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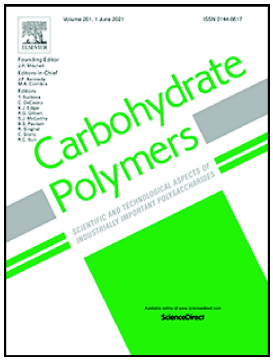

Biomedical engineering of polysaccharide-based tissue adhesives: Recent advances and future direction

Hanieh Shokrani, Amirhossein Shokrani, Farzad Seidi, Muhammad Tajammal Munir, Navid Rabiee, Yousef Fatahi, Justyna Kucinska-Lipka, Mohammad Reza Saeb

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Biomedical Engineering of Polysaccharide-based Tissue Adhesives: Recent Advances and Future Direction

Hanieh Shokrani[1,2], Amirhossein Shokrani[3], Farzad Seidi[1,*], Muhammad Tajammal Munir[4], Navid Rabiee[5], Yousef Fatahi[6,7], Justyna Kucinska-Lipka[8,*], Mohammad Reza Saeb[8,*]

[1] *Jiangsu Co–Innovation Center for Efficient Processing and Utilization of Forest Resources and International Innovation Center for Forest Chemicals and Materials, Nanjing Forestry University, 210037 Nanjing, China*

[2] *Department of Chemical Engineering, Sharif University of Technology, Tehran, Iran*

[3] *Department of Mechanical Engineering, Sharif University of Technology, Tehran, Iran*

[4] *College of Engineering and Technology, American University of the Middle East, Kuwait*

[5] *School of Engineering, Macquarie University, Sydney, New South Wales, 2109, Australia*

[6] *Department of Pharmaceutical Nanotechnology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

[7] *Nanotechnology Research Centre, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

[8] *Department of Polymer Technology, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland*

*Corresponding authors: F.S. (f_seidi@njfu.edu.cn), J.K-L. (juskucin@pg.edu.pl) & M.R.S. (mrsaeb2008@gmail.com)

Abstract

Tissue adhesives have been widely used for preventing wound leaks, sever bleeding, as well as for enhancing drug delivery and biosensing. However, only a few among suggested platforms cover the circumstances required for high-adhesion strength and biocompatibility, without toxicity. Antibacterial properties, controllable degradation, encapsulation capacity, detectability by image-guided procedures and affordable price are also centered to on-demand tissue adhesives. Herein we overview the history of tissue adhesives, different types of polysaccharide-based tissue adhesives, their mechanism of gluing, and different applications of polysaccharide-based tissue adhesives. We also highlight the latest progresses in engineering of tissue adhesives followed by existing challenges in fabrication processes. We argue that future studies have to place focus on a holistic understanding of biomaterials

and tissue surface properties, proper fabrication procedures, and development of magnetic and conductive responsive adhesives in order to bridge the huge gap between the present studies for clinical implementation.

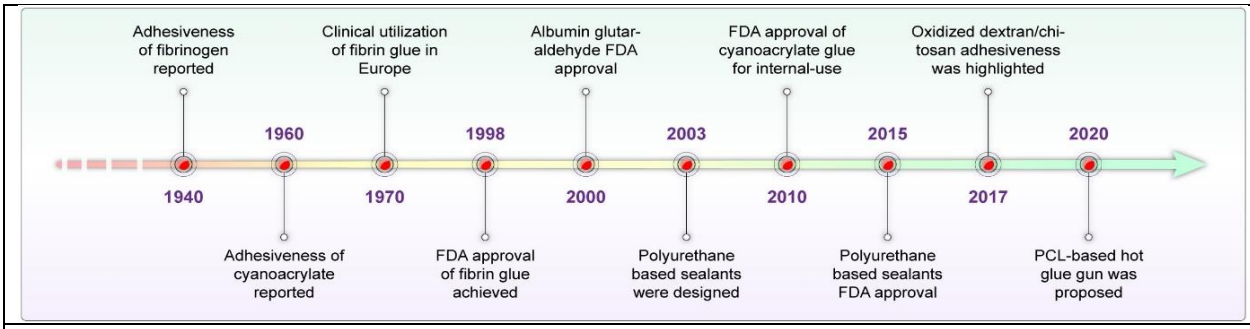
Keywords: Tissue adhesives; polysaccharides; bio-adhesives; bio-glue; biomedical engineering

1. Introduction

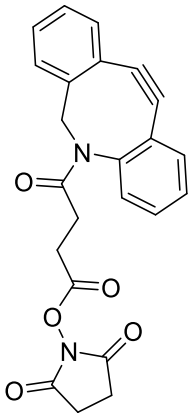
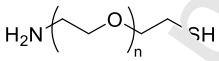
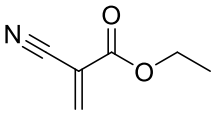
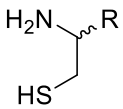
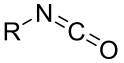
Millions of surgical operations have been carried out around the world and in almost all cases, surgeons have been willing to close the induced wounds preventing from the leaks, severe bleeding, preparing antibacterial barriers, as well as enhancing the healing process. Classical techniques consist clips and staples, which have been forecasted to own a global market value of US$15 billion annually by 2024 (Shagan et al., 2020; Taboada et al., 2020). Tissue-adhesives as hemostasis agents, sealants, delivery platforms as well as implantable biomedical devices have been widely under investigation in different areas of biomedical engineering, especially during the last three decades (Buchaim et al., 2019; Nam & Mooney, 2021; Shokri et al., 2022; Zhong et al., 2021). Correspondingly, **Table 1** (top) depicts the history of tissue adhesives, since 1940 till now. Despite such advancements, the applications of most of the existing adhesives have been challenging because they might cause further damages to the tissue and increase the level of potent inflammation and infection. Moreover, these systems have been known to be painful and could leave some unattractive scars on the surface of the patients' body.

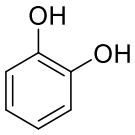
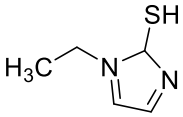
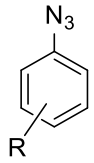
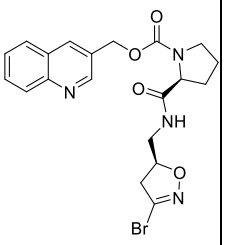
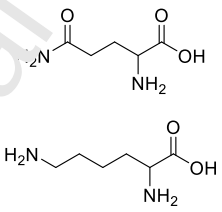
Table 1. (Top) A glimpse at the history and progression of tissue adhesives from early 1940 up to present (Balakrishnan et al., 2017; Chao & Torchiana, 2003; Coover, 1959; Ennker et al., 1994; Shagan et al., 2020; Spotnitz, 2014; Young & Medawar, 1940); and (bottom) functional groups attached to tissue surface and tissue adhesive biomaterials.

History of tissue adhesives progression (Balakrishnan et al., 2017; Chao & Torchiana, 2003; Coover, 1959; Ennker et al., 1994; Shagan et al., 2020; Spotnitz, 2014; Young & Medawar, 1940)



Different functional groups on the tissue surface and tissue adhesive biomaterials

Functional groups in adhesives	Chemical Structure	Functional groups on tissues	Chemical Structure	Pros and Cons	Refs.
NHS esters		Amine Thiol		Pros: High reactivity and spontaneous cross-linking Cons: Susceptibility to hydrolysis, and long-term storage requires a dry condition	(Bu et al., 2019)
Cyanoacrylates		Amine		Pros: Rapid polymerization process Cons: Toxicity issues for monomers, degradation products, including cyanoacetate and formaldehyde, and exothermal reaction	(Korde & Kandasubramanian, 2018; Leiro et al., 2018)
Aldehydes		Amine Thiol 1,2 aminothiol		Pros: High reactivity and spontaneous cross-linking Cons: Toxicity issues for glutaraldehyde and formaldehyde	(Zhang et al., 2018)
Isocyanates		Amine		Pros: High reactivity and spontaneous cross-linking	(Spring, 2018)

				Cons: Possible side reactions compromise the reaction with amines on tissues	
Catechol		Amine Thiol Imidazole		Pros: Versatile chemistry with a multitude of functionalities Cons: Oxidization process required to activate catechol	(Hofman et al., 2018; Thi et al., 2019)
Aryl azides		Amine		Pros: High reactivity and spontaneous cross-linking Cons: Possible side reactions compromise the reaction with tissue amines	(Ishihara et al., 2006)
Transglutaminases		Glutamine and lysine		Pros: Biocompatibility Cons: Slow reaction process	(McDermott et al., 2004)

Recently, some Food and Drug Administration (FDA) approved glues have entered the clinics. In a general view, we can categorize them into the internal and external ones on the ground of their applications. External bio-adhesives are usually utilized in topical medications, whereas the internal ones are generally used in intracorporal conditions (direct contact with body fluid and organs) (Fan et al., 2016; R. Li et al., 2022; Yuk et al., 2019). They can bind to the tissue surface not only in highly dynamic tissues, but also under wet conditions. They also pose antimicrobial activity, which is a requirement for efficient healing of tissue. However, most of them suffer from limited possibility of remote controlling over adhesion, low adhesion strength, and to some extent from the relatively high level of toxicity.

Considering all the above-mentioned, plenty of investigations are underway in order to find some nontoxic (nontoxic byproducts) and biodegradable adhesives, potent to strongly bind to the tissue in the wet and dynamic environment in addition to antibacterial properties. Different categories of glues, powders, nanoparticles, as well as hydrogels are suggested by different groups of scientists (Lu et al., 2020; Pan et al., 2020; Yazdi et al., 2021). In order to increase the biocompatibility of bio adhesives, researchers make good use of inspiration from the nature. To the best of our knowledge, polysaccharide-based hydrogels (especially chitosan and dextran) are top class of adhesive biomaterials, due to their optical properties, hemostasis activities, biocompatibility as well as inherent antimicrobial features (Pang et al., 2020; Sanandiya et al., 2019; Seidi et al., 2021; Xu et al., 2018). These polysaccharide-based systems can provide a warm, moist and self-healing microenvironment with desired natural biological properties, providing support for strong binding to the targeted tissue, particularly when combined with the other biomaterials or nano-materials (Shamekhi et al., 2018; Yazdi et al., 2020).

In this review article, we comprehensively overviewed the chemistry of tissue adhesives, along with mechanisms underlying the adhesiveness of polysaccharide-based adhesives, and applications of polysaccharide-based adhesives, i.e., wound dressing, hemostasis agent adhesives, antibacterial closures, drug delivery adhesives, cartilage treatment applications of adhesives, as well as implantable adhesives. The most recent or most innovative developments of polysaccharide-based adhesives are particularly highlighted. Although there exist some fantastic reviews about synthetic bio-adhesives (Nam & Mooney, 2021), methods of bio-adhesives preparation (Ryu et al., 2015), primitive tissue adhesives (Bhagat & Becker, 2017), their mechanism of action (Sánchez-Fernández et al., 2019; Zhu et al., 2018), their design strategies (Bao et al., 2020), and their origins (Bal-Ozturk et al., 2021), there is no article summarizing the most state of the art platforms and applications, especially polysaccharide-based ones, the most recent improvements, and the existing challenges in addition to the outstanding mechanisms. The results indicate that the main requirement of successful bio-adhesive development is pursuing interdisciplinary studies, which integrate the biological, chemical and mechanical interactions of tissue adhesives into a versatile bio-adhesive for a target tissue, where physicochemical characteristics of tissue adhesives are playing the main role. All the biological limitations such as the host immune response, bacterial activities and local environment characteristics should also be taken into account (Balkenende et al., 2019; Shokri et al., 2021). Several researchers addressed tissue specific

adhesives by consideration of the chemistry and biology of the targeted tissue in terms of physiological responses (Nam & Mooney, 2021).

2. Clinical and commercial glues

There are only a few bio-glues that reached the clinics despite considerable attempts made in academia, mainly because of some inevitable weaknesses of bio-glues at the current state of the knowledge. To name but a few, we can address cyanoacrylate glue, 2-octyl cyanoacrylate (Dermabond), and fibrin sealants. Cyanoacrylate glue is a clinical glue repetitively, which has been used frequently by dentists. It owns great wet adhesion, but produces toxic byproducts (like formaldehyde) after degradation. Likewise, Dermabond as a well-known clinical skin closure and fibrin sealants was used in cartilage repair surgeries suffer from uncontrollable swelling ratio and low adhesion when surrounded by blood components (Bhagat & Becker, 2017; Korde & Kandasubramanian, 2018; Taghizadeh et al., 2022). Albumin-glutaraldehyde is another example, which lacks bioactivity and induces undesired inflammatory reactions. In addition to the mentioned products, gecko- or worm-inspired glues are a class of nature-inspired tissue adhesives, which enjoy from sufficient adhesion to the wet environment, but their strength is far beyond the standard defined for plenty of wound closing applications (Pourjavadi et al., 2020; Romano et al., 2016). Surgiflo and Floseal are two commercial bio-glues. Surgiflo is reported as a gel based hemostatic adhesive that can be excreted from body after 6 weeks (this minimizes the body's immunological responses). However, its adhesion strength in humid environments is not desirable (Hao et al., 2022). Noteworthily, Floseal provides a very strong tissue adhesion in a vascular surgery. However, its appropriate degradation pattern is questioned (Binnetoğlu et al., 2022). Similarly, China Perfectseal 2-Octyle glue owns the same limitation. It is a liquid-based adhesives that initiates the polymerization after being exposed to the body moisture. Importantly, the chemical polymerization process undermines its degradation capacity. Even if China Perfectseal could decompose to its monomers (n-butyl cyanoacrylate), its toxicity concerns are remained (Chevallier et al., 2021). Bluestar silicone is another commercial product usable as wound and scar care, transdermal patches and wearable devices. According to the reliable reports, it owns acceptable adhesion strength as well as exceptionally high tear strength and elongation, in addition to being very flexible and durable. Since this product is utilized for external applications, its degradation issues are not challenging. However, further studies need to be

conducted to investigate the possibility of internal uses in parallel with the potential loading capability (Yildiz et al., 2022).

3. Chemistry of polysaccharide-based tissue adhesives

The wet adhesion of catechol group ($C_6H_4(OH)_2$) is clear and well-known. Typically, catechol group can enter Michael reaction with thiol (R-SH) and amine (R- NH_2) groups, which are abundantly present in the surface of tissue. This is the reason why biopolymers (natural or synthetic) conjugated with catechol groups are candidate tissue adhesives (J. Kim et al., 2020; Zheng et al., 2020). In this regard, catechol-modified biomaterials have been extensively studied. Additionally, scientists utilize some specific biomaterials like poly-L-lysine (PLL) as bridging molecules in order to increase the interfacial adhesion between the catechol groups and cells or tissues. For instance, a group of scientists chose hyaluronic acid (HA) as a platform for the functionalization with catechol groups where PLL was used as a bridging agent. Their results indicated that HA could sufficiently enhance the biocompatibility, and the whole scaffold was elegant in adhesion to the porcine skin. They also demonstrated that the resulting scaffold could increase the host tissue integration via angiogenesis enhancement (M. H. Kim et al., 2020; Shokrani et al., 2022; Singh et al., 2021; Xi et al., 2021). However, since the surface of tissue has a net negative charge in physiological conditions, HA with the same negative charge could not satisfactorily interact with the tissue. To overcome this limitation, scientists have proposed mussel-inspired chemistry (Bagheri et al., 2020; Pei et al., 2020; Wang et al., 2021). This approach works via the oxidation of dopamine conjugated macromolecules to adhesive quinonic groups, which can be facilitated using enzymatic oxidation (An et al., 2018; Feng et al., 2016; Granskog et al., 2015; Zarrintaj et al., 2018). Enzymatic crosslinking is another option for crosslinking of polymer catechol conjunctions in the presence of horseradish peroxidase (HRP) and H_2O_2. However, there are several variables in these reactions, such as biopolymer concentration, oxidizing enzyme, the design of biopolymer, catechol substitution degree, HRP concentration as well as H_2O_2, which may change the final adhesiveness (M. H. Kim et al., 2020; Snider et al., 2021). Furthermore, cytotoxicity and pH dependency of such reactions can limit their efficacy (Ryu et al., 2015). On the other hand, increasing the amount of sodium peroxide in reaction with aldehyde sodium alginate can bring about higher oxidation degree leading to formation of more aldehyde groups. The excess aldehydes react with the amine groups of

tissue (R- NH_2), thereby a higher adhesiveness may be induced and correspondingly a more stable crosslinking network may cause a sort of slower degradation pattern (Wu et al., 2017). Addition of polydopamine (dopamine possessing catechol group) nanoparticles is a well-known way to improve the adhesion characteristics of polysaccharides (Narayanan et al., 2020). Panday's results suggested that the addition of polydopamine nanoparticles (with a controlled size of 200 nm) to HA hydrogel can significantly increase the adhesion strength as a tissue glue (**Fig. 1**) (Pandey et al., 2021). However, no antibacterial activity was detected for this platform. Notably, photo-crosslinkable thiolated chitosan adhesive hydrogel is another choice, which speedily forms an *in-situ* hydrogel after exposure to the UV lamp (Frost et al., 2016; Zeng et al., 2016). However, it is not easily operable. Notably, *in-situ* formed hydrogels reveal the highest ability to adapt to the structural shape of the tears and wounds and appropriately stick to the crack wall. However, they lack required level of mechanical strength. For example, in cardiac bleeding, where the tissue strongly moves, the mechanical properties are underscored (M. Kim et al., 2020). **Table 1** (bottom) summarizes different functional groups on the tissue surface and tissue adhesive biomaterials.

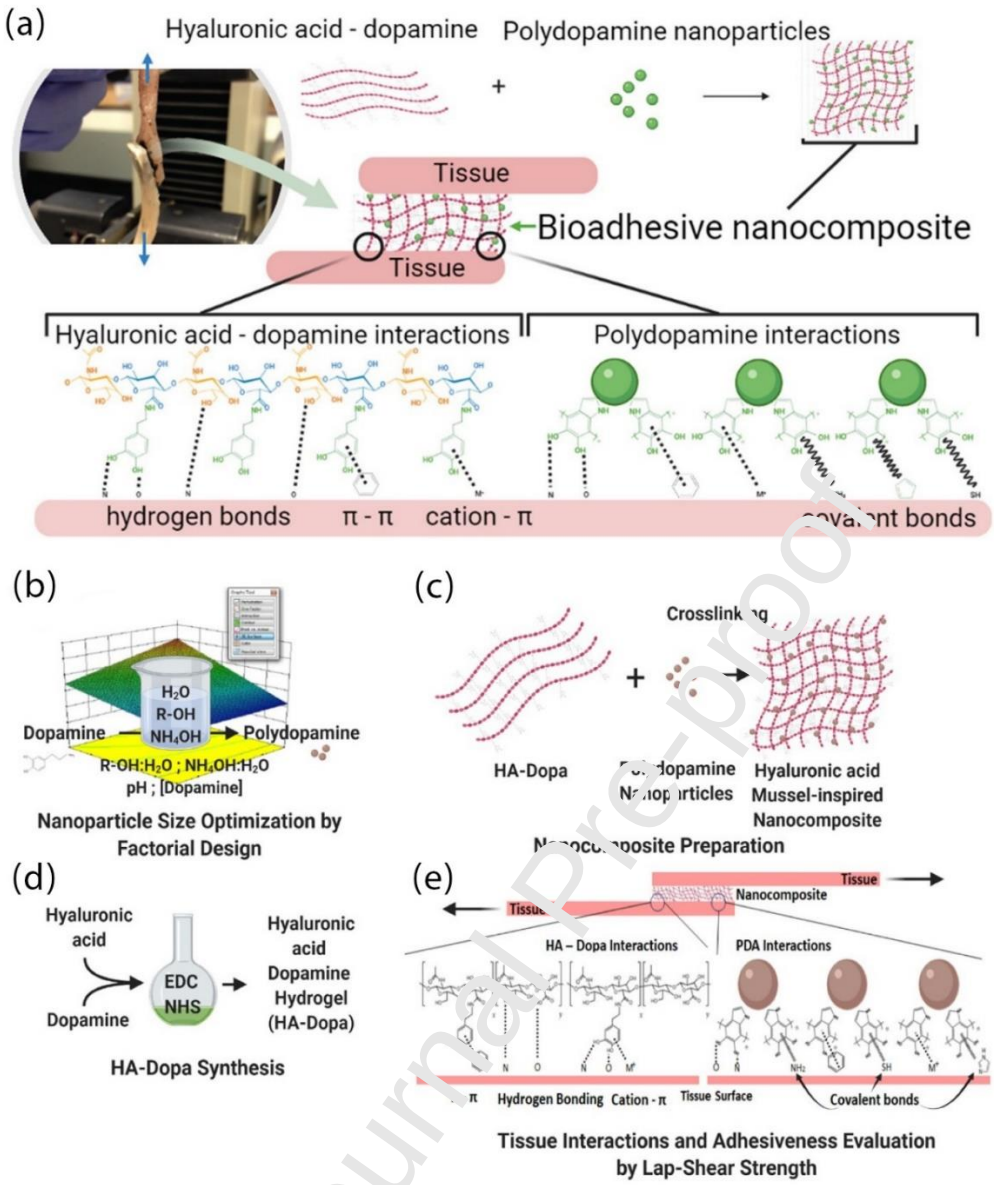


Fig. 1. (a) A general illustration of a bio-adhesive nanocomposite with polysaccharide base and possible interactions. **(b)** Dopamine nanoparticle size optimization process. **(c)** By using carbodiimide chemistry, the dopamine can be conjugated on the surface of hyaluronic acid. **(d)** Crosslinking with sodium periodate assists to form an adhesive nanocomposite. **(e)** The possible interactions between adhesive and tissue surface (Pandey et al., 2021).

4. Gluing mechanisms

The adhesion of a tissue adhesive depends on the interface properties, which itself can be divided into two components, adhesion layer and adhesive matrix. Adhesion layer is the layer which directly contacts with the tissue surface, whereas the adhesive matrix is the bulk network responsible for a series of physical properties such as swelling ratio, stiffness, as

well as energy dissipation (**Fig. 2a**). The direct adhesion can be driven via different mechanisms. The most outstanding adhesion mechanisms are chemical conjunctions, biological and biochemical coupling, electrostatic bonding, diffusion and physical entanglement (Aziz et al., 2015; Lih et al., 2012; Simson et al., 2013; Yang et al., 2020). The chemical conjunctions are also called covalent bonding, while the physical ones are usually called noncovalent interaction. The key function of all the mentioned mechanisms is to form firm connections with the tissue surface under physiological conditions, which usually is involved with blood or body fluid (Nam & Mooney, 2021; Villou et al., 2020). Additionally, the competition between blood (or body fluid) and tissue surface to interact with the functional groups of adhesive should also be taken into consideration (Yang et al., 2020; Yuk et al., 2019). Due to the fact that a real and practical adhesion is far more complicated than what theories predict, the gluing mechanisms typically take into account a combination of different types of interactions with one or two ones dominantly controlling the whole phenomenon (Bao et al., 2020; Hyon et al., 2014; Seidi et al., 2018). However, designing efficient tissue adhesive considering the main mechanism of gluing highly depends on the mechanical properties of tissue, which is often overlooked. For instance, the elastic modulus and stiffness of tissue adhesives should match those of tissue to avoid deformation when the body's normal stresses are applied (Guimarães et al., 2020).

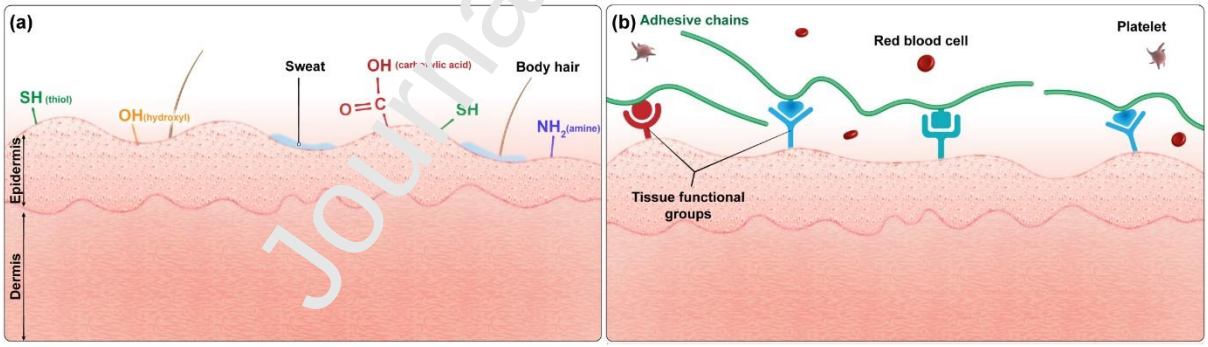


Fig. 2. (a) A schematic illustration of tissue functional groups, which directly attach to the adhesive matrix; **(b)** A schematic illustration of chemical conjunction between tissue functional groups (hydroxyl (OH),thiol (R-SH), amine (R- NH_2), carboxylic acid (C(=O)OH), lysine ($C_6H_{14}N_2O_2$) and the reactive groups of adhesives (catechol ($C_6H_4(OH)_2$), aryl azide (N_3) and cyanoacrylates (NC O_2CH_3)).

4.1. Chemical conjunctions

During the early stages of studying tissue adhesives, chemical conjunctions where usually considered as the dominant mechanism of gluing (Blacklow et al., 2019; Kim et al., 2018).

The chemical conjunctions were usually reported between the chemical functional groups of bio-adhesives and the biological surface. However, some other types of chemical conjunctions were reported as well (**Fig. 2b**). For instance, the chemical reactions between amino groups and carbonyl groups, the chemical reactions between the functional groups of tissue adhesives with the crosslinking agents, the enzyme-mediated reactions, as well as free-radical polymerizations (photo-initiated polymerization and thermo-initiated polymerization) were reported (Zhu et al., 2018). Interestingly, in addition to supporting adhesion, the chemical covalent bonds contribute to the formation of adhesively integrated matrix. Indeed, chemical conjugations prevent the disintegration of the bio-adhesives themselves (García & Smulders, 2016).

As mentioned earlier, one way to reinforce the chemical conjunctions in polysaccharides is to introduce aldehyde groups onto polysaccharide molecules using oxidation (Liu et al., 2021). Oxidation can take place after addition of sodium periodate. For instance, Hyon et al. introduced aldehyde functional group onto dextran, which interacted with amino groups on the tissue surface. Moreover, the existence of epsilon-PL (ε-PL), an oligomer of L-lysine within their matrix brought about additional amino groups to support the cohesiveness (Aziz et al., 2015; Hyon et al., 2014). As an example of enzyme-mediated polysaccharide-based bio-adhesive, Li et al. provided a chitosan-polyethylene glycol amine (PEG)-tyramine (CPT) hydrogel in which horseradish peroxidase and tyramines tied with each other through enzymatic oxidation (Lih et al., 2012). Elsewhere, Strehin et al. prepared a N-hydroxysuccinimide (NHS)-grafted chondroitin sulfate (CS-NHS) and six-arm PEG (PEG-$(NH_2)_6$) as a crosslinker. The cohesive strength was supported by the covalent amid bonds such that the NHS groups could effectively connect to the tissue surface to boost adhesive strength (**Fig. 3**) (Simsek et al., 2013; Zarrintaj et al., 2019; Zhu et al., 2018).

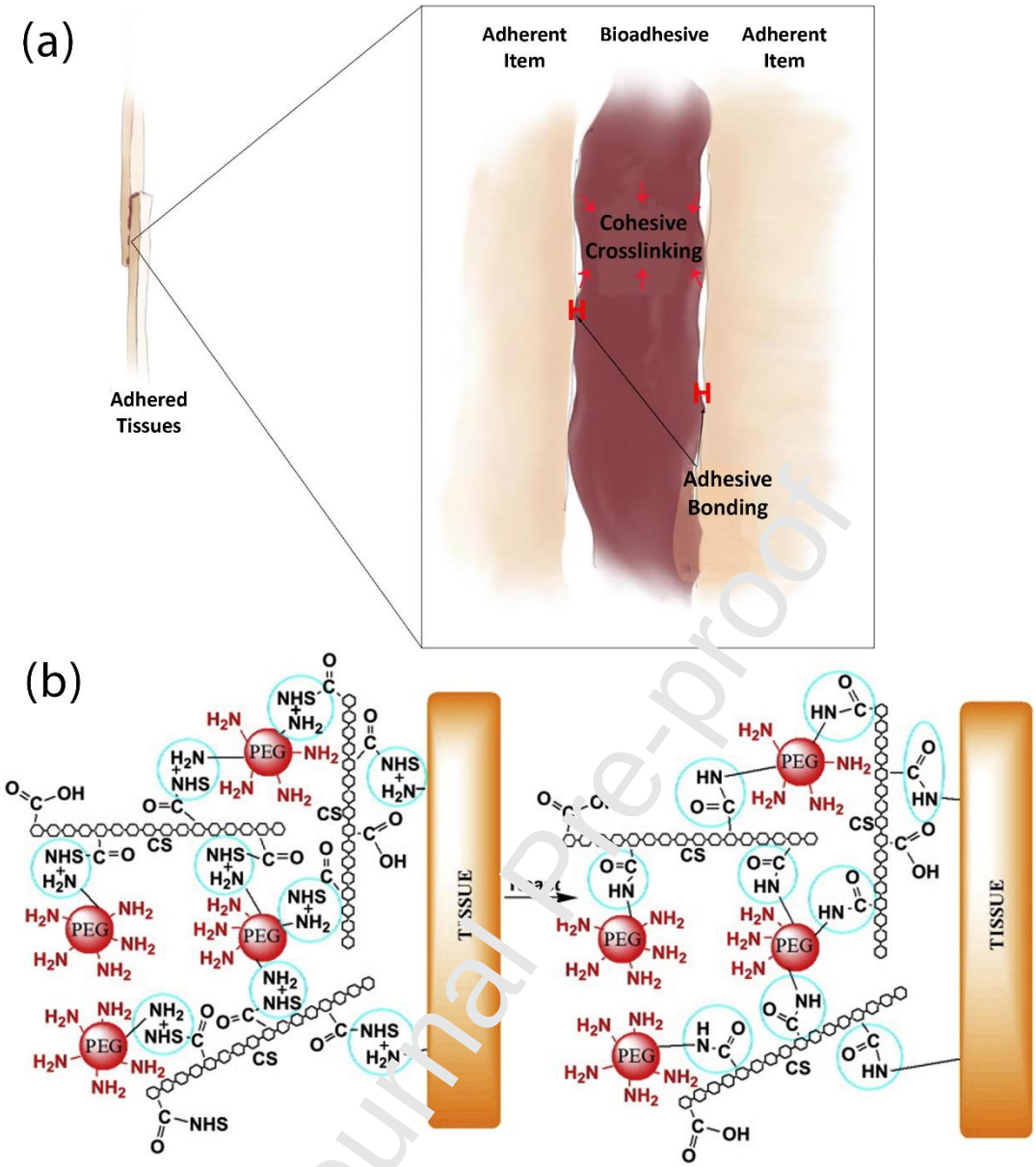


Fig. 3. (a) A general illustration of adhesives and cohesive forces (Cohesive crosslinking is within adhesive's thickness and adhesive bonding is between adhesive-adherent item interfaces); **(b)** The possible interaction mechanisms between chitosan, polyethylene glycol and N-hydroxysuccinimide (Strehin et al., 2010; Zhu et al., 2018).

4.2. Biological couplings

There are plenty of biomolecule-biomolecule interactions during metabolism of organisms, all of which can form bonds, known as possible biological mechanisms of gluing (**Fig. 4a**). Due to the fact that these bonds are originated from natural body metabolism, they are intensively biocompatible. They also do not require any specific condition (especial temperature or pH) and can occur under completely mild condition. Among common

examples of adhesion with biological mechanism are fibrinogen-thrombin interaction that happens during clotting cascade, biotin-avidin, and disulfate bonds with proteins (Gillman et al., 2020; Zhu et al., 2018). The biological coupling usually occurs at the same time as all other mechanisms because it is a part of the metabolic process. However, they are never enough where there is a serious demand for a bio-adhesive such as an extreme bleeding. Hence, more of effective mechanisms must be considered when designing an efficient adhesive (Wang et al., 2022).

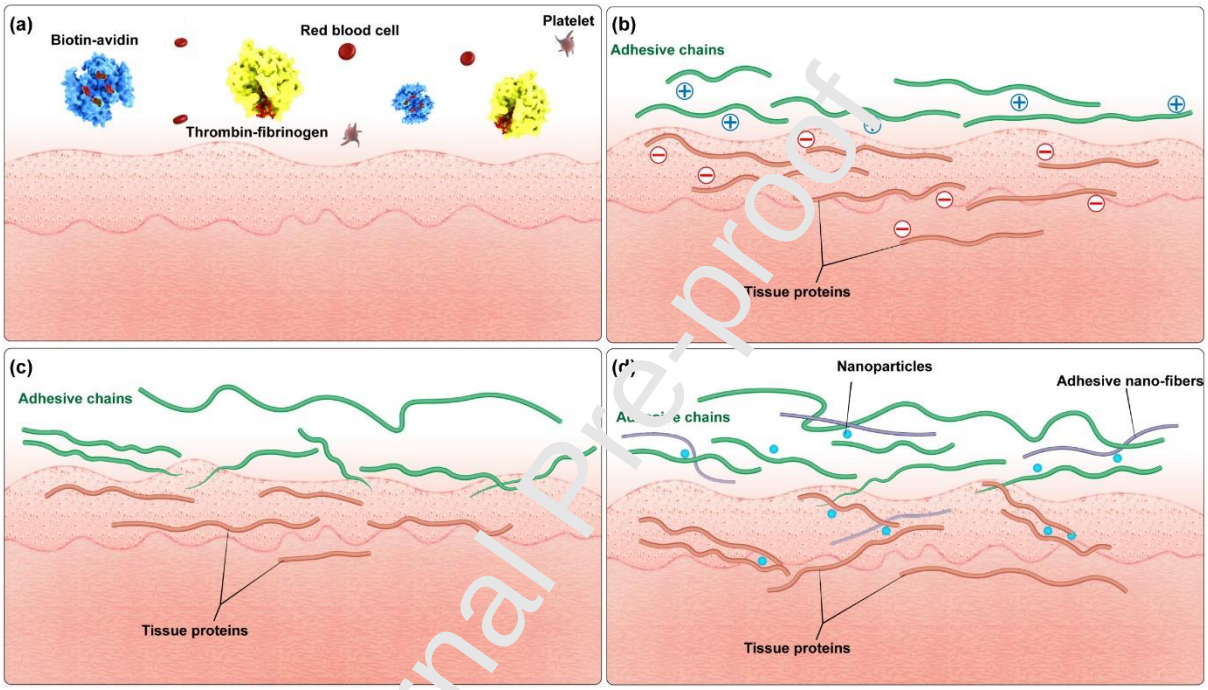


Fig. 4. (a) A schematic illustration of biological interactions between the biomolecules such as biotin-avidin and thrombin-fibrinogen; **(b)** A schematic illustration of electrostatic bonding between the tissue adhesive and the tissue glycoproteins (such as chitosan and mucin); **(c)** A schematic illustration of diffusion of adhesive's chains into tissue surface (it is strongly dependent on the molecular weight of chains, chains' length as well as tissue surface temperature); **(d)** A schematic illustration of physical entanglements between the adhesive (chains, nanofibers and nanoparticles) and tissue components.

4.3 Electrostatic bonding

Electrostatic bonding happens because of the existence of oppositely charged molecules present on the tissue surface and the adhesives (**Fig. 4b**). This oppositely charged components cause a double layer of electrons leading to dispersive force induction and electrostatic bonds. Alginate-calcium and starch-calcium are two important examples of electrostatic bonding of polysaccharide-based tissue adhesives (Gao et al., 2019; Lin et al.,

2019). Although this kind of bond formation does not play a key role in adhesion strength, reports indicate that it is determinative in muco-adhesion, which is very useful in drug delivery platforms (Yang et al., 2020).

4.4. Diffusion

When the adhesive and adherent surface are compatible enough, the interdiffusion of chains across the interface of adhesive occurs that can affect the adhesion strength (**Fig. 4c**). An important condition in this mechanism is the mobility of chains of both surfaces. Additionally, the surface of adhesive and adherent chains should be completely compatible with each other. However, this mechanism can be highly affected by the mobile chains' concentration, the chains' molecular weight, the chains' length, interface temperature as well as glass transition temperature (T_g), all of which can directly affect the mobility of chains (Bal-Ozturk et al., 2021). Finally, the contact time of polymer chains (adhesive and adherent chains) is another critical factor in diffusion process (Mansuri et al., 2016).

4.5. Physical entanglements

Recently, an outstanding study from Leibler et al. demonstrated that the presence of nanoparticles within the adhesive matrix can induce a new gluing mechanism useful for increasing the adhesion strength. Technically speaking, the presence of nanoparticles or nanofibers can play the role of connectors among protein chains of tissue surface (Kim et al., 2022; G. Wang et al., 2018). Unlike the chemistry-based tissue adhesion mechanism that occurs almost in all bio-adhesives, this type of adhesion mechanisms is relied on the physical entanglements (this kind of interlocking also includes hydrogen bonding and hydrophobic interactions (Daristotle et al., 2020)) and only occurs in the platforms that contain nano-scale components (**Fig. 4d**). However, it is indeed beneficial in terms of low-cost, convenient and applicable features for clinical translation (Taboada et al., 2020). Silica (SiO_2) and iron oxide are examples of biomaterials that can participate in this mechanism (Gao et al., 2017).

5. Applications of tissue adhesives in biomedical engineering

To date, existing tissue adhesives have plenty of applications in biomedical engineering including wound dressing, antibacterial closure, drug delivery, cell delivery, cartilage treatment as well as hemostasis agent (Zhu et al., 2017). These applications can be classified to internal-use and external-use applications of adhesives. External ones are usually utilized for sealing surgical wounds, in order to close the body surface. These adhesives (external) cannot be applied in inner cavities. In fact, limited by their biological properties, they cannot be in a direct contact with the inner organs (Han et al., 2017; Zhang et al., 2020). Unlike external adhesives, internal ones are utilized in a direct contact with the organs inside the body. Hemostasis agent during heart surgery is an example of internal-use adhesives (Annabi et al., 2015; Zhang et al., 2015). They have to possess a super biocompatibility and more of adhesion strength in comparison to the external ones. Generally speaking, in addition to a desirable adhesion, they have to have no toxic byproduct after degradation, no inflammatory or carcinogenic response, no irritating reaction, and be degradable by hydrolysis or enzymatic degradation (Pascual et al., 2016). Considering the mentioned requirements, polysaccharide-based tissue adhesives are of a great interest among the state of art studies. In this section, we will summarize different applications of polysaccharide-based tissue adhesives.

5.1. Antibacterial dressings

Bacteria-infected wounds and antibiotic abuse are worldwide issues for clinics and medical systems. So, designing a kind of multifunctional wound dressing with non-antibiotic-dependency is highly demanded. Plenty of studies have been conducted toward designing such systems. However, these systems require a specific mechanism of antibacterial activity or biomolecules delivery to fight against drug resistant bacteria (Han et al., 2020). Among all the proposed systems, polysaccharide-based platforms are more interesting to scientists due to their compatibility and inherent antimicrobial activities (**Fig. 5**) (X. Y. He et al., 2020). For instance, a group of researchers proposed a tissue adhesive nanocomposite with remarkable photothermal antibacterial features. They suggested that combination of N-carboxyethyl chitosan (CEC) and benzaldehyde-terminated Pluronic F127/carbon nanotubes (PF127/CNT) will provide a nice system for healing infected wounds. Based on their reports, this platform owns hemostatic features, stable mechanical properties, excellent tissue adhesiveness, pH

responsiveness, high water absorbance as well as great biodegradability. Its photothermal antibacterial activities is derived from the inherent antibacterial activities of N-carboxyethyl chitosan and release of moxifloxacin hydrochloride, which was already loaded in the hydrogel (J. He et al., 2020). According to Wang et al. reports, utilization of injectable adhesive polysaccharide-based hydrogel is a promising platform for sustained exosome release which has re-epithelization properties in addition to antibacterial ones. However, being non-self-healable and lacking self-recovery characteristics are two main constrains of plenty of the existing platforms (Suneetha et al., 2022; Wang et al., 2019).

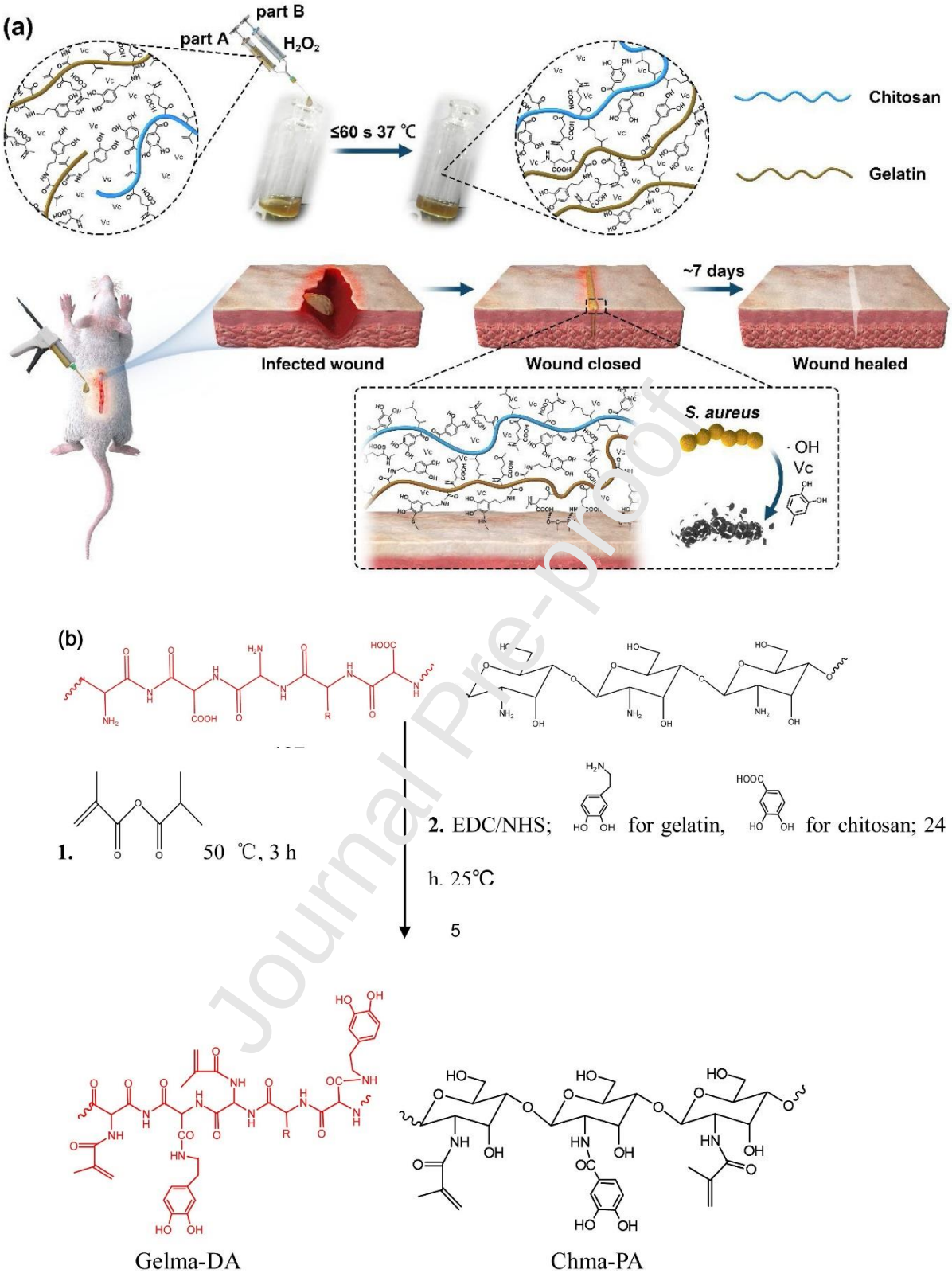


Fig. 5. (a) A general illustration of the origins of catechol ($C_6H_4(OH)_2$) and methacrylate (CH_2=C(R) $COOCH_3$)-modified chitosan/gelatin antibacterial actions. **(b)** The preparation process of gelatin methacrylate-dopamine and chitosan methacrylate-dopamine (X. Y. He et al., 2020).

5.2. Wound healing

There exist plenty of clinical wound dressing hydrogels that suffer from poor adhesiveness and cannot withstand the entered external damages. Moreover, their fixation process on the surface of wound is challenging due to lack of appropriate adhesiveness (Wu et al., 2018). Most of hydrogels with a single component cannot meet the required criteria. Therefore, recently attention has been directed towards composite hydrogels. Polysaccharide-based hydrogels are well-known for their biocompatibility, antibacterial activities and biodegradability (Jung et al., 2021). Hence, modification of these systems with catechol group-containing materials such as dopamine (because these materials increase the adhesion strength through oxidation and connecting to thiol (R-SH) containing substrates) will provide us with a great wound dressing platform (Kamoun et al., 2017; Shi et al., 2018; Xu et al., 2017). Among all the mentioned polysaccharides, sodium alginate and chitosan are the most prevalent ones. Reports indicate that sodium alginate has good toughness and self-healing properties (in addition to biocompatibility and biodegradability) and chitosan owns antioxidant properties which strongly supports the healing process (X. Y. He et al., 2020). For instance, a photo-induced adhesive hydrogel from carboxymethyl chitosan has recently been recommended. Accordingly, carboxymethyl chitosan combined polyethylene glycol (as crosslinker) was approved to be an antibacterial and antioxidant gel promoting wound healing process and upregulating Vascular Endothelial Growth Factors (VEGF). Such a smart system also demonstrated great angiogenesis effect as well as hemostatic performance (Wei et al., 2022). Notably, fabrication of bio glues using photo-gelation method is an effective and compatible technique of crosslinking for a wide variety of macromolecules without the need for chemical modification processes (J. Zhang et al., 2021).

5.3. Hemostasis agents

Tissue adhesives have a high potential for rapid hemostasis. These platforms can rapidly diminish the hemorrhage without any immune responses. However, their blood clotting rate, degradability (if they are injected to the internal sites, such as cardiac surgery), injectability, adhesiveness, irritation risks, as well as long-term inflammatory reactions are very important in clinical uses (Kamoun et al., 2017). Among all the natural biomaterials, polysaccharides, and especially oxidized cellulose, hyaluronic acid as well as chitosan are the most appealing options, to the extent that most of commercialized products are made of cellulose and oxidized cellulose (MacDonald et al., 2017; Narayanan et al., 2020; C. Zhang et al., 2021).

There exist some good studies that have minimized the inflammatory responses while maximizing the adhesiveness and hemostatic ability. For instance, Chitosan-catechol, inspired from mussel-adhesive-proteins, is a suggested platform by a group of scientists. Their reports show that this hemostatic structure has negligible toxicity and excellent adhesiveness. However, it suffers from unoptimized mechanical properties (Park et al., 2019). To overcome weak mechanical properties, Pang et al. proposed the addition of dextran dialdehyde (DDA) to chitosan (Pang et al., 2020). Also, reports show that combination of quarternized Chitosan with polydopamine as a cryogel can induce antioxidation properties to the excellent hemostasis performance and adhesiveness (Li et al., 2020). Despite adequacy of the studies conducted in designing hemostatic adhesives, the arterial and cardiac bleeding are still serious concern in view of the application criterion suggested for bio-adhesives, where they must adhere to a wet and strongly mobile surface. This is why the cardiac uncontrollable hemorrhage is a hassle. In this regard, Hong et al. designed a photo-reactive hyaluronic acid-based adhesive greatly mimicking the extracellular matrix and strongly adhering to the cardiac surface under UV light. Interestingly, this platform is able to withstand up to 290 mm Hg pressure, which is extensively higher than (almost three times) the normal blood pressure (60-160 mm Hg). However, the drug loading capacity of the mentioned system needs to be under further investigation (Hong et al., 2019).

5.4. Drug delivery

Wound dressing materials have been widely utilized to cover the wounds, not to be in direct contact with the external environment. However, plenty of the conventional dressings lack the anti-inflammatory functions, which can cause fibrosis and stricture, when it comes to deep wounds such as gastrointestinal wounds after endoscopic surgery. this is the exact reason behind the fact that practical delivery of drugs (e.g., corticosteroid) is necessary for improving healing process (Nishiguchi & Taguchi, 2020). Injectable hydrogels have attracted attention as delivery platforms. Among different polysaccharides, hyaluronic acid has attracted scientists due to great injectability, anti-inflammation profile, as well as self-healing performance (Mi et al., 2022). However, for internal cases, injectable hydrogels face some challenges. One important limitation is that they may detach from their location due the high blood shear stress and also, they may not be able to maintain their gel state for a long period of time at a location, where there exist a large amounts of body fluid (Fujiwara et al., 2021).

This limitation will be highlighted when it comes to drug delivery aims. Indeed, failing to maintain the gel state will bring about changing in release pattern and also, detaching from the desired location (because of blood flow pressure or presence of body fluid) will totally disturb the delivery profile. This is why the adhesion strength to the native tissue is of a great importance for such systems (Boda et al., 2020).

5.5. Cartilage and tendon injuries treatment

Cartilage is a tissue with limited regenerative capacity when it is damaged and tendon repair is a kind of unacceptably high failure process because of being unable to recreate the load transfer mechanisms, which necessitates fabrication of mechanically optimized tissue adhesives (Linderman et al., 2018). There exist two main treatment options for articular regeneration, arthroscopic meniscectomy or surgical interventions. However, results obtained from these two methods are not satisfactory (Sánchez-Fernández et al., 2019). Researchers are trying to design injectable biomaterials in order to provide a system with proper biological and chemical cues, regenerating a damaged cartilage. Reports indicated that hydrogels have high water content and great swelling kinetics which is able to provide a biomimetic extracellular media similar to the native cartilage tissue. It is also able to absorb the nutrient and metabolites, easily (Li et al., 2016). However, hydrogel adhesiveness to the native tissue is a main key factor. Otherwise, the diffusion process of nutrients will be failed and also, the scaffold will be scattered and will not be fixed in its accurate place. Hence, different chemical or physical cross-linking strategies of polymers have been employed to prepare an adequate cartilage regeneration system with high adhesiveness (Ren et al., 2015). Among biomaterials, the natural ones, especially agarose, silk fibroin, chitosan, alginate, gelatin, elastin, hyaluronic acid (HA), and chondroitin sulfate (CS) have shown a great performance due to great cell interactive properties (Kim et al., 2017). Noteworthily, CS is the most outstanding option because it is contained units of β-1,4-linked glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine, which are the major components of cartilage. According to reports, glucosamine has a key role cell migration and receptor binding. However, chitosan suffers from weak mechanical properties and cannot withstand a long-term *in vivo* duration (Han et al., 2018). As a good instance for application of polysaccharide-based tissue adhesives for cartilage treatment, An et al. proposed an enzymatic approach for fabrication of an adhesive hydrogel. Regarding the capability of hyaluronic acid and gelatin for meniscus repair, they utilized a tyrosinase mediated crosslinking to enhance the mechanical properties and regulate the kinetics of degradation (Fig. 6) (An et al., 2018). This platform also

enhanced the cartilage specific gene expression which is an efficient step toward its treatment. However, lacking antibacterial properties is a major threat to a highly inflamed area. Technically speaking, polysaccharide-based mussel inspired adhesives can be administered to the cartilage–tendon interface in anterior cruciate ligament (ACL) reconstruction (it is a kind of tissue graft located in knee to restore its functionality after damage) not only to enhance tendon-bone bonding strength, but also to improve the bony inward growth as well as both chondrogenesis and osteogenesis capacity of the bone–tendon interface (Yuan et al., 2021). For instance, 3,4-dihydroxy phenyl chitosan (BGC) bio-adhesive is designed not only to provide a very biocompatible media, but also to enhance the bio adhesion after being combined with soluble oxidants or cross-linking agents. Although this platform supports tenogenesis, it additionally increases the expression of collagen I and upregulates tenogenic markers, the mechanical optimizations need to be addressed (Fang et al., 2022). According to another study, utilization of chitosan in tendon healing platforms can reduce inflammation, modulate chemokine secretion and recruit tendon stem cells (Freedman et al., 2022).

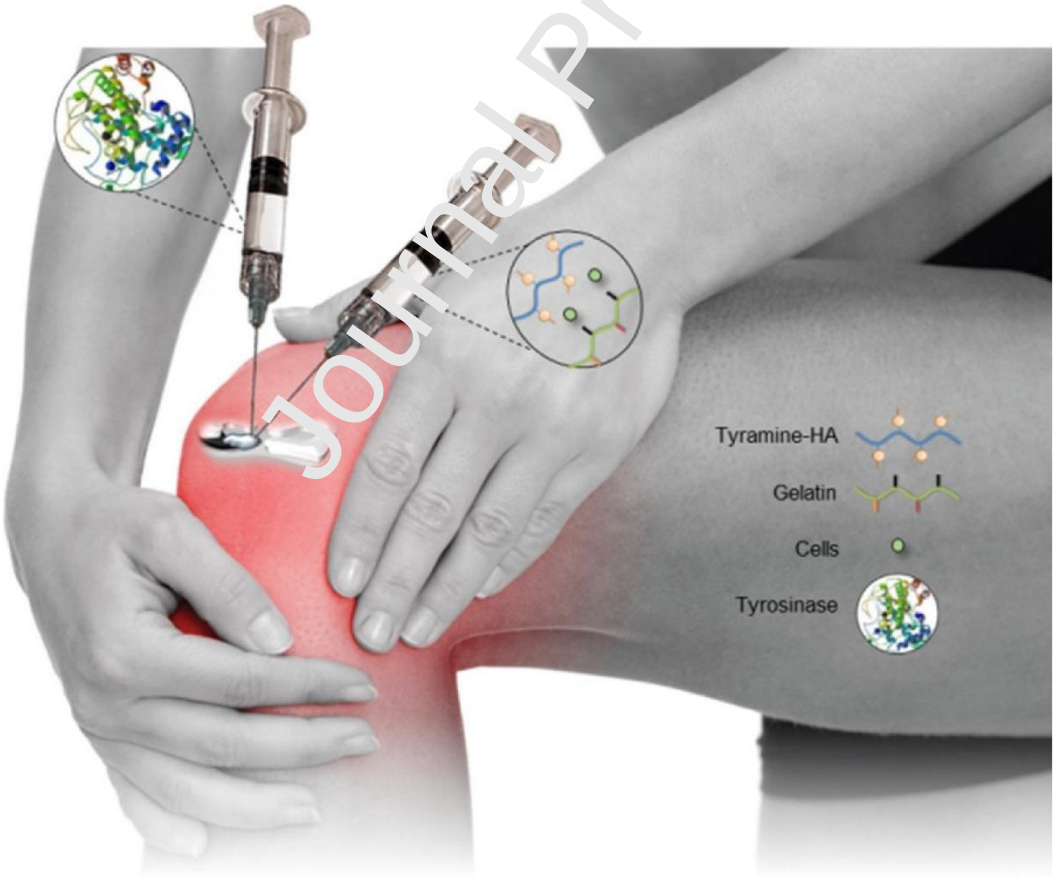


Fig. 6. A Schematic illustration of an injectable hydrogel from tyrosinase-mediated hyaluronic acid/gelatin for meniscus repair and the possible functional groups that attract each other (An et al., 2018).

5.6. Tissue adhesive sensors

High stretchability, high adhesiveness, conductivity as well as stability are the important criteria for implantable hydrogel sensors (YU et al., 2022; Q. Zhang et al., 2019). Combination of synthetic and natural polymers, metal nanomaterials, and carbon nanomaterials is referred to as a suitable platform for hydrogel sensors and monitoring applications (Agnol et al., 2019; Nam & Mooney, 2021). For instance, adhesive and healable soft human motion sensors have been under wide investigations in order to be used as healthcare monitoring devices (L. Wang et al., 2018; X. Zhang et al., 2019). There exist some studies that offer human-friendly hybrid hydrogels with robust adhesiveness (Liao et al., 2017; Liu et al., 2017). However, three main barriers have limited their application. Firstly, these systems require super stretchability, secondly, they need to be highly sensitive and conductive, and thirdly, they must own excellent adhesiveness. Otherwise, they cannot be applied as large-range human motion monitoring systems because weak adhesion makes them unable to induce firm contact with skin and so, they fail to record weak signals (Liu & Li, 2017). The next main problem is that peeling adhesion tests have revealed that the more we increase the toughness, the more adhesion and cohesion decrease. Therefore, it is challenging to prepare a hydrogel sensor that has both adhesiveness and toughness (L. Wang et al., 2018; Q. Zhang et al., 2019; X. Zhang et al., 2019). Some studies have reported that cellulose-based hydrogel sensors support us to have both options together (toughness and adhesiveness). For instance, Yang et al. demonstrated that presence of cellulose nanocrystals not only enhances all the mechanical properties, but also increases adhesive strength between different substrates such as skin, plastic, glass as well as steel (Amer & Chen, 2020; Yang & Yuan, 2019). Several polysaccharide-based adhesive sensors combined with tannic acid support fabrication of a platform with high reproducible adhesion strength, as well as oxidation resistance. **Table 2** shows different applications of polysaccharide-based adhesives.

Table 2. Different applications of polysaccharide-based adhesives.

Application	Materials	Pros	Cons	Refs.
Antibacterial	Chitosan, N,N′-Methylenebisacrylamide	robust mechanical strength, antibacterial	high dependency on crosslinker	(Sharma et al., 2019)

		and antifungal activity	concentration	
Antibacterial	hydro caffeic acid-modified chitosan	optimized gelation time, good mechanical properties, homogenous microstructure and high tissue adhesion properties, anti-infection capability, no significant cytotoxicity, situ antibleeding efficacy	no drug release profile	(Du et al., 2020)
Antibacterial	N-carboxyethyl chitosan, benzaldehyde-terminated Pluronic, carbon nanotubes	potential option for photothermal therapy, a suitable gelation time, stable mechanical properties, hemostatic efficacy, high water absorbency, and good biodegradability pattern, anti-infection capability, angiogenesis effect	no drug release capability	(J. He et al., 2020)
Antibacterial	Aldehyde pullulan, polyethylenimine (PEI)-linked PEO–PPO–PEO (Pluronic F127)	thermosensitive, injectable, self-healing, tissue adhesive, antibacterial, hemostatic, and UV-shielding polysaccharide-based scaffold, long-term exosome release	mechanical properties were not optimized	(Wang et al., 2019)
Wound Dressing	dopamine-grafted oxidized sodium alginate, polyacrylamide	efficient self-healing ability, exceptional tissue adhesiveness, tissue regeneration capability	no antibacterial effect or drug release pattern	(Chen et al., 2018)
Wound Dressing	catechol- and methacrylate-modified	injectable, applicable at body temperature	lower adhesiveness compared to the	(X. Y. He et al., 2020)

	gelatin and chitosan	without activation by UV, good adhesion to tissues, inherent antibacterial activity	exceptional ones, reported by other studies	
Wound Dressing	gelatin, adipic acid dihydrazide, oxidized sodium alginate	good adhesiveness, good biocompatibility, appropriate swelling ratio, good injectability	no antibacterial effect or drug release pattern	(Xing et al., 2021)
Wound Dressing	oxidized dextran, poly-L-lysine	low toxicity, well-controlled degradation rate, good mechanical properties, water stability, high tissue adhesiveness	no antibacterial effect or drug release pattern	(Matsumura et al., 2014)
Wound Dressing	aldehyde sodium alginate, amino gelatin	good gelling time, good swelling behavior, tunable bonding strength by varying the content of aldehyde groups, high tissue adhesiveness	no antibacterial activity, no well-defined degradation pattern and no drug release profile	(Yuan et al., 2017)
Wound Dressing	poly(ethylene glycol), chitosan	dissolvable in neutral aqueous media, good mechanical properties, facile gelation kinetics and high tissue adhesiveness	no antibacterial activity, no well-defined degradation pattern and no drug release profile	(M. Kim et al., 2020)
Hemostasis Agent	chitin nanowhiskers, carboxymethyl chitosan, dextran dialdehyde	high compressive stress, great adhesive strength, negligible cytotoxicity, degradable without long-term inflammatory responses, injectable, hemostatic efficacy	no antibacterial effect or drug release pattern	(Pang et al., 2020)
Hemostasis Agent	glycol chitosan-catechol	reduced adhesion of immune cells, great tissue adhesion and	no antibacterial activity, no well-defined degradation	(Park et al., 2019)

		hemostatic ability	pattern and no drug release profile	
Hemostasis Agent	polydopamine, sodium alginate–polyacrylamide	highly interconnected porous structure (~94% porosity), improved the cell proliferation, cell attachment, cell spreading, and functional expression of human skin fibroblasts, good hemostatic properties, rapid blood coagulation ability, great tissue adhesion	adhesiveness was checked using adhesion to plastic, skin, glass, computer screens, and leaves which can be far more different with human organs, no antibacterial activity, no well-defined degradation pattern and no drug release profile	(Suneetha et al., 2019)
Hemostasis Agent	chitosan and dextran	negligible cytotoxicity and minimal swelling in phosphate buffered saline, good tissue adhesive properties, good storage modulus, a good drug delivery vehicle,	no antibacterial activity	(Balakrishnan et al., 2017)
Hemostasis Agent	quaternized chitosan and polydopamine	excellent hemostatic performance, multifunctional tissue-adhesiveness, outstanding mechanical strength and easy removability, antioxidant activity, and NIR photothermal-enhanced antibacterial performance	no well-defined degradation pattern	(Li et al., 2020)
Hemostasis Agent	chitosan, tunicates	high platelet adhesion and blood clotting ability, two-fold greater adhesion	no antibacterial effect or drug release pattern	(Sanandiya et al., 2019)

		ability in wet condition than did fibrin glue, the electrospinning capability, fibrous structure		
Hemostasis Agent	starch, succinic anhydride and dopamine	biological adhesive and hemostatic capability, ease of operation, rapid sol–gel transition, porous microscopic morphology, good swelling ratio, good biodegradability, tissue-like elastomeric mechanical properties and excellent cyto- , hemocompatibility	no antibacterial effect or drug release pattern	(Cui et al., 2020)
Drug Delivery	gelatin-hyaluronic acid, tyrosinase	high mechanical properties, tissue adhesive function, good delivery to the desired area, sprayable hydrogel, good ability for cell and growth factor delivery	no antibacterial effect	(Kim et al., 2018)
Drug Delivery	chitosan, Pectin	mucoadhesive properties and oral therapeutic delivery capability, antimicrobial properties, pH-responsive delivery	no well-defined degradation pattern	(Boda et al., 2020)
Cartilage Treatment	Tyramine, hyaluronic acid, gelatin	modulated mechanical properties and degradation kinetics, tissue-adhesive properties, strong biocompatibility,	lower adhesiveness compared to the exceptional ones, reported by other studies	(An et al., 2018; Sánchez-Fernández et al., 2019)

		enhanced cartilage-specific gene expression		
Cartilage Treatment	polydopamine–chondroitin sulfate–polyacrylamide	good cell affinity, high tissue adhesiveness, facilitated cell adhesion and tissue integration, super resilience and toughness, biomimetic microenvironment for chondrocyte growth and cartilage regeneration	no well-defined degradation pattern	(Han et al., 2018)
Cartilage Treatment	Tyrosinase-crosslinked alginate sulfate tyramine	a strong increase in the expression of chondrogenic genes such as collagen 2, aggrecan and Sox9, human chondrocytes encapsulation capability, enzymatic crosslinking, strong adhesion to native cartilage and chondrogenic re-differentiation	no well-defined degradation pattern	(Öztürk et al., 2020)
Implantable Adhesives	titanium oxide polydopamine–perfluoro silica carbon dot-conjugated chitosan–polyvinyl alcohol-loaded tannic acid	capacitive reversibility that follows finger motion, strong adhesion to native skin, useful for artificial electronic skin	no well-defined degradation or depreciation pattern	(Pei et al., 2020; Ryplida et al., 2019)
Implantable Adhesives	cellulose nanocrystals	rapid UV initiation, compressive cycling sensibility at diverse pressure during 0.5, 1.0, and 1.5 Hz, flexible, applicable	no well-defined degradation or depreciation pattern	(Amer & Chen, 2020; Yang & Yuan, 2019)

		mechanosensory electronics and artificial intelligence, strong adhesion to native skin		

6. The latest advances in tissue adhesive applications

6.1. Cell therapy

HA can be easily functionalized with different functional groups via its carboxyl or hydroxyl group. This property causes HA to be a nice option for producing tissue adhesives. Additionally, HA poses some cell surface receptors such as CD44, ICAM-1, and RHAMM through which it can accelerate the cell-matrix interactions. Also, using the cell-matrix interactions, HA can activate the signal transductions that are integral for cell survival. Regarding these properties, are used as tissue adhesives for cell therapy and cell delivery (Samanta et al., 2022). For instance, using oxidative crosslinking, HA can be functionalized with catecholamine ($C_6H_9NO_2$) motif. This functional group can firmly bind to peptides and proteins on the tissue surface. The resultant hydrogel not only has great adhesion properties, but also it can provide a great media for human adipose-derived stem cells and hepatocytes viability after encapsulation. It also accelerates angiogenesis. Noteworthily, HA reveals an outstanding viscoelastic behavior in addition to immunomodulatory characteristics. Hence, this platform can be addressed as a practical scaffold for minimally invasive cell therapy. However, more of smart and innovative scaffolds are required modulating the local inflammatory microenvironment well as suppressing the potent oxidative stress in order to reach the clinical translation of regenerative and efficient cell therapy (Chen et al., 2020; Shin et al., 2015).

6.2. Cancer therapy

Recently, application of hydrogels as chemotherapy delivery platform is questionable. It is due to the fact that hydrogels suffer from instable network structure, weak mechanical properties as well as weak tissue adhesiveness (Buckner et al., 2016; Shalumon et al., 2018). A good chemotherapy platform not only owns a sustained release pattern, but also has a good tissue adhesiveness so as not to expose healthy cells to hazardous drugs. However, the fixation process of the platform is usually unsuitable being restricted by plenty of nerve networks, blood vessels, multiple glands such as lymph nodes as well as the mobility of the

organs. (L. Li et al., 2022). Having high bio-adhesive properties can enhance the efficiency of the fixation and minimize the drug exposure to the adjacent healthy tissue and simultaneously, it maximizes the drug penetration into the cancerous media (Wu et al., 2019; Zeng et al., 2021). For instance, a group of scientists fabricated a multifunctional nanoparticle-hydrogel (NP-gel) hybrid system for targeted delivery of anticancer drugs. They claimed that this new system can remarkably increase the tumor-specific drug penetration while it diminishes the exposure of adjacent healthy tissue to the drug. This polysaccharide-based system is consisted of two main components, doxorubicin (DOX) loaded phenylboronic acid-modified mesoporous silica nanoparticles (PBA-MSNs), and dopamine-conjugated hyaluronic acid (DOP-HA). This platform is reported to have unique adhesion properties because of acid-cleavable dynamic boronate bonds between catechol group and PBA groups, which plays the main role for minimizing the drug uptake of healthy cells (**Fig. 7**) (Wu et al., 2019). From a practical point of view, this novel platform seems to be a desirable and potent platform for local anticancer delivery.

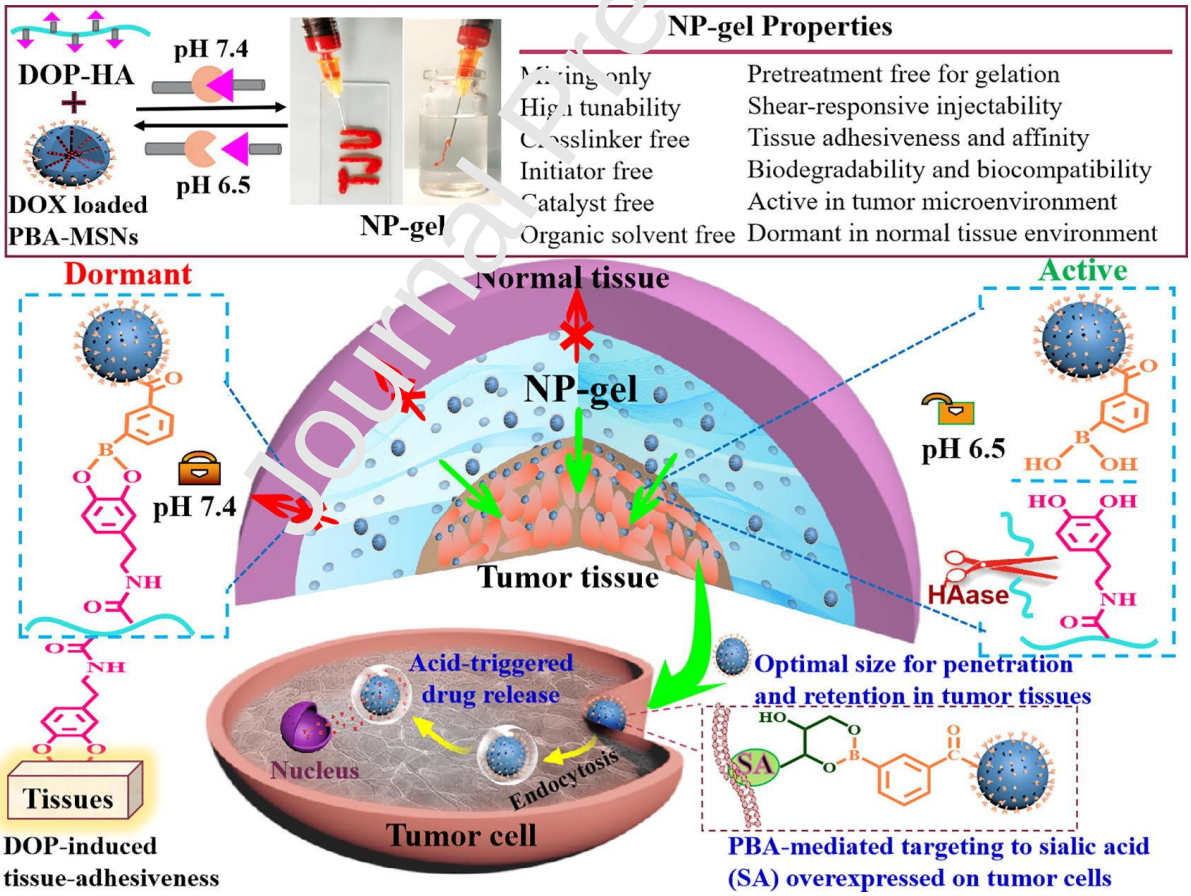


Fig. 7. A Schematic illustration of a nanoparticle-hydrogel hybrid formulation from silica nanoparticles and dopamine-conjugated hyaluronic acid which is loaded with doxorubicin. The system will be activated in an

acidic media and in the presence of hyaluronidase and it will release tumor-targeting and penetrative doxorubicin (Wu et al., 2019).

6.3. Cornea regeneration

Eyes have different protective mechanisms (such as producing tears) which rapidly washout the entered drugs. This is why conventional methods (such as suspension) cannot effectively deliver drugs to the targeted areas of eye. Likewise, ointments are not good options owing the fact that they undesirably change the tear's refractive index. To resolve the existing problems for ocular drug delivery, delivery agents must have bio-adhesive properties, which extend the contact time of drug in the eyes' media. Notably, the existing methods of treatment include using sutures and adhesives. Sutures are not only invasive, especially for such a sensitive tissue, but also cause astigmatism and carry a risk of infection. This is why utilization of soft and smart bio-adhesives is in the core of attention. (Barroso et al., 2022). Among all the natural biomaterials, chitosan and sodium alginate own great characteristics such as bio-adhesiveness, and inherent antibacterial activity, which make them potent options for ophthalmic formulations. For instance, Mowaffi et al. reported that chitosan and sodium alginate nanoparticles loaded with brimonidine (Celecoxib™), not only exhibited a desirable sustained release pattern (for 24 hours), but also they revealed high level of bio-adhesiveness (**Fig. 8** shows examples of polysaccharide-based adhesives for ocular drug delivery) (Trujillo-de Santiago et al., 2019).

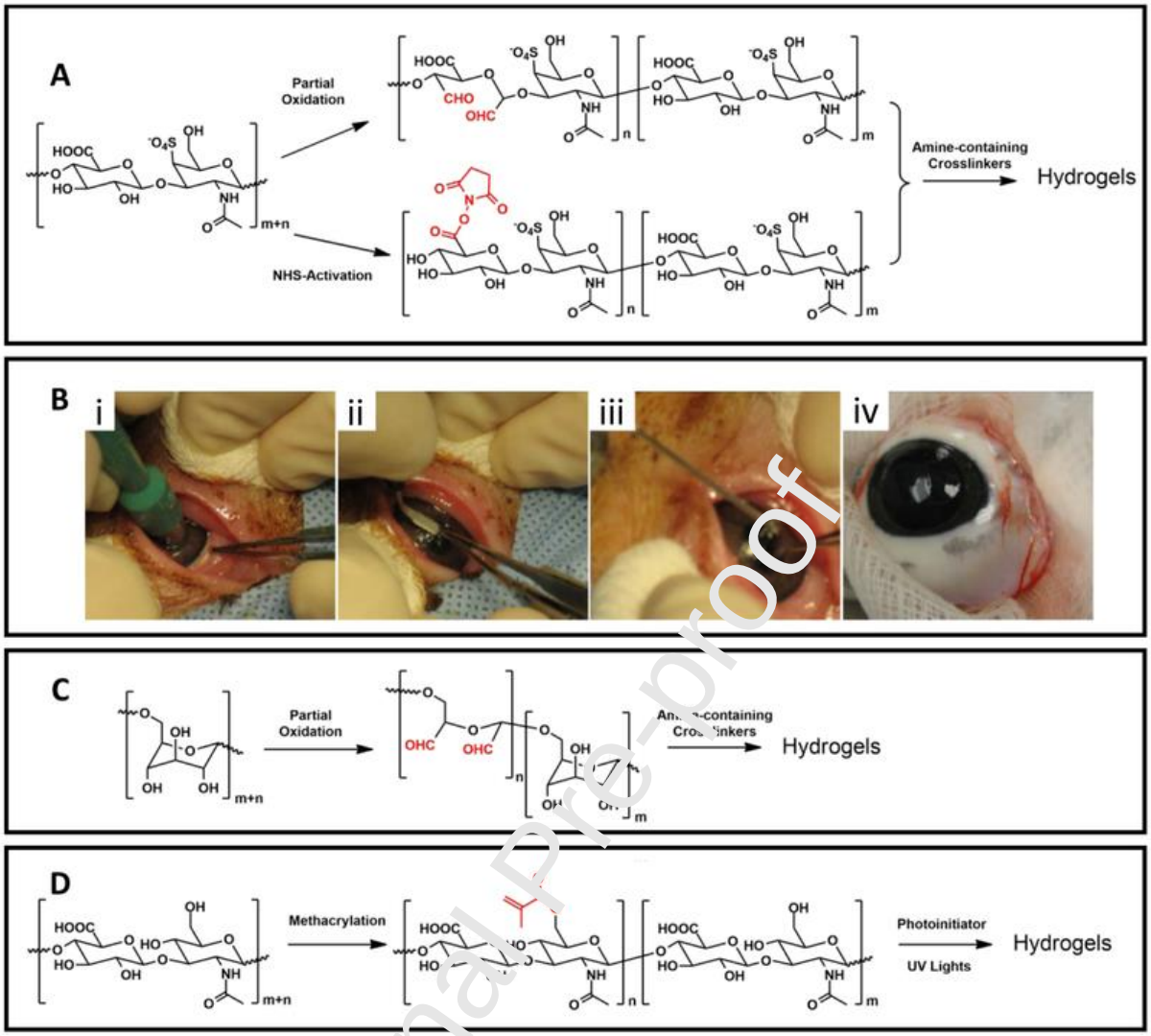


Fig. 8. Examples of polysaccharide-based adhesives for ocular drug delivery. **(A)** Chondroitin sulfate-based hydrogels; **(B)** NHS-modified chondroitin sulfate/amine PEG; **(C)** Dextran-based sealant; **(D)** Hyaluronic acid-based glue (Trujillo-de Santiago et al., 2019).

In addition to drug delivery, cell delivery to the damaged cornea is very important because regeneration of cornea is dependent on delivery of both epithelium-renewing limbal epithelial stem cells (LESCs) and human adipose-derived stem cells (hASCs). Because of the existing risks relevant to suturing of corneal implants, there is a serious need for fabrication of tissue adhesive platform in order to regenerate cornea. A group of scientists modified hydrazone-crosslinked hyaluronic acid (HA-DOPA) hydrogels with dopamine. In order to increase the quality of hASCs encapsulation, they conjugated thiolated collagen IV on the surface of hydrogel. Their results indicated that this novel platform own an excellent tissue adhesion

when implanted to the porcine corneal organ. It also has the ability to deliver cells to the targeted media, properly (Koivusalo et al., 2019).

6.4. Clinical imaging

Although tissue adhesives have been under plenty of investigations from different aspects, there is an essential demand for detecting them via clinical imaging modalities. To overcome the clinical barriers, internal tissue adhesives need to be monitored over time. It helps scientists to regularly check their chemical and biological status using state of art imaging methods like bioluminescence imaging technique (Mirzaei et al., 2022). However, very few studies have followed this topic. Although Shin et al. have reported a good internal adhesive platform that is detectable via image guided procedures, their proposed system is not natural. Indeed, we believe that such an internally used systems must be super biocompatible. So, polysaccharide-based bio-adhesives may be a better option in comparison to tantalum oxide/silica core/shell nanoparticles (TSNs) (Shin et al., 2017). However, their studies can be so inspiring for further investigations.

7. Concluding remarks and future challenges

Tissue adhesives have been widely used to prevent wound leaks, sever bleeding, bacterial activities, as well as to enhance drug delivery and healing process. Although they have been under plenty of detailed investigations, still there exist no platform with ideal properties for clinical uses. An ideal bio-adhesive needs to have sufficient adhesion strength, biocompatibility, non-toxicity of byproducts, acceptable antibacterial properties, controllable degradation, encapsulation capacity, detectable by image-guided procedures (for internal uses) as well as affordable price. In this review article, we have presented the chemistry of polysaccharide-based adhesives, their main mechanisms of action, their biomedical applications (wound dressing, hemostasis agent adhesives, antibacterial closures, drug delivery adhesives, cartilage treatment applications of adhesives, as well as implantable adhesives), and the most recent or most innovative developments of polysaccharide-based adhesives. Overall, polysaccharides due to some inherent properties such as antibacterial (chitosan), angiogenesis (HA), wound healing (alginate), and hemostasis (cellulose) are appropriate platforms for tissue adhesive formulations. Moreover, biodegradability of polysaccharides resolves the shortcoming of degradation in biological media, which is the case when using adhesives of other families like PEG. Another interesting feature of polysaccharides is their tunable surface functionality, which facilitates coupling with

complementary biomaterials used in tissue adhesive formulation (Xu et al., 2019). Almost in all the literature on polysaccharide-based adhesives the chemical mechanism of gluing has been highlights, which is promising indeed.

After careful review of the literature, we understood that there exist some specific unresolved problems and unanswered questions, which can be numbered:

1- Successful fabrication of the next-generation adhesives requires a deep understanding of biomaterials and tissue surface properties, all possible adhesion mechanisms, and clinical limitations. We need to consider the physical and biological properties of each specific tissue, which vary markedly among tissue types. The adhesion efficacy is strongly dependent on the tissue-specific properties, which needs to be under further investigation.

2- Despite considerable advancements in tissue adhesives fabrication methods, there exist some unmet needs such as non-controllable polymerization. Scientists need to focus on development of biomimetic adhesives, externally activated tissue adhesives, as well as multiple crosslinking strategies. Remarkably, economic limitations play a vital role in this pathway.

3- Fabrication of magnetic and conductive responsive adhesives for growth factor delivery is a serious clinical shortcoming, which needs to be under further investigations.

4- As mentioned above, a tissue adhesive as an anticancer delivery platform is highly required for clinical application of these systems. However, the main challenge is the need for minimizing the toxic drug exposure to the adjacent uncancerous tissue. Indeed, the drugs quite often are accumulated by the adjacent healthy tissue nonspecifically, because of the drug concentration gradient.

5- The advent of advanced methods for developing bio-adhesives is highly demanded. The available fabrication techniques are required to be time and cost effective, efficient, facile and tunable in terms of ultimate properties. In this regard, utilization of 3D printing techniques for fabricating curved structures, 4D printing strategies for creating stimuli-responsive platforms (which perform shape change as a function of time) as well as exploring design strategies via machine learning seem to own a most promising outlook.

6- Monitoring the long-term efficacy of the implanted adhesives is another issue. In fact, there is a need for monitoring the chemical, physical and biological properties of the implanted adhesives over time. Any change in tissue response, compatibility, adhesion and

cohesion can be integral. Investigations in this regard are still inadequate for an explicit conclusion.

Accordingly, there exist a huge gap between the number of investigations and the practical and standard clinical products. To bridge this gap, there is a necessity to better apprehend the barriers to clinical translation of tissue adhesives. It is believed that polysaccharides can be taken as game changers.

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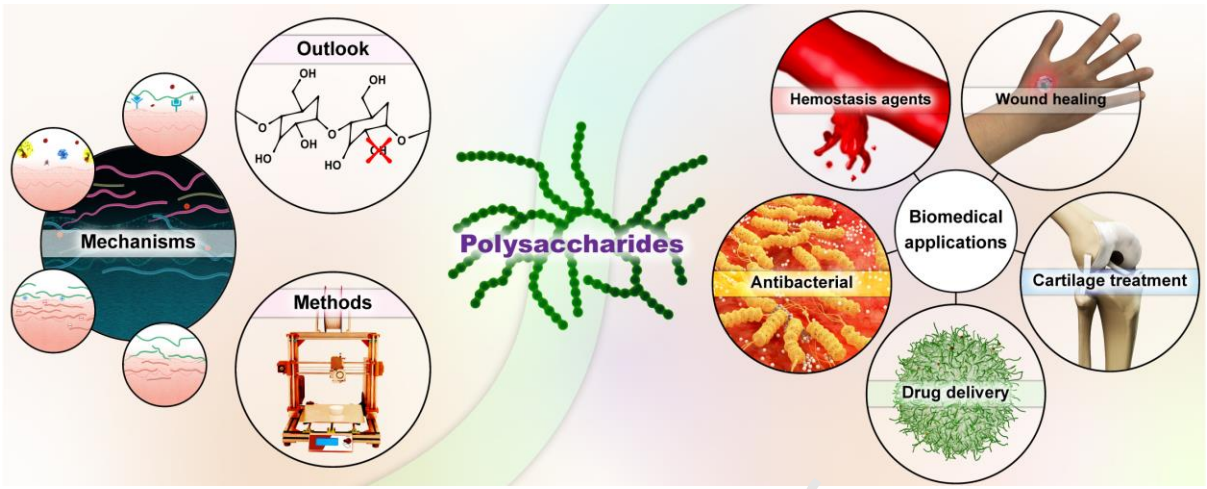
Declaration of interests

Hanieh Shokrani, Amirhossein Shokrani, Farzad Seidi (Corresponding author), Muhammad Tajammal Munir, Navid Rabiee, Yousef Fatahi, Justyna Kucinska-Lipka (Corresponding author), Mohammad Reza Saeb (Corresponding author), the authors of the work entitled **"Biomedical Engineering of Polysaccharide-based Tissue Adhesives: Recent Advances and Future Direction"** submitted to *Carbohydrate Polymers* declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



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