Published in final edited form as:
Macromol Biosci. 2013 March ; 13(3): 271–288. doi:10.1002/mabi.201200332.

Design Strategies and Applications of Tissue Bioadhesives

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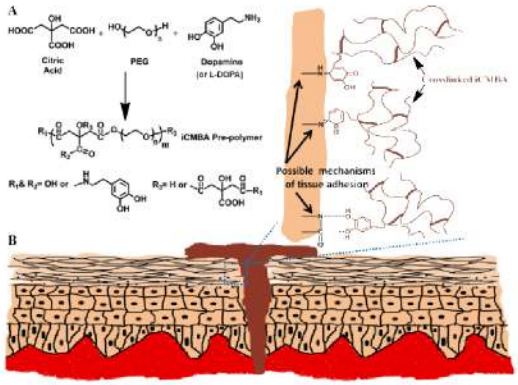
Abstract

In the past two decades tissue adhesives and sealants have revolutionized hemostasis and wound management in traumatic and surgical injuries. Various biological-driven glues and synthetic adhesives are clinically utilized either as an adjunct to conventional hemostats and wound closure techniques, such as suturing, or as a replacement to them. The ability to effectively and promptly control bleeding, thus, reducing the risk of complications due to severe blood loss, in addition to convenience of use render medical adhesive a highly suitable tool for wound management. This review focuses on existing tissue adhesive systems, their structure, functioning mechanism, indicated and off-label applications, and limitations. It also includes the latest advances in the development of new tissue adhesives as well as the emerging applications in regenerative medicine. We expect that this review will provide insightful discussion on tissue bioadhesive design and lead to innovations for the development of the next generation of tissue bioadhesives and their related biomedical applications.



Keywords

Bioadhesion; Biodegradable Polymer; Tissue Adhesive; Tissue Engineering; Wound closure

1 Introduction

The ability to control bleeding and wound closure dates back to ancient time when grass and leaves were used by prehistoric man as wound dressing.[1] In addition to grass and leaves,

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evidence of using suture to close wounds were documented as early as 1100 BC.[2] Suture has been the practice of choice for wound closure and bleeding control for many years due to its high tensile strength and low dehiscence. However, the high infection rate, inconvenience in handling, and concern over possible transmission of blood-borne disease through the use of needles are some reoccurring disadvantages of suturing. To address these problems, other techniques have been developed to help faster and more effective bleeding control and wound closure including utilizing various hemostasis agents, clips, staples, tapes, and tissue adhesives.[3] The latter technique has shown to be an effective method for wound closure and hemostasis in recent decades, hence, an enormous amount of efforts are being invested into developing new generation of tissue adhesives to improve upon existing adhesives.

Tissue adhesives are increasingly gaining more popularity in diverse areas of clinical applications, including wound closure and healing, drug delivery, implantation of medical devices, tissue engineering and dental and bone applications.[3, 4] Tissue adhesives and sealants are particularly important in situations that other techniques such as suturing are impractical or ineffective.[3, 5] In addition, this technique has demonstrated high efficacy in preventing massive blood loss caused by traumatic injuries or during surgeries where rapid bleeding control is vital to minimize any probable damages to patient's organs, which can occur due to hemorrhage-induced hypotension. Additionally, bleeding control during surgical operations has many advantages, such as preventing unstable hemodynamics, decreasing the need for blood transfusions, lowering operative time, minimizing the risk of infection, lowering overall mortality and morbidity rate, and reducing cost. In addition to tissue adhesives, hemostatic agents and sealants are also broadly utilized in bleeding control and preventing body fluid leakage.[5]

In the present literature review the structure, composition, functioning mechanisms, and performance of clinically used hemostatic agents, tissue adhesives and sealants (primarily in the United States, as shown in Table 1) are reviewed. In addition to materials and mechanisms as the primary focus, the review includes major reported applications and limitations of each adhesive system from clinical point of view. Furthermore, the results of previous and ongoing researches in developing new tissue adhesive materials and recent progresses in the field have been discussed. In addition to the typical applications in wound management and hemostasis, tissue adhesives have other diverse applications, such as in tissue engineering/regeneration and drug delivery, which will be concisely reviewed in the end. We expect that this review will provide insightful discussion on tissue bioadhesive design and lead to innovations for the development of the next generation of tissue bioadhesives and their related biomedical applications.

2. Hemostatic Agents

In a simple definition Hemostasis is referred to the stoppage of bleeding. During the biological hemostasis in the body three steps can be considered including formation of platelets plug, creation of fibrin clot through a complex coagulation cascade, and the final step, break-down of fibrin clot by plasmin enzyme (fibrinolysis). This physiological bleeding control system is usually sufficient to control blood loss for minor injuries and wounds. However, during a surgical operation or in severe trauma injuries, and in order to reduce preoperative and postoperative massive bleeding, employment of hemostatic agents, or simply hemostats, might be necessary to assist blood loss control.[6] While suturing is conventionally the primary choice to close wounds and stop bleeding, it is not always as effective and practical as it is required to be in order to satisfy clinical requirements, particularly when it comes to rapid bleeding control and blood oozing restrain.[7] To provide and maintain prompt and effective bleeding control, hemostats are utilized, particularly

during surgeries or trauma injuries. Ideal hemostats should be able to promptly and reliably control bleeding, be easily and rapidly prepared for immediate use, and be safe and affordable.[8]

Hemostatic materials may be categorized into mechanical agents and active agents.[8] The mechanical agents usually do not contain active biological materials such as thrombin. Gauze, sponges or any surgical packing, and adhesives acting as sealant or embolic agents are a few examples of mechanical hemostatic agents.[3, 8] Mechanical hemostats prevent bleeding by forming a mechanical barrier to flow of blood from an injured site. They can be in the form of powder, sponges, sheets or micro particles, which are used alone or in combination with active hemostats such as thrombin to enhance their hemostatic efficacy.[5] Porcine gelatin (such as *Gelfoam* and *Surgifoam*), bovine collagen (such as *Helitene*, *Avitine* and *Instat*) and oxidized regenerated cellulose (such as *Surgicel*) are some of the commercially available hemostats.[4, 5] Hemostats are also available in the form of viscose and paste-like flowable matrix (such as *Floseal* and *Surgiflo*), which can be injected to wound area. Most of these hemostats, are absorbed within 2-10 weeks post application.[5]

The main concerns over using these mechanical hemostats are possible allergic reaction of patients to bovine- or porcine-originated products, swelling of these products upon contact with blood and other body fluids resulting in compressive pressure on neighboring tissue, and probable foreign body reactions to these agents.[5]

On the other hand hemostatic agents containing active biological components, particularly thrombin, are referred to as active agents. These agents actively participate in the process of fibrin clot formation, when applied to wound location. For instance, thrombin interacts with patient's blood fibrinogen to accelerate fibrin clot formation. Thrombin is an enzyme, which can be of bovine, human or recombinant origin, and is available both as a stand-alone product (such as *Thrombin-JMI*, *Evithrom* and *Recothrom*) and in combination with gelatin matrix (such as *Floseal*). In the latter case when the matrix contacts the blood the gelatin swells and assists to block bleeding while thrombin accelerates the clot formation. This type of gelatinous matrix is degraded and absorbed within 6 to 8 weeks post application.[9] The major concern of using thrombin-containing hemostats is interfering with blood stream, thus intravascular injection must be avoided.[5] Moreover, bovine thrombin antigenic property and bovine Factor V impurities can stimulate human antibody formation and subsequently cause serious complications. Possible allergic reactions to bovine- and porcine-originated products and foreign body response are other issues to be watched when using this type of hemostats.[5]

Another widely used product, which can be categorized as an active hemostatic agent, is fibrin glue. Fibrin glue typically comprises two major components, thrombin and fibrinogen, which form a crosslinked adhesive gel upon mixing.[10] Fibrin sealants are further discussed elsewhere in this review.

3. Tissue Adhesives and Sealants

Tissue adhesives and sealants in the current context represent a group of liquid or semi-liquid compounds that can be applied to a tissue incision for the purpose of closing wounds, adhering to soft tissues and hemostasis. They comprise natural substances and/or synthetic chemicals, typically in the form of monomers, pre-polymers, or non-crosslinked polymers, which undergo polymerization or crosslinking reaction to form an insoluble adhesive matrix, when delivered to a tissue. An ideal tissue adhesive should:

1. be safe, sterilizable, nontoxic and easy to prepare
2. have required flow characteristics to be easily and precisely applied to desired area

3. rapidly solidify in the physiological condition to minimize bleeding and surgery time
4. demonstrate strong tissue bonding and adhesion for required period of time, hemostatic property, tissue healing and regeneration characteristics, and infection control
5. maintain required mechanical properties throughout healing process
6. be degradable and absorbable within reasonable period of time with no/minimal toxicity
7. easily and rapidly prepared for clinical use
8. be affordable and cost-effective to earn broad clinical acceptance.[3, 11, 12]

Tissue adhesives and sealants are categorized on various bases. In the present review, clinically utilized tissue adhesives and sealants are classified into two major groups based on the origin of their main component: 1. Naturally-derived glues, and 2. synthetic adhesives and sealants. A list of FDA (The US Food and drug Administration)-approved tissue adhesives and sealants including their chemical structure, applications, advantages, and limitations are summarized in Table 2.

Before further discussion about commercially available tissue adhesives, the definition of adhesion and adhesive, and different mechanisms of adhesion are briefly discussed in the next section, which can provide a better understanding on functioning mechanisms of tissue adhesives and their performance and facilitate innovations on new bioadhesive designs.

3.1 Adhesive and Adhesion; Theory and Mechanisms

An adhesive is a material, usually in the form of liquid or semi-liquid, that can bond objects together when applied to their surfaces and withstand separation by transferring applied loads from one substrate to another across the joint area. The terms adhesive and glue are usually used interchangeably. There are many advantages of using adhesives over traditional joints such as ability to join materials with different geometry and dimensions (e.g. thin or thick bodies), imrpoved and more uniform distribution of any applied stress over the joint area, which is especially crucial in dynamic loadings, ability of attaching similar and dissimilar articles, sealing the joint area, and convenience of use.[13, 14] Possible disadvantages of using adhesives in comparison with mechanical bonding techniques are lower service life, negative effect of harsh service environment on adhesives and adhesion strength, and inferior strength and toughness to some mechanical joints. If at least one of the substrates involved in an adhesion process is a biological body, the phenomenon is termed “bioadhesion”.[15] Several mechanisms for adhesion and bioadhesion have been described in literatures, which can be categorized into four main mechanisms including mechanical interlocking, chemical bonding, diffusion theory, and electrostatic theory.[13, 15] Although adhesion in a system might arise predominantly from one of these mechanisms, often a combination of various mechanisms is accountable in most adhesion systems. These adhesion mechanisms are briefly discussed in this section.

3.1.1 Mechanical interlocking—In the mechanical interlocking concept, adhesive material is believed to infiltrate into the pores and irregularities of adherends’ surfaces and mechanically lock into the microscopic surface roughness of the substrates that leads to binding to the surface. A well known example of this mechanism is the traditional tooth cavity filling method by means of amalgam, where adhesion between amalgam and the pretreated tooth surface is facilitated by mechanical interlocking. In order to obtain the required surface topography to achieve a good mechanical interlocking, the surface

pretreatment is essential. However, there are some uncertainties about how significant role this mechanism plays in adhesion, as some studies show that a good adherence can occur between smooth surfaces as well. Although mechanical interlocking may play an important role in the adhesion between roughened surfaces, other factors such as elimination of weak surface layers by surface treatment and enhancement in interfacial contact area due to those treatments are believed to have more contribution to adhesion strength than mechanical interlocking.[13, 14]

3.1.2 Intermolecular bonding—This is the major mechanism of adhesion between adhesive materials and substrates, which arises from interatomic/intermolecular forces and the bonds between atoms/molecules of adhesives on one side and the surficial atoms/molecules of substrates on the other. These forces include primary interactions or chemical bonds as well as secondary forces. Various types of primary forces or chemical bonds (also referred to as "Chemisorptions") can be formed across the interface of adhesive and adherends, such as covalent, ionic and metallic bonds. Since the primary bonds are of high energy, they will usually form a much needed strong adhesion. However, formation of strong primary bonds across interface sometimes needs special preparation techniques such as chemical modification of adhesive molecules by incorporating specific groups into the chemical structure of adhesive, and pretreatment of adherends' surfaces by means of primers, adhesion promoters and coupling agents.[13, 14]

Secondary forces such as hydrogen bonds, dipole-dipole interactions, London dispersion, and van der Waals forces can be of significant importance in adhesion. Although the energy of secondry forces is much lower than that of the primary bonds, in many adhesion systems only the secondary forces are accountable for bonding strength, particularly when a large number of sites for secondary forces is available in the interface between adhesive and substrates. In some studies a different approach has been taken to explain the adhesion between adhesive and substrate. In those theories intrinsic adhesion was ascribed to electron donor-acceptor interaction. In such a concept, Lewis acid and base are considered as electron acceptor and donor, respectively. In this manner hydrogen bond can also be classified as donor-acceptor interaction. Molecules with donor and acceptor properties are also able to form molecular complex that helps the bonding between these types of molecules and the formation of stronger adhesion.[13, 14] Chemical bonding is the major adhesion mechanism in bioadhesion, where the bonding between adhesive materials and tissue surface arises from primary chemical bonds, secondary forces, or a combination of both.

3.1.3 Chain entanglement—Chain entanglement theory has been proposed to explain, in particular, the adhesion of two similar polymers as well as binding between two different polymers. In this mechanism polymer macromolecules diffuse mutually over the polymer-polymer contact interface, which typically has a thickness of 1-100 nm, and forms a layer of interpenetrated polymer chains. For this chain entanglement to happen, the giant polymer molecules must have enough mobility. Thus, chain entanglement does not occur in highly crystalline and crosslinked polymers, neither in amorphous polymers below their glass transition temperature, due to lack of large scale molecule mobility. Additionally, the two interdiffusing polymers must be mutually soluble. One example, where this kind of inter-diffusion takes place, is when two plastics with similar solubility parameters are welded to one another. In such a welding, the mobility of polymer molecules is commonly facilitated by applying heat or solvent to the interface areas.[13, 14] In bioadhesive systems, diffusion mechanism has also been employed to explain some bioadhesion phenomena.[15] For example, in mucoadhesive drug delivery systems, interpenetration and entanglement of bioadhesive polymer chains and glycoproteininc network of mucus is believed to be accountable for the adhesion of polymer carrier to the mucus. The diffusion of polymer

chains into the network of glycoproteins (bioadhesion) occurs when they are brought in intimate contact and is a function of interface topological characteristics, diffusion coefficient of the macromolecule through the mucus network, chemical potential coefficient, and the difference between solubility parameters of bioadhesive medium and glycoproteins..[15]

3.1.4 Electrostatic bonding—When the surface of two materials with different electronic band structures are brought to a close proximity, the possible transfer of some electrons, which occurs to equalize the Fermi levels, might form a double layer of electron charge in the interface area. These charges are believed to induce electrostatic forces, which may play a significant role in the intrinsic adhesion of the two contacting surfaces. However, in the case of insulator substrates the charge build-up would be very slow and the number of available electrons might be limited, hence it would require a long time to build up charge concentration. Although the presence of electrostatic forces arisen from the charged double layers have been observed in some metals and semi-conductors, this mechanism does not play a significant role in adhesion of nonmetallic systems.[13, 14] However, this mechanism is believed to have a possible role in bioadhesion. For example, electron transfer in the contact area between a bioadhesive material and glycoprotein of mucus is thought to be one of the plausible mechanisms of mucoadhesion.[15, 16]

3.2 Naturally Derived Tissue Adhesives

The major components of the bioadhesive systems discussed in this section are either directly extracted from biological sources, such as human blood, or are based on proteins isolated from animals, such as porcine or bovine. These products can function without involvement of any other chemical reagents, for instance fibrin glue system, or in combination with active chemicals, such as aldehydes, which are used in gelatin-based glues.

3.2.1 Fibrin Glue —Fibrin-based glues are one of the most widely used tissue adhesives in clinical applications. The use of fibrin as a scaffold for tissue regeneration and local hemostatic agent was first reported as early as 1910's.[17, 18] During the first world war fibrin patches were used to control bleeding. In 1940's the combination of fibrinogen and thrombin were used as biological glue for human skin grafting.[10, 19] The use of fibrin glue took momentum when the ability of producing highly concentrated fibrinogen was developed, which led to making fibrin glue with stronger adhesion properties.[19] Fibrin glues had been in broad clinical use in Europe many years before it was approved by FDA in the United States in 1998 (*Tisseel*).

Fibrin glues mimic the last stage of blood clotting, during which fibrinogen is converted to fibrin clot through a complex coagulation cascade. The fibrin glue typically consists of two major components including concentrated human-derived fibrinogen (together with factor XIII and some other blood plasma proteins) and human or bovine thrombin in combination with calcium chloride solution as the second component.[19, 20] Upon mixing the two components, fibrinogen is converted to fibrin monomers by thrombin which consequently forms a polymer. In the meantime thrombin activates factor XIII (in presence of calcium chloride) into factor XIIIa, which stabilizes the network through the crosslinking of fibrin molecules by creating amide bonds and forming an insoluble clot (Figure 1).[19, 20] In order to prevent fibrinolysis (disassociation of fibrin clot, which happens by plasmin enzyme), an antifibrinolytic agent (such as aportinin) is used in some formulations. Depending on the amount of thrombin the clot formation can be adjusted to be reached within seconds with higher concentration of thrombin or after a couple of minutes as the thrombin concentration is lowered. The maximum adhesion strength is usually achieved within 3 to 5 minutes and is

directly proportional to the concentration of fibrinogen.[21] Family of fibrin glues has been broadly utilized in clinical applications. The majority of reported applications were in surgical procedures, to control bleeding and leaking during and, particularly, after surgeries.[4, 22] There are numerous reports on using fibrin glue as hemostatic agent and sealant in cardiovascular surgery, particularly to prevent bleeding from suture line and graft area, which is a common issue in this type of operations. [4, 20, 22-27] Fibrin sealants are also utilized in neurosurgery to seal cerebrospinal fluid after operation on the central nervous system and peripheral nerve repair and grafting.[22, 28, 29] The application of fibrin glues in treatment of gastrointestinal tract diseases such as in patients suffering from bleeding peptic ulcers has also been investigated with the aim of replacing surgical procedure by noninvasive endoscopic injection of fibrin sealant. This application demands sealants with specific flow and crosslinking characteristics to make them suitable for injection through lumen catheters and allow enough time for handling and injection.[22] There are also numerous reports on the applications and performances of fibrin sealants in a variety of medical disciplines such as plastic surgery and skin grafts,[30] ENT (ear, nose and throat) and head and neck surgery,[31] trauma surgery,[32] urology,[4, 22] and ophthalmology.[33]

Despite of having many advantages, such as fast curing, biocompatibility, and biodegradability, using fibrin glue might be associated with some risks and safety concerns. The thrombin from bovine source can trigger allergic reactions in some patients. Additionally, in reaction to factor V or thrombin from bovine source, some antibodies are produced that might cross-react with human clotting factor causing serious hemorrhage. There is also a risk of transmission of infectious agents to human when bovine-source thrombin is used.[34] Thrombin of human-source can be used in order to overcome these safety concerns.[34] Another issue in using fibrin sealant-despite the extensive efforts to minimize it, is the risk of blood-borne disease transmission, such as HIV and hepatitis A, B and C, as the result of using pooled human plasma for extracting fibrinogen and thrombin.[10, 35] To eliminate this concern some fibrin sealants make use of fibrinogen and/or thrombin that are derived from patient's own blood plasma (such as *Vitagel* and *Cryoseal System*). The side effects of using antifibrinolytic agents, which are used to prevent untimely fibrinolysis (breakdown of fibrin clot), are another possible area for concern associated with using fibrin glue.[10] Additionally, direct injection of the glue into large blood vessels can result in thromboembolic event and interfere with blood stream.[9] Another weakness of fibrin glues is their poor adhesion to tissue when compared to other adhesives such as cyanoacrylates and gelatin-resorcinol-formaldehyde/glutaraldehyde (GRF/GRFG).[36] Other disadvantages of fibrin glues are their long preparation time, which takes approximately 20 minutes,[37] need for ancillary equipments, and their inefficacy in high pressure bleeding.[19] Finally, fibrin sealants perform best when applied to dry surfaces, which is a limiting factor when wet tissue adhesion is required.

3.2.2 Protein-Based Adhesives—Another family of commercially available adhesives and sealants for clinical utilizations is based on proteins or protein-like compounds that undergo crosslinking reaction upon exposure to proper crosslinking agent, while simultaneously form covalent bonds with the tissue surface. Unlike fibrin glue, these adhesives do not resemble the physiological coagulation mechanisms.

One of the adhesives of this type is a gelatin-based glue called Gelatin-Resorcin-Formaldehyde/Glutaraldehyde (GRF or GRFG), which was developed in Europe in 1960's.[38] GRF/GRFG glues have been clinically utilized in Europe and Japan for the past few decades. Gelatin, a naturally occurring protein, is derived from collagen of bovine or porcine skin or bone. Depending on production method gelatin is categorized into type A, prepared by using acid extraction, or type B, which is conditioned by a base followed by acid extraction. Gelatin is a biocompatible and bioabsorbable material that can form strong,

transparent, and flexible gels and films, granting it suitable properties for medical application. However, due to its solubility in water and consequently low stability in aqueous environment, gelatin network requires to be stabilized through crosslinking in order to be used within physiological systems.[38, 39] Gelatin can be crosslinked by reacting with aldehydes, which decreases its solubility and increases the cohesive strength. The combination of gelatin and aldehyde was initially proposed as a tissue adhesive, but due to its poor performance in aqueous environment, a phenolic component (1,3-benzenediol), namely resorcinol or resorcin, was added to improve its strength through reducing the negative effect of water.[40]

GRF/GRFG glue (gelatin resorcinol formaldehyde/glutaraldehyde), also known as "*French glue*", is a two-component glue consisting of: 1) gelatin and resorcinol mixture; and 2) formaldehyde or formaldehyde/glutaraldehyde combination as polymerizing agent. The gelatin chains are crosslinked by aldehyde through polycondesation reaction with amine groups of gelatin. Simultaneously, reaction of aldehyde groups with amine groups of living tissue forms a strong bond with the tissue (Figure 2). Resorcin molecules are also linked to one another by aldehyde groups.[38, 40] Due to their strong bonding, even in the presence of moisture, this type of adhesive has been used in medical applications, particularly in Europe for the treatment of aortic dissections,[36, 41] liver surgeries,[42] gastrointestinal tract surgeries,[43] and urinary tract surgeries.[44]

Despite of being used for many years, particularly in Europe, the presence of formaldehyde, as a residue of unreacted aldehydes or as a degradation product, is a major point of concern due to its possible mutagenicity and carcinogenicity.[45] Therefore, some investigations have focused on using less toxic glutaraldehyde glyoxal.[45] In addition, developing other crosslinking techniques rather than using chemical agents can eliminate the risk of using aldehydes. Researchers reported synthesis of a tissue sealant that was prepared based on a photo-crosslinkable gelatin.[39] In another attempt a research group reported a hemostatic technology using photo-curable gelatins and a hydrophilic difunctional macromer. They developed hemostatic glue consisted of gelatin, poly(ethylene glycol) diacrylate, and ascorbic acid, all of which were dissolved in a saline solution and produced a swollen gel upon irradiation of the glue by visible light.[46] To our knowledge there is currently no FDA-approved GRF/GRFG glues in the United States. Nevertheless, a glue and sealant based on albumin-glutaraldehyde is available in the United States (*BioGlue*), which has FDA approval for application as adjunct to standard methods of hemostasis (such as suture and staple) in open surgical repair of large vessels (such as aorta, femoral and carotid arteries). This protein-based sealant consists of bovine serum albumin protein, which is crosslinked through linkage formation between amine groups of albumin protein chains by aldehyde groups of glutaraldehyde. The adhesion mechanism to tissue is similar to previously described GRFG glues (Figure 2). This kind of product has been approved and used for sealing large blood vessels, vascular prostheses and aortic dissection.[5, 47] However, as for GRFG glues, similar safety concerns of using aldehyde-containing products has limited their wide utilizations.[5]

3.3 Synthetic Tissue Adhesives

Various classes of synthetic adhesive polymers have been widely used as soft and hard tissue adhesives. Synthetic polymers are attractive because their structure and, consequently, material properties, including adhesion, degradation, mechanical, etc, can be controlled, tailored, and processed accordingly to suit specific applications. In this section, commercially available tissue adhesives that solely or predominately comprise synthetic substances and polymers are reviewed.

3.3.1 Cyanoacrylates—Invented by H. Coover in mid 20th century, cyanoacrylate-based adhesives, also known as *Superglue*, have been one the strongest and multipurpose adhesives available. They have broad applications from general household uses to medical applications. The general structure of cyanoacrylates (alkyl-2-cyanoacrylates) monomer, an alkyl ester of 2-cyanoacrylic acid, is shown in Figure 3. It is a liquid-state monomer that rapidly polymerizes at room temperature through an exothermic-anionic polymerization in the presence of nucleophile species, particularly hydroxyl ion, including water.[48]

The first cyanoacrylates adhesive used in clinical application for skin incision closure in Europe and Canada, was n-butyl-2-cyanoacrylates (*Histoacryl and Histoacryl Blue*) in 1980's. In the United States FDA approved the first cyanoacrylate adhesive with indicated application of topical skin approximation in 1998 (*Dermabond*), an adhesive based on 2-octyl-2-cyanoacrylate, which also contains plasticizer, radical and anionic stabilizers and colorant.[48] Another available medical adhesive from cyanoacrylate family is based on n-butyl-2-cyanoacrylate (*Indermill*), which was approved by FDA for closure of the topical skin incisions.[48]

The pending alkyl groups in cyanoacrylates (-R, Figure 3) largely influences the polymerization and properties of final polymer. Increasing the length of side alkyl group lowers polymerization rate and causes formation of polymers with less stiffness and more flexibility. Longer alkyl group also decreases the mechanical properties of polymer, such as tensile strength and modulus, and lowers adhesion strength. It also causes slightly less tissue response but increases the stability against hydrolytic degradation.[49]

Cyanoacrylate adhesives properties, such as strong adhesion, rapid setting time, instantaneous adhesion to tissue and their ease of use with simple preparation make them very attractive for clinical uses and are widely used in emergency rooms, dermatology and plastic surgery. There are some other reported applications, such as endoscopic intervention for gastric varices outside the United States.[50] They are also getting more popularity in dentistry applications, as tissue adhesive, in bonding orthodontic brackets, for dentures repair, etc.[51] On the other hand exothermic reaction, i.e. heat generation during polymerization, and concerns about toxicity of degradation products, namely cyanoacetates and formaldehyde, have imposed limitations in medical use of cyanoacrylate adhesives. Furthermore, despite of having fast polymerization and strong adhesion, it might lack required flexibility especially when used for soft tissue adhesion. This is particularly observed in cyanoacrylates with short alkyl groups such as methyl-2-cyanoacrylates.[48, 52] Polymers with short alkyl group and lower molecular weight (i.e. shorter polymer chain) degrade faster causing more histotoxicity, while high-molecular-weight polymers with longer side chain degrade slowly, which translates in producing less toxic degradation products.[48] However, this decelerates the rate of hydrolytic degradation of adhesive and even might result in a non-degradable polymer, which can cause medical complications.[49] There are also some other issues associated with cyanoacrylates adhesives including difficulties in accurate delivery due to its low viscosity, weak shear strength of joint area especially in the presence of water, high stiffness that can cause undesired consequence such as adhesion failure and tissue irritation, and infection due to existence of nonabsorbable polymer.[49] These disadvantages have limited the application of cyanoacrylate adhesives to topical skin approximation in the United States. Nevertheless, researchers are trying to address the problems associated with clinical utilization of cyanoacrylate adhesives in order to broaden their medical applications. For example, to address prolonged biodegradability issue, investigators developed absorbable adhesive polymers using more hydrophilic cyanoacrylates, which comprise, for example, methoxypropyl cyanoacrylates, instead of using alkyl cyanoacrylates such as n-butyl, isobutyl or n-octyl cyanoacrylates.[49] Plasticizers, stabilizers, accelerators, viscosity-adjustment agents and other additives might

also be included in the adhesive formulation to improve the properties of cyanoacrylate adhesives to make them more accommodating for broader tissue applications.

3.3.2 Polyethylene glycol (PEG)-Based Hydrogel Sealants—Another type of synthetic tissue sealants are polymeric hydrogels developed based on PEG. PEG is a well known nontoxic, non-immunogenic, biocompatible and FDA approved material, which has found many applications in modern medicine including surface modification of materials for enhanced biocompatibility and hydrogel for drug delivery.[53] This family of tissue adhesive is typically consists of chemically functionalized linear or branched PEG molecules. Depending on available chemical groups, these modified PEGs can be crosslinked upon mixing through chemical crosslinking or upon irradiation of light by photo-crosslinking of PEGs capped with a photo-reactive elements such as acrylate groups, to form a hydrogel adhesive. For example, one of the FDA approved PEG-based adhesives (*Coseal*) is composed of two four-armed PEGs (with pentaerythritol core), one of which has terminal groups of glutaryl-succinimidyl ester and the other is capped with thiols.[54] When the solutions of these two PEGs are mixed together (plus dilute solution of hydrogen chloride and sodium phosphate-sodium carbonate[5]), the polymer begins to crosslink and form a network through the reaction of thiol groups with the carbonyl groups of the succinimidyl ester, resulting in formation of a covalent thio-ester bond between PEG molecules (Figure 4).[54] The main indicated application of this adhesive is to seal suture lines and vascular grafts.[4] Another FDA approved PEG sealant (*Duraseal*), which consists of PEG ester and trilysine amine solutions, is used as an adjunct to dural closure for sealing CSF (cerebrospinal fluid) leakage following a neurosurgery.[5] Although PEG-based tissue adhesives offer many advantages such as rapid gel formation, adhesion to biological surface, biocompatibility of polymer and degradation products and inducing mild to moderate inflammatory response, there are some concerns associated with them including a swell ratio of up to 400% of original volume, which requires more caution when applying to closed spaces to avoid pressure build up on surrounding tissues (e.g. nerve compression).[5] In addition, it requires a relatively dry surface for better results.[4]

4. Recent Developments in Tissue Adhesive Technology

As discussed earlier, a number of tissue adhesive systems have already been approved by FDA for indicated applications and are commercialized. However, the performance inefficacy, safety concerns and limitations associated with the use of each of these adhesive and sealants have driven researchers to address those problems by developing new adhesives, which have better performance in biological environment, broader applications and fewer drawbacks. In this section, some of the recent developments in the field of tissue adhesives are discussed.

4.1 Urethane-Based Adhesives

In the recent decades, polyurethanes, a family of polymers synthesized based on polyaddition reaction between diisocyanates and diols, have been utilized in many medical applications such as bladders, catheters, cardiovascular applications, wound dressing and pacemakers.[55] Urethane (urea) chemistry is based on high affinity of isocyanate groups to nuclophiles such as hydroxyl- or amine-containing chemicals. Taking advantage of this feature, researchers tried to develop urethane-based adhesive systems. This type of adhesives typically consists of isocyanate-terminated pre-polymers, which form a polymer network in reaction with water molecules upon contact with wet biological environment. Simultaneously, these pre-polymers will covalently adhere to tissue through formation of urea bond between available isocyanate groups and protein amines available in physiological body (Figure 5). Various aromatic and aliphatic polyisocyanates with different

polyether/polyester diols have been used to synthesize tissue adhesives.[56-58] However, there are three major challenges associated with using urethane adhesives: prolonged set time, ether-based polyurethanes are not readily biodegradable, and toxicity and carcinogenicity of degradation products.[59] As mentioned earlier, an ideal tissue adhesive must solidify rapidly. Isocyanate-terminated pre-polymers usually exhibit long set time- in the order of tens of minutes, when no catalyst is used, which makes them unacceptable as tissue adhesives. This problem is more critical when aliphatic isocyanates, such as hexamethylene diisocyanate (HDI) are used. These isocyanates are employed in the place of more reactive aromatic isocyanates (such as TDI: toluene diisocyanate or MDI: methylene diphenyl diisocyante), which even though make the urethane formation faster, are more toxic and can result in releasing carcinogenic aromatic diamines, such as 2,4-diaminotoluene, upon hydrolytic degradation of urethane bonds. To address the issue of long set time a research group used more reactive fluorinated HDI.[57] In another attempt researchers utilized linear and multi-armed pre-polymers capped with more reactive Isocyanate groups.[58, 60] They synthesized Lysine di- and tri-isocyantes (LDI and LTI) that reacted with glucose and PEG with different molecular weight to yield isocyanate-capped pre-polymers. These pre-polymers are reportedly crosslinked within 30 sec to 2 min upon applying to tissue surface.[58] Using this type of isocyanates also diminished the safety concerns associated with aromatic isocyanates. To tackle the challenge of prolonged in-vivo biodegradability of polyether based polyurethanes, hydrolytically-degradable ester components (such as polylactide/poly-Ɛ-caprolactone) were incorporated into the structure of polyurethanes, which resulted in polymers with accelerated rate of degradation.[61] Despite of all these breakthroughs and other improvements in urethane chemistry and raw materials to address existing safety concerns, there is no FDA-approved tissue adhesive based on polyurethane to date.

4.2 Nature-Inspired Adhesives

Nature and natural phenomena have always been a major source of inspiration for human to develop and invent new materials and applications. Adhesive technology has not been any different. An outstanding example is biologically-derived fibrin glue, discussed earlier in this review. Adhesive materials are widely used by many organisms ranging from biofilm in microscopic bacteria to proteinous adhesives secreted by sea organisms such as mussels and barnacles. One of the most important features of the adhesive polymers produced by sea creatures is their capability to firmly adhere to any substrates (non-specific) in wet condition, where water must be displaced from the adherend surface. Furthermore, these adhesives show strong resistance against destructive effect of water, which often adversely influences the strength of many chemical bonds and, hence, the strength of adhesives.[12] In this section the adhesive systems that were inspired by adhesion strategy of these maritime creatures are discussed.

4.2.1 Mussel Adhesive Proteins—Tissue adhesives must effectively function in aqueous environment in order to be able to create strong adhesion to wet biological surfaces. Thus, understanding the adhesion mechanism of organisms that stick to wet surfaces can help the development of adhesives with strong wet-tissue adhesion for use in biological environment. One of these creatures that has been extensively studied, mostly through the works of H.J. Waite, is mussel.[62] Mussels, such as *Mytilus edulis*, secrete adhesive materials (also called Mussel Adhesive Proteins or MAPs) that enable them to firmly adhere to various underwater surfaces such as sea rocks and ship hulls, and resist detachments even in marine's harsh and wavy condition. Studies have shown that this strong wet adhesion is primarily due to the presence of a catechol-containing amino acid called L-3,4-dihydroxyphenylalanine (L-DOPA), a post-translational hydroxylation of tyrosine, in the structure of secreted mussels adhesive proteins.[62-64] Although the adhesion and

crosslinking mechanisms of MAPs are not completely known, it has been proposed that hydroxyl groups of DOPA are able to generate chemisorption to polar surfaces such as formation of hydrogen bonds to the hydrophylic surfaces.[62] Furthermore, under oxidizing or alkaline condition DOPA promotes the crosslinking reactions of MAPs through the oxidation of catechol hydroxyl groups to ortho-quinone, which triggers intermolecular crosslinking between MAPs, rendering cohesion and bulk elastic properties to these proteins. In addition, oxidized DOPA contributes in strong adhesion to biological surfaces, through the formation of covalent bonds with available nucleophile groups on these surfaces such as $-NH_2$, −SH, −OH and −COOH.[63, 65-67] Furthermore, DOPA is also able to undergo crosslinking through formation of a strong complex with multi-valent metals and metal ions, which are present in marine environment.[68] Figure 6 shows the schematic plausible pathways for adhesion and crosslinking reactions of dihydroxyphenyl-containing compounds.[66]

Considering the outstanding and unique properties of mussel adhesives such as fast curing, even in wet condition, and strong adhesion to non-specific surfaces, many researchers have tried to mimic the adhesion strategy of mussels to make bioadhesives that can robustly function in wet/dry condition. Initially researches focused on direct extraction and isolation of adhesive protein from mussels and other organisms as well as on genetically engineering these proteins.[69, 70] In one study adhesive strength of extracted MAPs crosslinked by different curing agent has been measured and compared with some cyanoacrylate-based adhesives.[71] It was concluded that, depending on curing system, the adhesion strength of MAPs could be higher than that of some cyanoacrylates with longer side chain (e.g. butyl and octyl cyanoacrylates) but was inferior to short-side-chain cyanoacrylate such as ethyl cyanoacrylate.[71] Since isolation and purification of MAPs from mussels is a complicated procedure with relatively low yield (10,000 mussels to obtain 1g of MAP),[72] there have been many investigations concerning synthesis of polymer adhesive mimetic of MAPs. In addition to studies about synthesizing DOPA-containing polypeptides,[73-77] researchers have also investigated the functionalization of other monomers/polymers with DOPA or compounds analogous to DOPA. A group of researchers reported modification of poly(ethylene glycol) (PEG) by DOPA.[78] They conjugated amine-terminated linear- and branched-PEG with DOPA and studied the crosslinking behavior and hydrogel formation of DOPA-functionalized PEG using different oxidation agent such as horseradish peroxide, hydrogen peroxide, sodium periodate and mushroom tyrosinase.[78-80] The reported gel times varied from seconds to hours depending on structure of pre-polymer, its spatial architecture, and the oxidation agent used. In a recent study, in-vivo performance of a synthetic glue based on branched-PEG functionalized with 3,4-dihydroxyhydrocinnamic acid (a catechol containing compound), which was crosslinked using sodium periodate solution, was evaluated in extrahepatic islet transplantation of a mice model. Minimal acute or chronic inflammation was reported while the interface with the tissue remained intact for up to one year, according to the reported results.[81] In another attempt, investigators reported synthesis of surgical meshes coated by DOPA-functionalized PEG and polycaprolactone (PCL). The presence of DOPA in the structure of the coating polymer rendered adhesion properties to the coated mesh, hence, reportedly eliminated the need for mechanical fixation of mesh and made it suitable to be utilized as a reinforcement for surgical repair of soft tissues.[82]

In a recent development we have successfully synthesized a novel family of biodegradable and strong wet-tissue adhesives based on mussel adhesive strategy with 2.5-10 times stronger adhesion strength than commercial fibrin glue (Figure 7).[83] These injectable citrate-enabled mussel-inspired bioadhesives, iCMBAs, were synthesized using a facile polycondensation reaction using FDA-approved and inexpensive materials including citric acid, PEG, and dopamine/ L-DOPA. Incorporating catechol group in the structure of

iCMBAs rendered them strong adhesion to wet tissue surface as well as crosslinking capacity for bulk cohesive strength. In addition, the presence of hydrolytically degradable ester bonds in the back bone of iCMBA polymers made this family of adhesives readily biodegradable without requiring any further modifications. This property provides iCMBA with a significant advantage over other investigated mussel-inspired bioadhesives, which typically require additional complex structural modifications to make them biodegradable.[84] In addition, the properties of iCMBAs, such as bonding strength, mechanical properties, and degradation rate could be tuned according to requirements. iCMBAs also exhibited good in vitro cyto-compatibility. In vivo study showed that iCMBA rapidly and effectively stopped bleeding and closed open wounds created on the dorsum of a rat animal model without the aid of other wound closure tools such as stitches or staples (Figure 8).[83] iCMBA did not induce any significant inflammatory response and was degraded and absorbed completely in rats (Fig 8E). Controlled biodegradation and bioabsorption are essential requirements for most biomaterials, which provide a scaffold for regrowth or regeneration of tissues as the materials undergo gradual degradation. iCMBAs properties make them promising for potential clinical applications such as sutureless wound closure and soft tissue engineering.[83]

The non-specific dry/wet surface adhesion of synthetic mussel-inspired adhesives has exposed a new ground for developing a new family of soft tissue adhesives that are not only capable of forming strong adhesion to wet tissues, but safe enough for utilization in human body without any adverse effect during application and degradation.

4.2.2 Gecko-Inspired adhesive—Geckos are capable of climbing and strongly attaching to vertical and inverted surfaces. Yet, temporary nature of this adhesion enables geckos to detach and reattach to the surface with high pace, making it possible for them to run fast over vertical and inverted surfaces. This extraordinary adhesion feature of geckos relies on millions of nano-structured hairs, called setae, covering gecko's soles.[85, 86] In sub-microstructure scales, capillary forces and van der Waals interactions are the main mechanisms for adhesion to hydrophilic and hydrophobic materials, respectively.[85] Inspired by geckos, researchers fabricated a gecko-mimetic adhesive based on micro-patterned pillars that were made of flexible polyimide films using electron-beam lithography and dry etching in oxygen plasma.[85] They reported that the adhesion strength these adhesives is directly proportional to the number of foot-hairs sticking to the surfaces and the flexibility of the pillars, which is required for attaching to rough surfaces.[85] However, the adhesion is adversely affected when the micro-patterned pillars are immersed in water. To address this problem, researchers took advantage of the combination of the sticking mechanisms of gecko and the adhesion power of mussels.[86] They prepared nanoscale pillars, similar to gecko foot hairs, out of poly(dimethylsiloxane)(PDMS) that was then dip-coated by a mussel-mimetic polymer film to create an adhesive with the capability of reversibly adhering to different surfaces in dry and wet condition.[86] By combining these two adhesion strategies, mechanical and chemical, they reported a significant increase in the adhesion strength between an individual pillar and the residing surface in dry and, particularly, in wet environment.

In another attempt a group of investigators reported the preparation of gecko-inspired tissue adhesive by making nano-patterned poly(glycerol-co-sebacate acrylate) (PGSA), which was then coated by oxidized dextran. The presence of dextran reinforces the covalent adhesion of nano-structured PGSA to wet tissue through formation of imine groups, which is the result of reaction between aldehyde functional groups of dextran and amine group of tissue proteins.[87] They have taken advantage of the elasticity and biodegradability of PGSA to prepare this reportedly biocompatible tissue adhesive.[87]

5. Applications of Bioadhesives in Tissue Engineering and Reconstruction

In addition to being utilized for wound management and hemostasis, bioadhesives are increasingly emerging in other bioapplications such as tissue engineering and regeneration. One of the biggest challenges of using biomaterials in regeneration of tissue defects is the discontinuity in the interfacial region between biomaterials and tissue, which can cause the failure of the integration between the two. To prevent this separation from occurring, various integration techniques, such as suturing and tissue adhesives, are employed. However, for different tissues with distinctive functional requirements, tissue adhesive with a specific set of properties might be necessary. Thus, to minimize the risk of failure, customized tissue adhesives are developed to tailor the requirements of a specific tissue. In a recent development, investigators employed adhesive moieties to promote graft integration in cartilage tissue repair/engineering. To enhance cartilage tissue repair, chondroitin sulphate (CS), a polysaccharide found in cartilage, was functionalized with photo-crosslinkable methylacrylate and chemically-crosslinkable aldehyde groups.[88] The modified CS was then used as a biodegradable injectable adhesive scaffold to integrate with surrounding tissues once injected for cartilage tissue engineering. On one side, methacrylate groups of modified CS created bonds with a hydrogel biomaterial (PEG diacrylate) through photo-crosslinking, while the aldehyde end of CS chemically bonded to tissue, Thus, a bridge between biomaterial and cartilage tissue was formed, which significantly promoted graft integration/bonding with the tissue so as to improve cartilage repair (Figure 9). It was reported that the repair of defected cartilage was significantly improved, when CS adhesive was used together with hydrogel.

One of the most extensively investigated tissue adhesives for tissue engineering applications is fibrin glue. One reported application of injectable fibrin glue is in cardiac tissue engineering, where damaged cardiac tissue was shown to benefit from using compliant adhesive scaffold to facilitate graft integration, reduce mechanical irritation and inflammation, and promote tissue regeneration. In one study fibrin glue was used as an injectable wall support and scaffold in myocardial infarction (MI) in a rat model.[89] The results indicated that fibrin glue could prevent wall thinning, especially after myocardial infarction. In another study by the same author, it was shown that using fibrin glue enhanced cell transplant survival, decreased infarct size, and facilitated blood flow to ischemic myocardium by improving neovascularization in a rat myocardial infarction model.[90] Fibrin glue was also used as an injectable scaffold containing adipose-derived stem cells to maintain the cardiac function in a rat model after MI.[91] It was reported that using fibrin glue together with the stem cells increased the cells retention, enhanced the graft size, improved heart function, and significantly increased arteriole density in the infracted area, when compared to the case of injecting the stem cells alone.[91]

Another reported off-label application of bioadhesives is to prevent seroma, which is a common postsurgical complication. Interruption of lymphatic system and vasculatures during surgery causes drainage and accumulation of serous fluids in the space created by surgery.[92, 93] If not treated, seroma can cause massive complications.[92] Biodegradable bioadhesives, particularly fibrin glue, are the most widely investigated materials against seroma formation. The role of fibrin glue in seroma prevention is believed to be twofold: first, by reducing the flow of body fluid into surgically-created space through sealing the damaged vessels and lymphatic systems; and second, through eliminating the generated dead space by gluing injured tissues in the surgical area.[92] The biomaterials used in sermoa prevention must be biodegradable and bioabsorbable within limited period of time to avoid complications related to the prolonged degradation. In the case of fibrin glue this period is in the range of 1-2 weeks.[22]

In another capacity bioadhesives have been playing a major role in controlled and site-specific drug delivery. Adhesion of a drug loaded vehicle to the surface of a biological target, not only increases the residence time of drug and improves its absorption by the targeted biological system, but can also influence the rate of drug release, thus, improving the efficacy of medications.[94] In this context the adhesion is due to interfacial forces between the bioadhesive on one side, and either cell membrane or its coating, such as mucus, on the other. The bioadhesive drug delivery systems have been investigated in many applications such as mucoadhesives for drug delivery to gastrointestinal tract, bioadhesives in nasal drug administration, and ocular drug delivery systems. The detailed mechanisms and applications of bioadhesives in drug delivery are beyond the scope of this review and have been investigated by researcher elsewhere.[94]

6. Conclusion and Future Trend

As systematically discussed in the present review, tissue adhesives and sealants bear numerous advantages over traditional wound management techniques, such as effective and rapid bleeding control, ease of handling, and overall cost-containing potential. Tissue adhesives are also shown to have significant potential in many off-label applications, especially in tissue engineering and regeneration, facilitating integration between biomaterials and tissues, and drug delivery. Given these capacities, more investigations are expected to focus on improving upon existing adhesives and developing new systems. Challenges of making ideal tissue adhesives, which can be utilized in various clinical applications, are multifold. Strong wet adhesion, safety and biocompatibility of adhesive materials, degradability without producing harmful byproducts to the body, ease of accessibility and use in clinical environment, and last but not least the cost of final product are among the challenges to be addressed. Considering their promising performances, new tissue adhesives developed based on different adhesion strategies, mussel-inspired glues for instance, might be the solution to many of those challenges. In addition, tissue adhesives can significantly influence damaged tissues engineering and reconstruction through enhancing graft integration between biomaterials, cells, and native tissue. Achieving this goal necessitates development of customized tissue adhesives, with particular properties to suit specific requirements of an application in tissue engineering and regeneration, or in targeted drug delivery, which adds another dimension to the exciting research territory of tissue adhesives.

Acknowledgments

This work was supported in part by a R01 award (EB012575) from the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and a National Science Foundation (NSF) CAREER award 0954109.

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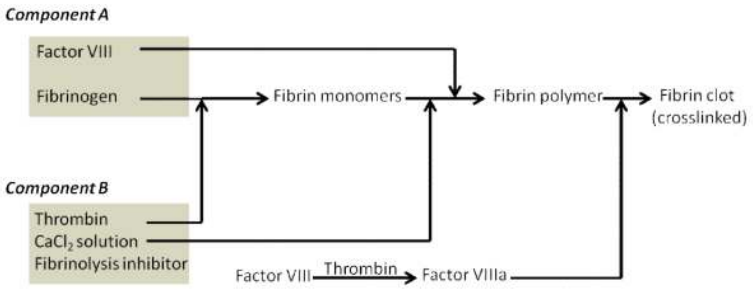

Figure 1.
Schematic diagram of functioning mechanism of fibrin glue, resembling the last stage of physiological coagulation cascade in the body.

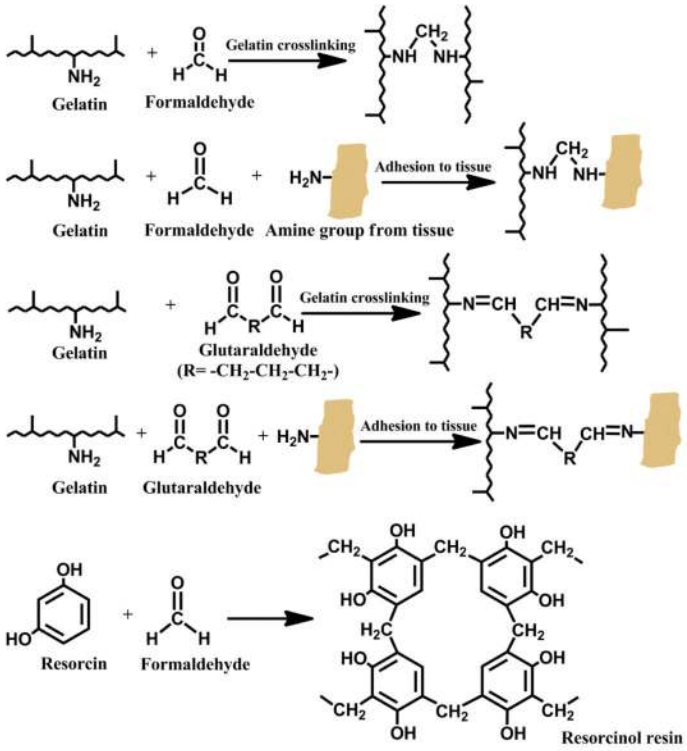

Figure 2.
Schematic adhesion and crosslinking mechanisms of GRF/GRFG glue (gelatin resorcinol formaldehyde/glutaraldehyde).

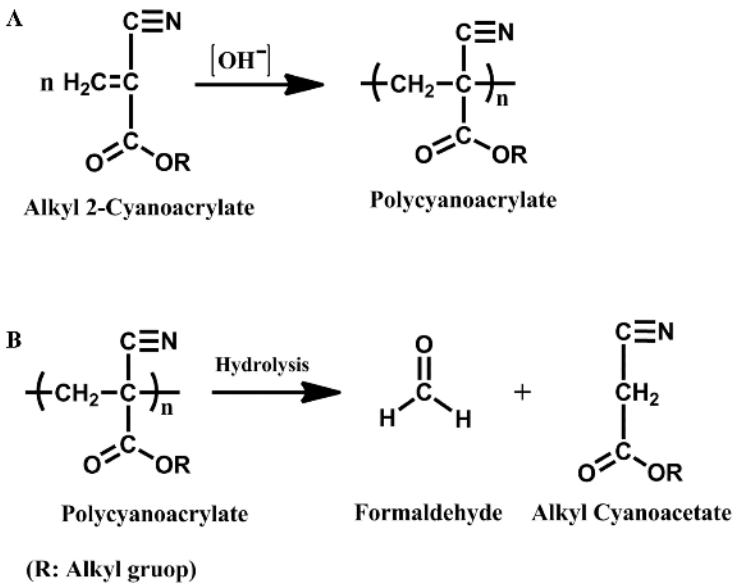

Figure 3.
Polymerization (A) and degradation (B) of cyanoacrylate adhesives.

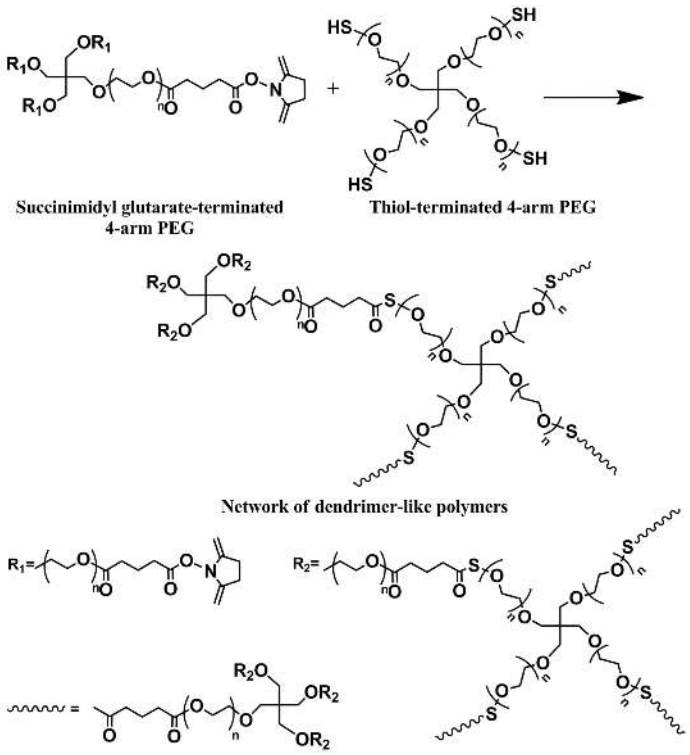

Figure 4.
Crosslinking and network formation of sealants based on dual-PEG (poly(ethylene glycol)) comprising two 4-arm PEGs capped with succinimidyl glutarate and thiol.

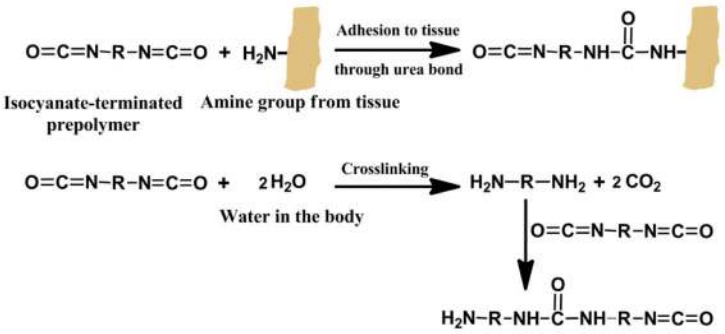

Figure 5.
Tissue adhesion and crosslinking mechanisms of urethane-based adhesives.

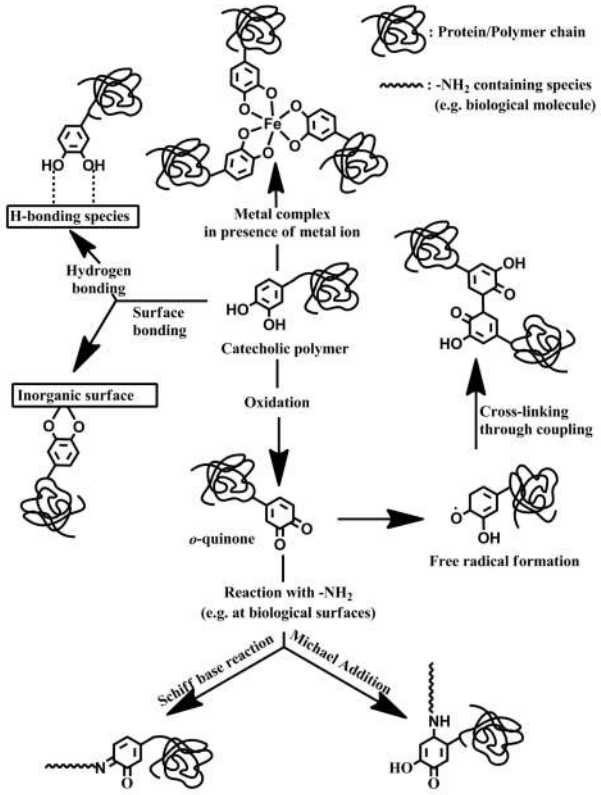

Figure 6.
Schematic diagram of plausible adhesion and crosslinking mechanisms of catechol-containing polymers, such as mussel adhesives.

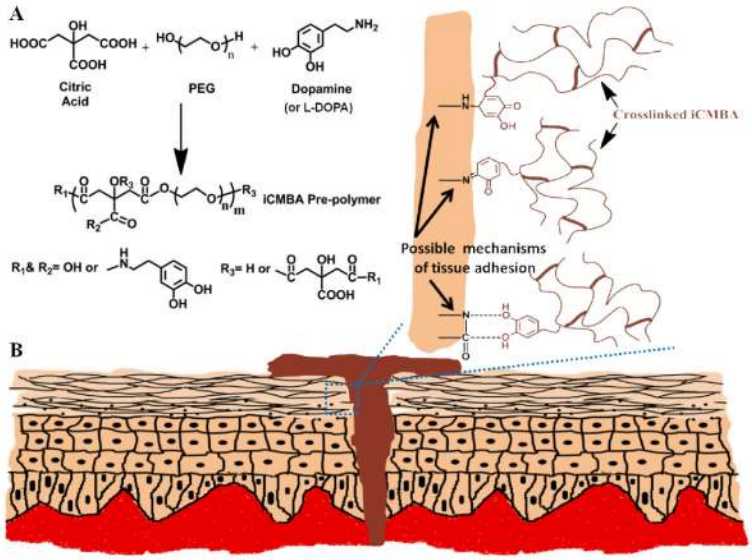

Figure 7.

Synthesis and plausible adhesion mechanisms of iCMBAs. (A) Schematic diagram of iCMBA synthesis using a condensation polymerization between citric acid, poly(ethylene glycol), and dopamine or L-DOPA. (B) Schematic representation of iCMBA adhesion to tissue and possible mechanisms.[82]

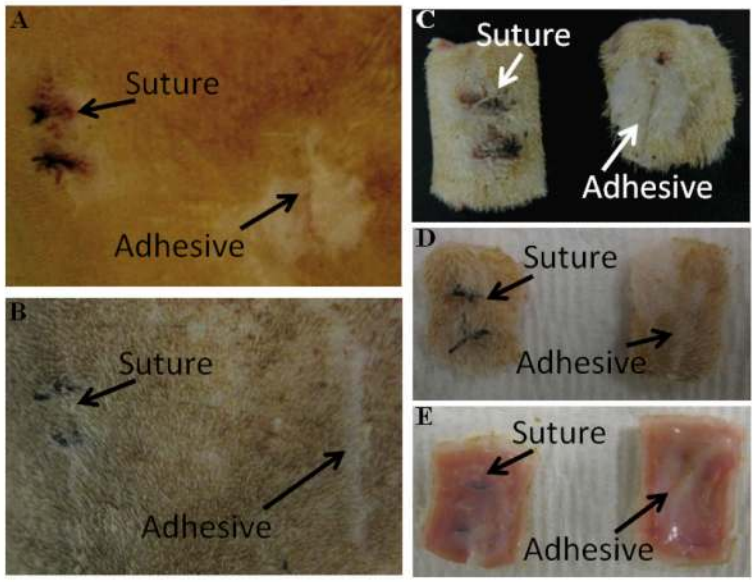

Figure 8.

Animal study of iCMBA in a rat model. Images of wounds created on rat's dorsum and closed by iCMBA adhesive and suture at (A) 7th, and (B) 28th day post surgery. The sections of skin tissue of sacrificed rats at the site of wounds, which were treated by iCMBA and suture: (A) 7 days, and (B) 28 days post operation. (C) The opposite side of (B). iCMBA exhibited better hemostasis and wound treatment properties than suture. [82]

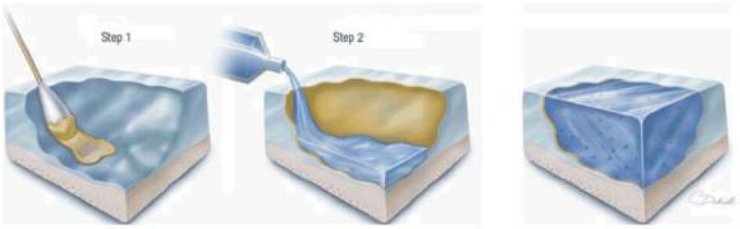

Figure 9.
Bioadhesive in tissue engineering. Schematic illustration of adhesion between biomaterial hydrogel (dark blue) to cartilage tissue (light blue) by means of a functionalized chondroitin sulphate (CS), which covalently binds biomaterial to cartilage tissue surface. Using modified CS adhesive resulted in improved integration between CS, the biomaterial hydrogel, and the native tissue (Reprinted by permission from Macmillan Publishers Ltd: NATURE MATERIALS [87], copyright (2007)).

Table 1

Various types of major hemostats, sealants, and adhesives, available for clinical use in the Unites States.

Type and major components	Functioning mechanism
Mechanical hemostats	-Available in various forms of powder, sponge, microfibrillar, sheets and flowable products, these hemostats swell upon contact with blood and mechanically impede bleeding.
Bovine collagen	
Porcine gelatin	
Oxidized regenerated cellulose	
Polysaccharide spheres	
Active hemostats	-Comprise thrombin as an active ingredient, which converts fibrinogen available in patient's blood to fibrin clot, accelerating cessation of bleeding.
Human pooled thrombin	
Bovine thrombin	
Recombinant thrombin	
Bovine gelatin with human thrombin	
Porcine gelatin with thrombin	
Sealants	-Typically consist of two or more components that undergo chemical reaction upon mixing, forming a solid body or hydrogel that seals the wound area.
Fibrin sealant and hemostat	
PEG based sealants	
Adhesives	- Create covalent/secondary bonds with biological surfaces, which result in adhesion to tissue and/or approximating wound edges to close wounds and control bleeding.
Cyanoacrylates	
Albumin and glutaraldehyde	

Table 2

FDA-approved tissue adhesives, sealants and hemostats available in the US market.

Bioadhesives/Sealants family	Product Brands (Chemical name)	Manufacturer	Indicated Applications	Pros	Cons	Reference
Cyanoacrylates	Dermabond (2-Octyl cyanoacrylate)	Ethicon Inc. (Johnson & Johnson Co)	• Topical applications to hold closed easily approximated skin edges from surgical incisions • Dermabond may be used in conjunction with but not in place of subcuticular sutures	• Fast polymerization • Strong adhesion • Ease of use • Relatively inexpensive	• Exothermic polymerization • Work best on dry surfaces • Prolonged degradation • Safety concern over degradation products • Limited to topical uses	[47-51]
	Indermil (n-Butyl-2-cyanoacrylate)	Covidien Inc.	• Closure of topical skin incisions that are simple, thoroughly cleansed, and have easily approximated skin edges • In conjunction with but no in place of deep dermal stitches • Microbial barrier			
	Histoacryl and Histoacryl Blue (n-Butyl-2-cyanoacrylate)	B. Braun Medical Inc.	• Closure of smooth and fresh skin wounds • Closure of skin in endoscopic incisions • Sclerosation therapy of large esophageal and fundal varices			
Albumin and Glutaraldehyde	BioGlue (Bovine serum albumin and 10%glutaraldehyde)	Cryolife Inc.	• As adjunct to standard methods of achieving hemostasis (such as suture and staple) in open surgical repair of large vessels (such as aorta, femoral and carotid arteries)	• Fast Polymerization, begins in 20-30 sec and reaches full strength in 2 min • Good adhesion to tissue	• Safety concerns over risk of glutaraldehyde toxicity • Relatively	[7],[46]
Fibrin glue	Tisseel (Human pooled plasma fibrinogen and thrombin)	Baxter Inc.	• As an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical • As an adjunct for the closure of	• Fast curing • Biocompatibility	• Risk of transferring bloodborne disease • Risk of allergic reaction Risk of infection transmission • Long preparation time • Ancillary equipment required	[10] [19-21] [33], [36]
	Evicel (Human pooled plasma fibrinogen and thrombin)	Ethicon Inc. (Johnson & Johnson Co)				
	Vitagel (Autologous plasma fibrinogen and thrombin)	Orthovita Inc.				
	Cryoseal system (Autologous plasma fibrinogen and	ThermoGenesis Corp.				

Bioadhesives/Sealants family	Product Brands (Chemical name)	Manufacturer	Indicated Applications	Pros	Cons	Reference
	thrombin)		colostomies • Vitagel is used during surgical procedures (except neurosurgery and eye surgery) as an adjunct to clotting when control of bleeding using suture or other conventional procedures is not effective, or seems impractical • The autologous Cryoseal system fibrin sealant is indicated for use as an adjunct to hemostasis on the incised liver surface in patients undergoing liver resection	• Biodegradability	• Poor tissue adhesion • Relatively expensive	
Poly(ethylene glycol) (PEG) based sealants	Coseal (2 four-armed PEGs: one capped with glutarylsuccinimidyl ester and the other with thiols, and dilute solution of hydrogen chloride and sodium phosphate-sodium carbonate)	Baxter Inc.	• Sealing suture lines and vascular graft	• Rapid gel formation • Fast hemostasis • Biocompatibility • Adhesion to tissue	• Risk of swelling • Possible allergic reaction • Relatively expensive	[7,8] [53]
	Duraseal (PEG ester powder and trilysine amine solution with FD&C blue No.1 dye)	Covidien Inc.	• Sealing of cerebrospinal fluid (CSF)			