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Surgical adhesives: Systematic review of the main types and development forecast

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ABSTRACT

Due to several advantages over traditional approaches (*e.g.* sutures and staples), surgical adhesives are excellent materials for wound closure. For several decades intensive research activities have been carried out to enhance the efficiency of the adhesives in different tissues and application conditions. This article provides a concise literature review of different types of adhesives in order to understand their structure–properties relationship. Some of the most important commercial adhesives available are presented and discussed in terms of limitations and applications. The recent advances reported in the literature that could provide new avenues to the development of more efficient adhesives inspired in nature strategies are also discussed.

Contents

Abbreviations: ASTM, American Society for Testing Materials; CSF, cerebrospinal fluid; DIN, standards and the Deutsches Institut Für Normung; DOPA, 3,4-dihydroxyphenyl-L-alanine; DNA, deoxyribonucleic acid; FDA, food and drug administration; GAG, glycosaminoglycan; GRF, gelatine–resorcinol–formaldeyde; GRFG, gelatine–resorcinol–formaldeyde–glutaraldehyde; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, immunodeficiency virus; HDI, hexamethylene diisocyanate; IEMA, 2-isocyanatoethylmethacrylate; IPDI, isophorone diisocyanate; mTG, microbial transglutaminase; PBS, phosphate buffered saline; PCL, polycaprolactone diol; PEG, poly(ethylene glycol); PGSA, poly(glycerol sebacate acrylate); PP, polypropylene; SEM, scanning electron microscope; US, United States; UV, ultraviolet radiation; vCJD, variant form of Creutzfeldt–Jakob disease.

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1. Introduction

The application of surgical adhesives appears as an extremely convenient method for wound closing. This fact is based on their main known characteristics, such as: fast application, less traumatic closure, less pain, no suture removal, excellent cosmetic result and localised drug release. In spite of the enormous efforts of the scientific community during the last decades, the currently available tissue adhesives still have significant limitations and drawbacks.

Surgical reconnection of injured tissues is essential for restoration of their structure and function. For many years, the mechanical fasteners such as sutures, staples and wires have been the most widely used methods for joining tissues. A useful fastener must hold the joined tissues in close proximity to allow adequate healing and stop the leakage of biological fluids while being able to resist tensile loads. Despite their common use in the clinic, these mechanical methods have some disadvantages. Besides the application of sutures being inherently traumatic to the surrounding tissue they are not suitable for inherently complicated procedures, such as stopping leaks of bodily fluids and air in blood vessels and tissues with rather low cohesion energy such as lung, liver, spleen and kidney. Also, the accuracy of positioning of the mechanical union may be extremely difficult when working in regions of the body not easily accessible. Therefore surgical adhesives, including tissue adhesives, have emerged because they provide attractive alternatives to suturing or stapling since they exhibit some advantageous features, such as haemostasis sealing of air leakages, elimination of the risk of needlestick injury to the surgeon, reduction of surgery time, tissue handling and blood loss by the patient, mitigation of surgical complications (*e.g.* infection), easy application, quality and strength of seal and no removal requirements [1–3].

Besides this, they really become an asset in situations where mechanical fastening is undesirable [2].

Tissue adhesive can be broadly defined as any substance with characteristics that allow for *in situ* polymerization to cause adherence of tissue to tissue or tissue to non-tissue surfaces, as for prostheses, to control bleeding (haemostats) and to serve as a barrier to gas and liquids (sealants) [3,5]. Many different tissue adhesives and haemostats have been developed over the past 30 years based on different materials.

In general, the adhesive must be easy to use, safe and, above all, it must have good adhesion properties, however the required properties are strongly dependent on the surgical specialty and procedure, in which the adhesive will be used. For example, to control a small oozing in a facial reconstruction, a more slowly polymerized adhesive that in a reconstruction of a portion of the aorta [6], is required.

The surgical adhesives should have, however, some common essential requirements. They must hold the two sides of the tissue together until it has enough mechanical strength to properly support wound healing and they should be biodegradable. In addition they must also polymerize in a moist environment, be gradually metabolised by the surrounding tissue without foreign-body response [7], be inexpensive and prevent tissue deformation [8].

Currently there are several types of commercially available tissue adhesives, which are traditionally classified into three categories: natural or biological, synthetic and semi-synthetic and biomimetic adhesives.

The biological tissue adhesives (*e.g.* fibrin glues, collagen adhesives) are really effective in some applications, but since they are derived from autologous tissue they are rather expensive and of limited availability.

Fibrin glue presents relatively weak tensile and adhesion strengths and requires a labour-intensive preparation just prior to application. Furthermore, thrombin and fibrinogen, which are the main components of the fibrin glues, obtained from human blood can, if not properly screened, cause viral infections such as immunodeficiency virus (HIV) and hepatitis and/or immune deficiency syndrome [1,9]. Concluding, biological glues are expensive, often exhibit

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relatively poor mechanical and tissue-bonding properties, and are potentially pro-inflammatory because most of them are based on proteins [10,11].

Semi-synthetic and synthetic surgical adhesives such as gelatine–resorcinol–formaldeyde (GRF), urethane prepolymers and cyanoacrylate have also been proposed during recent years. These adhesives present several disadvantages such as low bioabsortion and metabolic rates, cytotoxicity (low biocompatibility), low adherence to wet surfaces and chronic inflammation induced by the release of some of the respective degradation products such formaldehyde (which causes inflammation and possesses carcinogenicity potential) from GRF and cyanoacrylate polymers and aromatic diamine from aromatic polyurethanes [1,9]. Despite the good adhesion results obtained using non-aromatic urethane prepolymers based adhesives, the curing time presented is too long to cope with the surgical requirements [12].

The cyanoacrylates are an important group of tissue adhesives, used since the Vietnam Era [4]. In cosmetic surgery, they are used in multiple situations to avoid using skin sutures, but its application beyond skin reapproximation is unwise and potentially dangerous and can induce infection risks and tissue necrosis [13,14].

Therefore, for the discussed reasons, synthetic adhesives are in general not suitable for current internal use in surgery, and tissue adhesives based on natural polymers, cross-linked via biochemical reactions, offer a more compatible alternative to most of the synthetic adhesives. This fact is due to their composition, since they can mimic the same crosslinking process that naturally occurs during the blood coagulation [15].

It is pertinent to develop improved adhesives and methods of tissue adhesion for use in connection with living tissues [9]. During recent years an active area of research is related with the characterisation and development of mimicking adhesive materials found mainly in mussels and geckos because new classes of biomimetic polymers are poised to provide the next generations of surgical adhesives. Different publications have appeared related to strategies based on the development of recombinant deoxyribonucleic acid (DNA) technology to obtain large amounts of mussel adhesive proteins, which due to the adhesion properties presented in wet environments are considered to possess the potential required to become practical bioadhesives for diverse applications [16].

2. Natural or biological adhesives

Surgical adhesives and sealants based on natural polymers, cross-linked via biochemical reactions, offer in general a more biocompatible alternative to synthetic glues [10]. The main biological adhesives will be described then in detail. Note that among them, the most used are the fibrin and collagen based adhesives.

2.1. Fibrin sealants

Fibrin sealants are made from a number of components produced from pooled human plasma that enables the adhesive to mimic the final stages of blood clotting [17]. The most basic fibrin sealants consist of combinations of thrombin and fibrinogen [4]. Fibrin sealants generally contain two main components, fibrinogen (with or without factor XIII and fibrinectin) and thrombin with a small amount of calcium chloride, and in a few cases antifibrinolytics like aprotinin [18,19] as presented in the scheme of Fig. 1. Such products create a deliverable clot with dual function – haemostatic and sealant. These sealants use the same basic processes the body uses for haemostasis and tissue adhesion [4].

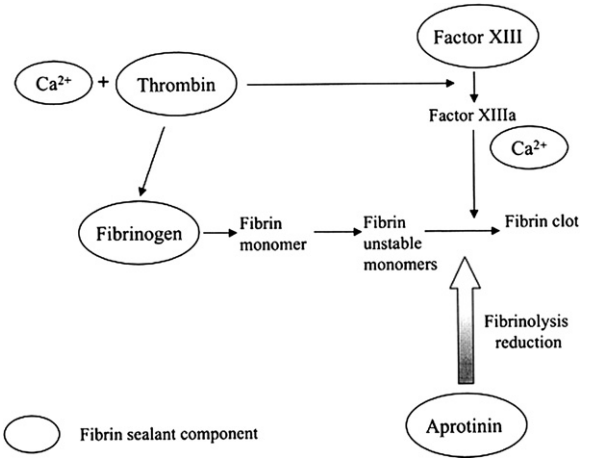

Fig. 1. Scheme of fibrin formation process, highlighting the fibrin sealant components.
Adapted from [94].

Formulations of fibrin glues available in the United States are local blood bank products and the commercial products are, for example, Hemaseel APR (Haemacure Corp., Quebec, Canada), Tisseel VH (Baxter Healthcare Corp., Deerfield, IL) and Crosseal™ (Human) (OMRIX Biopharmaceuticals Ltd., Brussels, Belgium) [4,20]. This type of biologic tissue adhesive has the longest history and by consequence the widest range of applications, such as: in cardiovascular surgery for haemostasis [21,22]; in neurosurgery for dural closure, to prevent cerebrospinal fluid (CSF) leaks, and to repair dural leaks [23–25]; plastic surgery to control burn bleeding after debridement [26] and as adjuncts in surgery necessitating flaps [27]; for sealing air leaks from lung procedures [28] and even as treatment for bronchopleural fistulas [29]. In addition, head and neck surgeons use them after radical neck dissections to treat lymphatic leaks [30], and trauma surgeons have applied them to spleen and liver lacerations [31].

The work presented in [32] has shown that fibrin sealants decrease bleeding in total knee replacements (arthroplasty procedure).

Despite their elasticity, the reduced mechanical strength of fibrin-based adhesives, mainly under wet conditions (*e.g.* in the presence of significant amount of blood) [33–38], makes them unsuitable for supporting tissue joints with significant tensile loads and to be applied on wet substrates [36,39]. Therefore, when these glues are used to counter brisk bleeding during surgery, generally they are used in combination with sutures or staples [33,34,40,41] or applied with a carrier sponge [42].

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The commercial fibrin sealant Crosseal™, the human protein, bovine component–free fibrin sealant, shows very efficient to reduce ecchymoses and hematoma formation in patients undergoing rhytidectomy [20]. Recently, fibrin components have been incorporated into a bandage that can be applied by first responders who provide pressure for the few minutes required for fibrin to undergo gel formation [43].

Since the plasma products are derived from pooled donors this type of adhesive, if not properly screened, may induce the risk of disease transmission [44], even knowing that heat inactivation and solvent/detergent extraction are used to reduce the risk of viral contamination. On this matter, recently, Horowitz and Busch [45] calculated the viral transmission safety margins of fibrin sealants for human HIV, the hepatitis virus, and parvovirus. In their study, the calculated risk for parvovirus transmission was 1 in 500,000 vials for fibrinogen even though the risk for HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), and hepatitis A virus (HAV) was very low (1 in 10^{15} vials for both fibrinogen and thrombin), and the risk for vCJD (variant form of Creutzfeldt–Jakob disease) could not be excluded. Moreover, fibrin sealants can be the cause of a severe allergenic effect such as anaphylactic shock, in some cases followed by death [46,47].

To avoid the problem of the possible contamination, virus-inactivated fibrin sealants were developed. These sealants offer an excellent biocompatibility and low toxicity; however they have a complex preparation procedure, slow curing and rather poor bonding strength [10]. Briefly, we can say that fibrin sealants are commonly used because they have low residual risks of infectious transmission and are naturally broken down by fibrinolytics [4].

Two new types of fibrin sealants have recently been developed for severe haemorrhage control. One type is a foamy fibrin sealant and the other type is a dry fibrin sealant [8].

2.1.1. Sprayable-foam fibrin sealant

The fibrin based sealants can be formulated as an instillable foam [48]. The tests performed show that the sprayable fibrin foam significantly reduced bleeding, resulting in a 56 and 66% reduction in blood loss when compared with untreated or placebo-treated animals, respectively and 100% survival in a severe parenchymal haemorrhage, created by partial resection of liver lobes in anticoagulated rabbits [49]. It is worthwhile to note that in terms of blood formulation and mortality rate, the foam formulation presents superior behaviour to the correspondent liquid form [8].

2.1.2. Dry fibrin sealants

The dry fibrin sealants can be obtained from different combinations of fibrin and fibrinogen, from human or animals, lyophilized on a backing material.

In the past decade two types of such sealants have emerged, TachoComb®, clinically used in Europe and consisting of a thin layer of lyophilized human fibrinogen and bovine thrombin, applied to one side of a sheet of equine collagen [50] and TachoComb® H and TachoSil® [51] produced both with human fibrinogen and thrombin, being that the first also contains bovine aprotinin. Despite the achieved success in the control of the haemorrhage of major parenchymatous organs [52], to compare the effectiveness of these agents with other haemostatic sealants used to control severe bleeding during the clinical surgery, more *in vivo* data are still needed [8].

Anema et al. [19] related the development of an absorbable fibrin adhesive bandage (AFAB) that is a concentrated mixture of lyophilized fibrinogen and thrombin deposited in polyglactin backing. This system appeared to have potential in producing rapid haemostasis because even though stable when dry, when placed in contact with liquids, such as blood, it forms a gelatinous clot almost immediately. Moreover is easy to use and convenient to storage.

Several studies with animals described in [53–60] demonstrate that the dry fibrin sealants significantly decrease blood loss during haemorrhage. Despite the efficiency these sealants are very expensive and, in the dry form, present stiffness, which limits its use [8]. To reduce the associated costs as well as the pathogen agent's transmission, recently some authors [60–62] investigated the potential of a salmon fibrin bandage as an alternative to the current dry fibrin sealants.

The combination of dry fibrin sealants with other haemostatic products, such as cellulose-based Surgicel [63] and gelatine-thrombin based FloSeal have been studied [64], but the resultant materials have not been tested in severe bleeding situations.

Elvin et al. [65] reported a new crosslinking process for fibrinogen using a ruthenium-based photochemical reaction using visible light illumination. This process allows obtaining an elastic hydrogel biomaterial from native fibrinogen through the dityrosine formation. The bonding strength of this photocrosslinked fibrinogen is at least five times higher than Tisseel™, a commercial fibrin tissue sealant. Moreover the *in vitro* tests demonstrate that the components of the photochemical reaction were non-toxic.

Later on Elvin et al. [66] carried out a skin-repair study in rats using photochemically crosslinked fibrinogen as a sealant. Their results indicated minimal inflammatory response, with good healing, new collagen formation and neovascularisation at the wound repair site. Since the performed tests shown that it can strongly sealed tissue within 20 s of application this sealant has potential in surgical applications where rapid curing and/or high strength are needed.

More recently Bjork et al. [67] developed a cross-linking method to form dityrosine both in fibrin and collagen based engineered tissues using a ruthenium–sodium persulphate and visible blue light. This crosslinking method allows increasing three times the mechanical strength and ten times the stiffness by controlling culture duration prior to cross-linking and light exposure time. Moreover it is quick, non-toxic and minimally inflammatory.

2.2. Collagen based adhesives

The adhesives based on collagen adsorb blood and coagulation products on its fibres, trapping them in the

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interstices and effectively adhering to the wound. This biopolymer also induces platelet adhesion and aggregation, and activates coagulation factors [68–71].

However, collagen-based haemostats can swell with tissue compression. As a consequence, it cannot be used for ophthalmologic or urologic surgeries [6].

Collagen-based adhesives are relatively new and they show significant potential [4]. They present a low risk of disease transmission because they are produced from mammalians, and have been used in different medical applications such as surgical suture materials, haemostatic glue, and wound dressings [72–75]. Two of these adhesive types are approved for use in the United States; FloSeal (Sulzer Spine-tech, Anaheim, CA) and Proceed (Fusion Medical Technologies, Mountain View, CA). They are chemically identical compounds, made from a combination of bovine collagen and bovine thrombin [4]. These products work by providing a matrix for the clot and enhancing coagulation by delivering fibrinogen to the area. FloSeal is advised for vascular surgery haemostasis [76] while Proceed is appropriate for prevention and treatment of cerebrospinal fluid (CSF) leaks [77], and it has a longer applicator tip. Both products can be considered relatively inexpensive [4].

The literature [68] suggests that another collagen product, CoStasis (Cohesion Technologies, Inc.) produced with autologous human plasma, bovine collagen and thrombin provides significant improvement in control of surgical bleeding in general, as well as cardiovascular, hepatic and orthopaedic procedures.

New crosslinking agents derived from citric acid have been used to prepare collagen sealants with sufficient bonding strength and low toxicity as reported in [78,79]. The capacity of this glue to bind collagen castings is similar to the aldehyde glue (GRF glue®), 11 times higher than a fibrin-based glue (Bolheal) but lower than the cyanoacrylate glue (Dermabond®). Concerning the biocompatibility and the resorbability, this sealant exhibited very good properties, indicating its applicability as a soft tissue bonding agent.

As drawbacks this sealant requires a long time (10 min) to reach sufficient bonding strength, which may represent a difficulty for its use in clinical applications.

The work presented in [80] describes the evaluation of the performance of two produced atelocollagen (a telopeptide-free collagen that is non-immunogenic) based adhesives, Bleestop A (2% esterified atelocollagen in 75% ethanol + 1% $CaCl_2$ + 0.71% 3,4-dihydroxyphenyl-L-alanine (DOPA) + 0.1% tranexamic acid in distilled water) and Bleestop B (2% esterified atelocollagen in distilled water + 1% $CaCl_2$ + 0.71% DOPA + 0.1% aminocaproic acid in distilled water). The results of the performed tests show that the bleeding was controlled immediately after application of Bleestop A and partial adhesion was observed after 30 s. More than 95% of the resected surface area was attached after 1 min. In Bleestop B, similar results were found; partial adhesion was registered after 30 s. More than 95% of the resected surface area was attached after 45 s. Histologic evaluation showed that Bleestop A and B rapidly confer adhesion between both resected tissue surfaces. The adhesion strength of Bleestop A and B was better than the negative control (no adhesives used group) and showed the same adhesion strength as the positive control group (Tissucol/Tisseel, Duo Quick group, a commercial fibrin sealant) after 3 min [80].

Despite the excellent results obtained until now with collagen-based compounds, a long-term study to better explore their benefits in surgery is required.

2.3. Gelatine based adhesives

The materials that can form gels *in situ* are envisioned as injectable matrices for controlled drug delivery or injectable scaffolds for tissue engineering [81–84].

They are attracting considerable attention for a large variety of soft tissue applications, since they may serve as adhesives to bond tissue or seal leaks (either gas or fluid) [85].

Some authors [86,87] described the properties and uses of Floseal™ (manufactured by Fusion Medical Technologies, Inc., Mountain View, CA, USA and distributed by FloSeal Baxter Medical, Fremont, CA, USA), a topical haemostatic agent. It consists of cross-linked gelatine granules and thrombin, both from bovine origin. The referred product proved to be efficient to solve problematic bleeding occurred during surgery in several anatomic sites and surgical procedures, such as femoral bypass. The gel formation can also be achieved by physical means using self-assembling peptides [88–90] stimuli-responsive materials (*e.g.* poly-N-isopropylacrylamide) [91,92] and through biological approaches based on blood coagulation (*e.g.* the fibrin sealant) [93–96]. It is also possible to achieve gel formation using the crosslinking components from marine adhesives (*i.e.,* the mussel glue) [39] as well as low molecular weight phenols or phenolic residues on natural or synthetic polymers [97–105]. Mimicking phenol-mediated crosslinking operations used by insects to generate a crosslinked network for processes to harden its integument [106,107] or seal wounds [108,109] also affords a gel.

Elvin et al. [110] showed that a photochemically crosslinked gelatin-based tissue sealant demonstrated high adhesive strength (>100 kPa), high elasticity (>600% extension to break) and high tensile strength (ca. 2.0 MPa). This dityrosine-crosslinked biomaterial was well tolerated *in vivo*, with minimal inflammation, good wound healing and effectively sealed lung, vascular and gastrointestinal defects.

Furthermore, when combined with fibrinogen, a photochemically crosslinked gelatin-based biomaterial promoted cell growth *in vitro* [111] and may represent a useful tissue engineering scaffold. Other relevant types of biological crosslinking operations result from the transglutaminase-catalysed reaction that occurs during blood coagulation [112].

Over the years different adhesives based on gelatin and gelatin cross-linked with an aldehyde were developed, such as GRF where gelatine–resorcinol are cross-linked with formaldehyde and gelatine–resorcinol–formaldeyde–glutaraldehyde (GRFG) that is cross-linked with glutaraldehyde. Some *in vitro* studies [113–115] showed that a calcium independent microbial transglutaminase (mTG) can crosslink gelatin to form a gel within minutes. The

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gelatin mTG adhesive can bond even with moist and wet tissue, and the adhesive strength is comparable to, or even better than, fibrin based sealants. The potential of the gelatin-mTG adhesive as a surgical sealant, concerning bonding strength, was evaluated using porcine skin as a model, and initial *in vivo* studies were performed using a small animal (*i.e.,* rat) and a large animal (*i.e.,* pig) [86]. Since the gelatin-mTG adhesive mimics fibrin crosslinking, the gel-forming mechanism is analogous to that for fibrin-based sealants. The work described in [86,114] compared the potential of the gelatin-mTG biomimetic adhesive to the more established fibrin sealants. The *in vitro* comparative studies already carried out show that when gel formation occurs under moist conditions the gelatin-mTG adhesive confers greater bonding strength than fibrin sealants [114]. However, the *in vivo* comparative tests have not yet been performed.

The *in vivo* tests made with the gelatin-mTG adhesive [86] indicate that this adhesive gel adheres to tissue within a relevant timeframe (<5 min), in the presence of modest amounts of blood and results in appropriate mechanical strength to serve as a haemostatic sealant in the absence of sutures. In addition the gelatin-mTG adhesive has some relevant advantages that should be stressed: (i) it does not require the use of an external stimulus or a reactive reagent, (ii) since their components are not derived from human blood, they would be readily available and inexpensive and (iii) the formation of the biomimetic clot would be independent of the patient's coagulation state. Despite the promising results, the biocompatibility and biodegradability of the referred adhesive, as well as its potential to promote wound healing, have not been analysed [86].

Currently, one of GRFG adhesives, with the trade name BioGlue (CryoLife Inc., Kennesaw, GA) is approved in the United States for the limited use of assisting in the repair of aortic dissection. This product is a combination of bovine albumin and glutaraldehyde glue. Note that in this glue the formaldehyde component is left out due to toxic issues. In other countries, different types of GRFG glues are used for both vascular and pulmonary procedures. BioGlue fills in the dissection, since it closes the cavity and provides a stronger arterial wall for the repair [115,116]. The inflammatory effects and long-term reaction to BioGlue also need to be better described before the United States (US) FDA authorises the expansion of its application [4]. Other GRFG type glues are being explored for use in thoracic and general vascular cases [117].

2.4. Polysaccharide based adhesives

2.4.1. Chitosan sealants

Chitosan is a polysaccharide produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi. It is usually derived from chitin via deacetylation by enzymatic or alkaline treatment. The haemostatic property of chitosan is well known, and the development of a patented product called Hem Con™ [118] has demonstrated that these sealants are capable of controlling severe parenchymal and large venous haemorrhage in a swine model of severe liver injury [119]. The efficiency of the referred product for both military [120] and civilian uses [121] has been shown by clinical data. A new version of the product Chitoflex®, showed better performance in a lethal groin-injury model in goats [122].

Chitosan sealants based on powder have also been developed. As an example Celox™ is a patented preparation in the form of granules prepared from more than one type of chitosan with a large surface area [123]. Its efficiency as a haemostatic product was confirmed by Kozen et al. [123] and Kheirabadi et al. [124]. The work developed by Klokkevolt et al. [125] shows that chitosan, when applied in lingual incisions, effectively decreased intraoral bleeding time.

A lased activated adhesive based in chitosan used in anastomosis nerves was successfully performed, as demonstrated by Lauto et al. [126]. This author also demonstrated that this type of adhesives efficiently repair intestine tissue causing only localised thermal damage *in vivo* [127].

An insoluble chitosan hydrogel resulting from the photo crosslinking (by a short UV radiation) of the chitosan molecules, successfully seals air leakage from lung incisions and bleeding from the artery.

This tissue adhesive may be suitable to skin wound closure and in situations that require an urgent haemostasis, such as medicine disasters [37,128].

Despite the arterial catheterization is currently applied in diagnostic and therapeutic procedures, due to inadequate haemostasis, complications in this procedure may occur. The work performed by Hoekstra et al. [129] shows that the use of a microcrystalline chitosan (MCCh) sealant via an arterial sheath at the completion of catheterization may improve haemostasis. Chitosan based adhesives also successfully closed scleral lacerations, as described in [130].

2.4.2. Alginate based glues

Alginate, also called algin or alginic acid, is an anionic polysaccharide distributed widely in the cell walls of brown algae, where it, through binding water, forms a viscous gum. In extracted form it absorbs water quickly; it is capable of absorbing 200–300 times its own weight in water [131].

To mimic the adhesion mechanism of algae, a new polysaccharide formulation composed of alginate, calcium ions and phloroglucinol has been developed [10,132].

The addition of the phloroglucinol and calcium ions to the alginate aimed to facilitate the formation of a 3D network capable of binding to the tissues, even after prolonged exposure, over 2 months, of the adhesive to an aqueous environment.

2.4.3. Chondroitin sulphate glue

Chondroitin sulphate is a sulphated glycosaminoglycan (GAG) composed of a chain of alternating sugars (N-acetylgalactosamine and glucuronic acid). It is usually found attached to proteins as part of a proteoglycan.

A chondroitin chain can have over 100 individual sugars, each of which can be sulphated in variable positions and quantities. Chondroitin sulphate is an important structural

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component of cartilage and provides much of its resistance to compression [133].

Wang et al. [134] describe the development of glue prepared with chondroitin sulphate and functionalized with aldehyde and methacrylate groups. This adhesive can be applied to bind both the native cartilage tissue and a biomaterial implant, due to a chemical reaction between the aldehydes and the amine groups of the cartilage collagen. The methacrylate groups participate in the polymerization to solidify the implant material. The developed adhesive is appropriate in situations where the integration of implants with surrounding native tissue is fundamental for immediate functionality and long-term recovery, even because *in vitro* and *in vivo* studies confirmed that the biological adhesive promoted extracellular matrix production and tissue regeneration in cartilage defects.

To secure flaps in posterior lamellar keratoplasty a chondroitin-sulphate–aldehyde based adhesive was also developed [135] and the comparative tests performed revealed that flaps sealed with the novel tissue adhesive had reduced astigmatic changes compared with those sutured.

3. Synthetic and semi-synthetic adhesives

The synthetic and semi-synthetic class of adhesives include cyanoacrylate based adhesives, polymeric hydrogels, dendrimers and urethane based adhesives.

3.1. Cyanoacrylate adhesives

The commercial synthetic adhesives based on cyanoacrylate (*e.g.* Dermabond® and Liquiband®) are liquid monomers that on contact with various anionic substances, such as water or blood, polymerize into long chains, creating a flexible film that bridges the wounds and holds the apposed wound edges together [34,136,137]. They guarantee adequate adhesive strength and mechanical properties for applications on living tissues. Despite having quicker polymerization [138], some reports [139–141] show that, when compared with other adhesives, they are easier to use. Other advantage is that they provide an acceptable cosmetic, making it suitable for external application [7,11].

The use of cyanoacrylate tissue adhesives is well described in the literature for closure of skin wounds [142–146] and when used for this application, the compound lasts for 7–10 days [4]. The 2-octyl cyanoacrylate (Dermabond®) is a standard tool frequently used by surgeons worldwide for small lacerations and for wound closure of the body [147–149]. Due to the fact that 2-octyl cyanoacrylate meets many of the required properties, the Food and Drug Administration (FDA) approved it for use in 1998. Nowadays, the benefits of this tool are well known and appreciated by plastic surgeons. The product is used in multiple situations to avoid using skin sutures in cosmetic surgery [13] and by emergency room physicians to close smaller cuts or reapproximate lacerations that have deep support sutures [149]. It is especially useful in superficial or small wounds in children where its use has averted the trauma of needles [150]. Because it is waterproof, Dermabond® requires no dressing [4]. Not only the different surgical subspecialities are using 2-octyl cyanoacrylate, but Dermabond® is also indicated for skin graft fixation among other applications [151–153].

The use of Dermabond® has, however, risks, complications and negative aspects. One negative aspect is clearly the high price of 2-octyl cyanoacrylate compared to suture solutions. More important for the patient is clearly the possibility of a foreign body reaction occurring as a complication after the use of 2-octyl cyanoacrylate. Some authors [154,155] speculated about the hypothesis of a foreign body reaction after the use of 2-octyl cyanoacrylate, but they could not prove their theory because no histopathological analysis was published, so far. More recently Dragu [156] proved that a foreign body reaction occurred when using Dermabond® to treat a superficial wound of the right wrist in a patient. Moreover, in clinical trials, the number of infections was relatively low, with a reported maximum of 8% frequency [153,157–159]. Therefore, there is no doubt that in general the use of 2-octyl cyanoacrylate seems to be clinically safe.

The other cyanoacrylate approved for use in the United States, Trufill n-BCA (Cordis Neurovascular, Inc., Miami Lakes, FL) is a combination of n-butyl cyanoacrylate and tantalum powder. This cyanoacrylate is delivered through the arterial system to stop bleeding in atrioventricular malformations and is then removed during repair and, as Dermabond®, it is stronger than their fibrin sealant counterparts. However, both products are not bioabsorbable; the body cannot break them down [4].

Despite the fact that cyanoacrylate glues create a strong flexible bond, which lasts for a few years, they can only be used externally because they cause an intense inflammatory response and are toxic when making contact with noncutaneous surfaces as described by Singer et al. [160]. These adhesives were used in the Vietnam war to assist with wound management, before an associated risk of carcinogenicity was discovered [161].

There are some documented reports of internal cyanoacrylate use, but application beyond skin reapproximation is unwise and can be potentially dangerous to patients [4].

Glubran2 (GEM s.r.l., Viareggio, Italy), a modified n-butyl-2-cyanoacrylate tissue adhesive with high adhesive and haemostatic properties, is a class III (for internal and external surgical use) medical-surgical product which fulfils the requirements of the European Directive on Medical Devices 93/42/EU. Moreover, it has been approved for endoscopic use in Europe. Glubran2 is largely used in laparoscopic and traditional surgery, and in interventional radiology [7]. It is diffusely applied on skin, eliminating the need for suture removal and providing good cosmetic results. *In vivo* applications of Glubran2 evidenced its good haemostatic and adhesive properties, in particular in bonding biological tissues to each other or with prosthetic implants. The adherence appeared tenacious instantly after application and consolidated its strength during completion of the polymerization process, allowing rapid and efficacious results both in open and in laparoscopic surgery.

Recently Kull et al. [11] evaluated the adhesive and mechanical properties on biological substrates of Glubran2

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in comparison with fibrin glue (Tissucol/Tisseel; Baxter Healthcare, Deerfield, IL) according to American Society for Testing and Materials (ASTM) standards and the Deutsches Institut Für Normung (DIN) standards, respectively. All tests performed showed the intrinsic tensile strength of polymerized Glubran2 and its capability to promote a higher-resistance bonding among biologic tissues, in comparison with fibrin glue, giving strong indication of its usefulness in surgical and endoscopic practice, especially in a wet environment [11]. The surgical glue, Glubran2, as well as the Glubran was evaluated concerning the cytotoxicity, blood compatibility and antimicrobial activity by Montanaro et al. [7].

In general terms, developed tests show that cytotoxicity was severe with the undiluted glues, and it was acceptable when glues were diluted. On the contrary, blood compatibility was acceptable for the intended use of the glues. No difference was found between Glubran and Glubran2 after polymerization. Neither Glubran nor Glubran2 inhibits bacterial growth from the strips of *Bacillus subtilis* var. niger, but can hamper the spread of contamination of a high number of bacteria introduced into the test materials [7].

3.2. Polymeric hydrogels

Another synthetic tissue adhesive is based on a polymeric hydrogel made from poly(ethylene glycol) (PEG) and is used both as a fluid barrier and as a haemostatic agent [10]. The FDA-approved product in this category is FocalSeal-L (Genzyme Biosurgery, Inc., Cambridge, MA). This product is applied to tissue and a light source is used to photopolymerize the reactive double bonds and activates its adhesion. It is worth to point out that this product takes some time to be applied and set. The compound is bioabsorbable and the degradation takes approximately 3 months [4]. FocalSeal-L has been proved useful in decreasing air leaks after major thoracic surgery, but its role in decreasing costs and length of hospital stays is unclear [162]. It was also tested in wound closure and in haemostasis in anestomic bleeding [163,164].

Since the photoactivation makes application time of FocalSeal-L quite long, difficult and nearly impossible in haemorrhagic situations, similar products that do not require the same activation sources are being developed.

One PEG based polymer, CoSeal (Cohesion Technologies, Inc., Palo Alto, CA), is currently being used in Europe for similar purposes [4]. The comparative tests performed with CoSeal and a traditional haemostatic agent such as gelfoam/thrombin for managing anastomic bleeding during aortic reconstruction after implantation of Dracon grafts show no adverse consequences. So, the obtained results as well as an economic analysis developed and the FDA approval for CoSeal use in vascular reconstruction, support its use in the above referred application [165–168].

SprayGel (Confluent Surgical, Inc., Waltham, MA) is a sprayable hydrogel that adheres to the tissues for a period between 5 and 7 days and subsequently is hydrolysed into water-soluble molecules and absorbed. This polymeric gel has been shown safe in gynecologic and colorectal procedures, including in the closure of ileostomy [169,170].

The works [171,172] described the results of the application of hydrogel glues in rabbit eyes. This type of glues demonstrated to be minimally toxic to eye, can be used to path retinal breaks and to repair the sciatic nerve gap injury. When tested in this application DuraSeal™ demonstrates strong adhesive power and produced appropriate nerve regeneration [172].

The potential use of a sprayable *in situ* formed hydrogel as tissue sealant and as an adhesion barrier, to regulate biological adhesions in cardiovascular preclinical models, was studied by Bennett et al. [173]. A PEG based polymer was also tested as sealant in fluid leaks [174].

AdvaSeal (Ethicon Inc., Johnson & Johnson Medical KK, Somerville, NJ) is a bioabsorbable PEG based photocrosslinkable hydrogel with visible light and currently clinically used for sealing of pulmonary air leakage.

The investigation developed by Tanaka et al. also demonstrates its effectiveness in treatment of acute aortic dissection [175,176].

Adherus surgical sealants (HyperBranch Medical Tech, Inc., Raleigh, NC) are a family of biodegradable synthetic hydrogel sealants that polymerize in the presence of moisture, setting the tissues immediately after application. They are approved for sale outside of USA for cranial, ophthalmic, spine and hernia procedures [177].

3.3. Dendrimers

Dendrimers consist of highly branched macromolecules of low polydispersivity, with well-defined structures and numerous functional end groups that may provide several possibilities for biomedical applications [178]. In order to overcome the drawbacks of using sutures for the corneal wound repair [179] as well as for corneal cataract incisions [180] the performance of dendrimer based adhesives has been studied.

The work by Degoricija et al. [181] describes a photocrosslinkable dendrimer that provides an excellent seal in preventing the eye from leaking at high pressures and a barrier against the influx of surface fluid into the wound site when tested in porcine eyes.

3.4. Urethane based adhesives

Among the synthetic materials, recently, the urethane-based adhesives have been considered to be promising due to the possibility of being biodegradable and biocompatible.

In addition, if these polymers are synthesised in the form of prepolymers, they have the capacity to react with amino groups of proteins present in the biological molecules, which promotes the adhesion between the tissues as a result of the formation of urea linkages [1] in a very fast way (Fig. 2).

Lipatova [182] describes the synthesis of a polyurethane adhesive already tested in renal surgery [1], endocrinology [183], pancreatic occlusion [184] and in orthopaedic procedures to bone fixation [185]. The results show that the degradation products do not present any toxic effect and that the glue is auto sterile and assure intensive haemostasis.

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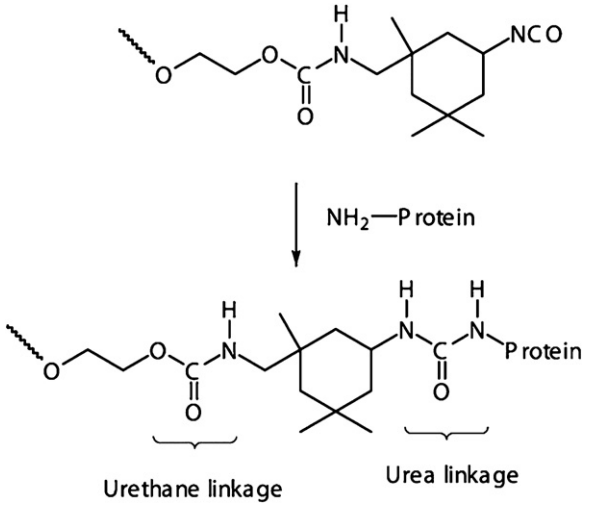

Fig. 2. Reaction between a prepolymer and the amino groups of a protein resulting in a urea linkage [189].

The work of Phaneuf et al. [186] presented the development of a new polyurethane sealant, consisting in a polyether based polyurethane containing carboxylic acid groups to seal the interstices of the prosthetic vascular grafts and create "anchor" sites that favour the proteins attachment.

Urethane based adhesives can also be applied with success is cosmetic surgery. For example, a lysine derived sprayable urethane adhesive (TissuGlu; Cohera Medical Inc., Pittsburgh, PA) shows to be effective in preventing the formation of seroma (excess fluid accumulation under the skin) that frequently occurs following the abdominoplasty procedure [187]. Since TissuGlu is non-toxic, resorbable, forms a strong bond between tissue layers and contributes to natural healing, CE Mark approval allows TissuGlu to be sold in the European Union [188].

The urethane based adhesives present the advantage of being biodegradable if they are synthesised from some natural molecules, such as castor oil as shown in Ferreira et al. [1].

The mentioned reference relates the development of a biocompatible and biodegradable urethane-based bioadhesive containing free isocyanate groups that result from the reaction of castor oil with isophorone diisocyanate (IPDI). The results show that the NCO groups of the adhesives are stable enough to be kept under storage conditions as long as humidity is avoided. Nevertheless, even in water saturated conditions, it takes 7 days for the hydrolysis of all the NCO groups to occur. The performed tests also reveal the non-haemolytic character of the adhesive [1].

Ferreira et al. [189] synthesised urethanes by reaction of polycaprolactone diol (PCL) either with IPDI or with hexamethylene diisocyanate (HDI). PCL is a biodegradable aliphatic polyester already approved by the US FDA [190,191] and that has been used in several medical applications, such as drug delivery systems [192], resorbable sutures [193] and also as a material for tissue regeneration [194]. The products of PCL degradation are either metabolised by being included in the tricarboxylic acid cycle or eliminated by renal secretion [195]. The results obtained show that the PCL + IPD polymer is able to promote adhesion between the aminated substrates, but the surface energies of the urethanes were proved to be low, which was consistent with the high thrombosis values induced by them. The haemolysis tests performed conclude that, after the extraction with phosphate buffered saline (PBS) solution, the haemolytic potential of the urethanes disappeared even though they previously presented a haemolytic character. The PCL + IPD polymer can eventually have a clinical application, once it is proved that clinical benefits are shown to overcome the risks and the referred values of haemolysis are within acceptable limits [189].

The several studies [1,182,190,196] that have already been made to develop one component urethane prepolymers to be applied as bioadhesives proved that, despite the good adhesion results, the curing time is too long to match surgical demands. Since compared with prepolymer systems the UV curable adhesives offer major advantages, such as fast-curing rate, localised curing and control of the polymerization heat evolution, they seem to be ideal for application to weakened and diseased tissue [197].

To overcome this disadvantage of urethane adhesives, Ferreira et al. [12] report the modification of PCL with 2-isocyanatoethylmethacrylate (IEMA) to form a macromer that was easily crosslinked via UV irradiation by the use of a photoinitiating agent (Irgacure 2959 by CIBA®), which proved [198] to be well tolerated over a wide range of cell types and chemical concentrations [12].

The several techniques used to characterise the crosslinked polymer allowed the conclusion that the percentage of polymer swelling was low, which indicates that the volume increase *in situ* will not be significant and surrounding tissues damage will not occur. The adhesive was also able to promote efficient adhesion between the aminated substrates, as showed by the results of the strength tests made with gelatine pieces [12]. The developed polymer was photocrosslinked to obtain new membranes, specially prepared to be submitted to biodegradation tests. The referred tests were carried out in human plasma, during 6 weeks and led to a weight loss of around 10%. The scanning electron microscope (SEM) analysis made after this period showed that the membranes are uniformly porous and allowed to observe fibrin fibres on their surface [12]. This capacity of fibrin fibre formation in the membrane surface just confirms the thrombogenic character revealed by the haemocompatibility studies performed.

When in direct contact with blood, the synthesised material could be classified as slightly haemolytic, however, this haemolysis was eliminated when the samples were subjected to extraction with PBS solution (indirect contact). This result does not mean, however, that this material cannot have a clinical application, because values of haemolysis are within acceptable limits [12].

4. Biomimetic adhesives

To promote adhesion underwater or in a wet medium is a considerable challenge for the adhesives because the presence of water beyond the weakening of the

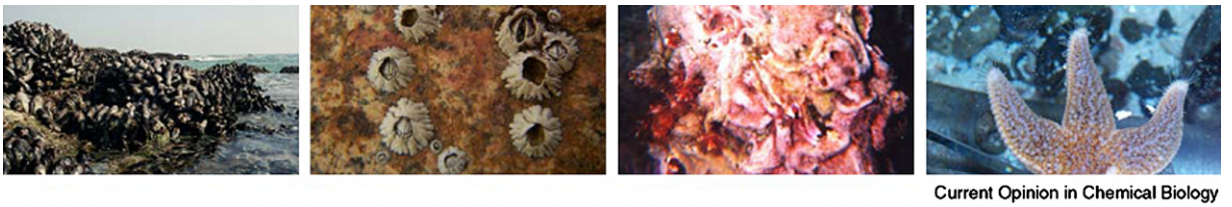

Fig. 3. Left to right: mussels, barnacles and tube worms sticking to rocks. A starfish is shown adhering to a sheet of glass [205].

intersurface physical adhesive forces, such as the van der Waals and acid–base interactions, may also alter chemical bonds [199]. Adhesive joints that need to withstand a wet environment created by body fluids are required for tissue adhesives. One significant alternative for synthetic reactive glues like cyanoacrylate [158] or bioderived glues like fibrin [137] that, in spite of giving an effective wet adhesion, present some disadvantages, are the bioinspired underwater adhesives. Gecko and beetle inspired micro-texturing of the surface [200,201], glues inspired by marine bioadhesives such as mussel proteins [202,203] or both in combination [204] are examples of these adhesives.

The oceans are filled with an amazing variety of biological materials including mussels, barnacles, tube worms, algae, and starfish that are making glues or cements for staying fixed in place (Fig. 3) [205]. The algae, for example, produce and secrete adhesives that form permanent, strong and flexible underwater bonds to a variety of substrates.

Some studies have shown that the adhesives produced by *Fucus serratus* are multicomponent polymeric materials composed of polyphenol and alginate, which is cross-linked by divalent calcium ions [206,207]. Following the biomimetic approach, the natural polyphenol was replaced with its synthetic monomer unit, phloroglucinol. The adherence capabilities of the biomimetic glue to a variety of substrates were of the same order of magnitude as those reconstructed from the alga [132].

Concerning the biomimetic polymers, mussels and barnacles have become major target for marine adhesion studies. Even so, we will focus only on mussels adhesives type because while studies on barnacle adhesion are still in relatively early stages [208,209] biochemical knowledge on mussel adhesions has been accumulated during the over past 25 years. We also analyse the recent developments referring to the gecko-inspired adhesives.

4.1. Marine mussel extract adhesives

In the beach, if we take a close look at how blue mussels (*Mytilus edulis*) adhere, we will see the byssal (or 'byssus' or 'beard') adhesive assembly, much like that shown in Fig. 4. Mussels affix themselves to surfaces by depositing a series (~10–40) of small (~2 mm diameter, ~0.1 mm thick) adhesive plaques, each connected to the animal using a long thread. An impressive amount of force is needed to break the adhesive bonding. Mussels can even stick to Teflon (Fig. 4) [205].

One of the most explored biomimetic approaches, which encompass artificial materials that mimic natural forms, is the development of adhesives based on the marine mussels [132]. Mussels, which are a common food throughout the world, have been studied as a potential source for a water-resistant bioadhesive [210,211].

Mussels produce and secrete specialized adhesives that allow themselves to attach in marine environments, which are typically characterised by salinity, humidity, tides, turbulence, and waves [210]. They adhere tightly to surfaces underwater using the byssus secreted from their feet, which consists of a bundle of threads. At the end of each thread, there is an adhesive plaque containing water-resistant glue that enables the plaque to anchor to wet solid surfaces [212]. These mussel adhesive proteins have been considered as potential underwater bioadhesives due to their many fascinating features [210,213–215]. Even mussel based adhesives are much stronger than other polymer-based adhesives such as epoxy and phenolic resins, it is flexible and elastic. And most importantly, mussel adhesive protein maintains its adhesion in wet environment and can also attach to various substrates, including plastic, glass, metals, and living body substances. Adhesions of mussel adhesive proteins (extracted and

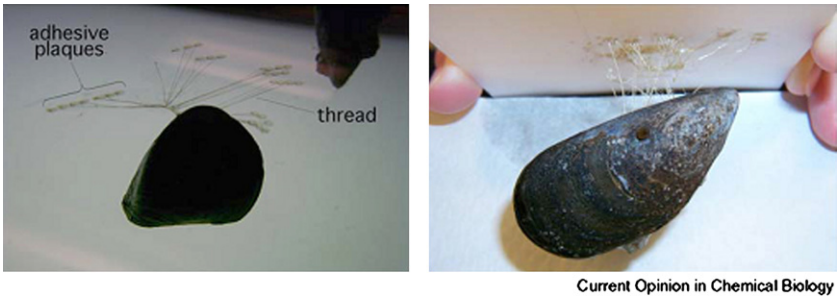

Fig. 4. A marine mussel clinging to a glass sheet (left) and Teflon (polytetrafluoroethylene, right). Note the attachment system comprising many adhesive plaques and threads [205].

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recombinant) to various solid materials have already been verified [97,216–220].

Burkett et al. [221] describe a method to quantify the adhesion strength of mussels. On high energy surfaces such as aluminium, mussels stick with strengths of almost 300 kilopascal (kPa), or a little over 40 pounds per square inch (psi) [221]. By comparison, common synthetic adhesives such as poly(vinyl acetate) (PVA, 'white glue') with ~900 kPa and cyanoacrylate 'super' glue with ~8000 kPa are stronger [197] but the mussel has plenty of sticking power for its life in the turbulent waters.

Recently, studies on attaching of mussel adhesive proteins to living body substances, especially porcine skin [2], and diverse types of mammalian cells [220,222,223] have been also performed.

Strong and water-insoluble mussel adhesives have attracted interest for potential uses in diverse biotechnological applications because they could be used as cell and tissue adhesives, and have the added advantages of being environmentally friendly as they are biodegradable [224], apparently harmless to the human body and do not impose immunogenicity [213,214,224,226]. Beyond this they are environmentally friendly and are efficient for use under aqueous conditions.

Three distinct types of collagenous proteins from byssus thread [226–228] and six distinct foot proteins type from adhesive plaque [212,216,229–233] have been identified. Studies revealed that mussel adhesive proteins that are closer to the adhesion interface have a higher proportion of DOPA residues [229–232] and that mussel adhesive protein analogues without DOPA showed a greatly reduced ability for adhesion [98,99,219]. DOPA residues also enable mussel adhesive protein molecules to cross-link by oxidative conversion to DOPA-quinone [98,99]. The reactive quinine is thought to provide the water-resistance characteristics of mussel adhesion [98,99].

Ninan et al. [2] describe the process of mussel adhesive protein ("mussel extract") from *M. edulis* feet as well as its adhesive properties. The results of the tests performed show that (1) mussel extract is capable of forming strong tissue joints (~1 MPa) in the end-to-end configuration, given adequate curing time; (2) the time required for mussel extract to reach the maximum adhesive strength on porcine connective tissue substrate is between 12 and 24 h, (3) mussel extract joints are similar in strength to fibrin joints, although they cure more slowly than fibrin and (4) mussel extract curing kinetics is very sensitive to moisture.

Chivers and Wolowacz [234] reported a very weak bond strength due to the delay in the curing of adhesives, that probably results from the difficulty in removing moisture from the mussel extract when the interface was not exposed to air.

In order to avoid this problem of very weak bond strength some authors [235,236] have studied the effect of the addition of various chemical cross-linkers on the strength and on the biocompatibility of mussel extract.

Despite having been identified as the major protein responsible for the mussel adhesive properties and the thorough examination of its adhesive properties and biocompatibility, its practical applications have been severely limited by the uneconomical extraction and unsuccessful large scale production. The natural extraction used to isolate mussel adhesive proteins is a labour intensive and inefficient process, requiring around 10 000 mussels for 1 g of the fp-1 (foot protein from the mussel specium *M. edulis*, which was the first identified and the most studied mussel) adhesive protein [39,229,237,238]. The chemical extraction process used does not yield pure or individual adhesive proteins [16]. Therefore, to the best of our knowledge, bioadhesives developed from marine are not commercialised yet.

Recombinant DNA technology has also been used to obtain large amounts of their components for further conventional adhesion tests and practical applications. Genetic production of fp-1, that is considered a key protein for adhesion of mussels in wet environments, has been attempted in several expression systems [216,238,239], but they have failed for several reasons [217,238,239].

The work of several researchers [216,217,239–242] concerns other mass production technologies for functional recombinant mussel adhesive developed without success. The development of novel hybrid type of mussel adhesive protein fp-151, which is easy to purify and presents significantly greater production yields, is described in [219,220]. This purified recombinant protein had comparable adhesion characteristics to recombinant Mefp-5 that is a plaque specific protein and contains the highest DOPA level (~30 mol%) among mussel adhesive proteins [220,232].

The results show efficient adhesion and good biocompatibility for various cell types including both anchorage-independent and anchorage-dependent cells, as well as good adhesion to laboratory plastic consumables, such as polypropylene (PP).

The macro-scale adhesion strength tests of recombinant fp-151 in comparison with the commercially available tissue adhesive fibrin glue, as a positive control, showed that the shear strength of fp-151 was about four times greater (~0.8 MPa) than that of fibrin glue (~0.2 MPa), when cowhide square pillars (10 mm × 10 mm) and 10 mg samples were used [16]. The development of other hybrid types of mussel adhesive protein for specific application as cell-adhesion biomaterial is reported by Hwang et al. [222].

Recently, diverse marine mussel inspired adhesives were studied to be used in different applications, mainly for prosthetic mesh fixation [243] islet transplantation at extrahepatic sites [244] and to repair ruptures of gestational fatal membrane [245].

4.2. Gecko-inspired adhesives

The ability of gecko feet to adhere to rough, smooth, vertical and inverted surfaces [202,248] has prompted the study of gecko-like morphology and their impact on the adhesive properties.

Autumn et al. [247] and Pennisi [248] show that the fibrillar arrays, which cover the bottom of gecko feet, maximize the interfacial adhesion to surfaces, mainly because the adhesive footpads are decorated with a dense array of fibrils (setae); each setae has numerous terminal

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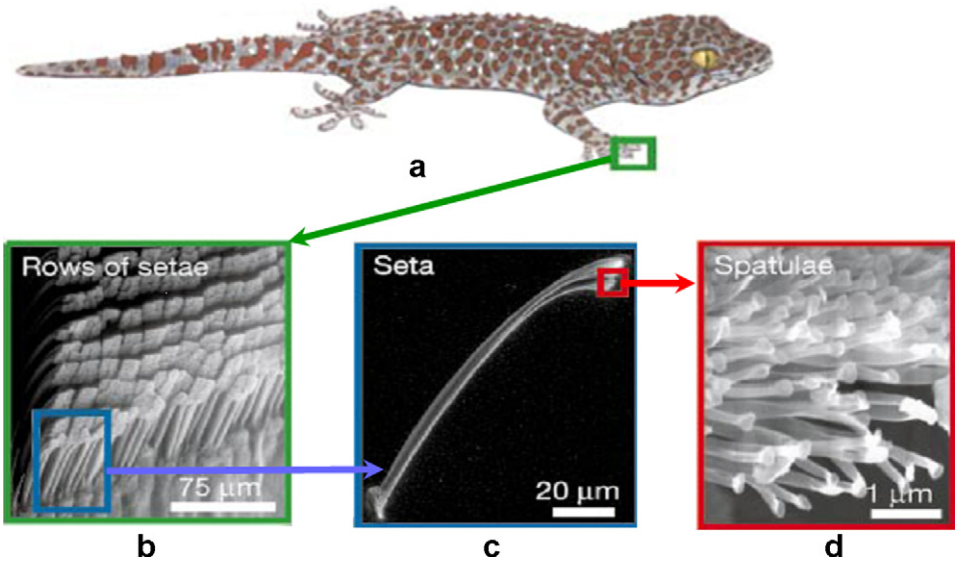

Fig. 5. Hierarchical structures of a Tokay gecko. (a) Optical image of a Tokay gecko; (b) SEM image of a setae array (*i.e.*, rows of setae from a toe); (c) SEM image of a single seta; (d) SEM image of the fine terminal branches of a seta, called spatulae or spatular pads [251].

projections (spatulae) that are 200–500 nm in length. The adhesion of these spatulae to the surfaces is controlled by the combination of van der Waals [247,249] and capillary forces [250] (Fig. 5 [251]).

Based on this knowledge, in recent years a gecko mimetic adhesive has been optimized for a wet tissue-like environment, which proved effective under water with reversible noncovalent bonding to inorganic surfaces [204].

In the study described in [200] an elastomeric, biocompatible, and biodegradable gecko-inspired tissue adhesive was developed from a biocompatible and biodegradable elastomer combined with a thin tissue-reactive biocompatible surface coating. This adhesive is based on poly(glycerol sebacate acrylate) (PGSA), a tough biodegradable elastomer with elastic and biodegradation properties, that can be tuned for specific tissue applications and can be easily doped with growth factors or drugs. Tissue adhesion was optimized by varying dimensions of the nanoscale pillars, including the ratio of tip diameter to pitch and the ratio of tip diameter to base diameter. Coating these nanomolded pillars of biodegradable elastomers with a thin layer of oxidized dextran significantly increased the interfacial adhesion strength on porcine intestine tissue *in vitro* and in the rat abdominal subfascial *in vivo* environment. The authors developed a biocompatible tissue adhesive with promising covalent cross-linking to wet tissue, obtained through combined morphology and chemistry effects, that may have application in medical therapies ranging from suture/staple replacements/supplements; waterproof sealants for hollow organ anatomoses; mesh grafts to treat hernias, ulcers, and burns; and haemostatic wound dressings [200]. The work described in [252] describes tape-based tissue adhesive that shows appropriate to prevent air leaks in lung resection procedures, haemostatic wound dressing and mesh grafts to treat ulcers, hernias and burns among other applications.

5. Choosing the tissue adhesive

Despite many studies and several products marketed in the area of surgical adhesives, to date no single type and form of tissue adhesive fills all medical and surgical needs.

This is due to the fact that it is not easy to develop a unique adhesive that presents biocompatibility, biodegradability, sustainable haemostatic action, strong adhesion to moist tissues, non-interference of the healing process, ease of use, appropriate long shelf-life, good cosmetic results, inexpensive and mainly that is suitable for all kinds of living tissue, that present different intrinsic characteristics.

Concerning the different types and forms of commercial and in development tissue adhesives, we can conclude that, in general, the fibrin-based adhesives are more effective in most of the wide range of applications than others sealant materials; although they are expensive and potential virus transmitters. In the dry form, the fibrin sealant is, so far, the best product to control severe haemorrhage. Despite the bioadhesives based on collagen and gelatine, have also presented good performance as haemostats, they do not succeed in stopping severe bleeding. Chitosan based adhesives are also widely used in haemostasis, presented different properties depending on molecular weights and deacetylation degree.

Contrarily to natural tissue adhesives, that activated the blood coagulation, the haemostatic properties of the synthetic ones result from the physical barrier formed during their polymerization. The cyanoacrylate based adhesives, mainly due to their cosmetic results and toxicity when in contact with noncutaneous surfaces, are specially recommended to skin wound closures. Polymeric hydrogels are effective as a fluid barrier and as a haemostatic agent mainly in sealing suture line bleeding.

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Table 1
Applications of some of the main adhesives types and brief description of the tested products.

Adhesive type	Surgical functions	Products tested	References
Natural or biological			
Fibrin	– Haemorrhage control, wound closure and tissue anastomoses, reduce ecchymoses and hematoma formation, sealing and repair leaks, treat lacerations and tistulas, control burn bleeding after debridement and fixation of bone fractures	– Fibrin liquid sealants (Hemaseel APR, Tisseel VH, Crosseal®) and foam, dry sheet, power with different fibrinogen and thrombin composition	[19,20,23–31,48]
Collagen	– Haemostasis for general surgery (*e.g.* cardiovascular, hepatic and orthopaedic procedures) retroperitoneal injuries	– Bovine microfibrillar collagen, bovine thrombin, suspension mixed with an equal volume of plasma during application (CoStasis®)	[69–71,68]
	– Haemostasis in vascular surgery	– Bovine collagen particle–bovine thrombin (FloSeal)	[76]
	– Haemostasis in adenoidectomy spine surgery	– Bovine collagen particle–bovine thrombin suspension (Proceed®)	[77]
Gelatin	– Haemostasis in a variety of surgical procedures and anatomical sites (*e.g.* femoral bypass)	– Gelatin particle–thrombin suspension (FloSeal®)	[86,87]
	– General vascular and pulmonary procedures	– Gelatin–resorcinol–formaldeyde –glutaraldehyde	[115–117]
	– Repair of aortic dissection	– Bovine albumin–glutaraldehyde glue (BioGlue®)	[115,116]
Polysaccharides			
Chitosan	– Haemostasis in lingual bleeding	– Chitosan	[125]
	– Nerve anastomosis	– Chitosan and crosslinker (indocyanine green or genipin)	[126,127]
	– Haemostasis in carotid artery, seal lung air, skin wound closure	– Photo-crosslinkable chitosan with azide and lactose moieties	[38,128]
	– Sealing materials puncture sites	– Microcrystalline (MCCh) chitosan gel	[129]
	– Closure of scleral lacerations	– Chitosan film without laser welding	[130]
Alginate	– Binding the tissues, even after exposure to an aqueous environment	– Alginate–calcium ions and phloroglucionol	[8]
Chondroitin sulphate	– Bind both the native cartilage tissue and a biomaterial implant	– Chondroitin sulphate functionalized with aldehyde and methacrylate groups	[8,134]
	– Secure flaps in posterior lamellar keratoplasty	– Chondroitin-sulphate–aldehyde	[8,135]
Synthetic and semi-synthetic			
Cyanoacrylates	– Superficial skin wound closure	– Liquid cyanoacrylates (Dermabond® and Liquidband®)	[142–146,160]
	– Cosmetic surgery, skin graft fixation, close small cuts or reapproximate lacerations	– 2-Octyl cyanoacrylate (Dermabond®)	[13,149,151–153]
	– Endoscopic, laparoscopic, traditional surgery and interventional radiology procedures	– Modified n-butyl-2-cyanoacrylate (Glubran2)	[7]
Polymeric hydrogels	– Inhibiting suture line bleeding	– PEG sealants: tetra-succinimidyl and tetra-thiol-derivatized PEG (CoSeal®)	[165–168]
	– Gynecologic and colorectal procedures (*e.g.* closure of ileostomy)	– PEG sealants: tetra-succinimidyl and amine PEG (SprayGel®)	[169,170]
	– Incisional cerebrospinal fluid leak after posterior fossa surgery, retina reattachment, nerve sciatic anastomosis, vascular closure	– PEG sealants: tetra-succinimidyl PEG and tri-lysine amine (DuraSeal™)	[171–173]
	– Sealing of fluid leaks	– PEG sealants: polyester polyol acrylates and benzophenone	[174]
	– Sealing of pulmonary air leak, haemostasis in anastomotic bleeding wound closure	– Poly(ethylene glycol)-co-trimethylene carbonate-co-lactide (Mr 20,000) with acrylated end groups/eosin Y (FocalSeal L®)	[162–164]
	– Sealing of pulmonary air leakage; acute aortic dissection	– Poly(ethylene glycol)-co-poly(a-hydroxy acid) diacrylate macromers/2,2-dimethoxy-2-phenylacetophenon (AdvaSeal®)	[175,176]
	– Sealing in ophthalmic, cranial, spine and hernia application	– Adherus™ surgical sealant	[177]
Dendrimers	– Corneal wound repair	– Several dendrimers submitted to a photocrosslinking reaction and several dendrimers coupled together by a peptideligation reaction	[179]
	– Corneal cataract incisions	– Two component system formed by a dendritic polymer synthesised from the amino acids lysine and cysteine and a linear polymer–poly(ethylene glycol)–butyric dialdehyde	[180]

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Table 1 (*Continued*)

Adhesive type	Surgical functions	Products tested	References
Polyurethane	– Bone fixation, sealing of vascular graft, haemostasis in several surgery procedures	– Polyurethane	[182,185,186]
	– Preventing the seroma formation in abdominoplasty	– A lysine derived sprayable urethane adhesive (TissuGlu®)	[187]
Biomimetic adhesives			
Marine mussel extract	– Repair of gestational fatal membrane ruptures	– Catechol functionalized PEG (cPEG) whose molecules crosslink into a hydrogel after addition of sodium periodate	[245]
	– Islet transplantation at extrahepatic sites	– cPEG adhesive	[244]
	– Prosthetic mesh fixation	– Amphiphilic block copolymers constructed from PEG and polycaprolactone modified with 2 DOPA derivatives and with dopamine and DOA	[243]
Gecko inspired	– Sealing wounds and for suture and staple replacement.	– Poly(glycerol sebacate acrylate) (PGSA) presented nanomolded pillars coated with a thin layer of oxidized dextran	[200]
	– Suture/staple replacement/supplements, water proof sealants for hollow organ anastomoses, air tight seals to prevent air leaks in lung resection procedures, haemostatic wound dressing and mesh grafts to treat ulcers, hernias and burns	– Tape-based tissue adhesive	[252]

Adapted from [8].

Although not yet in the market, dendrimers based adhesives have been considered a suitable product to eye leaking prevention and corneal application. Urethane based adhesives are widely used in medical devices and can also be successfully applied in cosmetic surgery to prevent fluids accumulation.

Concerning the biomimetic adhesives, although still being studied, we believe that in a near future protein engineering and DNA gene technology have potential to produce new tissue adhesives with special properties.

The decision of which adhesive to use in a given situation can be much easier when the properties of the adhesives are known. Table 1 presents, in detail, the recommended applications for the main adhesives types, as well as the tested products.

Due to several contradictions found in the literature about the effects of surgical adhesives [253–258], their application in practice is sometimes more complex than it seems at first sight. Gilly et al. [259] show that when surgical adhesives are used correctly they are very powerful tool. However, their study also suggests that using them improperly makes the problem worse, because if the adhesive polymerizes before the tissue is approximated, it serves as a crosslinked barrier to wound healing.

As happens with other technologies, the proper use of tissue adhesives requires the expertise of surgeons with experience. The efficacy of an agent will improve as surgeons learn to maximize the benefit of its properties and to provide maximum support; they must be used correctly based on proven experience in the right patients [4].

6. Conclusions and forecast

Nowadays, tissue adhesives provide great adjunctive surgical support, and it is expected that they will continue to expand as we learn more about their biodegradation, safety and scope of applicability.

The key factor for the successful use of tissue adhesives is that their specific indications/limitations must be understood by the surgeon, which will allow him to choose the best adhesive. The tissue adhesives serve to augment but do not replace techniques that surgeons have used for years [4].

We can conclude that, in general, the attachment of adhesives to living tissues has not been studied so far in sufficient detail. Since the existing models are not sufficient, the strength of the adhesive joint should be determined experimentally, according to standard tests, on living tissues under conditions that are close to a real surgical situation.

It appears impossible to develop an adhesive suitable for all kinds of living tissue because they present different functions, physico-chemical characteristics, rate of regenerative processes, type and degree of saturation with enzymes, *etc*. Therefore, it will be necessary in the near future to synthesise and investigate several types of medical adhesives focusing on the requirements of the final application.

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