Bio-Based Adhesives for Orthopedic Applications

Subjects: Orthopedics

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Bone fracture healing involves complex physiological processes that require biological events that are well coordinated. The process of fracture healing has been upheld through various treatments, including bone implants and bio-adhesive utilization. Bio-adhesion can be interpreted as the process in which synthetic or natural materials adhere to body surfaces. Bio-based adhesives have superiority in many value-added applications because of their biocompatibility, biodegradability, and large molecular weight. The increased variety and utilization of bio-based materials with strong adhesion characteristics provide new possibilities in the field of orthopedics in terms of using bio-based adhesives with excellent resorbability, biocompatibility, ease of use, and low immunoreactivity.

adhesion bio-based adhesives bio-polymers

1. Sources and Types of Bio-Based Adhesives

Bio-based adhesives can be classified into internal and external ones in accordance with their function and application conditions. Internal bio-based adhesives are largely used in intracorporal conditions with direct contact to organs, tissues, and body fluids. Internal bio-based adhesives have two specific characteristics, i.e., the bio-based adhesives should be able to dissolve in a liquid solution without adding the organic solvent to the primary constituents. Moreover, the primary constituents of bio-based adhesives must be capable to conduct cross linkage. Internal bio-based adhesives are developed to be in contact with internal organs and fluids frequently, so bio-based adhesive must have minimum toxic content along with aqueous solutions. Bio-based adhesives have special characteristics that can set up their adhesive function as it were when it is conducting cross-linking with the substrate in a wet environment just like the internal organs that have liquid circulation with rich blood supply. Toxicities due to long-term application and adverse effects may happen in the patient's body, in case the bio-based adhesives applied inside the body are unable to dissolve and degrade in body fluids which are excrete by excretion system. In general, external bio-based adhesives are applied in topical medications, e.g., epidermal grafting and wound closure [1][2][3][4].

Cyanoacrylate-based tissue adhesive is the most broadly utilized type of external bio-based adhesive. The application of this material can be found at wound dressings treatment, plastic surgeries, and skin transplantations. Some examples of cyanoacrylate-based bio-adhesive are Trufill n-BCA and Dermabond. USA Food and Drug Association (FDA) have approved these types of bio-based adhesives. Cyanoacrylates are distinguished by points of interest, such as their short time for bio-adhesion and improved bonding strength. Nevertheless, in application at

tropical zones formaldehyde and respective alkyl compound of cyanoacrylates can be harmful to the human body. This toxic component can also act as carcinogenic agent that can cause tumor or cancer if used for long time period separated from the common complications like necrosis, thrombo-embolic, and septic complications. Cyanoacrylates could see expanded utilization in numerous applications in case the optimum brittleness and adhesion strength of the material can be optimized by adjusting the length of alkyl groups [5].

Other common synthetic polymers, used in bone adhesive applications are polyurethanes, poly(methyl methacrylate)s (PMMAs), and polycyanoacrylates. Polyurethanes can be synthesized from polyisocyanates and polyols using ultraviolet light orcatalyst. Shifting the orientation of the molecule, chemical groups, cross-linking, and crystallinity of polyurethanes makes this material degrade optimally when utilized as bio-adhesive. If the composition of the molecule, degree of cross-linking, and stiffness of polyurethanes are tuned, these polymers can show diverse properties, suitable for a wide variety of applications, such as bio-based adhesives, wound dressing treatment, tube of catheter, and bone fillers. Since polyurethanes have been widely utilized as bio-based adhesives for soft tissue and sealants, they have found a recent application as bone adhesives. The mechanism that occurs when these polymers physically adhere to bone is through hydrogen bonding, but also through chemical process that involve the arrangement of urea bonds through reaction of the amine at mineralized collagenous extracellular matrix of bone with carbamate group of polyurethanes. In any case, the biomedical environment stability of this material in long-term utilization is still questionable, whereas degradation of this polymer through hydrolysis and enzymatic process is reported by several studies concluding that the degradation caused by in vivo utilization is negligible [6].

Kryptonite is a polyurethane-based polymer used as bone adhesive. Recent studied have reported its successful functional adherence to bone tissue in order to get vertebral augmentation, cranial reconstruction, and sterna closure. Kryptonite covers calcium carbonate powder, castor oil-based polyol, and a reactive isocyanate. However, for utilization as bone cement the formulation of this polymer still should be optimized. In addition, a novel adhesive which has foam-like form consisted of 4,4-methylene diphenyl diisocyanate (MDI)M which was polyurethane-based polymer, a polycaprolactone-based polyol with biodegradable properties and hydroxyapatite particles reinforcement was developed in order to achieve applications of bone-to-bone bonding. Based on the mechanical testing, it can be concluded that a four-fold improved adhesion yields a better result compared to conventional PMMA cement. However, this four-fold improved bio-adhesion is still not considered adequate to attain optimal bone healing since bio-adhesion of PMMA adhesives to bone tissue is slightly low. The cytocompatibility of this adhesive is firstly assessed in vitro which affirmed the good result. At that point, the healing of broken frog hind limb tarsus bone was conducted as the in vivo response. The tissue immunological response of the adhesive material is found based on histological results that comparable to control specimens of bone tissue. However, the estimate impediments of the animal species hold the appropriate evaluation of adhesive to bone bonding strength. In this manner, in order to convincingly as certain the biocompatibility of this material, long-termin vivo studies are required [6].

Actually, PMMA cements show weak bio-adhesion to bone in damp conditions because of hydrophobic properties of this material. Mechanical interlocks with the porous bone are formed when PPMA adhesive is placed. In common, PMMA is encapsulated by fibrous instead of hard tissue, but unfavorable tissue reactions have been

reported for bio-adhesives from PMMA-based. In spite of the fact mutagenesis has been reported in bacteria related to utilization of PMMA but carcinogenesis still unknown to be associated with these biomaterials. During application of the PMMA, heat can be released to the surrounding bone tissue caused by an exothermic polymerization reaction that eventually might lead to thermal necrosis. Numerous endeavors have been reported to improve the adhesion of PMMAs to bone, such as bone pre-treatment, intermediate bonding agent application, and PMMA cement chemical modification [1][3][7][8].

In the first place, cyanoacrylates were developed for household, automotive, and construction industries. Dermabond®, Indermil®, Glubran®, and Histoacryl® are examples of cyanoacrylate-based soft tissue bio-based adhesives that are already commercially available. Although this biomaterial has been utilized in clinics as bone glue, cyanoacrylates have not been purposed particularly for application as bone bio-based adhesive. Cyacrin was a cyanoacrylate adhesive, used for the first time in 1963 for bone adhesive, but this material was characterized by high infection rate, no adhesion after the placement, formation of fistula, and several local reactions. Furthermore, Biobond is an ethyl cyanoacrylate which, mixed with polyisocyanate and nitrile rubber, yields better initial results based on in vivo testing. Carcinogenicity is associated with cyanoacrylates that have short alkyl chains due to the releasing of formaldehyde and cyanoacetate caused by erosion of the polymers that happen through hydrolysis reaction. Because of that, American Food and Drug Administration banned methyl cyanoacrylate-based adhesives for human use. Cyanoacrylates that have longer alkyl chain showed a gentler reaction in bone tissue based on further studies, due to steric hindrance and hydrophobicity that makes this material degrade slower. A cyanoacrylate-based adhesive called butyl 2-cyanoacrylate, known as Histoacryl® is already recognized for utilization in surgery to conduct wound closure because of its biocompatibility. Besides, several potential bone adhesives for fractures healing are also tested, such as butyl, isobutyl and octyl 2-cyanoacrylates. However, inadequate bonding strength for stabilization at fracture location after six weeks, cytotoxicity, and inflammatory responses in undiluted form are reported in some cases, although cytotoxicity was appropriate when diluted with culture medium for ten times. For general, cyanoacrylates-based bio-based adhesives need more biocompatibility studies in order to better determine their utilization as bone adhesives [1][5][7][9].

There are numerous natural polymers that function as bone bio-based adhesives, mostly polymers consisted of animal-inspired bio-based adhesives, such as frog, sandcastle, mussel, polysaccharides, and fibrin glue [10][11][12][13][14][15][16][17]. The most broadly utilized material for soft tissue bio-based adhesives, sealants, and hemostatic agents is fibrin. Fibrin is a fibrous non-globular protein involved in the blood clotting mechanism. However, there are numerous factors that affect the fibrin gel architecture, such as thrombin and fibrinogen concentration, temperature of preparation process, pH, ionic strength, and concentration of calcium ion can affect the materials mechanical properties. The gel mechanical strength will be affected by the presence of Factor XIII covalently cross-linking with the polymer chains. Moreover, the adhesive strength of the fibrin-based adhesive can be affected by water, fat, and collagen contents. However, the adhesive strength of fibrin-based bio-adhesive against bone tissue is still low when compared to synthetic bio-adhesives (0.17 MPa), which can also be assumed due to the poor cohesive strength of the fibrin itself, although the fibrin-based bio-adhesive adhere to bone tissues through the formation of covalent bonds between carboxylic acid groups within the collagenous matrix of bone tissue with amino groups of fibrin or fibronectin. Based on the excellent biocompatibility, biodegradability, and cost-

effectiveness, fibrin-based bio-adhesive prove to be more superior to synthetic bio-adhesives such as cyanoacrylates. Therefore, these materials proved to be extensively utilized in orthopedic surgery. Currently, the fibrin-based adhesives are utilized for treatment to osteochondral defects. Accelerated revascularization of the osteochondral fragment can be achieved by using fibrin sealant in a thin layer form, this process also confidently followed by union and healing of bone fracture [1][18][19][20].

There are several important groups of polysaccharides utilized as soft tissue adhesives and hemostatic materials, such as chitin, chitosan, dextran or chondroitin. These materials yield biocompatible and biodegradable adhesives that are composed of natural sugar building blocks that are easy to prepare and apply [21][22][23][24][25]. A study reported the successful developed of novel biocompatible and degradable biopolymers based on a two-component bio-adhesive system (chitosan and starch). Based on biomechanical studies, it is known that these bio-adhesive polymers have better strength of bio-adhesion when compared to fibrin glue, but they also have a poorer strength of bio-adhesion than cyanoacrylates on bovine cortical bone specimens. Excellent biocompatibility was also demonstrated in *in vitro* cell testing, so this bio-based adhesive can be a promising candidate for clinical utilization [21][22][26][27][28].

A cellulose polysaccharides-based scaffold with good mechanical properties and suitability for load-bearing bone healing applications has been reported. Plant cell walls have a linear polysaccharide of D-glucose units linked by β(1→4) glycosidic bonds that are called cellulose. These materials have a particular strength and provide water-insoluble properties despite their hydrophilic nature because of the highly cohesive hydrogen-bonded structure that composed the cellulose fibers. The character of the cellulose made the scaffolds provide a good compressive strength, which is similar to the mid-range of human trabecular bone. Esterification reaction between the carboxylic acid groups within the bone tissue organic matrix and hydroxyl groups within cellulose was the main mechanism that provides the bio-adhesion of this material. However, in 24 h this adhesive exhibited a weight loss about 10–15% because of degradation under in vitro conditions. In order to decrease the degradation of this scaffold, its chemical structure should be modified for better tissue engineering applications [1][3][26][29][30].

In order to anchor themselves to in water or wet environment, saltwater animals, as well as marine worms, limpets, mussels, and oysters, produce bio-based adhesive proteins. In an environment that has various levels of salinity and humidity there is an organism like *Mytlius edulis* (blue mussel) that has the capability to adhere itself to a substrate, either inorganic or organic. Furthermore, a non-sticky material such as polytetrafluoroethylene (PTFE) can also adhere to this organism. However, there are some technical difficulties due to extraction and high production cost that hold this bio-adhesive to utilize widely in many practical applications. Moreover, large exogenous proteins produced from mussel adhesive utilization can trigger an allergic reaction based on in vivo examination. Because of that, there are many bio-mimetic polymers that have been developed in order to assess the characters and examine the constituents that provide mussels with substantial adhesive capability. Based on the research, it is known that a high concentration of compound at the interface of adhesive substrate of mussels endow this animal with strong adhesive ability. This compound belongs to the so called DOPA groups. Furthermore, it was found that $Fe(DOPA)_3$ was formed from cross-linking reaction between high concentration iron on mussel adhesive with cathecolic hydroxyl group of DOPA. The concentration of iron in mussel bio-adhesives is

actually higher (100,000 times) than its concentration in the peripheral water. Ultimately, the bonding between protein and protein or bonding of protein and surface for adhesion actually occurs when iron induces the oxidation of DOPA to produce an organic radical [1][31][32][33][34].

Because bone is made up of both organic and inorganic components, the type of bio-adhesion that bone has, either to organic or inorganic chemicals, has become the most important factor to take into account in the process of developing bone bio-based adhesives. Because the carboxylic acid and the hydroxyl groups from the catechol of DOPA can establish ionic bonding with calcium, there is a presumption that DOPA could adhere to bone tissue. The process of in vivo maturation of new bones takes place when DOPA stimulates the formation of bone tissue. Additionally, the newly growing bones have a density that is comparable to that of normal bone, as well as in vitro osteogenic differentiation of osteoblast cells. The creation of adhesives modeled after mussels is also being carried out by mixing DOPA, also known as 3,4-dihydroxyphenethylamine (dopamine), with synthetic polymers and hydrogels such as PEG, Pluronic®, and PMMA co-polymers recently. Because of the development that was carried out, a wide variety of tissue bio-based adhesives and hydrogels are now manufactured. However, their potential use as bone bio-based adhesives has been the subject of intensive research [27][35][36][37][38][39][40].

Phragmatopoma calafornica is another marine animal that has inspired researchers in developing bio-based adhesives. This animal produces a bio-based adhesive, commonly known as sandcastle glue. This bio-based adhesive is made of polyphenolic proteins that function as shield for the animal by pasting sea shell, sand, and grains together. These proteins are oppositely charged polyelectrolytes which coagulate due to pH changes. The protein produced by this animal can be a promising bone bio-based adhesive material since the presence of phosphate and amine side groups. The Australian frog *Notaden bennetti* is known to secrete a protein-based material which can produce a sticky elastic hydrogel rapidly. This protein is considered as frog glue. It is known that there are proteins (55–60% of dry weight) rich in glycine (15–16 mol %), proline (8–9 mol %), glutamic acid/glutamine (14–15 mol %), and 4-hydroxyproline (4–5 mol %) which compose this frog glue. Research indicated that this frog glue can solidify spontaneously and function well as a bio-based adhesive in wet environments by creating a proteinaceous pressure-sensitive adhesive. This frog glue can conduct covalent bonding with amines which consist in collagen matrix of bone because the main proteins contain carboxylic acid groups. It is reported that the glue performed significantly better than fibrin glues, although this bio-based adhesive did not perform better as cyanoacrylate in a repair model of ovine meniscal cartilage. This frog glue also enhanced bone-tendon fixation in an ovine model of rotator cuff repair. However, further research must be performed to examine its utilization as a bio-based adhesive for orthopedic applications; even this material has a good in vivo biocompatibility and resorbability. Overall, the distinctive characters of the frog bio-adhesive suggest that a bio-mimetic co-polymer can have a substantial potency for utilization as bone bio-based adhesive [1][2][30][32][37][40][41][42].

Another material that can be considered for utilization as a bio-based adhesive is from the ceramics group. It is already know that there are various ceramics materials that can be utilize in orthopedic application including calcium phosphate and hydroxyapatite [43][44][45]. Hydroxyapatite can actually be synthesized chemically from the precipitate of calcium and phosphate. However, this material can also be synthesized from natural resources

included clam shells, egg shells, or animal bones like bovine bone [46][47][48][49][50][51][52]. Hydroxyapatite was chosen as bio-based adhesive material in orthopedic application because of its biocompatibility and bio-activity, since hydroxyapatite is actually a natural matrix of human bone which constructs the bone tissue along with protein and other organic compound [53][54][55][56][57].

2. Preparation of Bio-Based Adhesives

Based on the numerous studies that have been conducted in order to examine the bio-adhesive synthesis and preparation, it can be concluded that there are two major process used to produce a bio-adhesive, i.e., polymerization and cross-linking [3][7][21][32][58][59][60]. The cross-linking process usually utilizes some type of bonding that can happen in the reaction, including hydrogen bonding, ionic bonding, host–guest interaction, hydrophobic bonds, imine bonds, disulfide bond, Acylhydrazone bonds, Diels-Alder reaction, boronate bonds, and oxime bonds [59]. In orthopedic surgery and orthodontics, poly(methyl methacrylate)s (PMMA) has been widely used. The polymerization of methyl methacrylate (MMA) via a free radical process utilizing an azo compound or peroxide as an initiator is a method to produce PMMA. Commercially, polymerization can be conducted, i.e., in bulk, solution, suspension, or emulsion. A viscous paste will be formed after blending these constituents which solidify via monomer radicals or anionic polymerization [1][6].

The polymerization process can be carried out at room temperature without the need of a heating step, the addition of a catalyst, or the application of pressure thanks to the profound reactivity of these materials. The reaction that must take place in order to generate these materials begins with the anionic polymerization of the monomers, which is triggered by water. The acrylate bond can be broken by a nucleophilic attack carried out by weak bases such as water or amines. In order to accomplish bio-adhesion to bone, an electron-withdrawing nitrile group polarizes the acrylate bond. Because of this, the acrylate bond is susceptible to nucleophilic attack by weak bases, such as the amines that are found in the collagenous matrix of bone tissues. Increasing the length of the alkyl chain can, in general, result in greater polymerization rates, stronger bonding strengths in bone tissues, and can form more flexible chains [5].

Mixing a solution that contains a fibrinogen source (from plasma, platelet-rich plasma), or heterologous/autologous cryoprecipitate) and factor XIII with another separate solution consisting of thrombin source (bovine, human, or recombinant), anti-fibrinolytic agent, and calcium to prevent rapid fibrinolysis is the most common method that is used to produce fibrin-based adhesive systems. When brought together, these substances cause the formation of a clot that is devoid of cells. During this process, thrombin cleaves fibrinogen, which results in the production of soluble fibrin monomers. These monomers then self-assemble into loosely aggregated fibrils via hydrogen bonding, and then into a more robust cross-linked fibrin polymer via covalent bonding. Thrombin also activates factor XIII, which, in the presence of calcium, provides for the formation of covalent bonds between fibrin polymer chains. However, a considerable amount of preparation is required before employing this adhesive made from biomaterials [1][18].

Starch was oxidized with periodic acid in order to produce aldehyde side groups, and chitosan was used as the amino-group carrier throughout this process. In the bio-based adhesives system, amino groups that are present in the surrounding tissues will react with aldehyde groups in a manner analogous to that of chitosan. After being mixed together in water, the two components produce a Schiff's base, which results in a covalent cross-linking that allows for a strong adhesion to tissue. This is accomplished by the production of covalent bonds. The bio-based glue had the potential to form bonds with any other exposed amino groups, such as those that are present in shattered bone for example. In addition, increasing the bio-adhesion strength to bone can be accomplished by conjugating starch or dextran compounds with 3,4-dihydroxy—phenylalanine (DOPA) [21][22][26][27][28]. A study reported that free radical copolymerization of monoacryloxyethyl phosphate (MAEP), dopamine methacrylate (DMA), and acrylamide (Aam) are used to produce bio-mimetic adhesive complex. This bio-based adhesive has the capability to bond wet bones together either in vitro and in vivo, demonstrating suitability for utilizing in the reconstruction of craniofacial fractures, and showed good degradability and osteoconductivity [1].

A successful strategy to address cell-behavior on biomaterials was also presented by the plasma enhanced–chemical vapor deposition (PE-CVD) of polyethylene oxide-like (PEO)-like coatings [61]. Moreover, Tris(trimethylsiloxy)silyl (M3T) containing methacrylate copolymers with low surface energy were designed and synthesized [62].

Chitosan thiomer derivatives are utilized in order to produce a novel three-dimensional (3D) scaffold with potential soft tissue repair applications. A covalent coupling reaction was conducted to synthesize amino acid-grafted chitosan (cysteine, CHICys) and N-acylated chitosan (11- mercaptoundecanoic acid, CHIMerc) derivatives, and hydrogel scaffolds were produced by freeze-drying process. They were comprehensively characterized by swelling and degradation behaviors, NMR, FTIR, and Raman spectroscopy, SEM, and X-ray microcomputed tomography [63].

A series of chitosan-graft- polypeptides were synthesized by ring-opening polymerization of three N-carboxyanhydrides (NCAs)—3,4-di- hydroxyphenylalanine-N-carboxyanhydride (DOPA-NCA), cysteine-NCA (Cys-NCA) and arginine-NCA (Arg- NCA)—using partial-NH2-protected chitosan as an initiator since inspired by the mussel foot protein and chitosan-based macromolecular adhesives. Based on the result, these copolymers demonstrated good biodegradability and low cytotoxicity for application in orthopedic implant and scaffold [64].

3. Characterization of Bio-Adhesives

3.1. In Vitro Methods

3.1.1. Shear Strength Measurement

The strength of bio-adhesion is commonly characterized by using mechanical testing, including crack growth assessment, peel test, and shear strength test. In the case of mucoadhesive assessment, shear strength measurements are commonly utilized to measure the forces within the mucus layer that slides each other in a

parallel direction to the contact plane. Another method that can be utilized to measure the mucoadhesive strength is the flow channel method. The method assesses the shear strength by measuring the force needed to get the particle of adhesive from the mucin gel surface using forced humid air via flow cell. Furthermore, in order to assess the development of crack yielding from the dental implant, the bending tests were also conducted in the application of bio-based adhesive in orthodontic. The cracks are usually produced as a result of polymerization due to the shrinkage of the composite materials used in the implant. Characterization and interpretation of the bending test results is conducted using Griffith's energy balance model. For example, the teeth elastic energy (usually the average elastic energy of tooth and the dental implant material) and the crack surface energy is set up using this balancing model. The experimental crack development assessment will decide the strain energy release rate or the stress intensity while the Poisson's ration and modulus of the implant material will calculate the fracture energy [1][2][3][32][65].

3.1.2. Peel Strength Evaluation

Fractographic techniques, e.g., transmission electron microscopy (TEM) or scanning electron microscopy (SEM), are used in order to assess the quality of the dental implants-surface after performing the tensile test. American Standards for Testing and Materials (ASTM) with various tests are conducted on the interface of adhesion and the substrates. In order to obtain better shear strength, peel strength, and adhesion failure temperature, a pressure-sensitive adhesive (PSA) is formed as a composite material by supplementing it with montmorillonite, an organo-clay based element [63].

3.1.3. Flow through Experiment and Plate Method

The flow through channel method, which is the macro-scale measure of flow rate that can yield the depletion of bio-adhesive coated over the substrate sphere, is conducted to measure the mucoadhesion of DDS. The biophysical assessment method is conducted to measure the fluctuation in sedimentation coefficient that emerges due to the molecular weight change through an analytical centrifuge. The Wilhelm plate method is used for surface tension evaluation by utilizing natural or synthetic mucus rather than a conventional water medium. This method is known for use as macro-scale bio-adhesion assessment method. This method is conducted by coating a plate with any polymer material before the changes in interfacial properties and the bio-adhesion property are measured with respect to time [1][2].

3.2. Ex Vitro Methods

3.2.1. Adhesion Weight Method

A specific test method is developed in order to determine the weight of adherent particles that emerged in the interior mucous layers of guinea pig digestive tract due to the ion exchange. The particle size effect and adhesion charge after 5 min of time with the pig's digestive tract was determined using this method. Based on the result it is recommended that the weight of the digestive tract increased due to bio-adhesion. However, when a larger change

within the biological tissue emerged due to regeneration or degeneration of the digestive tract tissues, this method will posture a diminished reproducibility of the data [1][2].

3.2.2. Fluorescent Probe Methods

Fluorescent probe methods could determine the relationship between the polymer molecules and epithelial cell membranes. The formulation of an orally utilized bio-based adhesive polymer can actually be improved by knowing its structural requirements. The investigated bio-based adhesives can be tagged on to the cell membrane which consists of proteins and the lipid bi-layer membranes and the variations in fluorescent spectrum are noted. Excimer and monomer bands are two different Pyrene bands shown by these materials, and environmental viscosity will administer the ratio of these bands. Because of that, by assessing the bands ratio, the viscosity changes can be noted. Based on this result, it can be concluded that the adhesion strength is directly related to the viscosity change. The bond between polymer and protein membrane can be observed using a quantitative method (fluorescence depolarization), while the interactions of soluble polymers can be compared with that of peel of the cell [1][2].

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