

An overview of functional biolubricants

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Abstract: At present, more and more diseases are associated with the lubrication dysfunction, which requires a systematic study of the complex lubrication behavior of tissues and organs in human body. Natural biomacromolecular lubricants are essential for maintaining ultra-low coefficients of friction between sliding biological interfaces. However, when the surface lubrication performance of tissues or organs destroys heavily, it will bring friction/shear damage for sliding contact interfaces. Therefore, the application of exogenous biological lubricating materials to improve the lubrication situation of damaged tissue or organ interfaces has attracted extensive attention of researchers. In this review, based on a simple summary of lubrication mechanism at sliding biological interface, we systematically introduce the research progress of several kinds of representatively biolubrication materials, including eye drops, tissue anti-adhesion agents, joint lubricants, and medical device lubricants. Meanwhile, the lubrication mechanism and individual advantage and shortcoming for each of these synthetic exogenous lubricated materials are clarified. Correspondingly, the important lubrication application functionality of these biolubricant materials in typically medical surgery scenes, such as dry eye syndrome, tissue adhesion, arthritis, and interventional medical devices, is discussed. Finally, we look forward to the future development direction of artificial biolubricant materials.

Keywords: biolubricants; eye drops; tissue anti-adhesion; arthritis treatment; medical devices

1 Introduction

Friction and lubrication phenomena exist widely in nature, while the biological lubrication is important and necessary for normal function operation of human body [1]. The interface between sliding biological surfaces commonly maintains a highly efficient lubrication state with ultra-low coefficient of friction (COF), which can be attributed to the typical biolubrication mechanism [1]. Biolubrication phenomenon happens to human body almost all the time, and every one of our organs and tissues need good lubrication to resist the shearing-induced damage. We blink 20,000–30,000 times a day, but we feel almost no pain resulted by friction because the

tear consisting of mucins, hydration layer, and phospholipid between the corneal and the eyelid can be regarded as the lubricated layer that gives a very low COF (~0.005) during blink [2]. The process of foods getting into the stomach is interesting. It depends on not only the movement of the muscles of the digestive system, but also the lubrication assistance from the biomacromolecule mucus secreted by the esophageal mucosa [3]. In the process of running or even jumping, even though articular cartilage bears huge external loads, it can still maintain low COF and near-zero wear based on synergistic contribution from glycoprotein boundary lubrication and the synovial fluid lubrication [4]. Similar lubrication feature also exists in buccal environment [5]. The hard teeth

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and soft tongue can synergy work well in chewing, resulting from the necessary lubrication role of boundary synovial film formed by saliva proteins [6]. For example, when the oral lubrication film is destroyed, such as drinking coffee or wine, it will generate the feeling of astringency in the mouth [7]. Therefore, it can be said that the normal function operation of organs and tissues of the human body is inseparable from natural biolubricants. For eyes, the lubrication dysfunction of tears will lead to dry eye syndrome [8], and the lubrication dysfunction of the esophagus may result in swallowing difficulties [3], and the destruction of the lubricating membrane in the mouth readily leads to the occurrence of xerostomia [7]. Especially, a failure of articular lubrication system commonly induces increased wear of cartilage and thus osteoarthritis (OA), which gives rise to severe pain and swelling of joint [9–11]. Among them, the fluid biolubricants have been proved to act important roles in maintaining the normal operation function of organs, which can minimize the occurrence of disease symptoms such as dry eye syndrome, tissue adhesion, and arthritis (Fig. 1).

Meanwhile, even though it has been reported that the extraordinary lubrication performance from natural biolubricants is the synergistic effects of many factors, such as adsorption, hydration, and fluid viscosity, macromolecular mucin chains in biolubricants are indispensable for friction-reduction [12–15]. Commonly,

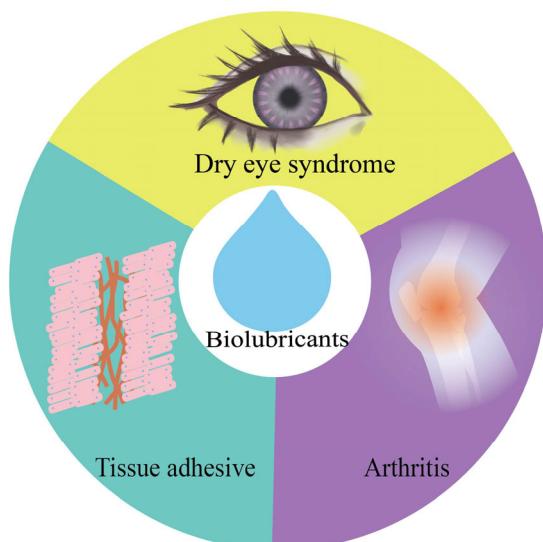


Fig. 1 Schematic diagram shows the important functionality of biolubricants in minimizing the occurrence of disease symptoms such as dry eye syndrome, tissue adhesion, and arthritis.

mucin is one kind of highly glycosylated proteins, and elongated protein core (interrupted by short, non-glycosylated motifs) carries a large amount of negatively-charged glycan chains (Fig. 2(a)), while the proposed lubrication mechanism is that the formation of a sacrificial mucin surface layer and hydration lubrication (Fig. 2(b)) [16]. Mucin, which exists widely in tears, saliva, and synovial fluid of joints, responsible for cartilage lubrication, is also called recombinant proteoglycan 4 (PRG4) [11, 12]. The most typical feature of mucins is that they can easily attach to the surface of tissues or organs, which is the basis and prerequisites for its key role of lubrication [17]. Besides, mucins are large linear molecules, and the structure of them is similar to bottle-brushes, which are easily hydrated to form good hydration layer in body fluid [18–20]. Especially, the hydration of mucin chains is important for the lubrication improvement in mouth, e.g., the salivary mucins deficiency is the main factor causing xerostomia [12, 21]. Both the adsorption and hydration of mucins are conducive to the extraordinary lubrication of the sliding biological interface. Taking tears as an example, the tear membrane is composed by mucins, liposomes, and the aqueous layer produced by the lacrimal gland [17, 22]. Among them, mucin chains adsorb on the eyeball to form a continuous hydration layer to lubricate the shearing

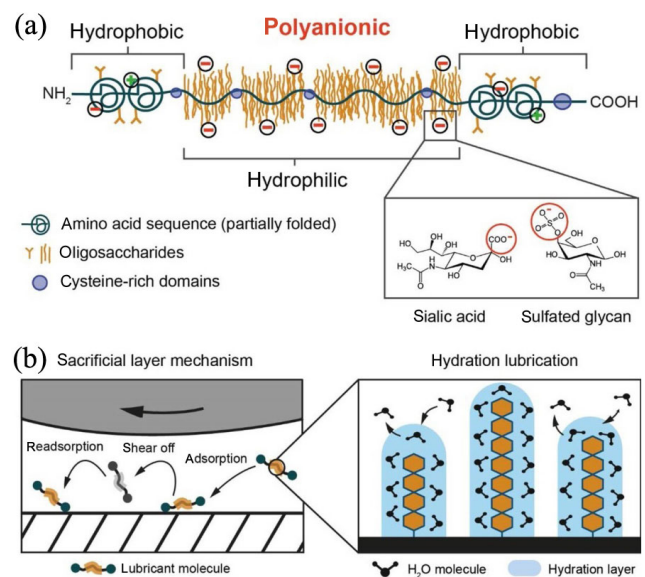


Fig. 2 (a) Schematic illustration of the macromolecule structure of natural mucin lubricants. (b) Proposed interface lubrication mechanism of mucins. Reproduced with permission from Ref. [16], © Elsevier B.V. 2019.

surfaces [23]. Insufficient secretion of mucins may deteriorate the lubrication performance of tears, finally resulting in dry eye syndrome [22]. Overall, almost all the lubrication phenomena occurring in human body depend on mucins, thus understanding the biolubrication mechanism of natural mucins and then developing artificially synthetic lubricants are extremely important and urgent.

2 Lubrication mechanism at sliding biological interface

2.1 Elastohydrodynamic lubrication

In order to avoid the direct contact of friction pairs, the effect way to decrease friction between sliding substrates is to use lubricants with certain viscosity to form continuous fluid film, and this lubrication mechanism is called elastohydrodynamic lubrication in engineering tribology [24–26]. Similarly, the separation of sliding biological tissue or organ interfaces by natural biolubricants is also an important way to maintain efficient lubrication for human body. The lubrication performance of elastohydrodynamic lubrication is mainly determined by the properties of fluids. Most biolubricants in human body are non-Newtonian fluids, and their rheological properties tend to be thinned by shearing [27–29]. For example, the viscosity of hyaluronic acid (HA), the main component of synovial fluid, is relatively high at static state, but it decreases obviously after applying wide range of shearing stresses [30, 31]. Similarly, the saliva (10 mPa·s) in mouth at the low shear rate is much more viscous than that of it (1 mPa·s) at the high shear rate [27]. The shear thinning rheological property of biolubricants is the key to maintain the elastohydrodynamic lubrication [32]. When contacted with sliding biological interface, lubricants can form continuous fluid film between shearing surfaces to separate the movement surfaces. Besides, the shear thinning rheological properties of biolubricants can also play a key load-bearing role [33–36].

2.2 Boundary lubrication

Another important lubrication mechanism in biological lubrication is boundary lubrication [37–39]. Lubricants

can generate boundary films at sliding surfaces to improve the local lubrication performance, which is independent of the viscosity characteristics [39]. Most of the boundary lubrication films in human body are formed by biomacromolecules (mucins, phospholipid, HA, and so on). These biomacromolecules can adsorb on biological surfaces and form a thin hydration layer for boundary lubrication [40, 41]. On account of low viscosity as typical Newtonian fluids, easily flowing between biological interfaces, and other inherent properties, pure water as a lubricant is undesirable, especially under a high load condition [42, 43]. However, as for the biological lubrication system, the addition of biomacromolecular into water can overcome its disadvantages of low viscosity and easily flowing. Therefore, the biological lubrication system based on water system can still keep a stable lubrication film under high loads and achieve efficient lubrication performance [44–46]. In addition, the regimes of biological lubrication often appear together, that is, the synergistic effect of elastohydrodynamic lubrication and boundary lubrication makes the biological interface present low COF. For example, HA has high viscosity in the synovial fluid of joints, which can play an elastohydrodynamic lubrication role between the cartilage interfaces [47]. Besides, they can also play a role of boundary lubrication by assembling with mucins to form a bottle-brush aggregation [48].

2.3 Hydration lubrication

In recent decades, Klein et al. [41, 49–51] has proposed a water-based lubrication mechanism known as hydration lubrication. Hydration lubrication is commonly found in human body. The strong interaction in lubricants and water molecules forms an effective hydration layer between the sliding surfaces to maintain the excellent lubrication performance [49]. Figure 3 shows the formation of the hydration layers and the mechanism of hydration lubrication. In general, water molecules are electrically neutral, but they have a strong dipole due to the remaining charges on hydrogen and oxygen atoms, which make them interact strongly with the charged groups, and can be around the charged groups to form hydration layers [51, 52]. On the other hand, the process of dehydration

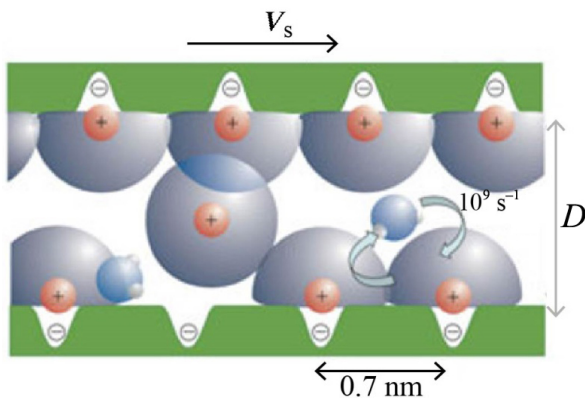


Fig. 3 Proposed hydration lubrication mechanism when two charged surfaces confining hydrated counterions slide past each other. V_s represents the velocity of top surface sliding past the bottom and D represents the surface separation. Reproduced with permission from Ref. [49], © The author(s) 2013.

requires a large energy, which makes it difficult for water molecules to move away from the charge. Therefore, such dense and stable hydration layers formed at the friction interfaces can bear huge normal loads. At the same time, the repulsion effect between hydration layers can avoid them overlapping each other. In addition, the water molecules in hydration layers can flow freely, and the moving water is better able to adapt to the external shear forces, which are useful to reduce friction at the sliding interface. At present, artificially synthetic biolubricants are mostly featured with hydrophilic groups in order to realize hydration lubrication. The mechanism of hydration lubrication is different from the classical lubrication mechanism, which is a new friction theory that can be used to explain the boundary lubrication in aqueous medium. Therein, the fluid hydration layer formed around positive and negative ions, zwitterionic, and polar groups are the core contents of the study of hydration lubrication [53].

In fact, dry eye syndrome, dry mouth, and osteoarthritis are all common diseases resulting from the dysfunction of hydration lubrication between the contact surfaces of tissues [7–9]. The most typical feature of these cases is the decreased amount of secreted lubricants along with the quality deterioration, which results in the appeared friction between the contacted biological surfaces. In addition, the adhesion of tissues during surgery is also the other kind of typical case of insufficient hydration lubrication at sliding biological interfaces [54, 55]. Therefore, in

order to improve the local lubrication performance of damaged tissues or organs, artificially synthetic exogenous water-based biolubricants are extremely necessary for the treatment of those above symptoms. Aiming at highlighting the mechanisms of biolubrication, this review takes dry eye syndrome, tissue adhesion, and osteoarthritis as representative examples, and then systematically describes the current research progress of different types of synthetic biolubricant materials.

3 Functional biolubricants

3.1 Biolubricants in treating dry eye syndrome

Dry eye syndrome is a tear secretion obstacle disease with dry eyes as the main symptom, which is easy to cause itchy eyes, eye sore, and sensitive to external stimulation because of insufficient secretion of tears [56–58]. Especially for severe dry eye syndrome patients, it is commonly accompanied by eye swelling and even corneal lesions, which may result in diminution of vision [59, 60]. Tears are composed of the innermost mucins, the hydration layer in the middle, and the outermost layer of phospholipids [61, 62]. The main lubrication regime of tears is boundary lubrication from the hydration layer of adsorbed mucins [62]. When the secretion mucin amount reduces, the local boundary lubrication is affected along with the feeling appearance of friction between eyeball and tissue mucosa. In addition, the role of phospholipids in the outermost layer can effectively prevent the volatilization of water [63]. When the phospholipid secretion amount is insufficient, the hydration layer in the middle is unstable, which causes the lubrication dysfunction. From the viewpoints of biotribology, dry eye syndrome is a typical lubrication failure case resulted from insufficient tear lubricant production. Therefore, artificially synthetic tear lubricants are indispensable in the treatment of dry eye syndrome.

At present, the artificial tears on the market are mainly divided into two kinds: gel type and aqueous type [64–66]. Aqueous artificial tears are mainly composed of physiological saline solution, hydrosoluble lubricants (propylene glycol, polyethylene glycol (PEG), and hydroxypropyl cellulose), and osmotic

protectant (glycerol) [64, 67]. Lubricants in artificial tears can effectively enhance the hydration and lubrication performance of the eyes to make up for the deficiency of the insufficient tear secretion. However, for dry eye syndrome patients caused by the decrease of liposome, artificial tears just contain hydrophilic lubricants are not ideal. Based on this, artificial tears containing liposomes, which can supply the insufficient secretion of phospholipids and delay the evaporation of tears to improve the lubrication performance of the eyes, have shown satisfactory results in treating dry eye syndrome [68]. In addition, HA has been widely used in the preparation of artificial tears because of its good water retention ability. Compared with the other lubricants, HA also has excellent viscoelasticity, which can further prolong the retention time of artificial tears on the eyes [69]. The water retention feature of HA can also be significantly improved with the increase of the concentration. Ahmed et al. [70] found that artificial tears containing 0.3% HA had the best water retention effect in experimental dry eye.

Therefore, improving the concentration of HA in artificial tears appropriately may show more effective treatment effect for dry eye syndrome. Besides, as an active macromolecule, HA can also improve the vitality of corneal epithelial cells and promote the physiological function of cell repair except lubrication performance [71]. Based on the advantages of HA, artificial tears containing HA have attracted more attention from researchers at present. Simmons and Vehige [72] added HA acid to carboxymethyl cellulose to prepare artificial tears with excellent lubrication properties, which generates positive effect in treating dry eye syndrome. Especially, the HA not only changes the rheological properties of artificial tears with obvious shear thinning effect, but also prolongs the retention time of artificial tears on the eyeballs. Rangarajan et al. [64] added HA to hydroxypropyl guar (HPG) to form artificial tears, which exhibit better lubricity and longer retention time on the ocular surface than those of HPG alone (Fig. 4(a)). In addition, bovine serum is also used as artificial tears to treat dry eye syndrome.

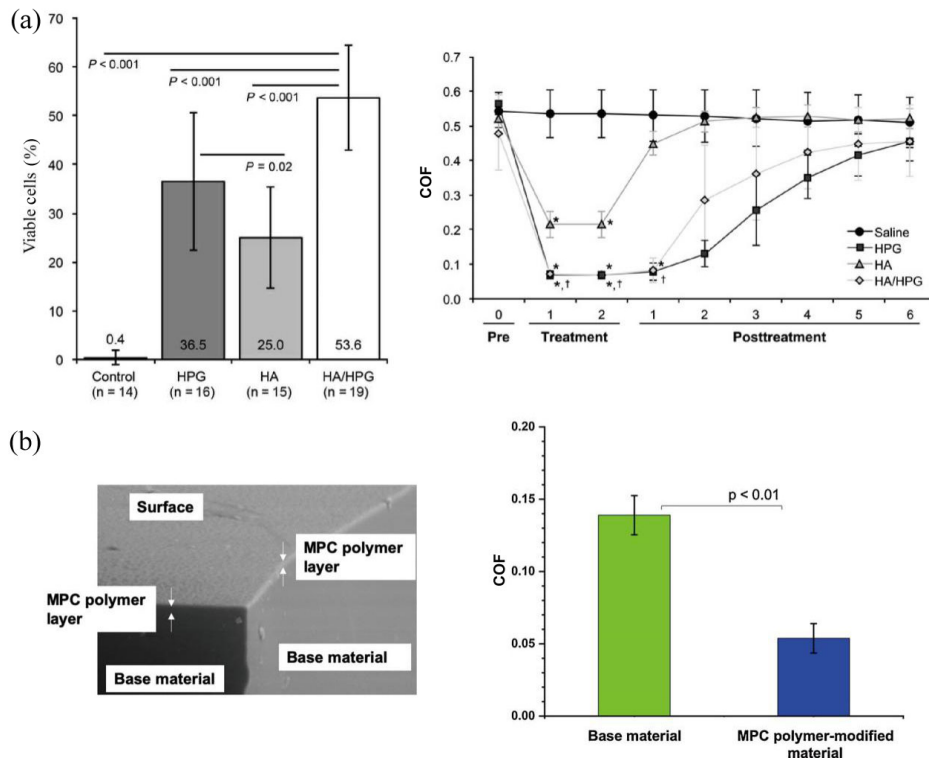


Fig. 4 (a) Left: hydration protection against the desiccation of HPG, HA, and HA/HPG; right: COFs of saline, HPG, HA, and HA/HPG. Reproduced with permission from Ref. [64], © Rangarajan et al. 2015. (b) Left: ESEM 3D image of 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer layer on the top of the base silicone hydrogel contact lens material in the 100% relative humidity environment; right: COFs of base contact lens material and PMPC polymer-modified contact lenses. Reproduced with permission from Ref. [73], © Elsevier B.V. 2020.

Although bovine serum is not effective for improving the lubrication performance of eyes, it contains a large number of proteins that can maintain the osmotic pressure of tears steady [74], and the proteins can inhibit the apoptosis of corneal epithelial cells and alleviate symptom of dry eye syndrome [75]. Compared with the traditional artificial tears with excellent lubrication performance, bovine serum mainly provides physiological functions in treating dry eye syndrome.

Aqueous artificial tears are convenient to be used and show excellent effects in alleviating mild dry eye syndrome, but gel artificial tears may be more useful for severe dry eye syndrome. Gel artificial tears can prolong the retention time of lubricants in eyes and reduce the injection frequency. Gel artificial tears also present obvious rheological feature of shearing thinning, which can make up the deficiency of insufficient mucin secretion to enhance the interface lubrication performance of eyes effectively [66]. In addition, the viscosity of gel artificial tears can be regulated according to the needs of different patients with dry eye syndrome. However, gel artificial tears with high viscosity may cause blurring vision, and gel lingering in the eyes for a long time is easy to accumulate, which makes the eyes feel uncomfortable [56]. Hence, the proper viscosity of synthetic gel tears with long retention time and low effect to eyesight is necessary. Artificial tears indeed relieve the symptoms of dry eye syndrome by improving the lubrication performance of eyes. At the same time, patients can also choose aqueous artificial tears and gel artificial tears through considering the severity of the symptoms. However, it should be pointed out that most artificial tears contain preservatives, and long-term use will cause damage to corneal epithelial cells. What's more, the lubricating molecules in artificial tears may damage the tear film and affect the normal secretion of tears, and improper use artificial tears will even aggravate the symptoms of dry eye syndrome.

The number of eye problems related to contact lenses such as mild dry eye syndrome is on the rise because more and more people wear contact lenses. It is estimated that nearly 140 million people around the world now wear contact lenses because of eyesight problems [76]. Since the contact lenses touch with the cornea directly, the lubricity of them has to be

considered to ensure the lubrication system of eyes to keep normal. At present, contact lenses are mainly divided into two kinds according to the synthetic material feature: rigid gas-permeable lenses (RGPLs) and soft contact lenses (SCLs) [77]. RGPLs are mainly made of polymethyl methacrylate (PMMA) materials [78], while SCLs are mainly made of silicone hydrogels [79]. Meanwhile, silicone hydrogels have excellent oxygen permeability and other popular advantages to be used as contact lenses. However, the lubrication performance of synthetic silicone hydrogels is not ideal because of its poor surface wettability [80]. Therefore, it is of great significance to develop SCLs with excellent lubrication performance. Assembly of natural or artificial lubricant is highly effective for improving the lubrication performance of SCLs. HA is commonly used as contact lens care solutions due to its excellent water retention ability [81] and good biocompatibility at physiological environment. When soaking into the solution containing HA, the HA can enter into the surface gel network of SCLs and then release slowly during wearing process to improve the local wettability/lubricity [82]. Another way is enhancing the lubrication performance of contact lenses by chemical anchoring of functional macromolecules directly. Yu et al. [83] prepared one layer of poly(dimethyl acrylamide) (PDMA) film on the surface of the contact lenses through hydrophobic initiator, which indeed improved the lubrication performance without changing the transparency and oxygen permeability of the contact lenses. Shi et al. [73] prepared one layer of hydrophilic PMPC on the silicone hydrogel contact lenses, and the COF of the contact lenses with anchoring PMPC layer was reduced by 80% compared to the blank contact lenses (Fig. 4(b)). As mentioned above, improving the lubrication performance of eyes by using artificially synthetic tears is a positive way to treat dry eye syndrome. Furthermore, assembly and anchoring of lubricated polymer macromolecules are both necessary to enhance the lubrication performance of contact lenses to inhibit the development of dry eye syndrome.

3.2 Biolubricants in resisting tissue adhesion

Postoperative tissue adhesion has always been a

difficult problem to solve in surgery, which is easy to cause intestinal obstruction, abdominal pain, infertility, and other complications, and even requires a second operation in serious cases which aggravate the pain of patients [84–86]. According to the statistics [55], tissue adhesion occurs in more than 90% in abdominal surgical. Therefore, how to prevent tissue adhesion has important significance in clinical practice. In general, the mechanism of tissue adhesion is mainly because of the rapid proliferation of fibroblasts and the secretion of a large number of collagen fibers to form fibrin network, which eventually lead to the adhesion of adjacent tissues [87, 88]. The generation of tissue adhesion is a part of tissue healing process, and the purpose of anti-tissue adhesion is to achieve a balance between tissue healing and adhesion, so as to reduce the formation of tissue adhesion while not interfering with tissue healing [89]. From the point of biotribology, improving the lubrication or separation performance between the sliding tissue interfaces is an effective strategy to inhibit the formation of tissue adhesion, because it is difficult for the cellular pseudopod to form a strong focal adhesion on lubricated surface to achieve anti-tissue adhesion.

At present, biological materials to prevent tissue adhesion mainly include aqueous lubricants, barrier membranes, and injective hydrogels [87, 90, 91]. Aqueous biolubricants based on biomacromolecules including chitosan, HA, and sodium alginate solution, all have lubricative and physiological effects. For example, the hydrophilic carboxymethyl chitosan is widely used in anti-tissue adhesion. In addition to the excellent aqueous lubrication performance due to the existence of large amount of COOH, carboxymethyl chitosan also exhibits physiological effect of anti-inflammatory to inhibit the fiber cell hyperplasia [92]. Similarly, HA is also used as functional biolubricants to prevent tissue adhesion due to the excellent water retention ability and anti-inflammatory effect [93]. The reason to prevent tissue adhesion by aqueous biolubricants can be attributed to their excellent hydration ability. Besides, natural biolubricants such as chitosan and HA are both biocompatible, which can be completely degraded and will not injure the normal tissue *in vivo* [94]. However, due to the easy fluidity and poor adhesion of aqueous biolubricants

at sliding tissue interface, they are easily lost on the wound surface of the tissues, resulting in non-ideal anti-tissue adhesion effect [95]. At the same time, despite the degradation of lubricating macromolecules will not damage tissues *in vivo*, the degradation rate of them is fast in most cases, which will also affect the local anti-adhesion effect.

Based on this, barrier membrane and hydrogels with specific fixed and adhesion features along with adaptive degradation time *in vivo* are widely used in anti-tissue adhesion [96]. The raw materials for preparing barrier membrane and hydrogels in anti-tissue adhesion should be biocompatible and degradable, such as polylactic acid (PLA), PEG, and poly(ϵ -caprolactone) (PCL) [86, 87]. The barrier membrane can isolate the tissue interface effectively for several days to prevent adhesion during the healing process. However, the lubrication performance and adaptability to complex traumatic surfaces of barrier membrane are undesirable compared with aqueous biolubricants. Hence, improving the lubrication performance and compatibility of the barrier membrane are necessary. Cheng et al. [97] synthesized one kind of novel poly((dopamine methacrylamide)-co-(2-methacryloyloxyethyl phosphorylcholine)) (poly(DMA-co-MPC)) copolymer lubricant by radical copolymerisation method (Fig. 5(a)). The as-synthesized poly(DMA-co-MPC) copolymer lubricant contains both of functional adsorption and hydration groups, which enables it to successfully decorate onto the PCL nanofibrous membrane, exhibiting excellent anti-adsorption feature to fibroblasts from the extreme hydratability of PMPC chains (Fig. 5(b)). Compared with the bare PCL nanofibrous membrane, COF of this lubricative nanofibrous membrane decreased by about 65% (Fig. 5(c)), demonstrating the great potential application in anti-tissue adhesion.

Injectable hydrogels as functional biolubricants can be served as good anti-tissue adhesion materials in surgery due to their excellent tissue compatibility [98, 99]. Bioactive macromolecules, such as sodium alginate, HA, and chitosan derivatives, can be used to prepare the anti-adhesion lubricating hydrogels. These hydrogel materials can obviously extend the anti-adhesion time in comparison to aqueous biolubricants [100, 101]. Among them, injectable

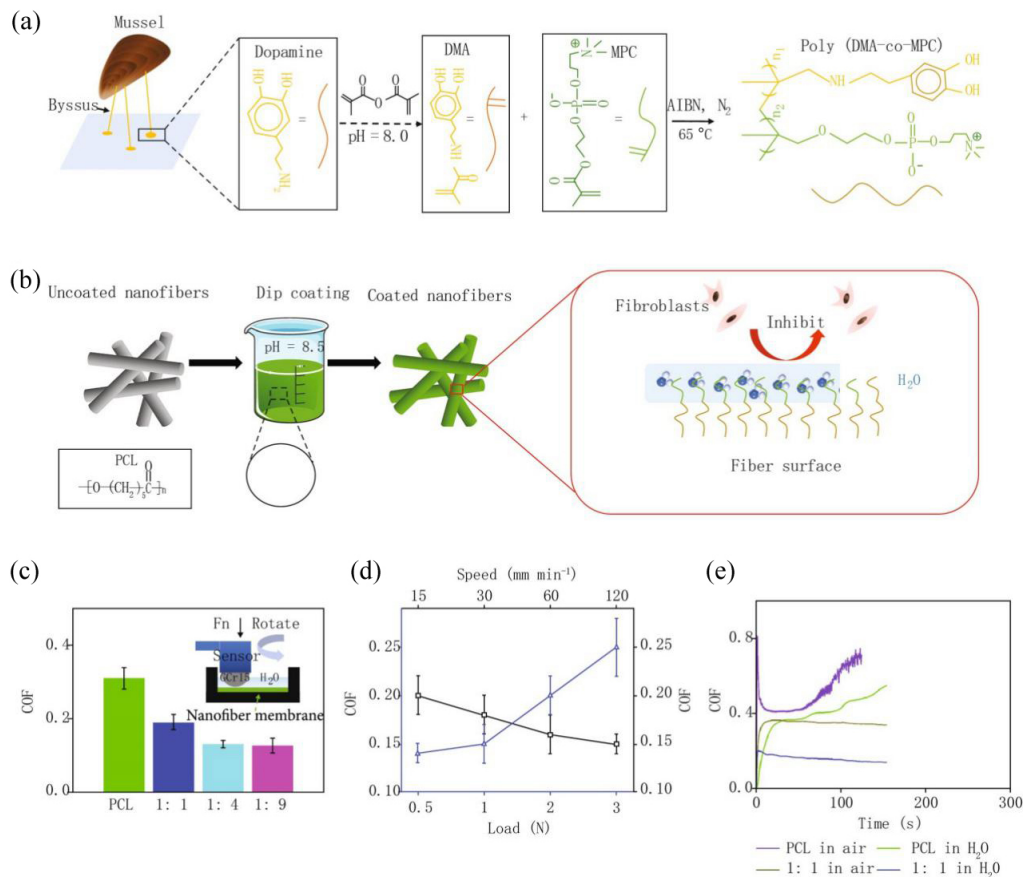


Fig. 5 Lubricative PCL nanofibrous membrane. (a) Synthesis processes of poly(DMA-co-MPC) (AIBN is azobisisobutyronitrile) and (b) schematic illustration of the fabrication of lubricative nanofibrous membrane by dip-coating method. (c) COFs of PCL nanofibrous membrane and poly(DMA-co-MPC)-modified nanofibrous membrane (with different ratios of DMA: MPC) (d) COFs of poly(DMA-co-MPC)-modified nanofibrous membrane under different loads and rotation speeds. (e) COF–time curves for PCL nanofibrous membrane and 1:1 poly(DMA-co-MPC)-modified nanofibrous membrane tested in air and water. Reproduced with permission from Ref. [97], © Liang Cheng et al. 2020.

in situ curable hydrogel material system has attracted considerable attention of researchers due to the convenience in terms of anti-tissue adhesion. The most common injectable hydrogel system is based on the dynamic Schiff base reaction between amino and aldehyde, and the typical one is the Schiff base reaction between chitosan and aldehyde dextran [102]. This kind of injectable hydrogel is constituted by natural polysaccharides that can be completely degraded *in vivo* without causing damage to tissues and cells [103]. Besides Schiff base reaction, Fujita et al. [104] used three kinds of synthetic PEG macromolecules with different functional groups (aldehyde, aminoxy, and catechol) to solidify into injectable hydrogels *in vivo* by the oximation reaction (Fig. 6(a)). Compared with the control samples, this injectable PEG-functionalized hydrogels exhibit good mechanical

properties, excellent anti-adhesion effect, and the lowest average adhesion intensity score by employing a rat cardiac adhesion model (Figs. 6(b)–6(e)), which makes it present a good application prospect in the prevention of adhesion in post-surgical cardiac. In addition, synthetic zwitterionic polymers with good biocompatibility have also demonstrated excellent lubrication performance and good anti-adhesion ability. Based on this, Zhang et al. [105] prepared a viscous, injectable hydrogel formed by zwitterionic poly(carboxybetaine acrylamide) (PCBAA) solution. This kind of injectable PCBAA hydrogels can completely prevent the fibronectin from adsorbing to the injured surface *in vivo* within 24 h after surgery (the initial development of adhesion) and significantly reduce the adhesion of fibroblasts *in vivo* after surgery.

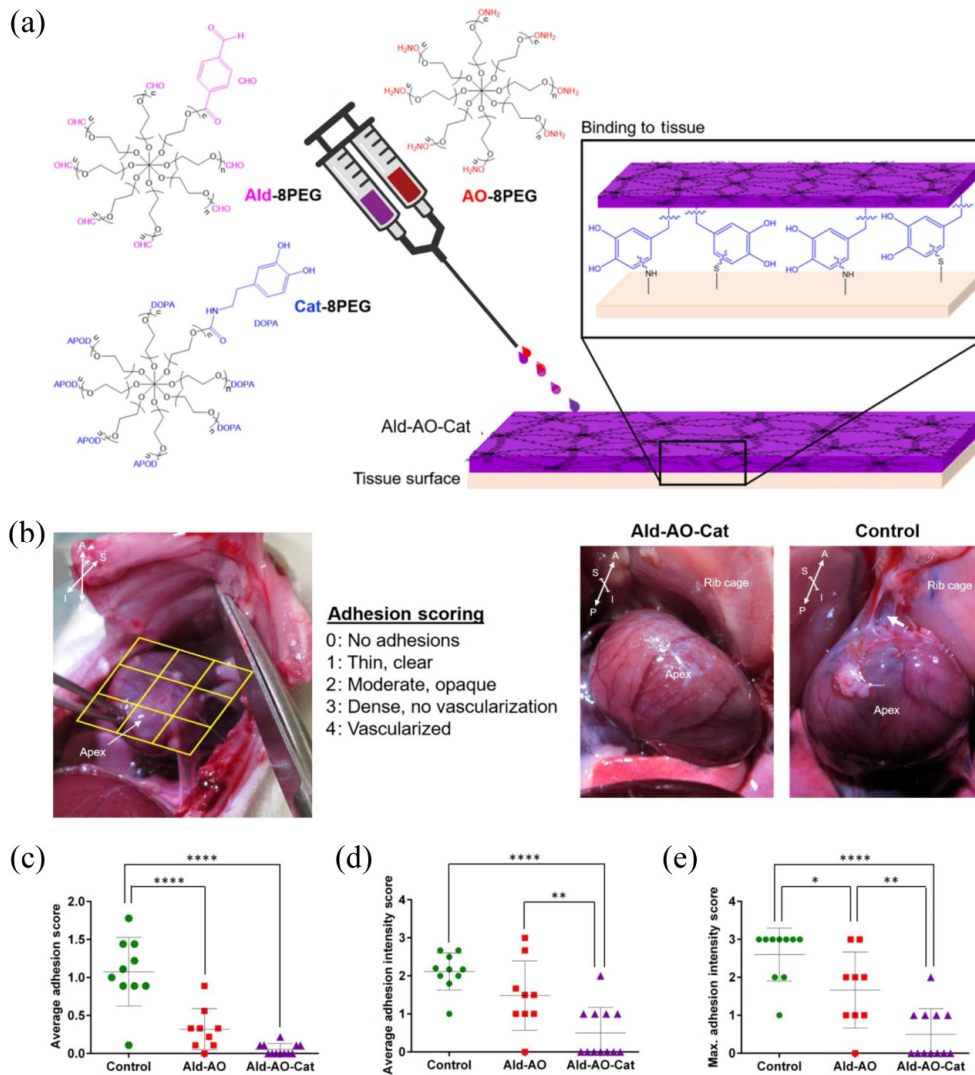


Fig. 6 (a) Schematic diagram showing the fabrication process of injectable catechol-functionalized PEG hydrogels of Ald-AO-Cat based on three distinct 8-arm star PEG polymers (Ald-8PEG, AO-8PEG, and Cat-8PEG). (b) Ald-AO-Cat hydrogels are used as functional anti-tissue adhesive, and the reduced adhesion formation phenomenon was observed after 2 weeks upon the application in rat surgical model. (c–e) Average adhesion score, average adhesion intensity score, and maximum adhesion intensity score of control sample, Ald-AO, and Ald-AO-Cat hydrogels. Reproduced with permission from Ref. [104], © The Author(s) 2021.

Objectively, postoperative tissue adhesion is indeed a difficult problem that needs to be solved in surgery. Even though scientists have made significant breakthroughs in this field, it still lacks ideal or practical anti-adhesion lubricating materials to prevent tissue adhesion completely in clinical now. Among the various methods of postoperative anti-tissue adhesion, natural or synthetic aqueous biolubricants are good choice, but their interface retention and anti-degradation properties should be improved. Even though the functionalized barrier membranes can inhibit tissue adhesion effectively and have been widely

used in clinic, they still show shortcomings when dealing with complex three-dimensional trauma surfaces. Recently, injectable lubricating hydrogels demonstrate significant advantages including adaptive mechanical behavior, long retention time against tissues, compatibility for complex wound sites, and favorable degradation behavior, which exhibit the most potential application in clinic.

3.3 Functional joint biolubricants

Natural joint system exhibits highly efficient lubrication behavior, and the COF between sliding cartilage

surfaces can be extremely low (0.001–0.03) [106]. The extraordinary lubrication feature of joint system can be attributed to the synergistic contribution from cartilage surface and synovial fluid. Articular cartilage is mainly composed of collagen fibers, and chondrocytes are distributed among the fibers of articular cartilage to maintain metabolism [107]. The surface of articular cartilage layer is extremely smooth and elastic, which not only plays a role in lubrication, but also can absorb and buffer external stress to protect joints [108, 109]. The surface network of articular cartilage is filled with water and contains an amount of charged biomacromolecules, which can form effective boundary hydration layer to achieve low friction at the cartilage interface [110]. In addition, synovial fluid in joint cavity also plays an important role for friction-reduction [111]. The synovial fluid is mainly composed of HA, polyproteoglycan, and lubricine (Fig. 7(a)) [112]. Among them, HA, as the main component in synovial fluid, is a linear polysaccharide with a huge molecular weight of up to millions of daltons, and can bind an amount of water molecules in body fluid environment to separate the sliding cartilages [112, 113]. Benz et al. [114] and Tadmor et al. [115] have systematically studied the mechanism behavior of HA on joint lubrication. Meanwhile, HA can significantly increase the viscosity of joint synovial fluid which is essential for achieving the elastohydrodynamic lubrication of joints [116]. In addition, HA can also bind with

phospholipid which is easily anchored to the surface of phospholipid vesicles to prevent phospholipid from being degraded by phospholipase [117]. The synergistic effect of HA and phospholipid can significantly improve the hydration lubrication performance of synovial fluid.

Proteoglycan aggregate is a natural hierarchical bottle-brush that plays an important role in cartilage lubrication (Fig. 7(b)), in which the hydrophilic sugar side chains can immobilize large amounts of water molecules while its backbone can interconnect to other segments or adsorb onto the surface [118]. Previously, Klein et al. [112, 119, 120] have well revealed the lubrication mechanism of polymer brushes. The polymer brushes are contracted under dry condition and can ionize in aqueous solution to keep a highly swelling and stretching state [121]. The ions produced by ionization make the inside of polymer brushes possess high osmotic pressure to prevent the interface of them contacting [49]. Correspondingly, the directions of osmotic pressure and external loads are on the contrary, which can effectively resist applied loads to enhance the lubrication performance [49]. In addition, the hydration of the polymer brushes makes the fluid layer form at the sliding interface to decrease the local COF [112]. More importantly, these “bottle-brush” biomacromolecules not only act as flowing lubricants, but also can assemble on the surfaces of cartilage to form a boundary lubrication layer to reduce friction

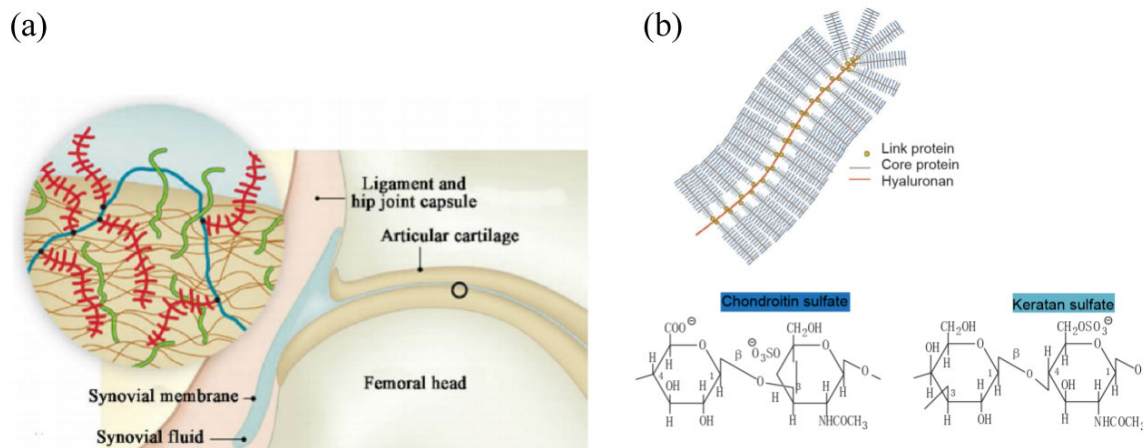


Fig. 7 (a) Illustration of the natural articular cartilage system and functional biomacromolecules: HA (blue), polyproteoglycan (red bottle-brush-like molecules), and lubricine (green). Reproduced with permission from Ref. [112], © The American Association for the Advancement of Science 2009. (b) Illustration of the bottle-brush structure of polyproteoglycan. Reproduced with permission from Ref. [118], © The American Association for the Advancement of Science 2008.

[122, 123]. For HA, glycoprotein, and polysaccharide, all of them belong to the polyelectrolyte containing hydrophilic groups, which can be highly hydrated in aqueous solution to form hydration lubrication layer at the sliding interface [112].

Intuitively, the obvious deficiency of these above biomacromolecules in joint system is the basic feature for people with arthritis (osteoarthritis and rheumatoid arthritis). The deterioration of articular cartilage and the loss of natural lubricating biomacromolecules would inevitably induce joint dysfunction [124–127]. Therefore, from the perspective of biotribology, injecting natural or synthetic biolubricants becomes a key mean in the treatment of arthritis.

The content of HA tends to decrease significantly with the occurrence of arthritis, resulting in the viscosity reduction of synovial fluid to deteriorate the lubrication performance of joints [128]. Therefore, injecting natural HA into joints cavity is an effective way in treating arthritis [129]. Apart from improving the viscosity of synovial fluid and restoring elastohydrodynamic lubrication, HA also has anti-inflammatory effect to inhibit the development of arthritis [130]. Similar to HA, natural chitosan (cationic glycan that exists in nature) can be also used as functional biolubricants to treat arthritis as well [131]. Besides, chondroitin sulfate (CS) and glucosamine are further widely used as treating arthritis in clinical [132, 133]. In addition to natural biological lubricants, artificially synthetic biolubricants also exhibit the excellent effect in the treatment of arthritis. Wathier et al. [134] synthesized a polyanion biolubricant by ring-opening metathesis polymerization of methyl 5-oxanorbornene-2-carboxylate (Fig. 8(a)). This as-synthesized polyanion lubricant can significantly increase the viscosity of synovial fluid in the joints, showing an extremely low COF at the cartilage sliding interface compared with saline, synvisc, and bovine synovial fluid (BSF) (Figs. 8(b)–8(c)). The excellent lubrication performance of this polyanion lubricant may be attributed to the extreme hydration degree of anion groups in polymer chains.

Inspired by typical “bottle-brush” structure of natural biomacromolecule, synthesizing brushed biolubricants with excellent lubrication performance to treat arthritis has attracted extensive attention. Spencer et al [135, 136] has prepared series of brushed lubricants with

PEG as side chains and investigated the relationship between the side chain feature and lubrication performance. The backbone of brushed-lubricants is positively-charged poly L-lysine (PLL) or polyallylamine (PAAm), while the side chain is the flexible PEG (Fig. 8(d)). Compared with the 2-(4-(2-hydroxyethyl)-1-piperazinyl)ethane sulfonic acid (HEPES) buffer, the as-synthetic PLL-g-PEG or PAAm-g-PEG exhibited the good lubrication performance (Fig. 8(e)). Meanwhile, the positively-charged PLL or PAAm can bind onto the surfaces with opposite charge through electrostatic interaction to form a boundary lubrication layer [137]. The length and grafting density of the side chains have the great influence on the lubrication performance for the brushed lubricants [138]. In addition, Pettersson et al. [139] synthesized one kind of novel bottle-brush polyelectrolyte lubricant by copolymerizing ethylene oxide-methyl ether methacrylate (PEO₄₅MEMA) and methacryloxyethyl trimethylammonium chloride (METAC). The as-synthesized polyelectrolyte lubricant could adsorb onto the substrate surface through electrostatic interaction in the shearing process to form a stable boundary lubrication layer, while its lubrication performance was highly related to the number of chain density of each segment.

In spite of the fact that macromolecular lubricants have positive effects in treating arthritis, most of them degrade too fast at physiological environment. Commonly, patients with arthritis need to inject aqueous lubricants once a week to maintain the lubrication and viscoelasticity of damaged cartilage, which may increase the risk of joint infection [140]. In addition, both of natural and synthetic aqueous macromolecular lubricants are still insufficient in eliminating the inflammation. Therefore, it is necessary to synthesize multifunctional biolubricants with synchronous lubrication performance and anti-inflammatory effect. Meanwhile, with the great development of nanoparticle synthesis technology, functional nanoparticles loaded with anti-inflammatory drugs have been widely used for the treatment of arthritis [141–145]. The anti-inflammatory drugs can slowly release from nanoparticles and then arrive in the damaged site of cartilage to reduce the local inflammation [146, 147]. Although exhibiting the good treatment effect, the lubrication performance of bare synthetic drugs-loaded nanoparticles such as gold

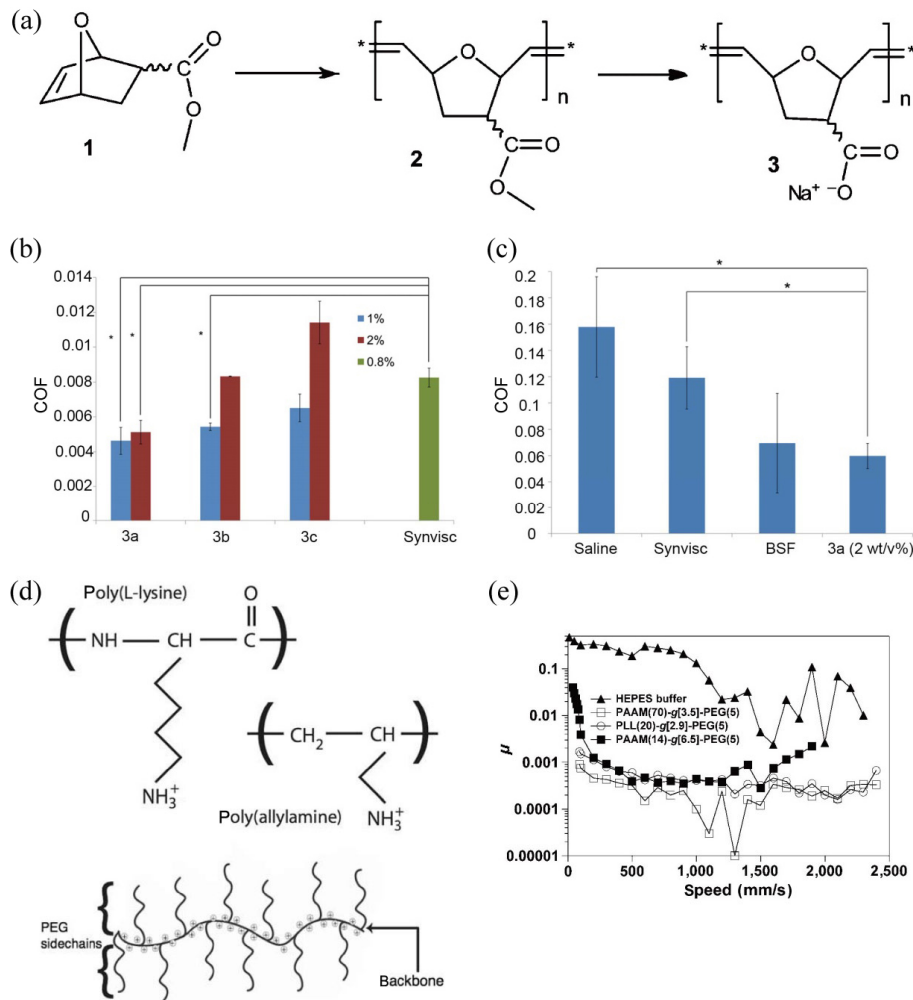


Fig. 8 (a) Schematic illustration of the process of preparing sodium poly(7-oxanorborene-2-carboxylate). (b) COFs of 1% and 2% sodium poly(7-oxanorborene-2-carboxylate) aqueous solution at different molecular masses on metal surfaces (3a represents 2.5 MDa; 3b represents 3.2 MDa; 3c represents 3.7 MDa; synvisc represents sodium hyaluronate). (c) Difference of COFs of 2% sodium poly(7-oxanorborene-2-carboxylate) aqueous solution (2.5 MDa), saline, synvisc, and BSF on *ex vivo* human cartilage–cartilage. Reproduced with permission from Ref. [134], © American Chemical Society 2013. (d) Structure of poly L-lysine (PLL) and polyallylamine (PAAm) and schematic structure of polymer brush which PEG as side chains, (e) COFs (μ) of PAAm-g-PEG and PLL-g-PEG. Reproduced with permission from Ref. [135], © Springer Science+Business Media, LLC 2008.

nanoparticles, chitosan nanoparticles, silica nanoparticles, and poly(lactic-co-glycolic acid) (PLGA) nanoparticles is unsatisfactory. In order to improve the lubrication performance of synthetic nanoparticles, surface modification strategies were commonly used to graft hydrophilic polymer chains. As shown in Fig. 9(a), Zhang et al. [148–151] grafted the charged polymer brushes chains from the surface of hard silica nanoparticles to prepare one kind of novel biolubricants with simultaneous lubrication performance and anti-inflammatory effect. These functional silica nanoparticles can be used as an

effective intra-articular injective lubricant in the treatment of rat osteoarthritis. Except for hard silica nanoparticles, as one kind of novel polymer-based colloidal particles, soft microgels exhibit adaptive modulus compatibility against cartilage along with good biocompatibility [152]. The internal network of microgels can swell sufficiently in water to achieve typical viscoelastic state for resisting the external force, while the surface-anchored polyelectrolyte chains are beneficial to realize good hydration, resulting in its extraordinary lubrication performance [153, 154]. Furthermore, the swelling network of microgels can

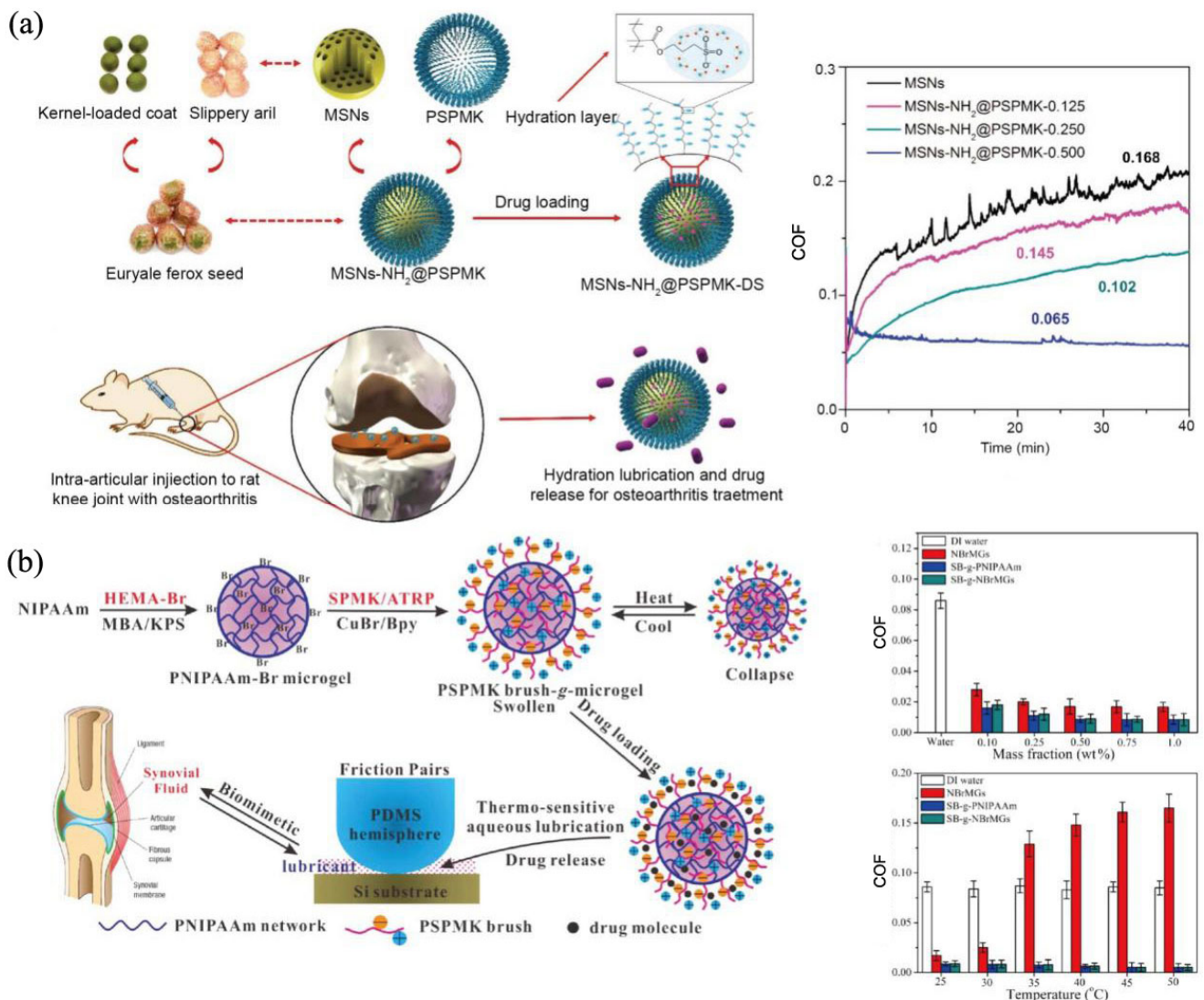


Fig. 9 (a) Left: schematic diagram of modified silica nanoparticles as lubricants to treat arthritis; right: COFs of modified silica nanoparticles under different circumstances and hematoxylin-eosin (H&E) staining and safranin O-fast green staining of the cartilage sections after the treatment of rat destabilization of the medial meniscus-induced osteoarthritis at eight weeks after surgery. Reproduced with permission from Ref. [148], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018. (b) Left: schematic illustration of the fabrication of PSPMK brushes-grafted poly(N-isopropylacrylamide) (PNIPAAm) microgels; right: COFs of the PSPMK brushes-grafted PNIPAAm microgels under different conditions. Reproduced with permission from Ref. [156], © American Chemical Society 2014.

be used to load drugs, while the functional lubricating microgels exhibit huge application potential in the treatment of arthritis [155]. As shown in Fig. 9(b), Liu et al. [156] grafted hydrophilic polyelectrolyte brushes of poly(3-sulfopropylmethacrylate potassium salt) (PSPMK) from the surface of the microgels by surface-initiated atom transfer radical polymerization (SI-ATRP) method, and then loaded the anti-inflammatory drug of aspirin into microgels to prepare one kind of novel microgel biolubricants.

The as-prepared functional microgels not only showed excellent lubrication performance, but also can realize the temperature controlled release of the aspirin, demonstrating great potential in osteoarthritis treatment.

In recent years, injectable hydrogels have also been widely investigated in bone repair and treating arthritis [157, 158]. The damaged wound site of cartilage layer can be well repaired by injectable hydrogels [159], due to its similar biochemistry feature as natural extracellular matrix [160]. Kim et al. [161] designed

a hybrid hydrogel containing a polymer aggregate azide-functionalized block copolymer. This hybrid hydrogel exhibited the good effect of nitric oxide scavenger and sequential drug release functionality. As shown in Fig. 10, PLA-*b*-PEG- N_3 copolymer and azide-functionalized HA (HA- N_3) could be rapidly gelled *in situ* via a “click” cycloaddition reaction. Meanwhile, in order to achieve rapid and selective nitric oxide responsiveness, a dialkyne-functionalized NO-cleavable crosslinker of N,N-(2-amino-1,4-phenylene) dipentyn-4-amide (DA-NOCCL) was

absorbed into the HA- N_3 skeleton. In addition, the PLA-*b*-PEG- N_3 crosslinked with DA-NOCCL and HA- N_3 , which can not only load anti-inflammatory drugs of dexamethasone, but also enable the hybrid hydrogel to acquire self-healing lubrication behavior. In combination with anti-inflammatory drugs, the hybrid injectable hydrogel is effective in alleviating the symptoms of rheumatoid arthritis.

Wei et al. [162] prepared a hierarchically structured injectable hydrogels based on PEG and HA for cartilage repairing and osteoarthritis treatment. The preparation

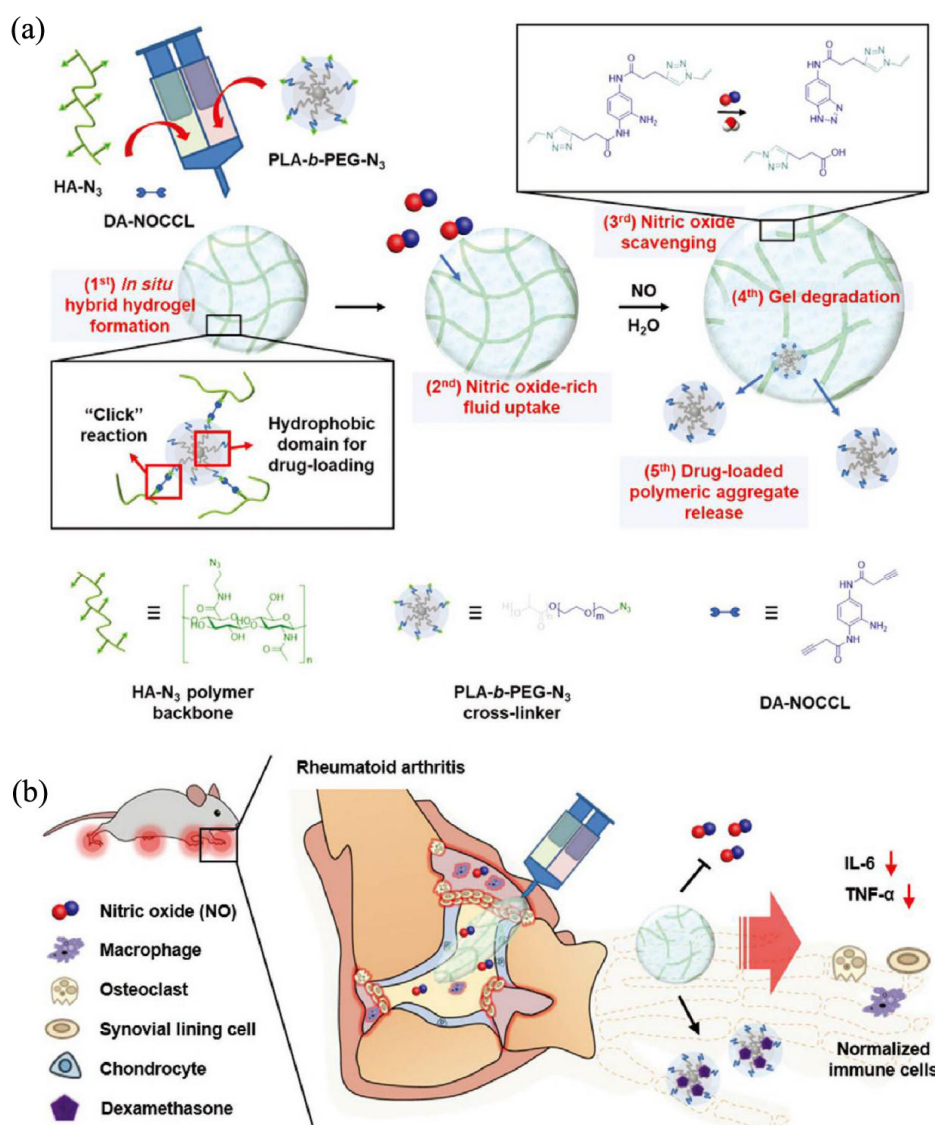


Fig. 10 Schematic illustration of the hybrid gel for combinatorial treatment of rheumatoid arthritis. (a) Chemical structure of the hybrid gel. Self-healable *in situ* hydrogel cross-linked with DA-NOCCL reacts with and scavenges NO to further release the drug-loaded polymeric aggregates for the combinatorial treatments. (b) Combinatorial treatment of rheumatoid arthritis with M-NO gel. M-NO gel directly scavenges overproduced NO and releases anti-inflammatory dexamethasone, depending on the severity of the diseases with NO concentration as a hallmark. Reproduced with permission from Ref. [161], © Wiley-VCH GmbH 2021.

process of hierarchically structured injectable hydrogel is shown in Fig. 11(a). Mesenchymal stem cells (MSCs) can induce differentiation chondrocyte, and short fiber (denoted as F_k in Fig. 11(a)) can assemble into spheroids to prevent MSCs from being destroyed after injection. To improve the mechanical property of the injectable hydrogel, another short fiber (denoted as F_c in Fig. 11(a)) was filled into them. Besides, F_c was loaded with anti-inflammatory drug of celecoxib (CXB) that can release continuously in joints. This injectable hydrogel has dual effects of anti-inflammatory and cartilage regeneration. Inspired by the wet adhesion feature of mussels, Zhang et al. [163] developed one kind of novel exosome (EXO)-integrated injectable adhesion hydrogel (AD/CS/RSF/EXO) through crosslinking of alginate-dopamine (AD), CS, and regenerated silk fibroin (RSF) protein. This kind of injectable hydrogel exhibited strong adhesion performance against tissue in wet environment along with good biocompatibility, which can accelerate the cartilage defect regeneration *in situ* and extracellular matrix remodeling after injection in rat patellar grooves (Fig. 11(b)). Furthermore, EXO released from hydrogel can recruit bone marrow-derived MSCs into hydrogel.

Different from aqueous biolubricants and nanoparticle-based lubrication materials, injectable hydrogels are more likely to highlight their physiological effect by coating non-MSCs, growth factors, etc. [164]. Based on this, it is of great significance to develop injectable lubricating hydrogels with simultaneous physiological treatment effect, repair functionality, and lubrication performance.

3.4 Functional biolubricants and coatings for medical devices

With the rapid development of medical device industry, surface lubrication treatment technologies have got great attention. Among them, medical catheters have been widely used in drug delivery, drainage, and blood delivery [165]. Commonly, medical catheters are generally prepared by hydrophobic or inert polymer materials, which results in their poor surface lubrication performance [166]. The high friction force between tissues and the catheter may result in inevitably tissue damage and infection. Therefore, it is necessary to improve the lubrication performance of the medical catheters. Meanwhile, artificial biolubricants, such as glycerin and silicone oil, are usually applied onto the surface of the catheters to

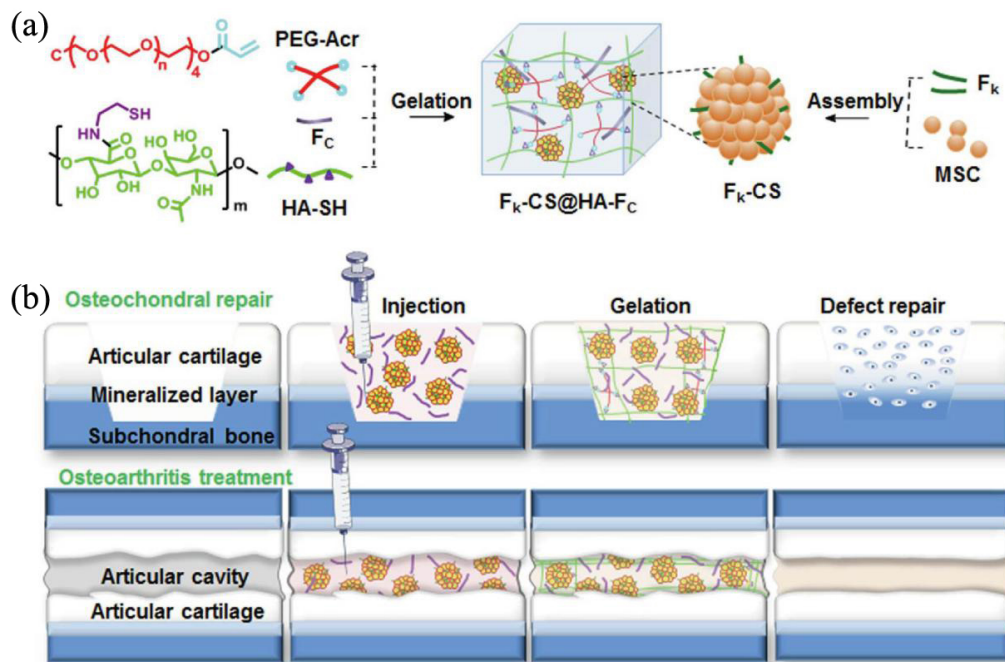


Fig. 11 (a) Schematic illustration of the process for hierarchically structured injectable hydrogel. (b) Therapeutic process and effects of injectable hydrogel on osteochondral defects and osteoarthritis. Reproduced with permission from Ref. [162], © Elsevier B.V. 2021.

enhance the interface lubrication performance in clinical [167, 168]. However, the coated biolubricants are easy to fall off from the catheter during the shearing process, which finally affects the lubrication efficiency. Besides, the adhesion and retention capacity of these hydrophilic polymers are very poor, especially on the surface of silicone-based devices [169, 170]. In the future, some functional adhesion groups, such as phenolic hydroxyl, ether chains, and silicone segments, could be introduced to improve the local interface retention capacity of artificial biolubricants.

In order to address these problems, lubricants-based hydrophilic polymers are permanently modified onto the surface of the catheter by coating solidification strategy [169, 171]. The hydrophilic lubrication coatings are generally crosslinked or non-crosslinked polymer network layers with an amount of hydrophilic chains, such as polyacrylamide (PAM), polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and natural macromolecule chitosan and HA [172]. Photo- and thermal-curing are two common methods used to prepare hydrophilic lubrication coatings [173, 174]. Compared with thermal-curing, photo-curing has a faster solidification speed, while the obtained hydrophilic coating exhibits better stability and lubrication performance. Yong et al. [165] grafted hydrophilic hydrogel lubricating layer on the surface of medical catheters by ultraviolet (UV) crosslinking of acrylamide monomer mixture in agar. The hydrogel layer-coated surface of medical catheters not only decreased 10 times of the COF, but also effectively inhibited the protein adsorption *in vivo*.

Over the past decades, polydopamine (PDA) coating has been regarded as a universal modification technology on various substrates [175, 176]. Firstly, PDA coating could be used as a bifunctional adhesive layer for chemically coupling macromolecular lubricant on the surfaces of biomaterials and devices. Song et al. [177] developed the dopamine–mucin composite coatings by using a simple two-step dip coating method, inspired by the excellent wet adhesion ability of mussels. In a typical case, PDA coating was immobilized on the polydimethylsiloxane (PDMS) and polytetrafluoroethylene (PTFE) substrates, and then the PDA-decorated substrates were immersed into mucin solution to construct double-layer composite coating by interface non-covalent chemical reaction.

As expected, the good lubrication property of mucin significantly reduces the local interface friction along with the weak tissue damage, indicating its great potential in the field of medical devices. Moreover, PDA coating could be used to load functional biolubricants under dynamic crosslinking deposition process. Wei et al. [178] reported a facile and universal method to prepare hydrophilic, low friction, and antifouling coating by dopamine-assisted codeposition of chitosan graft zwitterionic copolymer lubricant. The as-prepared codeposited coating showed low friction feature ($\mu \approx 0.015$) and good antifouling feature, implying its important application potential in biomedical devices and implants. Subsequently, Wei et al. [179] proposed a one-step strategy to construct ultralow-friction coating applicable for diverse biomaterial surfaces with the copolymerization of dopamine and hydrophilic monomers. The resulted coating showed ultralow-friction performance ($\mu \approx 0.003$) in pure water. This coating strategy could be used for the modification of the catheter, which can dramatically improve the surface wettability and the lubrication performance of the catheter device.

4 Conclusions and outlook

In this paper, we briefly reviewed the lubrication mechanism of natural macromolecular lubricants, while the importance of mucins in human body lubrication was emphatically introduced. Subsequently, we systematically introduced the research progress of several kinds of representative exogenous biolubrication materials, including eye drops, tissue anti-adhesion agents, joint lubricant, and medical device lubricant. These functional biolubricants cover both of natural biomacromolecules and synthetic polymer lubricants. The importance of different kinds of exogenous biolubricants for maintaining the normal operation of tissues and organs was emphasized, while the advantages and disadvantages of these biolubricants (macromolecule, injectable hydrogel, and nanoparticle) in improving the interface lubrication performance at the sliding tissue–tissue or tissue–device interfaces were discussed (Table 1).

Based on our humble understanding, we propose that the future development of biolubricants should

Table 1 Application fields, advantages, and disadvantages for different kinds of biolubricants.

| Type | Application field | Advantage | Disadvantage |
|---------------------|---|--|-----------------------|
| Macromolecule | Dry eye syndrome, tissue adhesion, arthritis, and medical devices | Convenience | Poor retention |
| Injectable hydrogel | Dry eye syndrome, tissue adhesion, and arthritis | Drug-loaded, good mechanical property, and long retention time | Poor fluidity |
| Nanoparticle | Dry eye syndrome, tissue adhesion, and arthritis | Drug-loaded | Difficult degradation |

consider the following points. 1) Although the lubrication mechanism of natural biomacromolecule lubricants (mucins, phospholipid, and HA) has been investigated *in vitro*, the specific lubrication behavior in human body environment still needs further research. In addition, the physiological activity about natural biomacromolecule to maintain the lubrication performance between sliding tissue interfaces should also be verified. 2) Even though some of the natural biomacromolecule lubricants exhibit extraordinary friction-reduction effect, the extraction cost is very high, and the mass production is difficult, which limits their wide range of applications in multi-fields of medical devices. By contrast, the synthetic biolubricants show great advantages, which should be paid more attention. 3) The synergy consideration of the surface hydration and adsorption is the basic design principle for developing novel synthetic biolubricants. 4) Taking into account further treatment and repair functions, drug-loaded nanoparticle-based biolubricants or injectable hydrogel biolubricants are good candidates in the future. (5) Degradation and metabolism properties of the synthetic biolubricants should also be considered seriously with considering future clinical applications. (6) Due to the common loss problem of fluid biolubricants under dynamic shearing environment, the available coating technologies *in situ* would be popular in the future.

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Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

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