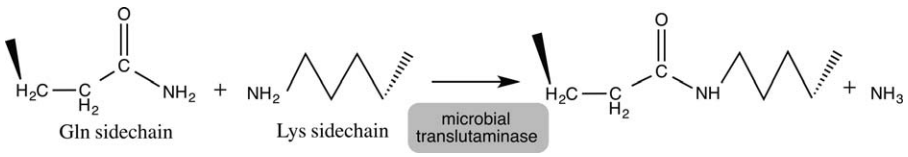

FIGURE 3. Crosslinking of Gln and Lys residues of gelatin by mTG. (Reproduced from Ref. 21).

argued that the GRF glue may become innocuous if an optimal composition of the components can accomplish a polymerization with no residual formaldehyde.[61] There is substantial evidence that GRF glue has beneficial effects on perioperative bleeding and on the incidence of reoperation.[63,64] Surgical application of GRF glues is recommended in cases in which tissue integrity is poor, hemostasis is challenging, and high bonding strength is absolutely imperative.

Enzymatically crosslinked gelatin (gelatin-mTG adhesive). Gelatin can be used as a sealant in combination with a microbial transglutaminase (mTG),[34] which is capable to catalyze its crosslinking.[21,65,66] mTG catalyzes the formation of a covalent bond between a free amine group of a peptide-bound Lys and the acyl group at the end of the side chain of a peptide-bound Gln, with the production of a molecule of ammonia (Figure 3).

The safety of mTG for medical applications has not been extensively tested, but it is worthwhile to note that this enzyme is approved for food uses. Both gelatin and mTG are commercial products obtained from sources that raise less concern than blood. The mTG-catalyzed crosslinking of gelatin does not require low MW compounds (that is, monomers, initiators, and crosslinkers) prior functionalization of the polymer backbone, nor photopolymerization. The current *in vitro* evidence indicates that the gelatin–mTG adhesive is effective under wet conditions[21,34] and that this adhesive confers strengths comparable to other soft-tissue adhesives like fibrin based sealants.[34] The resulting crosslinked network resorbs as a result of normal proteolytic processes. Viscosity and elasticity of the glue (but not its adhesive strength) depend on gelatin type and concentration.[67] One limitation of the gelatin-mTG adhesive is that the protein forms a physical gel at room temperature, and it needs therefore to be warmed to 37 °C prior to use, which could be inconvenient for surgical techniques. Additional long-term studies are required to ensure the biocompatibility and biodegradability of this adhesive and to assess the potential of the gelatin-mTG adhesives to promote wound healing process.

Photocrosslinked gelatin. The synthesis of a tissue sealant based on a photocrosslinkable gelatin was recently reported and the formulation showed high elasticity while retaining excellent adhesive strength.[68] In this case, self-associating proteins, for example, resilin and fibrinogen, can be covalently crosslinked via di-tyrosine bonds within seconds using visible light.[68] Elvin et al. proved that naturally self-associating proteins that contain surface accessible Tyr residues can be crosslinked into polymers using the ruthenium-based photochemistry.[69] The main drawback of the photopolymerized gelatin is its high swelling ratio (over 240% within 24 h); in an attempt to reduce this swelling, gelatin was derivatized with phenolic residues to increase its amount of tyrosine residues.[68]

The potential of photocurable gelatin in tissue sealing was tested in a sheep surgical model[68]: the photopolymerized gelatin sealed a wound in lung from leakage of blood and air, with excellent post-surgery outcomes. In another study, a photochemically crosslinked gelatin sealant was used in rabbit and canine gastrointestinal models with good mechanical and biological outcomes; the sealant demonstrated high elasticity and adhesive strength and good tissue integration.[70]

The effectiveness of a gelatin-based adhesive was evaluated in an experimental study on rat's liver: the results pointed out its efficacy in the establishment of a good tissue adhesion and hemostasis.[71] Sato et al. reported a case where the use of gelatin-resorcinol-formal glue was effective in the treatment of postoperative fistula following a low anterior resection in colorectal surgery.[72] Despite all the advantages of this material, potential contamination with animal infective agents is still the major concern on the use of gelatin.

Albumin-based glues. Albumin–glutaraldehyde adhesives are able to establish covalent bonds with functional groups on the tissue surface, thus creating an elastic seal. These glues also adhere to synthetic graft materials through mechanical bonding within the interstices of the graft matrix. The reticulation of bovine serum albumin (BSA)/glutaraldehyde tissue adhesives occurs by a condensation reaction between amino groups of Lys residues in the BSA protein and glutaraldehyde. Albumin–glutaraldehyde glues tend to degrade slowly and they can persist at the repair site for up to 2 years after application.[73] The commercial formulation BioGlue® (Cryolife, Kennesaw, GA) is a tissue adhesive composed of BSA mixed with glutaraldehyde and is able to adhere to tissues and to synthetic graft materials. It is currently being used as an adjunct for securing hemostasis at vascular anastomoses.[74,75] The effectiveness of BioGlue® in preventing air leakage in pulmonary surgery was demonstrated on rats.[76] In a pilot clinical study, the usefulness of BioGlue® for the treatment of high transsphincter anal fistulas was reported.[36] An improper use of albumin–glutaraldehyde glues was reported to cause negative outcomes in case of excessive application.[77] An *in vivo* study on rabbits reported that the release of glutaraldehyde upon polymerization could cause a certain extent of cytotoxicity when applied on lung and liver tissue.[74]

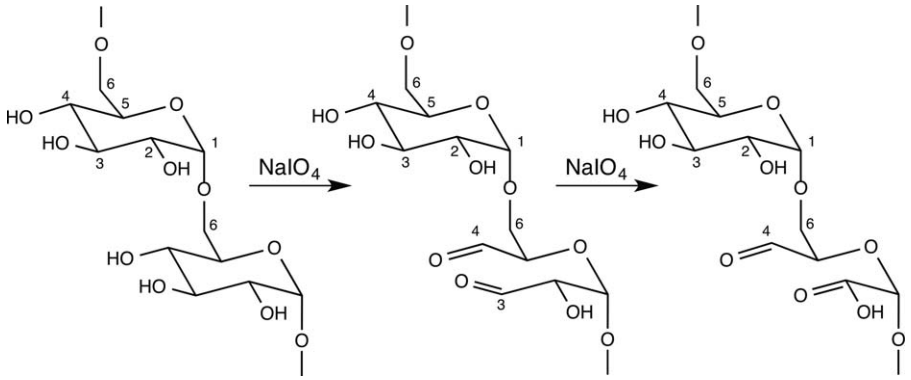

FIGURE 4. Oxidation of dextran to yield reactive dextran aldehyde for adhesive formulations.

Polysaccharide-based adhesives

In nature, polysaccharides and proteins (or a combination of the two) are natural mediators of adhesion and have found many industrial and pharmaceutical applications over the past decades. They represent a very attractive class of biomolecules for various biomedical fields, including general surgery. In this field, two polysaccharides from marine source, alginate and chitosan, are particularly attractive owing to their biocompatibility, hydrophilicity, adhesiveness, and hemostatic activities.[78,79] These two polysaccharides have been used for the preparation of adhesive nanosheets.[80] As to polysaccharide adhesivity, it should also be mentioned that some microorganisms use acidic or neutral exopolysaccharides (that is, dextran, heparan sulfate, levan) to adhere to a variety of substrates.[81] Certain polysaccharides are able to form hydrogels that exhibit high swelling ratios; although this is a desirable feature when polysaccharides are used in modern wound dressing formulations, in general surgery procedures excessive swelling of polysaccharide-based adhesives can affect the compliance to the tissue. To reduce such behavior and to enhance adhesivity, these polysaccharides can be subjected to chemical modifications as described in detail in the following paragraphs.

Dextran-based adhesives. Dextran is an exocellular bacterial polysaccharide predominantly consisting of linear α-1,6-linked glucopyranose units, with some degree of 1,3-branching. This highly water-soluble polymer is produced in a sucrose-rich environment by *Lactobacillus*, *Leuconostoc,* and *Streptococcus* and is commercially available with different molecular weights. Dextran is also nontoxic and biocompatible and can be degraded through the action of different dextranases (α-1,6 -glucosidases) in various organs in the human body, including liver, spleen, kidney, and colon[82,83]; both the degree of branching and the molecular weight distribution affect its physicochemical properties.[84,85] Besides being highly water-soluble, dextrans are stable under mild acidic and basic conditions. Furthermore, these polymers contain a high density of hydroxyl groups, making them suitable for derivatization and subsequent chemical or physical crosslinking.[85] Dextran-based hydrogels can be used as surgical adhesives; for this application, reactive groups (for example, aldehydes) are introduced into the polymer chain.[38,86] The introduction of these groups can be accomplished by selective oxidation with periodic acid or periodate salts which causes the formation of a dialdehyde-dextran compound, with a free hydroxyl group next to the newly formed aldehydes (Figure 4).

Polysaccharides that have acquired aldehyde groups as a result of oxidation can react with amine groups of cell surface proteins of the tissues thus allowing bioadhesion.[87,88] Moreover, oxidized dextrans can react with amino groups of additional components like gelatins or aminated PEGs to form intermolecular crosslinks.[87] Recently, dextran-PEGs bioadhesives have been proposed as soft tissues sealants[39]; the cohesive integrity of dextran-PEGs formulations comes from imine bonds that form through a Schiff base reaction between amines and aldehydes (Figure 5).[89] The cohesive properties depend on the chemical structure of PEG (for example, number of arms), while tissue/material adhesion strength is primarily determined by the number of aldehydes in the oxidized dextran.

Recently a hydrogel tissue adhesive, obtained by reacting an oxidized dextran with a water-dispersable multiarm polyether amine (PEG) has been developed (ActaMax®): the crosslinking reaction occurs in water and the components undergo a Schiff base reaction to form a crosslinked hydrogel that reticulates within 1 min at room temperature. The formed adhesive is able to adhere to moist tissue and it degrades hydrolytically.[90] Dextran-PEGs adhesives were shown to be non-cytotoxic and noninflammatory, they do not pose the risk of viral contamination[90] and have been used in sealing small intestinal puncture.[39] In a recent experimental study, Artzi et al. applied this adhesive on a small bowel rat model: the average adhesion force to intestinal tissue was found to be higher than with fibrin sealant and close to cyanoacrylates.[89]

Chitosan-based adhesives. Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine residues with a variable number of randomly located N-acetyl-D-glucosamine units; it is produced by deacetylation of chitin, the structural component of the exoskeleton of crustaceans. This polysaccharide has drawn a lot

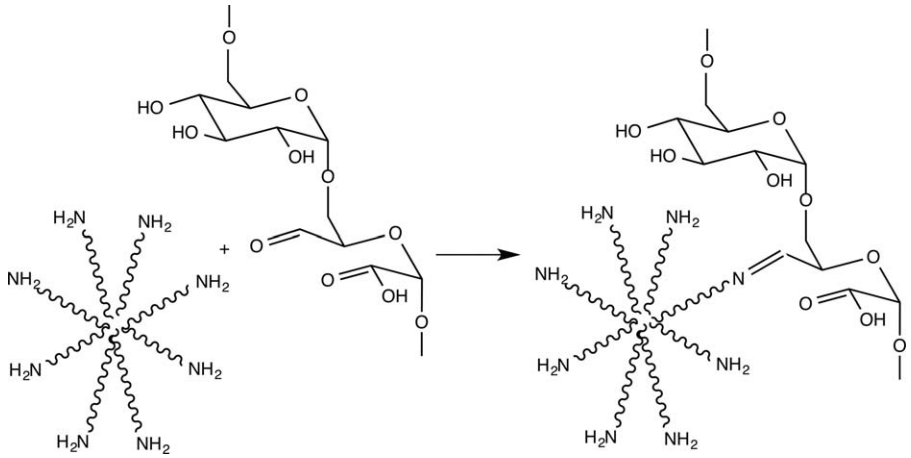

FIGURE 5. Dextran-PEG adhesive: the oxidized dextran aldehyde reacts with an aminated PEG to form a crosslinked hydrogel network through imine bond formation. (Reproduced from Ref. 89).

of attention in the biomedical field, because of its biocompatibility, antioxidant, and bacteriostatic properties.[91,92] Chemical modifications of its amino and hydroxyl groups provides a powerful mean to tailor its biological activity and to modify its physico-chemical properties. Owing to its basic nature, it has the ability to interact with anionic biopolymers, such as glycosaminoglycans, heparin, proteoglycans, and nucleic acids. This ability represents an important aspect in the development of soft tissues bioadhesives. However, despite pure chitosan solutions can establish molecular interactions with the target tissue, they lack cohesion and are not able to generate sufficient adhesion. Cohesion and adhesion can be increased by following various crosslinking strategies. Chitosan-based adhesives prepared through photochemical crosslinking reactions possess photoreactive inert groups (generally phenyl azides and diazirines) that become reactive when exposed to ultraviolet or visible light. A photocrosslinkable hydrogel based on chitosan, 4-azidobenzoic acid (Az)-chitosan® has been proposed for peripheral nerve anastomosis[93]; this bioadhesive was synthesized by conjugating Az with low and high molecular weight chitosans. Another commercially available chitosan-based product is SurgiLux®: the laser activation strengthens the adhesion of the formulation to tissue collagen through polymer chain interactions as a consequence of transient thermal expansion.[94] Its experimental use on intestinal tissue demonstrated good biocompatibility and negligible thermal damage as a consequence of irradiation.[35] Another crosslinking strategy was followed by Serrero and coworkers who reported the preparation of a hydrogel by adding a multifunctional crosslinker based on oxidized starch to chitosan[95]; owing to the aldehyde groups of the oxidized starch, adhesion can be achieved by the molecular interaction with collagen amine groups or with other proteins within the tissue.[87] Various physico-chemical parameters (chitosan concentration, molecular weight, degree of starch oxidation) were found to influence the adhesion properties of the formulations; adhesion tests demonstrated that low molecular weight chitosans were more effective than high molecular weight ones. This behavior was ascribed to improved mobility of the former macromolecules, which likely promotes a wider interaction surface with the tissue, hence an easier covalent or physical bonding with the biological substrate. However, no data about the biocompatibility of the system are available.

Synthetic adhesives. Performance limitations, safety concerns, and potential risks associated with the use of some natural-based adhesives (mostly proteins) have driven researchers to develop adhesives based on synthetic polymers. Synthetic adhesives are based on synthetic chemicals typically in the form of monomers, prepolymers, or noncrosslinked polymers, which undergo polymerization or crosslinking to form an insoluble adhesive matrix when delivered on a tissue.[2] Their three-dimensional structure as well as their chemical composition can be controlled to expose functional groups that can interact with biological tissues, thus providing bioadhesion.[28,96] Molecular weight of nonbiodegradable synthetic polymers should be under the threshold of renal excretion since these polymers have to be cleared by the kidneys.[97] In general, synthetic tissue-adhesives are not associated with the risk of infectious contaminations, although their biocompatibility and toxicity may represent an issue especially in the case of highly reactive components. Several synthetic adhesive materials are employed for general surgery applications: according to their chemistry, the main formulations are based on cyanoacrylates, PEG, and polyurethanes.

Cyanoacrylate adhesives. Cyanoacrylate tissue adhesives are currently the main synthetic polymeric sealants in clinical usage; they possess high bonding strength, very rapid setting time, and instantaneous adhesion to tissues. Some formulations are also reported to inhibit the growth of bacteria.[98] They are prepared as a single-component system that polymerizes at room temperature without the addition of a catalyst, solvent evaporation, heat, or pressure application. These adhesives require no external initiation for

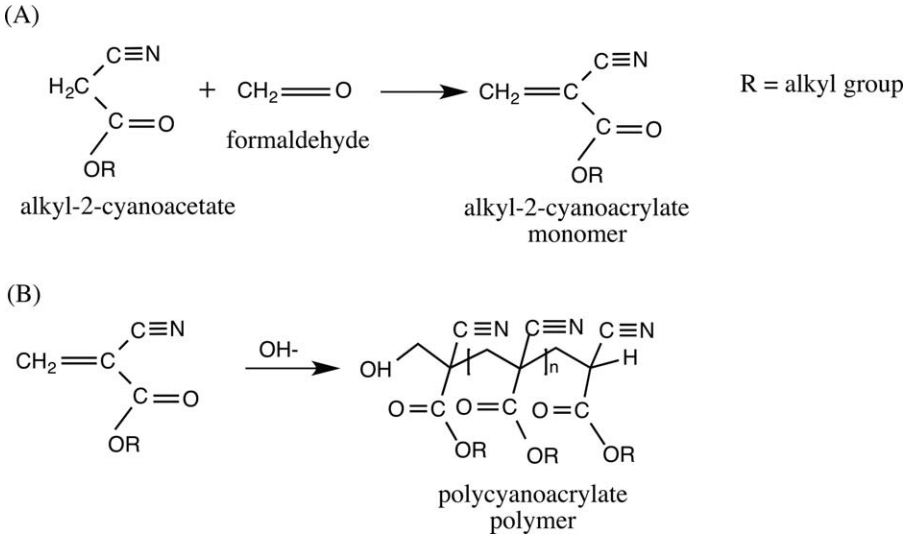

FIGURE 6. Cyanoacrylate chemistry: (A) Synthesis of alkyl-2-cyanoacrylate monomer and (B) polymerization reaction.

curing: cyanoacrylates can rely on small amounts of water to initiate the polymerization reaction and bonding occurs within seconds.

The basic cyanoacrylate monomer (alkyl-2-cyanoacrylate) is a low-viscosity liquid and is formed by combining formaldehyde and alkyl-2-cyanoacetate (Figure 6). The most common polymerization initiators for cyanoacrylates are the hydroxyl ions within water. Upon contact with wet tissues (such as skin, moisture, or blood), cyanoacrylates polymerize into a solid film that binds juxtaposed wound edges. Adhesion is achieved through two independent mechanisms: (i) molecular interaction via covalent bonding to proteins exposed on tissue surface and (ii) penetration of cyanoacrylate monomers into cracks and channels in the tissue surface (mechanical interlocking). For these reasons, cyanoacrylate adhesives are particularly effective on moist and porous substrates.[99,100]

In Figure 6, the general chemical structure and polymerization reaction of the cyanoacrylate adhesives is illustrated. The alkyl or carbon side chain —R has an important effect on the strength and physical properties of the glue. In comparison with complex, long-chain derivatives, straight, and short-chain monomers (—R = —CH_3 or —C_2H_5) form tighter and stronger bonds, which results in more rigid and brittle interfaces.[101] In contrast, by increasing the length or complexity of side alkyl group, the polymerization rate tends to decrease and interfaces with more flexibility are formed. Cyanoacrylate-based adhesives may also contain plasticizers, dyestuffs, thickeners, polymerization catalysts, anionic and radical stabilizers and other additives to make the formulation easier to handle and biologically safer. In the human body, cyanoacrylate adhesives undergo hydrolytic degradation, which takes place through nonenzymatic routes; the main degradation products are formaldehyde and the corresponding alkyl cyanoacetate. The degradation rate of cyanoacrylate polymers decreases with longer alkyl side chain, as a result of steric hindrance[102]; therefore short-chain derivatives degrade very quickly, resulting in a higher amount or local concentration of breakdown products, which are potentially harmful to cells and tissues and may cause inflammatory reactions and impair wound healing. High-molecular-weight polymers with longer side chain degrade slowly, which translates into producing less toxic degradation products; however, their persistence in the body may cause medical complications.[103] Although all cyanoacrylates arise from the same basic structure, subtle variations can dramatically change the properties of the compounds (flexibility, setting time, bond strength, viscosity, heat of polymerization reaction, biocompatibility, toxicity, and degradation profile). Cyanoacrylates have proven to be valuable in sutureless surgery: in many cases, wound closure can be safer, stronger, and more functional than with traditional suturing (that is, titches).[104] The development and clinical evaluation of these materials for general surgery was delayed because of safety issues; however, in the last decade a lot of efforts were devoted to cyanoacrylate applications other than cutaneous. An important use of cyanoacrylate formulations is for hemostatic purpose[105] like in anastomotic connections where there is a high risk of bleeding complication.[106,107] Cyanoacrylates possess several advantages for tissue approximation and their applications include wound closure or small Pfannenstiel incisional cuts performed during clean abdominal surgery.[13] To reduce possible inflammatory reactions and confer the desired adhesive strength and flexibility, novel cyanoacrylate-based formulations include additional components; as an example, the commercial formulation Glubran2® is a mixture of n-butyl-2-cyanoacrylate (monomer) and methacryloxysulpholane (monomer) and it displays anti-inflammatory properties.[108] Glubran2® has been tested for mesh fixation in Lichtenstein's inguinal hernia repair, with positive outcomes compared to traditional suturing methods.[109] In a recent

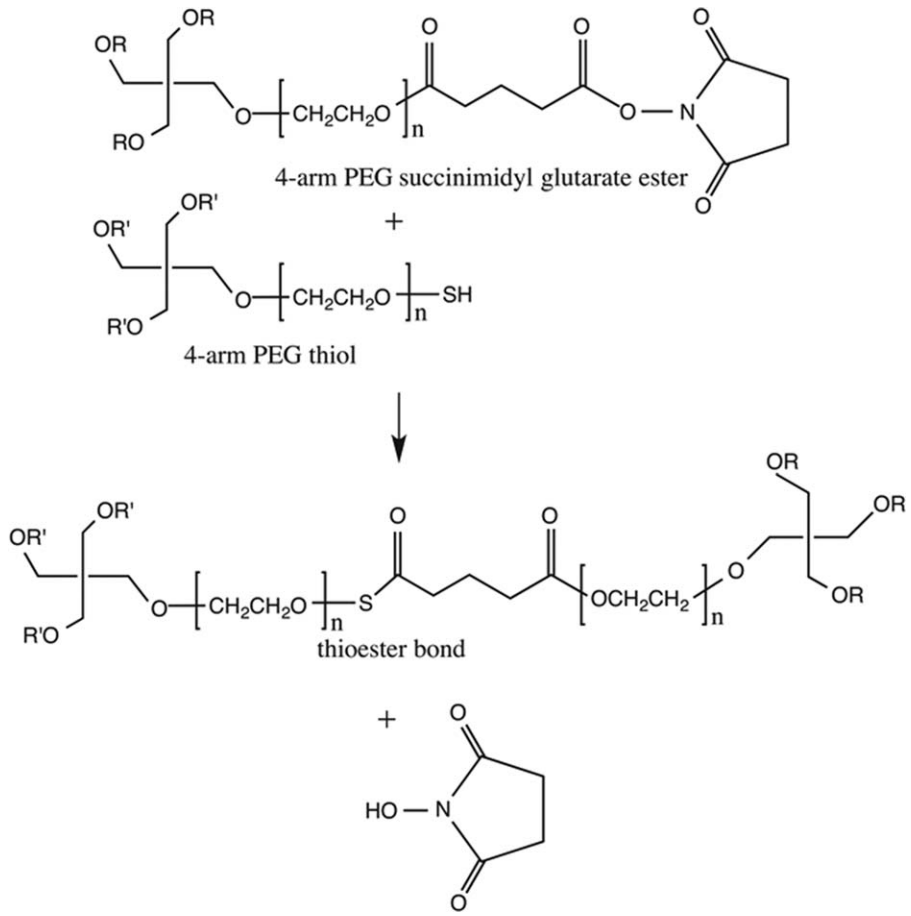

FIGURE 7. Formation of a 3D network by reaction of star-shaped PEG polymers in Coseal® PEG-PEG sealant: reticulation occurs by formation of thioester bonds and release of N-hydroxysuccinimide. (Reproduced from Ref. 49).

study, liver retraction was successfully achieved using *n*-butyl-2-cyanoacrylate glue in single-incision laparoscopic upper abdominal surgery.[110] A commercial 2-octyl cyanoacrylate (Dermabond Advanced™, Ethicon, Johnson, and Johnson Medical) was shown to reduce the rate of postoperative pancreatic fistula after pancreaticoduodenectomy.[111] The use of cyanoacrylate in surgical anastomosis for general surgery has been proposed as an alternative to microsurgery particularly in centers where facilities are unavailable and the financial implication is unbearable for the patient.[106]

PEG–BASED ADHESIVES AND SEALANTS

PEG is a neutral, biocompatible, and hydrophilic polymer widely employed in the biomedical field. It is soluble in aqueous solutions, which makes it a good candidate for hydrophilic and biodegradable systems. PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular weights and with a variety of end groups. Since it is not able to establish a bioactive interaction with biological matter, tissue adhesives based on PEG are prepared by grafting reactive moieties capable to establish covalent bonds with tissues; the resulting hydrogels can be employed as sealants for wound closure and as suture adjuvants to help hemostasis in the wounded site. For instance, Lee et al. described the preparation of PEG-based hydrogels modified through the coupling with L-3,4-dihydroxyphenylalanine endgroups conferring enhanced mucoadhesivity to the resulting hydrogels.[28] PEG-based adhesives are designed to provide a seal through covalent bonding to tissue surfaces while retaining flexibility and allowing a normal physiological dilation without stiffening, thus limiting mechanical stress.[112] PEG-based tissue adhesives are degraded through hydrolysis; they typically have a high swelling ratio and display a rapid degradation profile, which may represent a drawback for long-term wound reinforcement.[20]

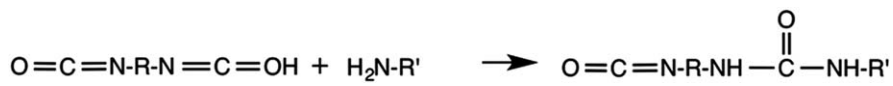

FIGURE 8. Tissue adhesion mechanism of urethane-based adhesive: $H_2N\text{-}R'$ represent tissue amines that react with isocyanate groups through urea bond formation.

TABLE 1. Summary Table of Adhesive and Sealant Classes of Materials for General Surgery Applications

Adhesive/ Sealant Class	Main Applications	Curing Mechanism	Pros	Cons	Ref.
Fibrin	Hemostatic agents in adjunct to common suturing techniques	Enzymatic crosslinking	Hemostasis possibilility to modulate adhesive properties by varing the composition	Poor adhesion in wet environment possible viral transmission and adverse response	(4,18–20,30,35 39–41,43,44)
Gelatin	Gluing of biological tissues	Chemical, enzymatic or photochemical crosslinking	Possibility to modulate the composition to prevent the formation of aldehydes binding in moist conditions biocompatibility and biodegradability	Presence of aldehydes high swelling ratio	(4,21,46,50–52,54,55)
Albumin	Hemostatic agents for cardiovascular anastomosis	Chemical crosslinking	Effective seal of vascular anastomosis adhesion to synthetic graft material	Slow degradation rates possible adverse reactions associated to glutaraldehydes	(59–61)
Dextran	Use as surgical adhesives and soft tissue sealants	Chemical crosslinking	Good adhesion in moist environment possibility to introduce chemical and physical crosslinking	Presence of aldehydes	(71–73,76,78)
Chitosan	Wound healing treatment and soft tissue repair	Photochemical crosslinking	Antimicrobial properties possibility to tailor physico-chemical properties by chemical modifications	Possible tissue damage upon thermal irradiation	(79–84)
Cyanoacrylate	Hemostasis, wound closure in sutureless surgery	Chemical crosslinking	Effective on moist and porous substrates high bonding strength possibility to modulate bonding strength, viscosity, and degradation profiles	Possible formation of poorly biocompatible degradation products	(13,85–92)
PEG	Suture and graft adjuvant, hemostatic agent	Chemical or photochemical crosslinking	Possibility to tailor physico-chemical properties of PEGs hydrophilicity and flexibility of hydrogels	High swelling ratio rapid degradation profile	(20, 26,76,91,100)
Polyurethane (PU)	Reduction of spaces where fluids can accumulate (abdominoplasty)	Chemical crosslinking	Good wettability possibility to tailor physico-chemical properties of PUs	Long setting time possible formation of poorly biocompatible degradation products	(4,24,25)

The commercial formulation Coseal® (Cohesion Technologies, Deerfield, IL) is composed of two types of four-arm PEGs (with a pentaerythritol core), one of which bears a glutaryl-succinimidyl ester as the terminal group while the other is capped with thiolic functions[2]; when the solutions of these two PEGs combine, the polymers begin to crosslink and form a network through the reaction of thiol groups with the carbonyl groups of the succinimidyl ester, resulting in the formation of a covalent thioester bond between the two multiarm PEG molecules and by the release of *N*-hydroxysuccinimide (Figure 7).[113]

The functionalized PEG end groups additionally react with functional groups (particularly amine groups) of the proteinaceous matrix to form covalent bonds, providing a chemical linkage between the PEG–PEG hydrogel and the surrounding tissue.[96] This formulation is proposed as a resorbable sealant for suture lines to prevent leaks.[27] Coseal® was tested for the reinforcement of intestinal anastomoses, although its use did not show a significant increase of bursting resistance.[114] In a similar study, a crosslinked hydrogels based on PEG and dextran aldehyde polymers was studied for the repair of intestinal wounds; this adhesive formulation exhibited considerable viscoelasticity and enabled to increase burst pressure.[39] In an experimental study on porcine model, a PEG-collagen hydrogel was applied to a pancreatic injury to prevent a pancreatic leak; the results showed that the PEG-based sealant could prevent a ductal leak following pancreatic injury.[115]

POLYURETHANE-BASED ADHESIVES (PU)

Polyurethanes are a family of polymers composed of two main components: isocyanates (containing two or more isocyanate groups per molecule) and polyols (containing on average two or more hydroxyl groups per molecule), which typically react in the presence of catalysts and a variety of other additives (such as chain extenders, crosslinkers and surfactants).[2] The properties of polyurethane are greatly influenced by the types of isocyanates and polyols employed. The wide variety of components and processing conditions, allow to tailor the adhesive formulations for the designed use.[116] The basis of polyurethane chemistry is the high reactivity of isocyanates, which can be assigned to the positive charge of the carbon atom in the cumulated double bond system of its N═C═O group. Urethane-based adhesives typically consist of isocyanate-terminated prepolymers that form a polymer network reacting with water molecules upon contact with biological environment.[2] These prepolymers covalently adhere to tissue through formation of urea bond between available isocyanate groups and amines of tissue proteins,[117] as shown in Figure 8.

Isocyanate-terminated pre-polymers usually exhibit long setting time (in the order of tens of minutes) when no catalyst is used, which limits their use as tissue adhesives.[2] To address the issues of long setting time and potential toxicity of degradation products, researchers incorporated new compounds in polyurethane synthesis: linear and multiarm prepolymers capped with more reactive and less harmful isocyanate groups are now widely used.[118] Urethane-based polymers display good properties as bioadhesives since they possess good wettability and capability to establish covalent interactions with body tissues. Recently, a Lys-derived urethane adhesive, TissuGlu® (Cohera Medical), was developed for large flap surgeries such as abdominoplasty. This glue is described as resorbable and nontoxic; it forms a strong bond between tissue layers and it eliminates or reduces fluid accumulation and the need for postsurgical drains. TissuGlu® was used on patients undergoing abdominoplastic surgery and the results showed that, in comparison to standard surgical closure techniques, it effectively binds tissue layers together, thereby reducing dead spaces where seroma can occur, while it also reduces post-surgery wound drainage.[26] More recently, a long term evaluation of TissuGlu® showed that it is capable of preventing the formation of seroma in a canine abdominoplasty model.[25]

To conclude, the main features of the adhesive and sealant interfaces for general surgery applications discussed in this review are summarized in Table 1.

CONCLUSIONS

In the field of general surgery, several clinical needs are being addressed by the use of adhesive and sealant interfaces; their use offers numerous advantages and it can be extended to further clinical situations that would benefit from the employment of sutureless techniques. Both synthetic and natural-based polymers are successfully being studied and employed and each adhesive class brings several advantages, although limitations related to the material features should always be considered.

Synthetic polymers offer several advantages especially in terms of mechanical performance but they can have limitations like poor biocompatibility and excessive stiffness; However, natural-based polymers typically form weaker interfaces but they are more similar to the macromolecular features of human tissues. When designing a new adhesive, the formulation has to be tailored for the specific target tissue, which means that since the early stages of its development, it must be conceived considering its clinical use. Hence, it is the medical application of the adhesive that dictates its features. This point should be taken into account when employing commercial adhesives for applications that were not designed for and it highlights that no universal solution has been developed so far in this field, given the wide morphological and functional heterogeneity of body tissues.

In the future, hybrid materials exploiting in a synergic manner the advantages of both synthetic and natural compounds will gain increasing importance. Within this challenge, bioinspired adhesive strategies that take inspiration from nature are expected to bring further impulse to this field of research toward novel solutions.

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