

Tissue Adhesives as Active Implants

Boaz Mizrahi, Christopher Weldon and Daniel S. Kohane

Abstract Tissue adhesives are substances that hold tissues together, and could be broadly applicable in medicine and surgery. In appropriate circumstances, such materials could be attractive alternatives to sutures and staples since they can be applied more quickly, causes less pain and may require less equipment. In addition, there is no risk to the practitioner from sharp instruments (Singer et al., Acad. Emerg. Med. 5(2):94, 1998), and they may obviate the need for suture removal (Coulthard et al., Cochrane Database Syst. Rev. 5:CD004287, 2010). An ideal surgical tissue adhesive should allow rapid adhesion and maintain strong and close apposition of wound edges for an amount of time sufficient to allow wound healing. It should not interfere with body's natural healing mechanisms and should degrade without producing an excessive localized or generalized inflammatory response (Mobley et al., Facial Plast. Surg. Clin. North Am. 10(2):147, 2002). The clinical and scientific potential of adhesives can be enhanced by a variety of functionalities that may not be directly related to their function as glues or sealants. Here we will review adhesives in general, with an emphasis on enhancements

B. Mizrahi, C. Weldon and D. S. Kohane (✉)
Department of Anesthesia and Perioperative Medicine, Division of Critical Care,
Children's Hospital Boston, 300 Longwood Avenue, Bader 6, Boston, MA 02115, USA
e-mail: Daniel.Kohane@childrens.harvard.edu

B. Mizrahi
Department of Chemical Engineering, Massachusetts Institute of Technology,
Cambridge, MA 02139, USA

B. Mizrahi
Operations Research Center, Massachusetts Institute of Technology,
Cambridge, MA 02139, USA

C. Weldon
Department of Surgery, Children's Hospital Boston, 300 Longwood Avenue,
Fegan 3, Boston, MA 02115, USA

that render those otherwise passive materials “active”. We note that some glues also have intrinsic secondary functionalities that can be direct or indirect consequences of their primary function, but that is not the focus of this chapter. (For example, they may augment local hemostasis directly, or by improving tissue apposition, without affecting clotting mechanisms (Reece et al., *Am. J. Surg.* 182(2 Suppl):40S, 2001)).

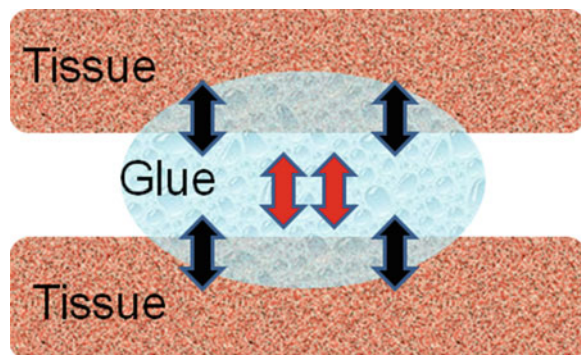
1 Categories of Adhesives

Tissue adhesives hold tissues together (and therefore are glues) but also can serve as barriers to leakage (and therefore can be sealants) when used for wound closure [74]. Achieving a strong bond (Fig. 1) is dependent upon obtaining close contact between the tissue(s) to be bonded and the glue (adhesive strength), and on the integrity of the glue (cohesive strength of the material) [47]. Consequently the causes of glue failure [67] can include: (1) adhesive failure—where the material detaches from the tissue and (2) cohesive failure—where the adhesive fails within itself. Even if the glue functions well, the tissue itself may tear; this may occur when both adhesive and cohesive forces are too strong.

Tissue adhesives can be divided into three main chemical categories: cyanoacrylates, fibrin sealant, and other cross-linkable polymers. They can be administered for a variety of clinical indications including wound closure [26], fistula repair, including in the bowel, blood vessels and bronchi [70], retinal fixation [30] and others. Cyanoacrylates are the strongest (~ 68 kPa, [2]) and are widely used for wound closure. Fibrin based materials, being weaker (~ 13 kPa, [2]) are applied as a sealant in many surgical procedures in conjunction with suturing. Hydrogels, collagen compounds, peptides and polyethylene glycol (PEGs)-based materials are also considered weak (4–17 kPa, [2]) and are therefore used as topical wound dressings or as sealants where mechanical properties are of less concern than with internal injuries (where wound dehiscence could be disastrous).

Below we detail a number of compounds used as glues. The list is not intended to be exhaustive but to provide a framework for the subsequent discussion of active glues.

Fig. 1 Types of glue strength: adhesive strength between the glue and the tissue (*black arrow*), and cohesive strength within the glue (*red arrow*)

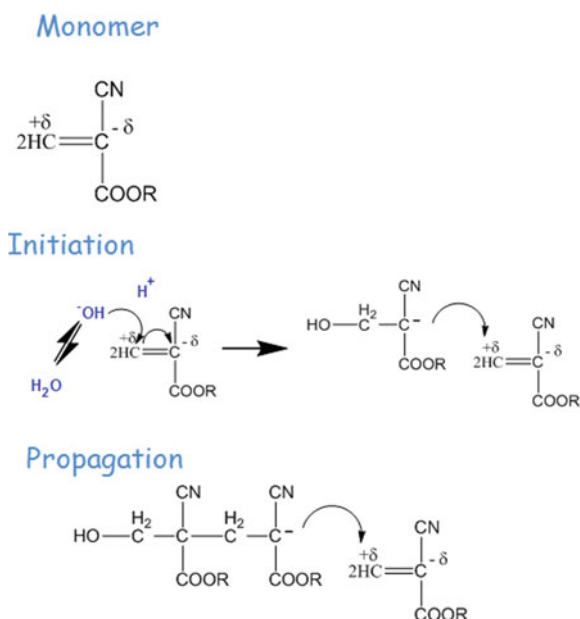


1.1 Cyanoacrylates

Cyanoacrylates were first synthesized in 1949 [3] and were first reported as tissue adhesives ten years later [18]. They are produced synthetically by condensation between cyanoacetic acid and a suitable alcohol followed by the Knoevenagel reaction [68]. The alcohol group will determine the nature of the final monomer by controlling the length of the side chain (e.g. by using methanol or octanol, 2-methyl cyanoacrylate or 2-octyl cyanoacrylate will be formed, respectively). The cyanoacetate oil formed is reacted with paraformaldehyde to form cyanoacrylate oligomers. High vacuum (~ 0.7 mm Hg) and heat ($150\text{--}180^\circ\text{C}$) are applied and depolymerization is carried out to produce clear and colorless liquids monomers. Usually, further purification by repeated vacuum distillations is utilized to get a medical grade material [33]. Since these monomers are highly reactive, polymerization inhibitors are added at this stage to prevent the monomers from hardening (polymerize) while being stored. Although polymerization may occur by one of three mechanisms—*anionic* (Fig. 2), *zwitterionic* or *free radical*—the first two mechanisms mentioned are strongly favored *in vivo* [86] by hydroxide or amine groups presented in the body, ultimately resulting in strong chains holding the two tissues' surfaces together.

Although cyanoacrylates are considered very strong and effective, their use—particularly within tissues—is limited by tissue toxicity, including necrosis, which occurs in the immediate vicinity of the cyanoacrylates. The toxicity of cyanoacrylate glues has been attributed to several factors including:

Fig. 2 The polymerization of cyanoacrylate tissue glue



direct toxicity of monomers such as methyl-2-cyanoacrylate [39] or of byproducts such as cyanoacetate and formaldehyde [87], insufficient tissue vascularization [2], and the heat from the exothermic nature of the reaction [21]. In addition, it has been postulated that the polymerization of the monomers may be initiated by the $-NH_2$ groups of glycosides or amino acids present on cell surfaces [42] thus damaging membrane lipids [84]. A second concern limiting the use of cyanoacrylates in tissues stems from the fact that they are hard and brittle, hence they may have insufficient flexibility for the dynamic nature of in vivo conditions [40]. As a result, cyanoacrylates are currently limited to external or temporary applications.

In general, the smaller the molecular weight of the side group, the quicker the rate of degradation. Accordingly, it has been shown that monomers with higher molecular weights may result in slower production of byproducts with resultant decreased inflammatory response [38]. This difference may be reflected in the fact that n-2-butyl cyanoacrylate (Histoacryl[®]), a monomer with a four carbon alkyl side chain, was not approved for the US market, while 2-octyl cyanoacrylate (Dermabond[®]), a monomer with an eight carbon alkyl side chain, was approved for use in the United States after it proved to be less toxic than cyanoacrylates with shorter side chains [79].

Cyanoacrylate tissue glues have found multiple uses. They have been used in the management of corneal perforations, corneal melts and wound leaks [2]. The cornea glue may also improve visual outcomes by obviating the need for sutures, which are associated with inducing astigmatism. In addition, they may create a more watertight seal, decreasing the risk of infection, thus reducing the chance of devastating intraocular infections such as endophthalmitis [5]. In dermatology, cyanoacrylate glues provide a flexible water-resistant coating with improved cosmetic outcomes. It was also found that patients, in particular children, prefer the concept of being “glued” over sutures and clips [9]. Recently, Dermabond was found to be superior for skin closure after repairing congenital cleft lip with or without associated palate defects [17]. In mammoplasties, Dermabond[®] was effective, safe, and had better cosmetic results than sutures [77]. Operative times and costs were also decreased, while patient satisfaction increased compared to traditional techniques.

1.2 In Situ Cross-linking Polymers

1.2.1 Fibrin Glue/Sealant

Fibrin tissue glue was first introduced in 1909 as an hemostatic agent, and was first used as an adhesive material in 1940 [78]. Fibrin based tissue adhesives are composed of purified fibrinogen and thrombin, and form a bond via the physiological cascade of coagulation (Fig. 3). Some additives such as Factor XIII, fibronectin,

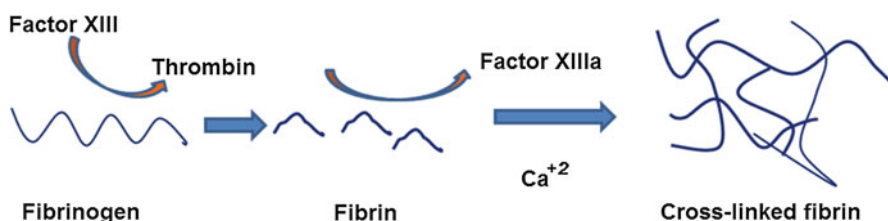


Fig. 3 Formation of cross-linked fibrin from fibrinogen

calcium chloride and the anti-fibrinolytic aprotinin may also be added to inhibit tissue fibrinolysis, and to control gelling time [4, 11, 89].

Since fibrin tissue adhesives are prepared from pooled human blood, there has been concern for potential viral transmission, in particular of hepatitis and human immunodeficiency virus (HIV) [24]. However, parvovirus (B19) has been the only documented virus transmitted from fibrin sealants to date [36]. Nowadays, these products are carefully screened so that the risk of viral transmission is considered minuscule compared to the risk with other biomaterials taken from donors [70].

Although fibrin glues are considered less toxic than cyanoacrylates their low adhesive strength limits their use in many surgical procedures [2]. For example, the strength of cystotomy closure with fibrin glue and 2-octyl cyanoacrylate were compared in a porcine model [50]. At 4 weeks postoperatively, the bladders were filled with saline to 200 mm Hg pressure and the cystotomy scars inspected for evidence of leakage. Four of six of the pigs treated with fibrin glue leaked, while none in the cyanoacrylate group had evidence of wound compromise. Ultimately, three pigs treated with fibrin glue died from urine leakage.

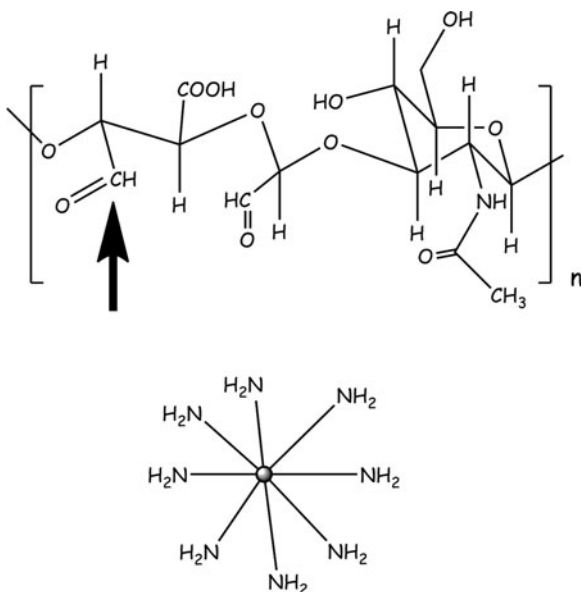
As a sealant, however, fibrin glue is very successful, especially in conjunction with sutures or clips. It has been used clinically in many settings including: anal fistulae closure to preserve sphincter function [94], prevention of esophageal leakage and stricture after esophageal reconstruction from caustic injury [75], prevention of cerebral spinal fluid leakage after durotomy during lumbar spinal surgery [35], hernia repairs [62], posterolateral spinal fusions [96], nerve anastomoses [90] and in cardiovascular surgeries [6].

1.2.2 Other In Situ Cross-linking Polymers

Water soluble polymers forming a three dimensional (3D) network at the site of injection have been used as tissue adhesives due to their safety, mechanical properties and ease of application. Cross-linking prevents early dissolution of the material in the body, and maintains cohesive integrity. Since it may be desirable that tissue adhesives degrade after healing has occurred, these compounds will frequently contain labile bonds in their backbone or in the cross-linking domains [28].

Several polymers, synthetic and natural, have been proposed for tissue adhesion, including poly(ethylene glycol) (PEG) [19], chitosan [43], laser- and

Fig. 4 Oxidized dextran (aldehyde is indicated by an arrow) and aminated star-shaped polyethylene glycol



non-laser-activated protein solders [1], porcine gelatin, glutaraldehyde mixed with collagen [49, 53] to name but a few examples. In situ cross-linking polymer systems can form non-self assembling systems (e.g. UV-light/irradiation) or can form spontaneously without the need of external triggers [85]. The bond formed between the two polymeric chains (cross-linking) can be covalent or can depend on weaker bonds, such as hydrogen bonds, van der Waals forces, ionic interactions or a molecule's side chain interactions [71]. Similarly, adhesive forces between the gel and the tissue can be due to covalent bonds formed between functional groups on one of the polymers (e.g. aldehyde) or by weak van der Waals or hydrogen bonds interactions (e.g. PEG compounds).

BioGlue[®] (Cryolife, Kennesaw, GA) is a surgical adhesive used in cardiovascular surgery, approved by the FDA and the EU as an adjunct in human vascular and pulmonary repair surgery [29]. It is composed of purified bovine serum albumin (BSA) and glutaraldehyde. The two components are dispensed by a delivery system comprised of a double-chambered syringe and an applicator apparatus. Once dispensed, the components are mixed within the applicator tip (a mixer) where the cross-linking begins. The glutaraldehyde molecules bond with the BSA molecules and, upon application to the tissue create an elastic seal independent of the body's clotting mechanism [48]. A pilot study [31] aimed to determine the feasibility of using BioGlue[®] to achieve hemostasis and to prevent urine leakage suggested that this glue provides adequate hemostasis during renal surgery, and decreased blood loss, transfusion rates and operative times.

Another two-component system [59] is made of aminated star-PEG (a star-shaped poly[ethylene glycol]) and high-molecular-weight dextran-aldehyde (Fig. 4). The two polymers are administered as viscous aqueous solutions that are

delivered through a dual-chambered syringe connected to a single injection needle, thus separating the compounds until the time of administration. Upon mixing, imide bonds are spontaneously formed through a Schiff-base reaction between the amine groups in the PEG molecule and the aldehyde groups of the dextran moieties. As a result, a network is formed in seconds. Cohesion strength is created by cross-linking between polymer chains, while adhesion forces are created by the reaction between the aldehyde and the amine groups in tissue. The aldehydes of the dextran are in excess of the amine groups in the star-PEG since they are responsible for both cohesion and adhesion. The adhesive mechanics of this glue varied with aldehyde content and with tissue type. For example: increasing aldehyde content from 8.8 to 14 and 20% resulted in moduli of 100, 500 and 744 kPa, respectively. Likewise, when moduli were measured for different tissues using a dextran with 20% aldehyde content, the highest modulus was measured in the duodenum, followed by the liver, heart and lung (724 ± 86 kPa, 431 ± 15 , 296 ± 60 and 72 ± 7 kPa, respectively). Thus, it was concluded that different tissues may require specific surgical sealants when applied.

PEG-based sealants have gained interest in recent years because they are considered safe, easy to apply, and very effective in sealing suture lines when cross-linked [19]. In order to provide a tight seal, PEGs can be cross-linked by chemical agents or by visible light. An example is the commercial product FocalSeal® (FocalSeal, Focal, Inc., Lexington, MA) which is composed of an eosin primer and an aqueous polymeric solution [69]. The primer is applied first, is absorbed by the tissue, and auto-cross-links. A polymeric solution composed of PEG is applied and cured by visible light (450–550 nm) [2]. FocalSeal® was effective in minimally invasive cardiac surgery, where limited exposure and tight quarters make accurate suturing difficult. This product was also found to be effective for sealing bronchial and parenchymal air leaks [37] and preventing leakage from the cut pancreas (the pancreatic stump) [83].

The preceding systems formed glues spontaneously upon application or mixing. Some, such as chitosan containing azide groups and lactose moieties [63] employ a triggering agent. After ultraviolet light (UV) irradiation, an aqueous solution of this material was used to glue two pieces of sliced ham to each other [65]. The binding strength of the chitosan hydrogel prepared from 30 to 50 mg/mL solutions was similar to that of fibrin glue. However, it was more effective in sealing air leakage from pinholes on isolated small intestine, aorta, and from incisions on the isolated trachea. Neither the tested gel nor its pre-crosslinked solution showed any cytotoxicity in cell culture of human skin fibroblasts, coronary endothelial cells, and smooth muscle cells. In vivo, all mice survived for at least 1 month after implantation of 200 μ L of photocrosslinked chitosan gel or intraperitoneal administration of the pre-crosslinked solution.

The catechol functionality of L-3,4-dihydroxyphenylalanine (DOPA) is thought to be responsible for the ability of marine mussels to form strong bonds with a range of substrates, a property shared by DOPA-coated surfaces [44]. DOPA moieties have been conjugated to polymers and peptides in efforts to develop tissue adhesives [81, 88]. However, the adhesive strength of these biomaterials

have not shown higher adhesive strength than that of fibrin sealant. This is believed to be the result of two major factors: (1) low adhesion forces due to intra- and/or intermolecular cross-linking reactions rather than with the surrounding tissue [45], and (2) the soft, flexible nature of hydrogel networks [66] that limits the cohesion forces within the material.

2 Active Tissue Glues

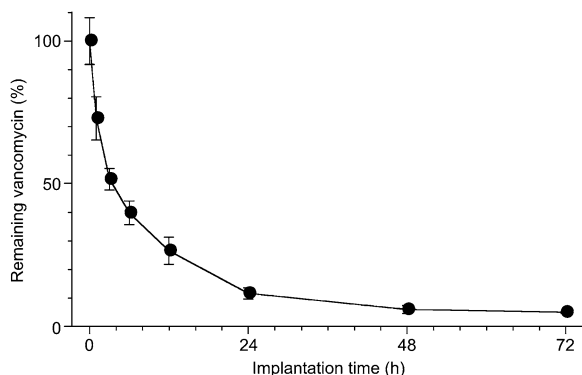
2.1 Tissue Adhesives Releasing Drugs

Tissue adhesives, in addition to being utilized as glues or sealants, can be used as drug delivery systems. The architecture of the material can be engineered to release its contents in the desired pattern directly to the target site. Local release by the glue enables the administration of controlled dosages, reducing the risk of adverse drug effects. Moreover, patient compliance with these drugs is assured as the agents are delivered at the time of the procedure and then released without the need for active participation on the patient's part. The release and the clinical benefits of several drug classes have been investigated utilizing this model, including antibiotics, chemotherapy, analgesics, growth factors, and gene vectors to name but a few. In some of these applications the adhesives are not used as glues or sealants, but simply as drug delivery (depot) systems.

2.1.1 Antibiotic Impregnated Glues

High local antibiotic concentrations at a wound site could prevent local infections (e.g. of surgical wounds) by providing local drug concentrations far in excess of what could be achieved by conventional dosing methods. A variety of formulations have been developed to achieve that goal. For example, vancomycin, teicoplanin, cephalothin and gentamicin added to the thrombin component of a fibrin glue [51] were released from that matrix for over 96 h in vitro, and exhibited antibacterial activity against clinical isolates of *S. epidermidis*. Similarly, amikacin released from a fibrin sealant/polyurethane mixture implanted subcutaneously in the anterior abdominal region of rats [60] was detectable in blood for 24 h, while the same dose given intravenously cleared after only 4 h. Moreover, peak local concentrations of amikacin in tissue near the glues were 210 times higher than when the drug was given systemically. A glue composed of aldehyde-modified dextran and poly (L-lysine) was able to reduce bacterial counts in adjacent subcutaneously implanted Dacron grafts inoculated with methicillin-resistant *S. aureus* [16, 56]. About 95% of the total antibiotic was released over 72 h (Fig. 5), and the local tissue concentration of vancomycin remained above the minimum inhibitory concentration throughout this period.

Fig. 5 Percentage of vancomycin remaining in aldehyde-modified dextran and poly (L-lysine) disks at time points after subcutaneously implantation. Reproduced with permission from Elsevier [56]



2.1.2 Release of Local Anesthetics from Fibrin Glue

A combination of fibrin glue and the local anesthetic lidocaine was developed to treat postoperative breast pain after subpectoral breast augmentation [97]. Although breast pain was observed for 1 week postoperatively for all groups, pain reported by patients in the group treated with the combination was significantly lower than that reported by patients who received lidocaine or fibrin glue alone. No complications were observed in any of the patients who participated in this study. Similarly, a fibrin glue containing lidocaine was used to relieve pain after tonsillectomy [41]. Tonsillar fossae were covered with fibrin glue containing lidocaine (dissolved in the thrombin solution) immediately after tonsillectomy. Patients began to eat normally after 3.78 days in the group administered with regular fibrin sealant compared to 2.83 days when the fibrin with lidocaine was used. In addition, the mean postoperative period for which analgesic administration was necessary decreased from 4.91 to 2.88 days when lidocaine was incorporated in the glue.

2.1.3 Release of Chemotherapy from Photocrosslinkable Chitosan Tissue Adhesives

In the management of cancer patients, local delivery may provide a high local concentration of anti-tumor drugs with decreased incidence of the side effects observed with systemic therapy [23]. A photocrosslinkable chitosan tissue adhesive (see Sect. 1.2.2 of this chapter) has been developed to deliver the antineoplastic drug paclitaxel [27, 63]. About 40% of the paclitaxel was released from the hydrogel into media (phosphate buffered saline) within 1 day in vitro, after which gradual release occurred for 3 days. The paclitaxel-containing hydrogel inhibited the growth of subcutaneous tumors induced with Lewis lung cancer (3LL) cells more effectively than those treated with plain chitosan gel or free paclitaxel injected subcutaneously at the tumor, for at least 11 days. Furthermore,

the paclitaxel-containing chitosan hydrogel markedly reduced the number of CD34-positive vessels in subcutaneous 3LL tumors, indicating a strong inhibition of angiogenesis.

2.1.4 Delivery of Growth Factors and Genetic Material from Tissue Adhesives

Although producing a system that releases biomacromolecules from a tissue adhesive can seem relatively simple (e.g. mixing one in the other), the macromolecules may have complex interactions with the surrounding matrix [80]. For example [13], when transforming growth factor beta-1 (TGF- β 1) was added to fibrin sealant, release was much slower when fibrinogen concentrations were increased, suggesting a binding affinity of TGF- β 1 with the fibrinogen. Varying the thrombin concentration though, had a lesser effect.

A matrix to promote wound healing has been developed by incorporating recombinant human epidermal growth factor (rhEGF) into a photocross-linkable mixture of glycidyl methacrylated chitoooligosaccharide and di-acrylated Pluronic F127 [15]. When this hydrogel was administered to dorsal burn wounds in the rat, epidermal differentiation was significantly enhanced compared to plain hydrogel. The in vitro release profiles of rhEGF were dependent on the degradation rates of the hydrogels (Fig. 6).

Fibrin sealant has also been used to release nerve growth factor (NGF) into the site of end-to-end sutured peripheral nerve. Stained sections revealed significantly increased regenerated nerve fibers distal to the anastomosis compared to groups that received NGF or fibrin sealant alone. Similarly, fibrin sealant containing glia-derived neutropic factor (GDNF) had a greater in vivo effect on neuron growth than did the free factor or the sealant alone [14, 91].

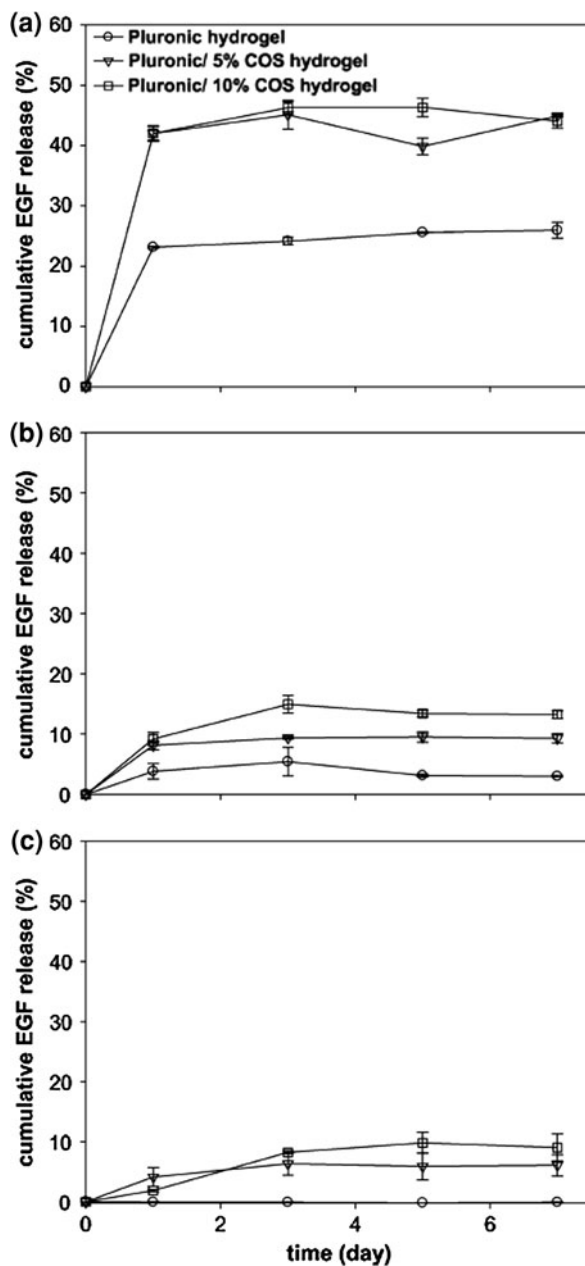
Fibrin sealant has been used to release adenoviral vectors encoding β -galactosidase [7]. Vectors released from fibrin resulted in higher numbers of rabbit cartilage cells expressing β -galactosidase in vivo than with vector alone.

2.2 Intrinsic Activities of Glues

2.2.1 The Anti-bacterial Properties of Cyanoacrylates

The antimicrobial properties of cyanoacrylate tissue adhesives were first reported in 1983 [25]. A link has been established between the polymerization process and the antimicrobial properties, in particular against Gram-positive microorganisms [72], perhaps by action against the bacterial cell wall [22, 76]. Similarly, 2-ethyl cyanoacrylate monomers applied onto the surface of bacteria cultures [73] inhibit the growth of *S. aureus* and *S. pneumoniae* (both Gram positive). A possible explanation to the higher sensitivity of the Gram-positive bacteria might be the

Fig. 6 Release profiles of rhEGF from a mixture of glycidyl methacrylated chitooligosaccharide and diacrylated Pluronic F127 with photo-irradiation times of 2 min (a), 5 min (b), and 10 min (c). The polymeric concentration of all hydrogels was 20% (w/w). Reproduced with permission from John Wiley and Sons [15]



strong electronegative charge on the cyanoacrylate monomer that reacts with the positively charged carbohydrate capsule of Gram-positive organisms [34]. While cyanoacrylates have less effect on Gram negatives, 2-ethyl cyanoacrylate monomers did kill *Escherichia coli* [73].

2.2.2 Anti-bacterial Barriers

2-octyl cyanoacrylate films have been shown to be effective barriers to bacteria, fungi, and yeast in vitro [58]. The barrier property of cyanoacrylate bandage was also seen in a wound model in swine [52]. *S. aureus* or *Pseudomonas aeruginosa* were inoculated on one side of a test bandage placed over a wound. Significantly lower numbers of inoculated bacteria were found among the cyanoacrylate bandage group compared with other groups treated with standard or hydrocolloid bandages.

2.2.3 Glues with Wound-Healing and Other Tissue-Active Properties

Photocrosslinkable chitosan is strong, elastic and is considered more effective in sealing air leakages than fibrin glue [64]. It can stop bleeding within 30 s of UV-irradiation and firmly adhere the cut edges of two pieces of skin [32]. It can also induce wound contraction and accelerate wound closure and healing [10]. Histological findings suggest that chitin and chitosan stimulate the migration of mononuclear and polymorphonuclear cells and accelerate angiogenesis and the formation of connective tissue [55]. Other studies [46, 61] suggest that chitosans possess antibacterial properties, owing to the cationic amines interacting with negatively charged residues on the bacterial cell surface [95].

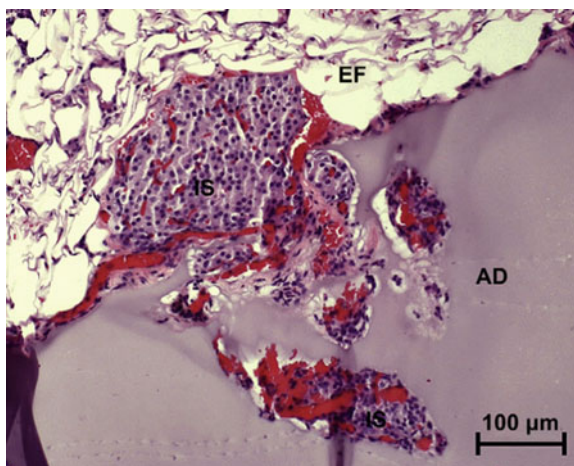
Experiments performed in our lab [92] suggest that some caution may be advisable in using chitosan and UV-cross-linkable chitosan in some contexts. Although in vitro experiments showed neither attractive interactions between the gels and the cells nor a proliferative or marked toxic effect, the same material applied in the peritoneal cavity of rabbits caused a granulomatous reaction in all animals, with resultant adhesion formation (“adhesion” in this context meaning an undesirable sticking together of tissues). Although chitosan’s adhesive and other proinflammatory properties may be beneficial in some biomedical applications, this may not be true in all contexts.

Chitin and chitosan gels have inhibitory effects on tumor angiogenesis and metastasis [12, 57], and can inhibit tumor cell proliferation by inducing apoptosis [57].

2.2.4 Glues for Islet Cell Immobilization

There is a great need for medical adhesives that effectively function on wet tissue surfaces with minimal tissue and cell response. A star shape PEG core with DOPA endgroups was suggested as a system for cell immobilization [8]. When aqueous solutions of this polymer were oxidized with NaIO_4 , each DOPA endgroup covalently attached to a neighboring DOPA, forming a 3D hydrogel structure. Donor islet cells were placed into the PEG-DOPA aqueous solution which was then oxidized. The encapsulated cells were then implanted in type 1 diabetic mice

Fig. 7 Photomicrograph of hematoxylin and eosin (H&E)-stained tissue explants demonstrating star-PEG-DOPA adhesive-mediated islet cell attachment to the epididymal fat pad surface. *AD*, adhesive, *IS* islet, *EF* epididymal fat tissue. Reproduced with permission from Elsevier [8]



(Fig. 7). This adhesive material maintained an intact interface with the supporting tissue for up to 1 year. The cells encapsulated within were able to maintain normoglycemia for over 100 days.

3 Conclusions and Future Directions

Surgical adhesives are attractive alternatives to sutures and staples [20]. They allow rapid adhesion and maintain strong and close apposition of wound edges [54]. In some cases, the tissue glues themselves contribute directly to the process of wound healing. A major potential advantage of tissue glues is their ability to release drugs directly to the wound. In this chapter, we presented the release of several drugs from various classes of tissue adhesives, with emphasis on the chemical and the physical properties of each system.

There is a great variety of adhesives, to which a range of active properties can be imparted. Further studies will be required to determine whether these new materials will translate into the clinical arena. The potential to modify these materials has barely been tapped. For example, the incorporation of nanomaterials [93] and/or of components that would allow triggered release of compounds [82] could further enhance their properties.

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