Bone-adhesive materials

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Abstract: Each year millions of people suffer from complex bone fractures which require proper external or internal fixation. This fixation is usually achieved by means of devices such as plates, pins and screws. These traditional fixation strategies are associated with severe drawbacks, which has prompted research and development of a variety of bone-adhesive biomaterials as alternative to traditional fixation strategies. However, a clinically applicable bone-adhesive biomaterial—in the form of a bone-glue or bone-adhesive membrane—that meets all requirements has not yet been identified. This review discusses the current state-of-the-art of bone-adhesive materials with a particular focus on their clinical requirements, mechanisms of action, and future perspective. To develop adhesive biomaterials with specific affinity to bone tissue, a more rational design should be implemented. This perspective article is intended as a starting point and inspiration for future research and development of suitable bone-adhesive materials.

1. Introduction

Every year millions of people suffer from complex bone fractures as a result of traumatic incidents such as sporting injuries, vehicle accidents and falls, or medical conditions such as osteogenesis imperfecta, osteoporosis, cancer-induced bone degeneration, or periodontitis. When alignment of the fractured bones is not well-maintained with the help of e.g. plaster casts, internal fixation is required to facilitate subsequent bone healing. To this end, metal plates, pins or screws are placed in unaffected areas of bone around the fracture. However, these conventional fixation methods are associated with numerous clinical problems. These disadvantages include high costs, the need for removal of these metal implants after bone healing, the occurrence of stress shielding and associated re-fractures, the risk for infection caused by transcutaneous fixation devices, impalement of tendons, muscles, vessels, and nerves as well as the difficulty to perform delicate surgery, e.g. to fixate fractures of small bone fragments around articulating surfaces.^[1, 2]

In view of the drawbacks of conventional fixation methods, novel bone-adhesive biomaterials such as bone glues would overcome a major surgical problem. A biodegradable and bone-adhesive glue would provide an easy and rapid method to fixate fractures without the need for removal after bone healing. Furthermore, their contact surface with bone is larger than traditional fixation devices such as pins or screws, which can allow a faster and more efficient healing.^[3-5] Moreover, their application to fix fractures around articulating surfaces or small bone fragments would be a major breakthrough. Furthermore, the lower stiffness of bone-adhesive glues would prevent stress shielding as observed for much stiffer metallic fixation devices, thereby maintaining bone quality and preventing fractures after surgical removal of fixation devices.^[6]

More than a century ago, Gluck pioneered the concept of bone-bonding materials using Lithocolle, which consisted of a resin, paraffin wax, red ochre and oil of turpentine.^[4, 7] In 1931, Hedri developed the first truly bone-adhesive biomaterial named Ossocol, which consisted of a mixture of collagen and fibrous protein. Its initial bone-adhesive strength and

bone-healing efficacy were satisfactory, but severe allergic reactions impeded its further clinical use.^[8] Since then, bone adhesives have been investigated extensively in view of the clear unmet clinical need, but no commercially available products are available which meet all the clinical requirements for bone adhesives. Most bone adhesives are based on synthetic polymers since their adhesive properties can be easily tuned by varying polymer characteristics such as their functional (side) groups, their cross-linking degree, and their viscosity and surface tension to allow formation of mechanical interlocks with the outer surface of bone. Conventional bone substitutes such as cements or bone void fillers are occasionally claimed to possess bone-adhesive properties, but these traditional biomaterials merely bond to human tissues by mechanical interlocking without exhibiting specific bone-adhesive properties.^[9, 10] This perspective article discusses the current state-of-the-art of both synthetic and natural bone adhesives by describing i) their clinical requirements, ii) their mechanism of action and iii) their specific advantages and disadvantages for future clinical applications.

1.1. Definition and Requirements of Bone-Adhesive Materials

Adhesion can be defined as the force that binds two dissimilar materials together when they are brought into intimate contact.^[11] However, a generally accepted definition for bone adhesives is not available yet. Generally, bone adhesives used for applications in e.g. maxillofacial, trauma and orthopedic surgery should meet the requirements summarized in **Table 1.**^[4, 5, 8, 12]

Table 1. Requirements for bone adhesives.

Adhesive and cohesive mechanical properties	<ul style="list-style-type: none"> • Strong adhesion to bone under clinically relevant situations (e.g. moist, bleeding, uneven surfaces) • Mechanical stability under tensile, compression and shear forces
Biocompatibility	<ul style="list-style-type: none"> • Non-toxic, non-teratogenic and non-carcinogenic • Biocompatible with surrounding tissues

	<ul style="list-style-type: none"> • Allow for fracture healing and bone regeneration
Biodegradability	<ul style="list-style-type: none"> • Biodegradable and bioresorbable • Tunable degradation rate • Non-toxic degradation by-products • Control over mechanical properties over time
Clinical handling behavior	<ul style="list-style-type: none"> • Easy and quick to prepare and apply • Rapid setting time
Miscellaneous requirements	<ul style="list-style-type: none"> • Sterilizable • Stable during storage • Cost-effective

Obviously, bone adhesives should be able to form a strong bond with bone tissue to create a mechanically stable interface under the influence of tensile, compressive and shear forces. Minimum levels of adhesion have not yet been clearly defined in view of the complex clinical scenario as well as the wide variety of testing methods to quantify adhesion strength. Nevertheless, Weber and Chapman proposed a minimum bond strength for bone adhesives of 0.2 MPa below which fixation strength was considered insufficient.^[3] Ideal bone adhesives should maintain sufficient strength during the main phases of bone healing, i.e. i) hematoma formation, ii) inflammatory response, iii) callus formation and iv) bone remodeling. As described in **Table 2**, bone adhesives should be able to withstand pH changes as well as the occurrence of bleedings. They must be compatible to bone, allow for fracture healing as well as regeneration of the surrounding bone without causing tissue irritation or necrosis. Ideally, bone adhesives should be degradable. The degradation process could be either biologically mediated by enzymatic and/or cellular processes (biodegradable) or chemically mediated by hydrolysis (bioresorbable). To ensure mechanical stability, the degradation rate of the bone adhesive should match the rate of bone healing. Average bone healing times range between 8–16 weeks, although these rates vary depending on the type and site of the injury as well as the age and health of patients.^[13] The degradation rate of bone adhesives should be tunable to

such extent that the cohesive and adhesive strength are maintained long enough to ensure sufficient fixation. Since the bone remodeling phase is only initiated after 3–4 weeks, bone adhesives should be stable for at least this period of time before actual degradation starts.^[14] Subsequently, the adhesive should degrade in a controllable manner. Gradual degradation rates are preferred over burst-type degradation profiles to avoid toxicity caused by high concentrations of degradation by-products and local inflammatory responses due to pH changes. Generally, degradation by-products should be non-toxic, non-teratogenic and non-carcinogenic at their specific *in vivo* release profile. They should be easy and quick to prepare and apply by clinicians, and once applied, they should set rapidly. Finally, they should be sterilizable, stable during storage and cost-effective.

Table 2. Phases of bone healing.

Phases of Bone Healing	Physiological Changes	Properties of Ideal Bone Adhesive
Hematoma formation	Bone and surrounding tissues bleeding	Good cohesion and adhesion on highly perfused bone tissue
Inflammatory response	pH decrease	Not affected by acidic pH
Callus formation	Osteoblast proliferation, cartilage resumption and bone replacement	Initiation of adhesive degradation
Bone remodeling	Remodeling of original bone structure	Final bone adhesive degradation

1.2. Mechanisms of Adhesion

Adhesive bonds can be established by means of i) mechanical interlocking, ii) chemical and/or iii) physical adhesion.

i) Mechanical interlocking

Depending on their viscosity and surface tension, adhesives can penetrate into substrate surface irregularities such as voids or fissures. If the absorbing component is a long-chain molecule or forms a long-chain molecule within the penetrated layer, the resultant mechanical interlocking between the adhesive and the substrate may result into a substantial bond strength.

Nevertheless, mechanical interlocking is usually not sufficient to ensure sufficient bond strength for bone adhesives.

ii) Chemical adhesion

This form of adhesion is known as chemisorption, and it is achieved by irreversible ionic or covalent bonding. Adhesives must be strongly attracted chemically to the surface of application in order to form strong bonds, and require the presence of reactive groups on the surface of both adhesive and substrate.

iii) Physical adhesion

When two surfaces are in close proximity, reversible secondary forces can be formed through dipole interactions between polar molecules, Van der Waals forces, hydrogen bonding, etc. The magnitude of the physical interaction energy is usually less than 19 kJ/mol. This is lower than primary bonds, such as ionic or covalent bonds, which typically range between 190–580 kJ/mol. Although these secondary forces are weak, the presence of multiple poles in large or complex molecules may contribute to considerable bonds strengths.

The mechanisms of action of the bone-adhesive materials described in this review are summarized in **Table 3**.

Table 3. Mechanisms of action of bone-adhesive materials.

Adhesive System	Mechanism of Adhesion	
	Chemical and/or Physical Bonding	Mechanical interlocking
Polyurethane	Covalent bond between carbamate group of adhesive system with amines present in bone collagen matrix, hydrogen bonds	
PMMA		Infiltration of the polymer chains into surface irregularities
PMMA related co-polymers	Ionic interaction between carboxylate anions of adhesive system with Ca^{2+} present on the surface of bone	Infiltration of the polymer chains into surface irregularities
Cyanoacrylate	Covalent bond between acrylate group of adhesive system with amines present in bone collagen matrix	
Fibrin glue	Covalent bond between amino groups of fibrin/fibronectin of adhesive system with carboxylic acid groups present in bone collagen matrix	
Oxidized Starch Polysaccharide	Covalent bond between aldehydes of adhesive system with amines present in bone collagen matrix	

Mussel-inspired adhesive	Ionic bond between catecholic hydroxyl and carboxylic acid groups of adhesive system with Ca^{2+} present on the surface of bone
Sandcastle-inspired glue	Covalent bond between amine groups of adhesive system with carboxylic acid present in bone collagen matrix, and ionic interaction between phosphate anions and catecholic hydroxyl of adhesive system with Ca^{2+} present on the surface of bone
Frog-inspired glue	Covalent bond between carboxylic acid of adhesive system with amines present in bone collagen matrix

2. Bone Adhesives Made from Synthetic Polymers

Polyurethanes, poly(methyl methacrylate)s (PMMA)s and polycyanoacrylates, are the most commonly studied synthetic polymers for application as bone adhesives.

2.1. Polyurethanes

Polyurethanes are a very versatile family of polymers. They can be synthesized from a wide variety of polyisocyanates and polyols in the presence of either a catalyst or ultraviolet light. The degradability of polyurethanes can be tuned by varying properties of the polymer such as molecular orientation, crystallinity, cross-linking and chemical groups present in the molecular chains. These polymers can exhibit different properties by tuning their molecular composition and their crosslinking degree and stiffness. They have been used in many applications including adhesives, bone fillers, catheter tubings and wound dressings.^[15, 16] Polyurethanes have been proposed as bone adhesives in view of their abundant use as soft tissue adhesives and sealants.^[17] These polymers can interact with bone either physically through hydrogen bonding or chemically through the formation of urea bonds upon reaction of the carbamate group of polyurethanes with amines present in the mineralized collagenous extracellular matrix of bone. However, their long-term stability in biomedical environments is still debated. While evidence of polymer degradation via hydrolysis or enzymatic degradation has been reported by several groups, other studies conclude that *in vivo* degradation is minimal.^[18]

Polyurethanes have been considered for application in bone glues from the 1950s and early 1960s onward. In 1958, a rigid polyurethane foam called Ostamer was developed to repair bone fractures, which was used in clinical trials. The polymer was prepared by reacting trihydroxyl resin with an excess of diisocyanate at the time of surgery with a catalyst. Carbon dioxide gas was formed to produce a porous sponge-like compound. Initially, this adhesive was claimed to be mechanically strong, cohesive, osteogenetic, non-toxic, and easily applicable during surgery.^[19, 20] However, further studies showed breakage of the polymer or loss of its bond to bone, wound infection, and tissue necrosis.^[21] Complete removal of the adhesive was necessary to stop persistent drainage. Therefore, its use for osteosynthesis was discontinued.

In the 1990s, a novel adhesive based on polyurethane containing calcium and phosphate was reported, which was evaluated successfully *in vivo*.^[22, 23] The adhesive enabled the re-union of a shaft fracture without causing any adverse reaction. However, more quantitative studies are needed to characterize the adhesion properties, bone healing efficacy and degradation *in vivo* of this bone adhesive.

Recently, a polyurethane-based polymer that comprises castor oil-based polyol, a reactive isocyanate and calcium carbonate powder called Kryptonite^[24] was reported to adhere directly and specifically to bone tissue.^[25–29] Although it has successfully been used clinically to achieve sternal closure, cranial reconstruction and vertebral augmentation, this formulation still needs to be optimized for application as bone adhesive.^[30–32] Also, a novel polyurethane-based foam-like adhesive which was composed of 4,4-methylene diphenyl diisocyanate (MDI)M, a biodegradable polycaprolactone-based polyol and reinforced with hydroxyapatite particles was developed and investigated for bone-to-bone bonding applications.^[33] Although the exact chemical structure is registered as trade secret, the main synthetic reaction is depicted in **Scheme 1**. In terms of mechanical testing, a four-fold enhanced adhesion compared to conventional PMMA cement was achieved. However, since adhesion of PMMA

cements to bone is rather low, this four-fold enhanced adhesion is still not considered sufficient to achieve optimal healing. The biological performance of this adhesive was initially assessed *in vitro*, which confirmed the cytocompatibility of the adhesive. Then, the *in vivo* response was assessed for the repair of defects of frog hind limb tarsus bone.^[33] The histological results indicated that the adhesive material produced a tissue immunological response similar to control specimens. However, the size limitations of the species prevented proper assessment of the adhesive bonding to bone. Therefore, long-term *in vivo* studies are needed to demonstrate the biocompatibility convincingly.

Scheme 1. Schematic representation of the synthesis of a polyurethane consisting of MDI and caprolactone-based diol.

2.2. Poly(methyl methacrylate)s and Related Co-polymers

Poly(methyl methacrylate)s have been extensively used in dentistry and orthopedic surgery, e.g. to anchor artificial joint prostheses.^[34–36] PMMA is produced by polymerization of methyl methacrylate (MMA) through a free radical process using an initiator, such as an azo compound or a peroxide. Polymerization can be carried out commercially in several ways, i.e. in bulk, solution, suspension or emulsion.^[37] After mixing these constituents, they form a viscous paste which hardens through either radical or anionic polymerization of the monomers. PMMA cements are hydrophobic and exhibit weak adhesion to bone, especially in wet environments. They act by forming mechanical interlocks with the porous bone in which the cement is placed.^[38] In general, PMMA is encapsulated by fibrous rather than hard tissue, but adverse tissue responses have hardly been reported for PMMA-based adhesives.^[35]

Carcinogenesis has not been associated with these biomaterials, although mutagenesis has been reported in bacteria.^[5] During application, an exothermic polymerization reaction undergoes resulting in the release of heat to the surrounding bone tissue, which ultimately could lead to thermal necrosis in bone tissue.^[39, 40]

Many attempts have been reported to enhance the adhesion of poly(methyl methacrylate)s to bone, for instance by i) pre-treatment of the bone,^[41] ii) application of an intermediate bonding agent,^[42–45] or iii) chemical modification of the PMMA cement.^[46–50]

In 2003, inspired by dentine bonding agents developed in adhesive dentistry, Erli *et al.* used an etching system which contained 37% of phosphoric acid to remove debris and to demineralize the surface of bone tissue and expose collagen fibers.^[41] This pre-treatment was followed by infiltration of a hydrophilic acrylic monomer (e.g. hydroxyethyl methacrylate, 4-methacryloyloxyethyl trimellitic anhydride, and/or glyceryl methacrylate) followed by infiltration with a more hydrophobic acrylic monomer (e.g. bisphenol glycidyl methacrylate, triethylene glycol dimethacrylate, and/or polyethylene glycol dimethacrylate) into the exposed collagen layer.^[42] After photo-polymerization, a composite of collagen fibers and resin was formed, thereby increasing the bond strength by two orders of magnitude.

An alternative approach to enhance the adhesion of PMMA cement to bone involves chemical modification of the polymer. For instance, cements were developed which consisted of 4-methacryloyloxyethyl trimellitate anhydride (4-META) and methyl methacrylate (MMA) as monomers with tributyl borane (TBB) as an initiator (**Scheme 2**).^[46–50] 4-META enhanced the infiltration of monomers into bone to create a hybrid layer, thereby forming a bond with bone tissue through hydrolysis of the anhydride group to form carboxylate anions which bind to calcium ions in bone. This modified cement enriched with hydroxyapatite particles showed a ten-fold increased adhesion to bone compared to conventional unmodified PMMA bone cement.^[47–50] Despite its clinical use in dentistry,^[51] its use as bone adhesive is still limited due to its lack of biodegradability.

Scheme 2. Schematic representation of the synthesis of PMMA/4-META cement.

Unfortunately, PMMA cements are not biodegradable. To solve this shortcoming, various researchers attempted to combine the reactivity of methyl methacrylates with the biocompatibility and degradability of polylactides.^[52–55] Polylactide polymers and co-polymers have been widely used to synthesize biodegradable orthopedic fixation devices and their mechanism of degradation is well established.^[56] Besides polylactides, other polymers have been co-polymerized with PMMA as well, including poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG), which are biocompatible but not biodegradable.^[53]

In 2005, Heiss *et al.* described a bone-adhesive system based on a low molecular weight alkylene bis(dilactoyl)methacrylate polymer.^[57] This viscous polymer polymerizes upon light irradiation to form highly branched, hydrolysable, biodegradable networks. Initially, the biocompatibility and adhesion to bone were reported as favorable, while its degradation did not interfere with physiological fracture healing.^[54, 55] However, adverse tissue responses were also reported in a long-term *in vivo* study where the adhesive was used to improve screw fixation.^[52, 55]

In 2017, Wistlich *et al.* attempted to improve the adhesion under wet conditions of a bone glue based on a photo-curable poly(ethylene glycol) dimethacrylate (PEGDMA) matrix. An interpenetrating network (IPN) was formed through *in situ* formation by addition of isocyanate functional six-armed star-shaped pre-polymers with ethylene oxide and propylene oxide statistically co-polymerized in the backbone in a ratio of 4:1 (NCO-sP(EO-*stat*-

PO)), as depicted in **Figure 1**.^[57] To adjust the workability, biodegradable inorganic fillers such as $\text{Mg}_3(\text{PO}_4)_2$ and/or $\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$ were added to the glue. Although the adhesion strength of this system exceeded its cohesive strength, this composite glue significantly increased the bonding ability of isocyanate containing glues to wet bone. The authors demonstrated that the composite glue was cytocompatible and easy to apply. Consequently, this study could open a new strategy towards the development of biocompatible and degradable bone glues that stimulate rather than impede bone regeneration but instead facilitate the process of bone formation upon fracture healing.

Figure 1. Schematic representation of the design of a bone glue based on a photo-curable PEGDMA matrix, NCO-sP(EO-*stat*-PO) and a ceramic filler.^[57] Copyright 2016, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

A particularly effective mineral-adhesive monomer called 10-methacryloyloxydecyl dihydrogen phosphate (MDP) was developed by Kuraray in 1981. It is synthesized by reaction of methacrylic acid, 1,10-decanodiol, and phosphoryl chloride. This monomer is used extensively in dentistry in bonding agents, resin cements, dental adhesives, and dental adhesive primers. This phosphate-containing monomer forms a very stable and strong bond with enamel and dentine.^[58–61] MDP is a hydrophilic phosphate monomer that increases resin diffusion and adhesion by causing acidic decalcification of teeth acting as a self-etching

primer.^[59] The adhesion mechanism of MDP is achieved by a combination of micromechanical interlocking and ionic bonding between the acidic phosphate groups of the monomer with calcium ions in hydroxyapatite, the main inorganic constituent of both enamel and dentine. Micromechanical interlocking is established as well due to infiltration of resin monomers into the surface irregularities created in the mineralized tissues. Although this monomer does not show signs of degradation, its strong and stable adhesion to hydroxyapatite, which is also the main component of bone tissue, renders this type of chemistry promising for the development of novel bone adhesives.

2.3. Polycyanoacrylates

Alkyl 2-cyanoacrylates are the most extensively studied group of bone adhesives. A variety of 2-cyanoacrylates esters can be synthesized by varying the length of the alkyl chain. The structure of cyanoacrylates studied for application as bone adhesives is shown in **Figure 2**. They are highly reactive and polymerize at room temperature without adding a catalyst, heating or applying pressure. Monomers react via anionic polymerization after being initiated by water. The acrylate bond is susceptible to nucleophilic attack by weak bases as water or amines. Adhesion to bone can be achieved since the electron-withdrawing nitrile group polarizes the acrylate bond and therefore it is susceptible to nucleophilic attack by weak bases such as amines present in the collagen matrix of bone tissues. In general, higher polymerization rates, stronger bond strengths in tissues, and more flexible chains are obtained by increasing the length of the alkyl chain.^[8, 62]

Figure 2. Structures of A) ethyl cyanoacrylate, B) butyl cyanoacrylate, C) isobutyl cyanoacrylate and D) isopentyl cyanoacrylate studied as bone adhesives.

Cyanoacrylate adhesives were first developed in 1959 for application as universal glues in households as well as the automotive and construction industries.^[63] Many cyanoacrylate-based soft tissue adhesives are already commercially available, including Dermabond[®], Indermil[®], Glubran[®], and Histoacryl[®].^[13, 64] However, cyanoacrylates have not been designed specifically for application as bone adhesive, although these biomaterials have been used in clinics as bone glues since the early 1960s. In 1963, a cyanoacrylate adhesive, called Cyacrin, was used for the first time to achieve adhesion to bone tissue. Reports regarding non-adhesion and displacement of the Cyacrin-glued bone fractures were followed by reports of high infection rates, non-adhesion, fistula formation, and severe local reactions.^[42, 65, 66] An ethyl cyanoacrylate combined with polyisocyanate and nitrile rubber, called Biobond, showed more favorable initial results in animals.^[42] However, cyanoacrylates with short alkyl chains were associated with carcinogenicity due to the fact that the degradation of the polymers occurs via hydrolysis, leading to release of formaldehyde and cyanoacetate.^[67, 68] Consequently, methyl cyanoacrylate-based adhesives were banned by the American Food and Drug Administration for human use. Further studies with cyanoacrylates with longer alkyl chain demonstrated a more benign tissue reaction, since they degrade slower due to steric hindrance and hydrophobicity.^[69] Butyl 2-cyanoacrylate, also known as Histoacryl[®], is a biocompatible cyanoacrylate adhesive, approved for use in surgery to achieve wound closure.^[67, 70] Butyl, isobutyl and octyl 2-cyanoacrylates have also been tested as potential bone adhesives for fractures.^[71–80] However, some cases reported insufficient bond strength for fracture stabilization after six weeks, inflammatory responses and cytotoxicity in undiluted form, although cytotoxicity was acceptable when diluted ten times with culture medium. Generally,

more biocompatibility studies for cyanoacrylates are required to be able to conclude if these polymers can be considered as bone adhesives.

3. Bone Adhesives Made from Natural Polymers

Bone adhesives made from natural polymers consist most frequently of polysaccharides, fibrin glue, mussel-, sandcastle-, and frog-inspired adhesives.

3.1. Fibrin-based Adhesives

Fibrin-based adhesives are the most widely used soft tissue adhesives, sealants and hemostatic agents.^[81–84] Fibrin is a fibrous non-globular protein involved in the clotting of the blood. Most fibrin-based adhesive systems are formed by mixing a solution containing a fibrinogen source (from plasma, platelet-rich plasma) or heterologous/autologous cryoprecipitate) and factor XIII, with another separate solution containing a thrombin source (bovine, human or recombinant), calcium and an antifibrinolytic agent (e.g. aprotin) to prevent rapid fibrinolysis.^[85, 86] When mixed, these agents form a cell-free clot, in which thrombin cleaves fibrinogen, yielding soluble fibrin monomers, which assemble first into loosely aggregated fibrils by hydrogen bonding and then into a stronger cross-linked fibrin polymer by covalent bonding. Thrombin also activates factor XIII, which facilitates covalent bonding of the fibrin polymer in the presence of calcium. However, a long preparation time is needed before use. A number of factors affect the fibrin gel architecture, which in turn affects the mechanical properties of the material, such as the pH, ionic strength, temperature, calcium ion concentration, thrombin concentration and fibrinogen concentration. The presence of Factor XIII will affect the gel mechanical strength by covalently crosslinking the chains. Water, fat, and collagen contents will have some effect upon the adherence of the glue.^[87] Although fibrin glue adheres to tissues via formation of covalent bonds between amino groups of fibrin or fibronectin with carboxylic acid groups present in the collagenous matrix of bone tissue,^[4] its adhesion strength to bone is low compared to synthetic adhesives (0.17 MPa),

which can be attributed to the low cohesive strength of the fibrin itself.^[12] However, fibrin glue has many advantages over synthetic adhesive systems such as cyanoacrylates in view of their excellent biocompatibility, biodegradability, and cost-effectiveness. Therefore, these materials have been extensively used in orthopedic surgery.^[88–90] Fibrin adhesives are currently considered a second-tier treatment for osteochondral defects.^[81, 90, 91] Using fibrin sealant in a thin layer results in accelerated revascularization of the osteochondral fragment followed by union and healing.

In 1985, Keller *et al.* evaluated the fixation strength of standardized osteochondral fractures in canine femoral condyles with fibrin sealant.^[92] The authors concluded that fibrin sealants can be used as a method of fixation of small, well-adapted, osteochondral fragments, providing reliable immobilization even though their initial tensile strength was low.

Recently, an autologous fibrin glue for bone tissue engineering of maxillofacial surgery was introduced by Azizollah *et al.*^[93] The glue consisted of fibrinogen, thrombin, fibronectin (factor XIII), anti-fibrinolytic agents (such as aprotinin and tranexamic acid), calcium chloride, and platelet growth factors. This autologous fibrin glue is an interesting scaffold for application as a hemostatic barrier by inducing and promoting angiogenesis and initiating early osteogenesis for oral and maxillofacial surgery. However, bone adhesion was not assessed.

3.2. Polysaccharide-based Adhesives

Polysaccharides such as chitin, chitosan, dextran or chondroitin are an important class of soft tissue adhesives and hemostatic materials.^[94–96] They are composed of naturally occurring sugar building blocks that generate biocompatible and biodegradable adhesives which are easy to prepare and apply.

Their use as bone-adhesive materials was investigated from the 2000s onward. In 2009, Hoffmann *et al.* developed a novel two-component bio-adhesive system based on

biocompatible and degradable biopolymers (chitosan and starch).^[97] Starch was oxidized with periodic acid to form aldehyde side groups, while chitosan was used as the amino-group carrier (**Figure 3**). Aldehyde groups react with amino groups present in surrounding tissues as well as with chitosan in the bio-adhesive system. The two components covalently cross-link after mixing in water by forming a Schiff's base, thereby enabling a strong bonding to tissue through the formation of covalent bonds. The glue can bind to any other exposed amino group such as for example those exposed in fractured bone. Additionally, to further increase the bonding strength to bone, the starch or dextran compound was conjugated with 3,4-dihydroxy-L-phenylalanine (DOPA). Biomechanical studies on bovine cortical bone specimens revealed that the glue possessed superior adhesion strength as compared to fibrin glue, but a lower adhesion strength than cyanoacrylates. *In vitro* cell testing demonstrated excellent biocompatibility, rendering this glue a potential candidate for clinical use.

Figure 3. Structures of A) chitosan, B) starch and C) starch aldehyde.

In 2011, Kumbar *et al.* reported the design and fabrication of novel scaffolds with good mechanical properties based on cellulose polysaccharides and their suitability for load-bearing bone healing applications.^[98] Cellulose, the primary structural component of plant cell walls, is a linear polysaccharide of D-glucose units linked by $\beta(1\rightarrow4)$ glycosidic bonds. This highly cohesive hydrogen-bonded structure provides cellulose fibers with exceptional strength and renders them water-insoluble despite their hydrophilic nature. As a result, the scaffolds showed a compressive strength in the mid-range of human trabecular bone. The adhesion was achieved by an esterification reaction between the hydroxyl groups present in cellulose and carboxylic acid groups present in the organic matrix of bone tissue. These adhesives degraded

under *in vitro* conditions, resulting in a weight loss of 10–15% over a period of 24 h. The scaffold chemical structure should be modified to decelerate its degradation for tissue engineering applications.

3.3. Mussel-, Sandcastle- and Frog-inspired Adhesives

Marine animals such as mussels, oysters, limpets and marine worms produce adhesive proteins to anchor themselves to some substrates in water.^[99] Blue mussel *Mytilus edulis* has the ability to attach itself to both inorganic and organic substrates at various levels of salinity and humidity.^[100] Moreover, this organism can even adhere to non-sticky materials such as polytetrafluoroethylene (PTFE). However, the practical use of mussel adhesives has been hampered by technical difficulties with extraction and high production costs.^[90] In addition, the danger of allergic reactions to such large exogenous proteins precluded the use of the mussel adhesives *in vivo*.^[8, 90] For these reasons, many studies have been carried out to evaluate the properties and components that provide mussels with great adhesive ability, and various mimetic polymers have been developed.^[101–103] It was found that DOPA groups, which are present in high concentration at the adhesive substrate interface of mussels, are responsible for their adhesive properties. Furthermore, it was found that the iron concentration of mussel adhesives is substantially higher (100,000 times) than its concentration in the surrounding water, and it cross-links with the catecholic hydroxyl groups of DOPA to form $\text{Fe}(\text{DOPA})_3$.^[104] Furthermore, iron induces the oxidation of DOPA to yield an organic radical to enable further protein-protein bonding or protein-surface bonds for adhesion.

This type of adhesion to both organic and inorganic compounds is highly interesting for the development of bone adhesives since bone is also a mixture of organic and inorganic components. The carboxylic acid group and the hydroxyl groups from the catechol of DOPA form ionic bonding with calcium, which seems to indicate that DOPA can bind to bone.^[105] The authors claimed that DOPA promoted the process of bone formation as evidenced by

the *in vivo* maturation of new bones with a similar bone density to the normal bone and the *in vitro* osteogenic differentiation of osteoblast cells.^[106]

DOPA or 3,4-dihydroxyphenethylamine (dopamine) was also incorporated into synthetic polymers and hydrogels such as PEG, Pluronic[®], and PMMA co-polymers in order to develop mussel-inspired adhesives. This approach has successfully produced a range of tissue-adhesive hydrogels.^[107–109] However, to date their suitability as bone adhesives has hardly been studied.

Another marine creature that has inspired researchers in view of its bio-adhesive properties is the worm *Phragmatopoma californica*, which produces an adhesive commonly known as sandcastle glue. This organism uses a glue made of polyphenolic proteins to create a protective shell for itself by gluing together sand, grains and seashell.^[109, 110] These proteins are oppositely-charged polyelectrolytes which condense due to pH changes. They contain phosphate and amine side groups, which are well-known bone-adhesive groups, thereby rendering sandcastle glue a promising bone-adhesive biomaterial.^[111, 112]

In 2010, a biomimetic adhesive complex coacervate was synthesized by free radical copolymerization of monoacryloxyethyl phosphate (MAEP), dopamine methacrylate (DMA) and acrylamide (Aam). A trace of fluorescein isothiocyanate (FITC) modified methacrylate was included for visualization of the co-polymer (**Figure 4**). It was capable of holding wet bone together both *in vitro* and *in vivo*, showed degradability, osteoconductivity and appeared suitable for use in the reconstruction of craniofacial fractures.^[110, 113]

Figure 4. Structure of a sandcastle mimetic co-polymer composed of MAEP, DMA Aam and FITC.

Notaden bennetti is an Australian frog that secretes a protein-based material which rapidly forms a tacky elastic hydrogel known as frog glue. Its most abundant protein (55-60% of dry weight) is rich in glycine (15-16 mol %), proline (8-9 mol %), glutamic acid/glutamine (14-15 mol %), and 4-hydroxyproline (4-5 mol %). Graham *et al.* indicated that the exudate from *N. bennetti* frogs solidifies spontaneously, creating a proteinaceous pressure-sensitive adhesive that functions well in wet environments.^[114] Since the main proteins contain carboxylic acid groups, adhesion to bone can be achieved by covalent bonding with amines present in bone collagen matrix.

In 2008, the glue was evaluated *ex vivo* in an ovine meniscal cartilage repair model, where it performed significantly better than fibrin glues, although it did not outperform cyanoacrylate.^[115] In an ovine model of rotator cuff repair, the glue enhanced bone-tendon fixation.^[116] Despite the good *in vivo* biocompatibility and resorbability, further investigations must be performed to assess its use as a glue for osseous fragments.^[117] Overall, the unique

properties of the frog glue suggest that a biomimetic co-polymer could have a great potential for application as bone adhesive.

4. Clinical Perspective and Conclusions

The use of internal fixation to heal bone fractures is associated with several drawbacks such as the need for removal of these metal implants after bone healing, the occurrence of stress shielding and re-fractures, and the risk for infection caused by transcutaneous fixation devices. Bone-adhesive biomaterials such as glues would be a much needed alternative to internal fixation, but the biomaterials proposed so far as bone adhesives are still associated with several shortcomings. A summary of the investigated application area *in vivo*, advantages and disadvantages of biomaterials with bone-adhesive properties is depicted in **Table 4**. In general, the synthetic adhesives that have been evaluated as bone adhesives were not intentionally designed for this specific application. Synthetic adhesives tend to exhibit a high adhesion strength, but they show relatively poor biocompatibility and degradability, while their degradation products are often toxic. Bone adhesives made of natural polymers are less frequently studied. Although these adhesives tend to be more biodegradable and biocompatible, their adhesion strength to bone is often lower than synthetic adhesives. The hydrogel-like nature of most natural polymers and their associated low cohesive strength render them more appropriate for use as soft tissue adhesive than as bone glues.^[12, 90]

Generally, to develop adhesive biomaterials with specific affinity to bone tissue, a more rational design should be implemented. It is an oversimplification to characterize bone adhesives in a general manner, since the physicochemical properties of bone vary depending on the type of bone, animal species, age, anatomical site, as well as the storage and treatment conditions for the various *in vitro/ex vivo* studies. Furthermore, standardized and reproducible protocols to test the adhesion strength of adhesives to bone should be developed since a wide

variety of different testing methods have been reported including the most common butt tensile strength tests, which compromises direct comparison between various tests.

We propose that the future of bone-adhesive materials will rely on synthetic biodegradable polymers designed for specific clinical applications by tuning characteristics of these polymers such as their chemical groups, the degree of cross-linking degree as well as their viscosity and surface tension.

Ideally, future bone adhesives should be designed from a clear knowledge of the chemical composition of bone. Bone tissue consists of an organic collagenous matrix (≈ 30 wt.%) reinforced by finely dispersed calcium phosphate mineral nanocrystals (≈ 70 wt.%).^[118] Biodegradable polymers such as PEG or alginate could be designed to attach tightly to bone tissue through functionalization with pendant chemical groups of high affinity with either organic or inorganic components of bone tissue. *N*-hydroxysuccinimide esters (NHS esters) are known to form strong covalent amide bonds with primary amines as present in the collagenous extracellular bone matrix.^[119] On the other hand, several functional groups are known to bind to Ca^{2+} as present in the mineral phase of bone tissue, i.e. hydroxyapatite. Bisphosphonates (BP) are anti-osteoporotic molecules that are known for their exceptionally strong affinity for hydroxyapatite.^[120] Therefore, BP-functionalized polymers could also strongly adhere to bone by forming ionic bonds between pendant BP groups and Ca^{2+} . Alternatively, organic compounds containing carboxyl groups with strong affinity for Ca^{2+} generally include full proteins, peptide sequences, single amino acids, and carboxyl groups as well as hydroxyl, catechol and sulfate groups.^[121] Furthermore, the adhesion to bone could be enhanced by increasing the amount of functional (side) groups with high affinity to bone in the polymer.

We anticipate that a more rational design of bone adhesive biomaterials will allow to replace the use of internal fixation to fix bone fractures in future. To this end, a suitable bone-adhesive technology should be developed first. Nevertheless, it should be stressed that besides

their bone-adhesive properties several other criteria related to e.g. upscaling under Good Manufacturing Practice (GMP) conditions, sterilization, GMP need to be met before towards commercialization and clinical translation of these medical devices can be considered. Most notably, these devices should be biocompatible under clinical conditions, sterilizable and stable upon long-term storage. Importantly, their industrial production should be scalable under GMP conditions in a regulatory compliant manner.

Table 4. Application areas, advantages and disadvantages of bone-adhesive materials.

Adhesive System	<i>In Vivo</i> & Clinical Application Areas	Advantages	Disadvantages
Polyurethanes	Cranial defects, shaft fractures, bone-tendon ruptures, implant fixation, used clinically in sternal closure	Versatile synthesis and degradation	Toxicity, variability in the material after synthesis
PMMA and related co-polymers	Fixation of bone fragments in midfacial region, osteochondral and cranial defects, mandibular and shaft fractures, dental adhesive, vertebroplasty, used clinically for implant fixation	Adequate healing of fractures	Low adhesive strength, lack of biodegradability, exothermic polymerization
Cyanoacrylates	Fixation of shaft fractures and mandibular defects, ossicular chain reconstruction, used clinically for osteochondral and cranial defects	Very strong initial bonding strength in wet environments	Toxic degradation products, poor biocompatibility, loss of adhesion over time
Fibrin adhesives	Fixation of osteochondral, periprosthetic, mandibular and cranial defects, bone transplantation, healing intra-articular and rotator cuff rupture or tear, used clinically for sinus augmentation	Good biocompatibility and biodegradability, hemostatic behavior	Low adhesive and cohesive strength, need of external fixation, risk of virus transmission
Polysaccharide adhesives	Shaft fractures, periodontal guided bone regeneration	Good biocompatibility and biodegradability	Low adhesive strength, excessive swelling of the adhesive
Mussel adhesives	Calvarial defects	Good adhesive properties under dry conditions	High production costs, long degradation times, poor biocompatibility, little amount of studies
Sandcastle adhesives	Craniofacial reconstruction	Good adhesive properties, degradability and osteoconductivity	Little amount of studies
Frog adhesives	Bone tendon ruptures	Good adhesive properties and biocompatibility	Little amount of studies

Conflict of Interest

The authors declare no conflict of interest.

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