

Historical Developments of Various Adhesives for Biomedical Applications

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Abstract

Adhesives are versatile and have been widely researched in recent decades due to their significant effect on health care with applications in various areas. Biomaterials have grown into an attractive research area where the need for exploration of biocompatible, efficient and economical bioadhesives has increased. Adhesives have been in use since ancient times by our ancestors for wound healing. There were many efficient materials derived from plant, animal and micro-organism sources which were used as adhesives. These adhesives have played a major role in surgery and wound healing. First-generation adhesives were found to have drawbacks with regard to adhesion in wet conditions and also toxicity associated with their synthetic nature. However, over time much advancement has taken place in this area and various biocompatible adhesives have been identified and isolated for surgical applications. Even the applications of adhesives have extended to unexplored areas like drug delivery and tissue engineering. In current decades, new bioadhesive materials have come into picture to meet the needs in drug delivery and wound healing. This chapter is aimed to cover the historical development

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of various adhesives for medical applications. In addition, various development phases of these adhesives along with the historical milestones have been covered. This chapter also enlightens the reader about most recent and updated applications of bioadhesives in biomedical sciences and finally highlights the important points to consider while exploring this field of adhesives for biomedical applications.

Keywords: Adhesives, drug delivery, biomedical application, tissue engineering, wound healing

1.1 Origin of Adhesives

Adhesive bonding has influenced day-to-day life of individuals. It has long history and versatile applications. There are many industries and technologies which contribute to the recent advancement of adhesives. Our early ancestors were unaware of the concept of an adhesive material. Historically, discovery of adhesive materials started with nature. Most of the adhesives were originated from plant and animal sources [1, 2]. In addition, a few reports have suggested that microorganisms such as algae, bacteria and other insects, amphibians including echinoderms, carnivorous, orchids, frogs, spiders are also prominent sources of adhesives. Many micro-organisms are reported to produce sticky material on the surface of their bodies [3].

However, there are numerous historical evidences in literature regarding adhesives to suggest that humans had used adhesives for thousands of years for making objects more useful, attractive and decorous. In addition, adhesives were used in making ornaments and weapons. Adhesives have evolved gradually. The understanding of adhesiveness had a long way from sticky material obtained in cooking to the various advanced adhesives available in recent times. The past transformation period in the history of adhesives was well recognized where the suggestion made by Roman author and scientist Pliny the Elder that Daedalus was credited for inventing glue. However, based on the technical consideration and archaeological evidence the Pliny's suggestion was denied and it became necessary to find out the origin of man-made adhesives [4].

Adhesives are used in wound healing, dressing or prevention of bleeding in the medical field. In the current developed era of medical technology, various applications have been found for adhesives [5]. Numerous theories and hypotheses have been postulated to explain and demonstrate the process of adhesion including van der Waals forces, chemical bonding and electrostatic attraction [6–11]. Historically, human ancestors including primitive people and homosapiens used adhesives in treating wounds and healing injury. They used grass and leaves to cover the wound area.

Primitive people used to close wound by sewing it together with muscle fibers and shreds of tendon. Large wounds were cleaned by inserting spikes along the edges of the wounds and then tying these together with clothes and tendons. Around 1100BC, the oldest sutures were first described in ancient Egyptian literature. Historically, sutures were recognized as blessed combination of preventing infection and wound healing. 4000 years back, plant derived gums were used in the form of adhesives [12]. In addition, tree resin and beeswax were applied as sealants or adhesives. However, the ancient Greeks, Egyptians and Indians preferred suturing to heal the wound. Perhaps, the major challenge is to find alternative to suture the wound.

In the middle of revolutionary era, many scientists tried to refine the sutures for getting to current advanced status. In the 19th century, the modified and advanced adhesives were explored, and rubber cements appeared. Still, the advancement in this field had to wait for the 21st century when the natural adhesives were transformed into novel compounds. In the past 40 years, paradigm shift has been observed in the development and advancement of adhesives in the medical field. New adhesives are also continuously developed taking inspiration from natural adhesive materials. In 1970, U.S. Clean Air Act and the formation of the Environmental Protection Agency and Occupational Safety and Health Administration were established. Even today, there are several types of adhesive materials available with good safety profile and sustainability. Furthermore, water-based adhesives, ultraviolet and electron beam cured adhesives, hot-melt adhesives have been developed. There are certain chemicals which are reported to be carcinogenic and toxic in nature, hence the approaches for removing residual organic solvents with minimal risk of toxicity are preferred. In the recent era scientists have developed pressure-sensitive adhesives (PSAs) in order to absorb a significant amount of fluid, and these are rubber based for ease of utility. Following this, the revolutionary change occurred where exploration of silicone-based adhesives came in picture, which provides comfort and promotes healing. In this digital era, the needs of patients have changed from conventional to frictionless and wearable adhesives in wound closure.

1.2 Prominence of Biomedical Adhesives in Wound Healing and Drug Delivery

The use of adhesives in wound healing and drug delivery gained importance as adhesives offered various advantages.

1.2.1 Wound Healing

Interest in tissue adhesives has gained prominence in the past half century. They were introduced as an alternative to adhesive tapes or bandages. Adhesive tapes and bandages are applicable for topical wound therapy, while tissue adhesives were aimed to control bleeding irrespective of site of injury, i.e., the major advantage is that these could also be used for internal applications [13, 14]. This paved the way for advances in surgery and wound healing. Various classes of adhesives were introduced with varied functionality and applications. Fibrin sealants were the first tissue adhesives with their first use dating back to early 20th century.

Cyanoacrylates were one of the earliest adhesives approved for wound healing. These are synthetic derivatives of acrylic acid widely used for surgical and traumatic wound repair. These have advantages like higher mechanical strength compared to other adhesives [15, 16]. Moreover, cyanoacrylate adhesives are cheaper compared to fibrin or collagen-based sealants. This led to their wide use in surgical applications [17]. Their development started in 1950s for medical use. However, the approval was obtained only in early 1980s for their use only as topical skin adhesive [18]. N-butyl-2-cyanoacrylate marketed as Histoacryl Blue (TISSUESEAL, USA) was the first cyanoacrylate used for tissue adhesive application [19]. The first U.S. Food and Drug Administration (FDA) approval of cyanoacrylate adhesive for internal use was received in early 21st century. This product was approved for topical application to close easily approximated skin edges of minimum-tension wounds of surgical incisions and for simple, well-cleansed, trauma-induced lacerations. Histoacryl Blue and Histoacryl Flexible may be used in conjunction with, but not in place of, deep dermal sutures [20]. However, cyanoacrylates suffer from drawbacks such as poor elasticity and significant toxicity due to their synthetic nature. This led to the development of safer biocompatible alternatives.

Fibrin sealants are another class of popular tissue adhesives. The use of fibrin sealants dates back to early 20th century with first use of fibrin reported in 1909 [21]. However, the popularity of fibrin sealants rose in 1940s [22, 23]. The sealant is of biological origin and is derived from human plasma. The sealant is formed as a crosslink of fibrinogen and fibrin in the presence of factor XIII and calcium as catalysts. The crosslink prevents blood loss causing effective wound healing [24]. The fibrin sealants are prepared from human blood [25]. The major advantage of fibrin sealants is that they are entirely of biological origin and hence there is no risk of toxicity. Moreover, the crosslink formed degrades slowly without any abnormal degradants formation. Thus, these became a popular alternative

for wound healing applications. These can also be used internally for sensitive areas thus increasing their spectrum of applications. However, these suffer from drawbacks like poor adhesion strength and reduction in efficiency under wet condition and long sealing time [26]. Moreover, sealants derived from different human sources vary in fibrin and thrombin contents thus affecting degree of adhesion. This can be avoided by pooling the plasma from various sources [27]. However, the pooled sources have risk of viral transmission and also bacterial growth when used without antibiotics [28]. Nevertheless, fibrin sealants are most popular adhesives with wide use in surgical interventions.

Gelatin-resorcinol-formaldehyde/glutaraldehyde glues are another earlier class of adhesives that have been continuously used since 1960s. Adhesives are also made with a combination of different components. Gelatin in the adhesive imparts elasticity to the adhesive. Formaldehyde-based adhesives have strong bonding while those based on glutaraldehyde have better *in vivo* stability. The mechanism of adhesion is due to crosslinking of polymer chains. The advantage of these adhesives is that they have higher adhesion strength compared to fibrin sealants which is similar to that of cyanoacrylate adhesives. However, poor adhesion in wet conditions and carcinogenicity due to aldehyde content limited their clinical applications [29–31].

Collagen-based tissue adhesives are one of the newer classes of adhesives. Collagen is also a biological component which forms a major part of extracellular matrix. It acts by triggering an intrinsic pathway for blood coagulation. The mechanism of adhesion is crosslinking. As it is derived from mammalian source the risk of infection is less likely. Thus, these have found wide use in wound healing and surgery. Few collagen-based products were approved like Costasis™/Dynastat™ (Cohesion Technologies) and FloSeal Matrix® (Baxter International Inc.) [32]. Like fibrin-based sealants, collagen sealants have slower curing rate for adhesive applications. Thus, the adhesion strength is lower compared to synthetic adhesives. Moreover, the collagen can swell upon tissue compression making it unsuitable for ophthalmic or neurologic surgeries [33]. Approaches to increase adhesion strength are being evaluated to make these ideal for wound healing.

Albumin-based adhesives are another class of tissue adhesives which rose to prominence in late 1990s. Albumin-glutaraldehyde adhesive marketed as BioGlue® Surgical Adhesive (CryoLife Inc.), is a two-component system consisting of bovine serum albumin and glutaraldehyde in stoichiometric ratio. Compared to other tissue adhesives from biological sources, these adhesives have higher tensile and shear strengths. Moreover, albumin-based adhesives are not derived from pooled sources and hence

risk of infection is very low. However, these require bloodless environment thus preventing their use in active bleeding. Similarly, presence of bovine serum albumin may cause hypersensitivity reaction in some individuals. Even glutaraldehyde was found to be toxic for cells which limits its uses [34]. More clinical studies are required to establish their use in surgery.

Biomimetic adhesives are the newest class of adhesives which are mostly nature derived. These were inspired by nature where these were used for protection from predators, self-healing and attachment to surfaces. Various bioinspired adhesives are being evaluated for application in wound healing and surgeries. Examples of bioinspired adhesives include mussel-derived adhesive proteins, barnacles, sandcastle worms, prolamine, gecko adhesives, etc. Unlike other adhesives which cause adhesion due to crosslinking, the bioinspired adhesives undergo chemical adhesion thus providing highest strength even under wet conditions [35]. Studies were performed using hydrogels along with these adhesive materials to improve adhesion.

1.2.2 Drug Delivery

Application of bioadhesives in drug delivery is a newer aspect in adhesive technology though these were evaluated much earlier. One of the first methods of drug delivery using adhesives is antibiotic delivery with fibrin sealants. Here the researchers used fibrin sealant as a matrix to control the drug release. Drugs evaluated ranged from ampicillin, ciprofloxacin to tetracycline [36]. Similarly, the application was expanded to include the delivery of chemotherapeutic agents. Even cyanoacrylate adhesives were successfully applied in delivery of antibiotic like vancomycin [37, 38].

Site-specific drug delivery gained importance to achieve either localized delivery (ophthalmic drug delivery) or enhanced systemic bioavailability (colonic and transdermal drug delivery). Various adhesive polymers were used for controlled delivery of drugs. These included chitosan, cellulose derivatives, methacrylate polymers, alginates, lectins and thiolated derivatives of these polymers. These were selected based on the purpose of application.

1.3 Generations of Bioadhesives

The term “bioadhesive” implies the adhesion of a synthetic or natural molecule to a biological surface which could be either a mucus surface or epithelial membrane [39]. The most extensively explored bioadhesives are a group of macromolecules that are hydrophilic in nature.

These macromolecules contain functional groups which are proficient to form hydrogen bonds with the biological surface. These functional groups include hydroxyl groups, carboxyl groups and amine groups. However, they are non-specific in nature in terms of adhesion and adhere to any surface but require moisture for the activation. Hence, they are often referred as wet adhesives. Nevertheless, once they are activated, they exhibit a strong adhesion to the surface. The bioadhesives may overhydrate and form slippery mucilage unless the water uptake is restricted [40]. However, if the adhesive joint is dried then it results in a strong adhesive bond. They are considered safe by regulatory agencies and are defined as “off-the-shelf” adhesives. These bioadhesives are referred as first-generation bioadhesives [41].

The most commonly used bioadhesives which fall under the category of first-generation bioadhesives are carbopol [42], sodium alginate [43], polycarbophil [44] and chitosan [45]. These bioadhesives are categorized as synthetic or natural bioadhesives. Carbopol, carbophil and poly(acrylic acid) are widely used synthetic bioadhesives. Natural or semi-synthetic bioadhesives include chitosan, xanthan gum, alginate, etc. Cellulose based bioadhesives are also explored widely including methyl cellulose, sodium carboxymethyl cellulose and hydroxypropylmethyl cellulose [46].

The bioadhesion of macromolecules to the biological surface occurs via interactions which include ionic bonds, covalent bonds, hydrogen bonds, hydrophobic bonds and van der Waals bonds. Ionic bonds are formed between the oppositely charged ions and covalent bonds are formed by sharing a pair of electrons. Hydrogen bonds are formed between electronegative atoms and hydrogen atoms [47], van der Waals forces are formed between the polar molecules, and hydrophobic bonds are formed as a result of hydrophobic interactions. Covalent and ionic interactions result in strong adhesion; however, hydrogen bonds, hydrophobic bonds and van der Waals bonds are quite weaker bonds [48]. The type of interaction manifested between the macromolecule and the biological surface is based on the property of the bioadhesive molecules, for instance, whether anionic, non-ionic and cationic in nature.

Interaction between the macromolecules and the biological surface is explained by the chemical bonds. However, to demonstrate the mechanism of formation of bioadhesion numerous theories have been proposed [49]. The transfer of electrons between the biological surface and macromolecules results as a consequence of difference in the electronic structures. This manifests adhesion between the adhering surfaces as proposed in electronic theory [50]. Wetting theory is applicable to liquid systems where the affinity of liquid to spread on the biological surface is calculated as

spreading coefficient considering the surface and interfacial tensions [51, 52]. Adsorption theory describes the adhesion between the biological surface and macromolecules resulting via hydrogen bonding or van der Waals forces where a bond is formed between the biological surface and the bioadhesive macromolecule [53, 54]. Diffusion theory explains the diffusion of chains of macromolecules into the biological surface. The diffusion of chains is driven by the difference in concentration across the biological interface, mobility of chains and the diffusion coefficient [55]. Mechanical theory suggests the interlocking of bioadhesive molecules into the rough surface of the biological membrane. Also, rough surfaces offer an enhanced surface area accessible for interaction along with an increased viscoelastic and plastic energy release during bond failure, which are considered to be more imperative in the process of adhesion than a mechanical effect [56]. Fracture theory is quite different from the rest of the theories where it relates the force required to detach two surfaces involved in adhesion to the adhesion strength [57]. These theories are proposed to explain the mechanism behind establishing adhesion. However, numerous factors affect the strength of adhesion which include molecular weight of bioadhesives [58], concentration of bioadhesive molecules/polymer [59], chain length and its flexibility [60], interpenetration of polymer into mucus gel layer [61], degree of hydration [62], charge and functional group on the macromolecule [63, 64] and pH of the environment [65]. Charge and functional group present on the macromolecule affect the degree of bioadhesion and result in nonspecific attachment to the site. Bioadhesion of macromolecules to the biological membrane is also influenced by hydration where the hydration promotes interpenetration of polymer chains into the biological surface. However, the excess hydration leads to the formation of slippery mucilage hampering the bioadhesive property. This resulted in exploring new generation of bioadhesives which are specific in adhesion to the desired site. The widely explored new generation bioadhesives are lectins and thiolated macromolecules.

Lectins structurally belong to the class of proteins or glycoproteins where they bind specifically to the carbohydrate moiety, for instance, bind to the glycosylated membrane components [66]. Nevertheless, lectins also mediate receptor adhesion leading to internalization via endocytosis or transcytosis. Thiolated macromolecules are the derivatives of polyacrylates or chitosan. Thiol groups are present in their structure which results in the formation of covalent bonds between the thiol groups and the cysteine groups in the mucus membrane [67]. The derived thiolated macromolecules are chitosan–thioglycolic acid [68] and poly(acrylic acid)–cysteine [69].

Thus, these new generation bioadhesives offer specific and strong bioadhesive property compared to the old-generation bioadhesives.

1.4 Timeline of Developments and Advances

The scientific community has made great progress in the creation of tissue regenerative bioadhesives for musculoskeletal tissues in the last few decades. Co-polymerization, cross-linking, mixing, and surface modification are only a few of the chemical modifications that have resulted in significant improvements in the basic physical properties. Despite potential improvements in adhesion strength and bulk modulus, existing bioadhesives have yet to attain mechanical qualities required to restore the functional properties of the majority of musculoskeletal tissues in a timely manner. However, there are only a limited number of *in vivo* studies on bioadhesives efficacy in tissue repair and regeneration that require further research.

According to a PubMed literature search, the number of papers with the term “tissue adhesives *in vivo*” has remained relatively constant in the last decade, however it only accounts for 6.7 percent of all papers searched for “tissue adhesives.” In the last 20 years, the number of publications with the key word bioadhesive has steadily increased and the number of papers with bioadhesives *in vivo* is also on the rise, accounting for more than 20% of all papers containing bioadhesives. These findings from the literature search would indicate a growing research interest in adhesive biomaterials with a biological purpose other than their typical role as tissue adhesives providing physical bonding, hemostasis, or sealing.

Since their FDA approval in 1998, fibrin tissue adhesives or tissue sealants have been the most extensively utilized bioadhesives in the United States. Fibrin is the only substance approved by the FDA for use as a hemostat, tissue glue, and tissue sealant at this time [70, 71]. In the past few decades, aldehyde-based adhesives, i.e., gelatin - resorcinol cross-linked with formaldehyde (GRF) and GRFG (GRF with glutaraldehyde) have been widely used for vascular, thoracoscopic, gastrointestinal, liver, and urinary track surgeries in Europe and Japan. BioGlue® 24 (CryoLife, Kennesaw, GA) is a glutaraldehyde-based protein-aldehyde system (PAS) that is commercially available. It is made up of two components: bovine serum albumin (BSA) and glutaraldehyde, and its bonding action is identical to that of GRF/GRFG. In 1999, the FDA approved iBoGlue® for use in the United States as an adjuvant to suturing or stapling for acute thoracic aortic dissection and cardiac surgery [72, 73].

The use of bioadhesives as a delivery vehicle is a relatively new concept [74]. Bioadhesives with high target efficiency are highly implemented as delivery vehicles even if the adhesive property is low as it is likely useful for the localized distribution of cells, growth factors, and small molecules on the target location. It would be more feasible to achieve high adhesion strength and mechanical properties that would be an effective treatment option for degenerative musculoskeletal diseases such as tendinopathy if a bioadhesive's sole purpose was to provide controlled delivery rather than to support cell and tissue ingrowth [75]. Furthermore, the development and application of bioadhesives as controlled delivery vehicles with significant clinical impact is gaining popularity [75, 76].

The *in vivo* degradation of bioadhesives is an important but understudied research area. The *in vivo* functioning of a bioadhesive is directly linked to its degradation rate, whether for mechanical support, cell and tissue ingrowth, or regulated distribution. Bioadhesives used in securing tissue grafts or filling tissue defects must degrade in a way that is balanced with the development and remodeling of new tissue. Similarly, the release kinetics of a bioactive molecule loaded into a bioadhesive as a delivery vehicle is heavily influenced by the degradation of the vehicle. Because of the inherent differences between *in vitro* and *in vivo* in terms of biochemical and mechanical environments, degradation of biodegradable materials *in vitro* often resulted in *in vivo* degradation [77–80].

1.5 Current and Future Applications

1.5.1 Wound Healing

Wound closure was the first application of tissue adhesives and hence much development has been carried out in this area compared to other applications. Cyanoacrylate derivatives have been widely used in endoscopy, skin closure, esophageal variceal bleeding, peptic ulcer bleeding, and internal applications [81]. Histoacryl (Braun, Melsungen, Germany) is the most famous of all cyanoacrylates that has been in use since long time. Similarly, Dermabond® (Ethicon, Inc., Somerville, NJ) is a 2-octylcyanoacrylate which is most famous for skin closure where the patients reported less pain and faster healing compared to other products [34]. Nevertheless, its use has declined due to the need for more biocompatible alternatives. Fibrin glues have been widely used for surgical applications. Fibrin glues have been utilized for hemostasis in cardiac surgery, vascular graft sealing, vascular surgery, thoracic surgery, hepatobiliary, and pancreatic surgery [82–85].

Similarly, fibrin glue was found to be useful in preventing bleeding from gastro-intestinal ulcers, fistulas and perforations [86–88]. It is also used in special cases like neurosurgery where fibrin glue has been used to seal cerebrospinal fluid (CSF) leakage. Albumin adhesives have been used for haemostasis in vascular and cardiac anastomoses. Marketed albumin glues like BioGlue have been effectively used in preventing pulmonary air leakage [89–91]. They are even widely used for treatment of fistulas. However, the presence of glutaraldehyde reduced its usage due to the risk of cytotoxicity. Poly(ethylene glycol)-based adhesives have been used as an adjuvant for suturing and grafting and also in hemostasis. Though they are effective surgical adhesives, their swelling and rapid degradation limited their use as an adjuvant for surgical applications [92]. Mussel-inspired adhesives being the latest entry in the arena of biological adhesives are being explored for tissue adhesive applications. Since isolation of mussel proteins from nature is a costly and inefficient process, the researchers have identified the critical component of mussel protein called dopamine (DOPA) which is essential for its strong adhesion [93]. Based on this finding, the researchers have synthesized various DOPA-based polymer derivatives which have been found to have higher adhesion strength compared to available tissue adhesives. For example, poly (γ -glutamic acid) hydrogel formed by combining with dopamine was found to have 10-fold higher adhesion strength in wet condition compared to the marketed fibrin sealant [94]. These adhesives were also widely researched for bone adhesion in combination with (an)other adhesive polymers like chitosan and dextran which led to multi-fold increment in adhesion strength [95, 96]. Good biocompatibility also enabled mussel-inspired adhesives to diversify their applications. Gecko-inspired adhesives were also applied for tissue adhesion. Based on the pillared structure of gecko, the researchers have synthesized polyimide hairs which showed excellent adhesion to the site of application [97]. However, the inability of the pillars to retain adhesion for long time and also in wet condition limited their use. To address this issue, novel modification techniques like coating the pillars with a synthetic adhesive material to mimic mussel adhesive have been implemented. This led to improved adhesion even in wet condition with adhesion maintained up to 1000 contact cycles [98]. Similarly, Mahdavi et al also developed similar nanopillar structure with variation in ratio of tip to base diameter and also tip to pitch diameter. This resulted in strong adhesion demonstrated in *in vivo* study [99]. Though, multitude of advantages can be explored through biomimetic adhesives like mussel and gecko, still numerous clinical studies need to be performed to establish the effectiveness of these new generation adhesives.

1.5.2 Drug Delivery

The adhesive scaffold can also serve as a rate-controlling matrix for various synthetic and biological agents [100]. This property was utilized by formulation scientists for an effective local delivery of drugs for increasing therapeutic effect and also to facilitate tissue healing [101]. Fibrin glues, being the most utilized and researched class of adhesives, were also evaluated extensively for drug delivery applications. The ease of altering the mechanical properties of fibrin glue structure through simple compositional changes provided an avenue for research in drug delivery. The tunable properties can be achieved by varying crosslinking time, fibrinogen content, calcium content, and thrombin content [81]. Even anti-fibrinolytic agents can also be added in the glue to delay the fibrinolysis, thus providing long lasting matrix for controlled release. These factors enabled loading of various types of therapeutic agents. Fibrin glues were found to be useful as temporary storage depots for growth factors like vascular endothelial growth factor (VEGF), nerve growth factor, bone morphogenic protein and platelet derived growth factor (PDGF) to aid in tissue engineering. Similarly, drugs like vancomycin, lidocaine, sisomicin, doxorubicin and 5-fluoro uracil were effectively delivered from the matrix of fibrin to elicit local effects. Recently, gene delivery vectors were also used in fibrin matrix for delivery [36]. However, the major drawback using fibrin glue is that it cannot serve as a depot for prolonged drug delivery as it degrades in days. This limits its wider application. Delivery of vitamins was also done with adhesives. Lazovic *et al.* prepared vitamin A and C soaked collagen dressing which led to improved healing compared with adhesive sheets without vitamins [102]. Similarly, elements like zinc were also loaded in wound dressings to promote healing. Also, poly(n-butylcyanoacrylate) based electrospun meshes were evaluated for delivery of chemotherapeutic agents like 5-fluorouracil where it was observed that the adhesive matrix sustained drug release for about 96 days [103]. These factors enable the tissue adhesives to be excellent drug delivery vehicles. Newer materials like mussel-derived molecules were also used for drug delivery applications. Talebian *et al.* prepared mussel-inspired biofibres which were able to control the release of doxorubicin drug and were also found to be better in treating cancer than an injectable doxorubicin [104]. Sunoqrot *et al.* [105] prepared polydopamine coated methoxy-poly(ethylene glycol)-b-poly(ϵ -caprolactone) nanoparticles loaded with rifampicin for gastro-retentive drug delivery. The coated nanoparticles showed higher mucin adsorption compared to the uncoated nanoparticles indicating enhanced adhesion due to polydopamine. *Ex-vivo* wash-off test also showed that the polydopamine coated

nanoparticles were able to reside longer on the stomach mucosa compared to uncoated ones. This indicated a potential gastro-retentive drug delivery application but needs to be explored extensively [105]. Zhang *et al.* prepared multifunctional mussel-inspired microneedles for transdermal drug delivery of glucocorticoid. The designed system was able to improve the adhesion of the device followed by controlled release over time to reduce osteoarthritis in an animal model [106]. Though these drug delivery systems possess multitude of advantages, much clinical data needs to be generated to prove that these systems would be ideal for further exploration in medical applications.

1.5.3 Tissue Engineering

Biological adhesives were assumed as candidates for tissue engineering owing to their excellent biocompatibility, low toxicity and biodegradability. These scaffolds were found to have milder immune responses compared to their synthetic counterparts. Tissue adhesives are widely used as scaffolds for tissue regeneration. The tissue engineering is done in two ways: either by injecting the scaffold and cells into the body or by culturing cells on the scaffold *in vitro* and then introducing at the target site. Adhesives like fibrin glues were effectively used in tissue engineering of cartilage tissue, cardiac tissue and bone growth [107]. Research studies found that the fibrin matrix was an excellent scaffold for growth of osteoblasts, myoblasts and chondrocytes. Collagen was also used as a scaffold for cartilage repair [108]. However, collagen-based scaffolds suffer from rapid degradation. Similarly, researchers have developed bovine serum albumin-based hydrogel scaffold for cardiomyocytes for cardiac tissue repair. Polymerized albumin scaffolds were found to be excellent candidates for growth and differentiation of mesenchymal stem cells [109]. The albumin scaffolds were also found to enhance bone formation in various model studies by various researchers making albumin one of first choices for tissue engineering applications. Unlike collagen-based scaffolds, albumin-based scaffolds were found to have longer life due to slow degradation which will aid in effective tissue regeneration.

Biomimetic adhesives have also been being effectively used in tissue engineering applications. DOPA from mussel adhesive protein is a widely employed material in tissue engineering applications. Polydopamine, a bio-inspired component from mussel adhesive protein is widely used for tissue engineering application. These polydopamine based scaffolds were used for skin, cartilage and nerve tissue repair. In a study the hydrogel consisting of polydopamine complexed with sodium alginate and polyacrylamide

facilitated skin fibroblast and keratinocyte adhesion, proliferation and expression [110]. In another study, a polyacrylamide hydrogel containing polydopamine-chondroitin sulphate facilitated increased cell adhesion thus improving cartilage repair [111]. Similarly the application of polydopamine also extended to neural regeneration where the scaffold systems employing polydopamine were found to promote nerve regeneration through improved adhesion of Schwann cells and neuronal stem cells [112]. Nevertheless, this application needs to be evaluated extensively to establish adhesives as an integral part of tissue engineering applications.

1.6 Summary

The earliest application of bioadhesives can be traced back to the 20th century. Since then, bioadhesives have been explored widely all over the world. However, the extraction of fibrin from human blood plasma and its use as a bioadhesive was initiated in 1940s where it was used as an adhesive for peripheral nerves. Fibrin was commercialized and approved in Europe in 1972 and by US FDA in 1998. The prominent use of bioadhesives has been in drug delivery and wound dressing and has resulted in exploration of new generations of bioadhesives and derivatization of existing bioadhesive molecules. The feasibility of tailoring the bioadhesives as per the requirements in the biomedical field is attracting attention from the scientific community. Hence, bioadhesives are being explored to meet the unresolved needs in the pharmaceutical and biomedical arenas.

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