Catechol functionalized (hyper)branched polymers as biomedical materials

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ABSTRACT

The catechol plays a variety of important roles in biological processes, prompting researchers to include them in the design of biomimetic biomedical materials. The low molecular weight and good water solubility of the catechol group (or its derivatives) make it a good candidate for functionalizing biomaterials that can be typically achieved by grafting it onto a polymer chain. To fully harness the powerful capabilities of catechols, one can think beyond grafting to linear polymer chains, towards hyperbranched polymers wherein at least one of the branches comprises at least one catechol moiety. In recent years, our lab has developed a number of approaches to synthesize multifunctional hyperbranched polymers with catechol functionalities for bioadhesives and wound closure applications. This review article focuses on the main synthetic approaches applied for introducing the important and versatile catechol building blocks within the (hyper)branched structure polymers. In addition, the applications of these polymers in various fields of biomedical research are highlighted as well.

Contents

1. Introduction

Catechol groups feature as a key component in many biological processes including pigment formation, neuron transmission, metal iron chelating, antioxidant properties, and robust adhesion (1, 2). One can take marine mussels possessing the ability to adhere strongly to surfaces, even in the wet and saline environment, as a fascinating example of a natural phenomenon associated with catechol groups. Researchers have found a mussel that produces 15 types of adhesive mussel foot proteins (mfps) where two of them in particular (mfp-3 and mfp-5) contain 20 to 30 percent of an amino acid called L-3,4-dihydroxyphenylalanine (L-DOPA) allowing them to act as a primer on a target surface (3, 4). In this case, DOPA, which is versatile in a chemical sense (participating in redox reactions, high affinity coordination of metal ions, and strong interfacial activity), have been identified by Waite and Tanzer to be responsible for the versatile adhesion of mussels (5). Researchers can take inspiration from such natural occurrences to drive the development of new materials (in this case adhesives), from the knowledge gleaned from nature. Recently, there have been several review papers published which focus on the synthetic approaches developed to design novel catechol-based polymer materials (6-8).

To date, two main routes have been utilized to produce polymer chains containing catechol groups. One method has been to graft the catechol group to a natural macromolecule, such as chitosan (9), hyaluronic acid (10), alginate (11), dextran (12), or synthetic polymers (8). In this approach, a limited amount of catechol groups was grafted onto the polymer chains. The second way has been to form linear polymer chains by radical polymerization of the mono-vinyl monomer bearing protected catechols (13). However, polymer chemists not only have a wide range of starting materials available for consideration, but the structural configurations can also be tailored to suit the requirement of the final product with architectures ranging from linear chains to tree like dendrimers. One such polymer architecture is termed a hyperbranched structure, which contains a multitude of branching points. Tailored branching significantly influences the physical properties, rheological and processing behavior of polymers (14). Numerous studies on polymer structure-property relationships have shown that controlled branching provides a

useful tool for the preparation of polymeric materials. A hyperbranched polymer (HBP) comprising a plurality of branches, wherein at least one of the branches comprises at least one catechol moiety, can be envisaged in order to fully harness the function of catechols. However, it is proverbial that the synthesis of HBPs is more difficult to control than the synthesis of the linear counterpart.

In the last decade, our group has been devoted towards producing adjustable chemical structures (cyclized/knotted, hyperbranched, and so on) through kinetic control mechanism (15-18). Based on the hypothesis that the HBPs functionalized with catechol groups may be more efficient as a bioadhesive and have a more broad application prospect, a series of catechol functionalized HBPs has been developed and the application potentials were explored (19-21). Our results revealed that HBPs with adjustable catechol content exhibited excellent and controllable adhesion properties. Based on our positive results, there is significant potential for further develop this technique towards clinical applications.

Catecholized HBPs should intrinsically possess excellent functional properties for a broad range of applications but research on catechol based HBPs is still at a very early stage. In this review, we summarize the state-of-the-art design and synthesis methods used to form HBPs equipped with catechol groups. This review will also highlight the applications of such polymers in the field of surgical adhesion/wound closure and antifouling coatings. Meanwhile, several unique aspects for the future developments of catecholized HBPs are discussed.

2. Design and synthesis of HBPs with catechol groups

The catechol group represents an important and versatile building block for the design of various biomaterials. Generally, catechol groups have been incorporated into macromolecules as main, side and end-chain group by employing various synthetic pathways (22). Molecules bearing catechols are easily oxidized into highly reactive quinones either by a strong oxidant agent such as NaIO4 (11) or an enzymatic oxidant (horseradish peroxidase combined with hydrogen peroxide, HRP/H$_2$O$_2$, for instance) (23),

but also by an alkaline aqueous solution (pH > 7.5) with oxygen as the oxidant (24, 25). Dopamine oxidation leads to dopaminechrome (**Fig.1**) following a multistep reaction pathway (oxidation and Michael addition) and dopaminechrome can be further converted to 5,6-dihydroxyindole and then self-polymerized to a polydopamine network (25). However, these oxidative polymerizations may result in the formation of an uncontrolled cross-linked network composed of a mixture of cross-linked products bearing mostly catechol and quinone groups as shown in **Fig.1.** These cross-linked structures are of prime importance in the field of coating materials, for its well-known advantage of being easily deposited on virtually all types of inorganic and organic substrates, including poly(tetrafluoroethylene) (PTFE) surfaces, with controllable thickness and durable stability (26-28). HBPs synthesized or functionalized with catechol groups are described in the following sections.

2.1 Conjugation of catechol on HBPs

Conjugation of catechol group to preformed polymer platforms has been the most widely recognized strategy. L-DOPA or dopamine is often chosen for such a purpose due to the simplicity of their structures, which can be easily grafted onto synthetic polymers. Researchers have taken pre-formed HBPs and functionalized the chain with catechol groups (29, 30). There are different chemical ligation methods for attaching catechol derivatives onto preformed (bio)polymers, such as grafting of catecholamines onto activated carboxylic acid functionalized polymers (**Fig. 2A**), grafting of catechols bearing a carboxylic acid group onto amino functionalized polymers (**Fig. 2B**) and grafting of catecholamines onto hydroxyl functionalized polymers (**Fig. 2C**). This chemical modification added an adhesive property to these polymers and enhanced its mechanical properties. The first strategy developed outlines reacting a polymer bearing carboxylic acid end-groups **(Fig. 2A1)** with a catecholamine such as L-DOPA, dopamine or its derivatives in the presence of an activator such as a water soluble carbodiimide (31). In a similar way, catecholamines can also be grafted to polymers bearing activated esters such as pentafluorophenyl, succinimidyl esters or triazole activated esters (**Fig. 2A2-4, respectively**) (32-34). Conversely, a catechol derivative bearing a carboxylic acid group

can also be grafted onto amine functionalized biomolecules and biopolymers. For example, 3,4-dihydroxyhydrocinnamic acid (DHCA) can be grafted to the amine groups by amide coupling, to introduce catechol groups to amine functionalized hyperbranched polyglycerol (HBPG) (29). In another way, hydroxyl-functional polymers can also be converted into *p*-nitrophenylcarbonate using *p*-nitrophenyl-chloroformate (NPC) as an activator, and finally grafted with catecholamines (35).

2.2 Polycondensation methodology

A dendrimer is a spherical, highly branched synthetic polymer with unparalleled molecular uniformity. Compared to dendrimers, which are difficult to synthesize, HBPs can be synthesized by simple one-pot polymerization strategies such as one-step polycondensation of $AB_n (n \geq 2)$ type monomers (36). In this method, A and B represent two different functional groups, which can react with each other, but cannot undergo a self-reaction. Unfortunately, these kinds of monomers are not always easily available due to synthesis complexity and commercial availability (37, 38). Polymerization of functionally symmetric monomer pairs such as A_2 and B_3 type monomers has received great attention in the last decade as an alternative approach to synthesize HBPs (39, 40). "$A_2 + B_3$" methodology has the advantage not only of allowing for better control over the degree of branching, but furthermore, the monomers are often commercially available. However, it is well known that direct polycondensation of A_2 and B_3 monomers generally results in gelation (41). In our lab, the polymerizations via "$A_2 + B_3$" have been used to create a type of poly (β-amino ester) polymer by combining commercially available dopamine with triacrylates (20). Soluble three-dimensional hyperbranched poly(β-amino ester) polymer termed poly(dopamine-co-acrylate) (PDA) with catechols and crosslinkable vinyl groups was obtained by tightly controlling the concentration, the ratio of A_2 and B_3 monomers, the reaction time and by stopping the polymerization via endcapping prior to the critical point of gelation (**Fig.3**). This one-step Michael addition procedure is relatively simple and does not require protection/deprotection schemes, does not generate by-products that must be removed through further purification steps, and is tolerant of many functional groups. Furthermore, the wide choice of commercially

available A_2 and B_3 monomers allows tailoring of the polymer structure and provides more facile route to a wide range of HBPs.

2.3 Chain polymerization of vinyl monomers

2.3.1 Free radical polymerization (FRP) of mono-vinyl monomers bearing catechols

Radical polymerization of the mono-vinyl monomers bearing protected catechols (borax, 2, 2-dimethoxypropane, dichlorodiphenylmethane or benzylbromide as protecting agent) occurs in water and leads to linear polymer chains (13, 42, 43). Catechol deprotection can be carried out in acidic medium leading to polymers bearing pendant catechols. During the radical polymerization of mono-vinyl monomers bearing unprotected catechols, the catechol groups (depending of the amount) can interact with the propagating radicals thus forming a (hyper)branched or crosslinked structure as depicted in **Fig. 4 (A)** (44). For example, mussel-mimetic p(DMA-co-MEA) was synthesized by copolymerization of DMA with MEA as shown in **Fig. 4 (B)**. By increasing the catechol content, an increase in the degree of crosslinking was achieved. It was reported that an optimal composition for the highest wet adhesion was found at a DMA concentration of 5 mol%. Polymers with a higher DMA content showed a larger decrease in stiffness because they were more hydrophilic and would take up more water. However, there is an inherent limitation to the use of FRP for mono-vinyl monomers bearing unprotected catechol containing monomers. When high amounts of catechol bearing monomers are used, control over HBP formation is poor/impossible and instead cross-linked materials are obtained (45, 46).

2.3.2 Controlled radical polymerization (CRP) of multi-vinyl monomers (MVMs) bearing catechols

Radical copolymerization of mono-vinyl monomers with a small amount of divinyl cross-linkers has been widely used for synthesis of branched polymers and cross-linked gels. However, highly branched polymers, including gels, are formed at a very early stage of polymerization with low monomer conversions when using the conventional free radical polymerization (FRP) method (16). Not surprisingly, the synthesis of soluble

branched polymers to high conversion without crosslinking had seemed impossible in the FRP of multi-vinyl monomers (MVMs). In 2000, chain-transfer concepts were used to suppress the gelation during the synthesis of HBPs in the FRP of MVMs. Although it becomes possible to rapidly obtain HBPs at high yields with this method, it was reported that a low concentration of MVM and a limited molar ratio of MVM to initiator (≤ 1) were required to ensure the formation of soluble HBPs, imposing restrictions on the degrees of functionality that can be achieved (16). Therefore, the resulting copolymers can only reach a limited degree of branching (DB) with extremely broad molar mass distributions. In order to overcome this limitation, one of the most robust controlled radical polymerization (CRP) techniques, atom-transfer radical polymerization (ATRP), has been used to regulate chain length and prevent gelation (47). In 2007, our group first prepared, through deactivation-enhanced ATRP, novel dendritic poly(DVB) (DVB = divinylbenzene) and poly(EGDMA) (EGDMA=ethylene glycol dimethacrylate) polymers from homopolymerizations of commercially available MVMs (48). No crosslinking and microgel formation were observed during the polymerization process with the overall monomer conversion up to 60%. However, HBPs with catechol groups cannot be synthesized by the ATRP method due to the possibility of catechol monomers chelating with the catalysts (cooper complexes).

In contrast to FRP, the deactivating nature of reversible addition-fragmentation chain transfer (RAFT) polymerization allows the preparation of highly branched copolymers using mono-vinyl and multi-vinyl monomers (49). RAFT polymerization has developed into one of the most versatile forms of CRP because it can be applied to a wide range of monomers. We synthesized a series of well-designed highly branched PEG-catechol based thermo-responsive copolymers via one-pot RAFT polymerization (21). HBPs composed of an interfacial adhesion segment (dopamine methacrylamide, DMA), a water-soluble segment (poly(ethylene glycol) methyletheracrylate, PEGMEA) or (N-(2-Hydroxyethyl) acrylamide, HEAA) and a branching segment poly(ethylene glycol) diacrylate (PEGDA) or poly(ethylene glycol) dimethacrylate (PEGDMA) were synthesized via RAFT polymerization **(Fig.5)**. A varying degree of photo-crosslinkable

(meth)acrylate moieties were incorporated within the 3D structure by choosing PEG-di(meth)acrylate as a divinyl cross-linker to allow on-demand photo-curing. This strategy allows multitudes of free catechol groups to be introduced into the hyperbranched structure by copolymerization with unprotected catechol based vinyl monomers, giving the monomer good adhesive properties towards skin and cardiac tissue (the two surfaces tested to date). The deactivating nature of RAFT polymerization renders possible the production of soluble HBPs with free catechol groups by copolymerizing with unprotected DMA monomer for biological and biomedical applications (50). A range of accessible monomers can be used for CRP, allowing the combination of DOPA (catechol), HEAA and various formulations of PEG in a highly controlled fashion.

3. Applications of HBPs with catechol groups

3.1 Tissue adhesives and sealants

Inspired by the mussel adhesive proteins, researchers have focused their strategies on the development of biopolymers (e.g., copolypeptides, polystyrene and PEGs) incorporating catechol functionality. So far, a variety of catechol-modified polymers have been reported, predominantly PEG-catechol hydrogel bioadhesives (32, 51, 52). Messersmith et al. studied linear and branched DOPA-modified PEGs containing up to four DOPA endgroups synthesized using standard carbodiimide coupling chemistry (53). These PEG-catechol polymers have not shown signs of cytotoxicity *in vitro* (54) and have also been successfully employed in *in vivo* studies (32). Therefore, mussel glue appears to be a potential candidate for sealing fetal membrane defects and preventing amniotic fluid leakage. 4-armed PEG hydrogel end-capped with dopamine was also researched by Cencer et al. to identify the optimal buffering pH for formulation of the adhesive (55). When tested as an adhesive for pericardium tissues, a formulation pH of 7.4 provided the ideal balance of curing rate, mechanical properties, and interfacial binding ability. The mechanical and sealing properties of this PEG-(DOPA)$_4$ mussel-mimetic tissue adhesive have been tested (56). Inflation tests of punctured and sealed membranes and *in vivo* experiments in midgestational rabbits showed that PEG-(DOPA)$_4$ glue is a promising clinically applicable sealant for fetal membrane repair (52, 57). However, its mechanical

properties need to be improved in order to allow the repaired membranes to withstand higher deformations and pressures. New catechol-functionalized PEGs are being developed with different branches (2, 4 and 8 arms) and concentrations. However, PEG-based bioadhesives still cannot be applied in applications requiring high fracture strength because of their physical weaknesses due to the flexible backbones of their polymer chains. Terminally-catecholized Poly (DHCA-co-4HCA) (DHCA, caffeic acid; 4HCA, p-coumaric acid), with an aromatic backbone was researched as a new bioadhesive (58). The introduction of aromatic components into the polymer backbone was found to be an efficient method to improve their mechanical and thermal performance (59).

To introduce higher adhesive strength into PEG based adhesives, our lab designed photo-activated highly branched PEG-catechol copolymers synthesized by a one-pot and one-step RAFT polymerization that could be crosslinked upon exposure to UV light for tissue closure applications. The synthesis procedure for a series of photo-crosslinkable PEG-catechol based adhesives, which combine a mussel inspired adhesion component L-DOPA with a biocompatible PEG segment in a highly branched structure, is described in **Fig. 5** (21). After 1 min of UV curing, approximately 10 kPa adhesion strength can be achieved under shear stress on porcine skin samples and 5 kPa adhesion under tensile stress in a bovine heart tissue wound model. Thus, these gels possess good adhesion to soft tissue, and considerable mechanical strength, thus addressing the limitations of PEG-based adhesives. It is worthy to note that a physiologically useful phase transition temperature (FTT-around 32°C), which immediately relates to the swelling behavior of the hydrogel, can be accomplished by altering the hydrophilic and hydrophobic block components in the polymers. Furthermore, the covalently formed hydrogels (except for the hydrophobic P(DMA$_{40}$-HEAA$_{30}$-PEGDA$_{30}$)) all exhibit negative-swelling in physiological conditions (unlike similar PEG-based systems) in response to the temperature, thus avoiding the possibility of mechanical weakening and tissue-damage associated with exothermic reactions (60). This novel class of thermo-sensitive copolymers with low cytotoxicity represents a facile and versatile synthetic route to

strong mussel-inspired polymer hydrogels with an accurately controlled swelling to fit in different clinical applications through variation of polymer composition and structure.

The hyperbranched poly(β-amino ester) polymer PDA described in **Fig. 3** were also tested as an adhesive precursor for applications as a tissue adhesive. Whilst cyanoacrylate based adhesives typically exhibit cellular toxicity (61), and fibrin based adhesives lack strength (62), PDA provides high adhesion capabilities without high cellular toxicity. PDA crosslinked by fibrinogen attains a high adhesion strength (37 kPa) in just 15 min which is substantial for applications such as incisional skin wound closure. The PDA adhesive showed a lap shear strength to wet porcine dermal tissue that was significantly higher than that of the TISSEEL® fibrin glue.

A mussel-inspired nanocomposite adhesive was also developed consisting of hyperbranched PDA matrix, curing agent and reinforcing hydroxyapatite nanoparticles as a possible alternative adhesive, which might address the problem of a lack of a safe and efficient sternal bone closure approach after median sternotomy as shown in **Fig. 6(A)** (19). Standard practice for sternal closure winds steel wires around the bones to immobilize them as they heal (63). However, the wires may cut through osteoporotic bone in a similar manner to cheese wires (many elderly cases), and are sometimes too weak if put under load (typically young males) (64). Our aim was to create a safe adhesive that cured to a high strength, but cured slowly so as to allow a surgeon reentry to the sternal cavity in a post-operative emergency. The PDA adhesive demonstrated a controllable curing speed designed to set over one week and a relatively low adhesion strength on the first day when loading compression (251 kPa) and lateral distraction force (171 kPa) as shown in **Fig. 6(B)**. The strength eventually increased to a high compression strength and lateral distraction strength after 7 days curing time,which is substantial to withstand the stresses *in vivo.* As such, PDA as a mechanically strong adhesive while allowing for reopening in the short term is ideal for sternal closure.

A PEG-citrate-based polymer functionalized with dopamine has been prepared by polycondensation reaction as shown in Fig. 7 (A) and demonstrated the potential for sutureless wound closure (Fig. 7(B) (65). The adhesive demonstrated 2.5-8.0 folds

stronger wet tissue adhesion strength over that of fibrin glue, while exhibiting a tissue-like elastomeric mechanical properties. The bioadhesives were able to stop bleeding instantly and suturelessly, and close wounds (2 cm long × 0.5 cm deep) created on the back of rats. Besides, the adhesive also facilitates wound healing, and are completely degraded and absorbed without eliciting significant inflammatory response. To modulate the swelling behavior of the adhesive, the adhesive was formulated with hydrophobic 1,8-octanediol to lower the percentage of PEG as the diol (66). The cured adhesive demonstrated a rubber-like behavior, which was suitable for mechanically matching soft tissues for better load bearing and stress transferring and resulted in stronger adhesive with improved swelling properties.

3.2 Antifouling coating

Control over biointerfacial interactions is a key aspect of biomedical device preparation ranging from implantable devices to drug delivery devices and nanomedicines. The rapid adsorption of proteins onto material surfaces and the subsequent host responses, including blood coagulation, inflammation, and irritation of the surrounding tissue, are major problems associated with biomedical devices in contact with body fluids (67). In many of these applications, coatings of bioinert materials are required that reduce or prevent non-specific interactions with the biological environment, such as proteins and cells. Among these approaches, minimizing the nonspecific adsorption of biomolecules by the robust immobilization of PEG on surfaces has been widely implemented. In contrast to these surface-specific interactions, catechols have played a role in a surface-independent anchor molecule (68), and as such have been used to mediate improved PEGylation of surfaces. Multiple catechols tethered onto the backbone of PEG resulted in a significant enhancement of PEGylation capabilities on various types of material surfaces including hydrophobic, fluorine-containing materials such as PTFE (35, 69, 70). For example, Boaz Mizrahi et.al present a one-step method to form a thick and stable surface coating, based on the aggregation of a short amphiphilic four-armed PEG-dopamine polymer (PEG$_4$-dopamine) into particles and subsequent surface binding by catechol chemistry (69). Therefore, contrary to PEG derivatives that are difficult to immobilize on synthetic

polymer surfaces, PEG-catechol provides a facile way for surface PEGylation of various types of surfaces and produces a biocompatible and fouling-resistant surface with tailor-made functions, which hopefully can be expanded to a wider range of applications. Catechol-functionalized zwitterionic polymers such as poly(carboxybetaine) (71), poly(carboxybetaine methacrylate) (72), and poly (sulfobetaine methacrylate) (pSBMA) (73) have been reported in the literature, demonstrated excellent antifouling capability due to their ionic hydration.

Although a lot of catecholic polymers have already been designed for surface coating, most of them are linear structures with a low density of catechol groups which takes a long time to form a thick and long-lasting polymeric coating (74). Theoretically, at equivalent grafting density, a branched polymer graft has higher efficiency in reducing protein interactions with the coated surface than that of its linear analogue (75). In order toform more stabilized particles and denser surface coverage compared to linear polymers of similar molecular weight, researchershave combined nature's amazing bioadhesive catechol with the excellent bioinert synthetic macromolecules HBPGs to prepare antifouling surfaces (76-78). HBPGs were functionalized by different amounts of catechol groups for multivalent anchoring and cross-linking because of its highly branched architecture. In Dr. R. Haag's lab, a set of new catecholic monolayer coatings have been developed to improve the antifouling performance of TiO$_2$ surfaces (77). The defined mono-layer formation and surface properties of catecholic HBPGs (HBPG-Cat) with and without reactive vinyl functionalities were described as shown in **Fig. 8(A)**. The importance of multivalent surface binding as well as covalent crosslinking for high surface coverage and long-term stability was revealed. They demonstrated that by increasing the number of catechol groups on the HBPGs, the stability and surface coverage could be significantly enhanced. Moreover, the inner-layer crosslinking of the coatings, by grafting and initiating vinyl groups, clearly improved their long-term stability. As a result, HBPGs with a catecholic functional degree of 10% (HBPG-Cat10) and HBPG with both catechol and vinyl functional degree of 5% (HBPG-Cat5) were identified as the best HBPG-Cat to prepare bioinert and stable monolayer coatings on

TiO$_2$ as shown in **Fig. 8(B)**. Their further research presented for the first time a simple and efficient approach for a material-independent hierarchical polymer multilayer architecture prepared by catechol functionalized hPGs with tunable chemical activity and bioinertness. Hyperbranched polyglycerols with appropriate amounts of catechol crosslinkers can form dense and crosslinked multilayers to shield the activity of the sublayers completely. These coatings perfectly prevent protein and cell adhesion (78). Antifouling coating can also be formed via tethering of hyperbranched polyglycerols on biomimetic anchors (76). Hyperbranched polyglycerols (HPG) bearing terminal thiol moieties (HPG-SH) were synthesized via anionic-ring-opening multibranching polymerization of glycidol from pentaerythritol and subsequent 1,1′-carbonyldiimidazole (CDI) coupling with cysteamine. As shown in Fig. 9 (A), bioinspired (1) N-dopamine maleimide (DM), (2) tannic acid (TA), and (3) polydopamine (PDA) were employed to produce monolayer, multilayer, and polymeric anchors, respectively, on stainless-steel (SS) substrates. Postfunctionalization of the biomimetic anchor-modified SS surfaces was enacted by tethering of HPG-SH via Michael addition or thiol–ene "click" reaction to confer surface hydrophilicity. The thickness and grafting density of HPG coatings could be controlled by tuning the degree of thiolation. In comparison to the pristine SS surface, the HPG-modified surfaces exhibited substantially reduced initial adhesion and inhibition of the biofilm formation of Gram-negative Pseudomonas sp. and Gram-positive Staphylococcus epidermidis (Fig. 9(B). These research findings have proved that the highly hydrophilic nature of HBPG in combination with added catechol end group provide significant advantages over current benchmark coatings based on PEGs in regard to stability and functionality, and that HBPG-Cat are promising candidates for antifouling applications.

4. Summary and future outlook

This review aims to present the most important and straightforward synthetic methods allowing the incorporation of catechol units into hyperbranched polymer structure and to highlight two potential biological applications. The ability for catechol groups to form strong reversible and irreversible interactions has been used to create a unique and

versatile platform for developing tissue adhesives and sealants with enhanced material properties. Messersmith group reported that the catechol form of DOPA bonds to wet titanium oxide surfaces with dissociation energies of 22 kcal/mol, the strongest noncovalent bond yet measured, providing support for DOPA's main role in interfacial adhesion (79). As catechol groups need to be oxidized to their quinone form in order to participate in intermolecular covalent crosslinking (which is critical for designing *in situ* curable materials and adhesion to biological substrates), controlling the redox reaction of the catechol will be critical to the success of these biomimetic adhesive polymers. Despite these advantages, the bond strength of most reported bioadhesives are still not strong enough for wet tissues. Development of mimetic adhesives in the future should focus on improving bond strengths at wet state to find broad application. Besides incorporating catechol moiety into the design of the hyperbranched polymer adhesive, other amino acid residues, different functional side groups (guanidyl, mercapto, cyanoacryl and double bond), anion-cation interactions should be taken into account to yield polymer adhesives with improved properties (80, 81).

The idea of using mussel-mimetic polymers for reducing or preventing fouling of surfaces is, at first thought, counterintuitive.The reason lies in the truth that catechols make outstanding surface anchors for antifouling polymers due to their affinity to oxide and hydroxide surface (82). For the same functional polymers, globular-shaped graft polymers and multi-armed polymer have also been reported to provide superior antifouling efficacy over that of their linear counterparts (69, 83). These findings provide a good incentive for the investigation of antifouling surfaces based on hyperbranched polymer coatings. However, as far as we know, recent studies on this topic are centered around hyperbranched polyglycerol (HPG).   We hope that more catechol-based hyperbranched materials will be reported in the antifouling field in the near future..

Acknowledgement

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Fig.1
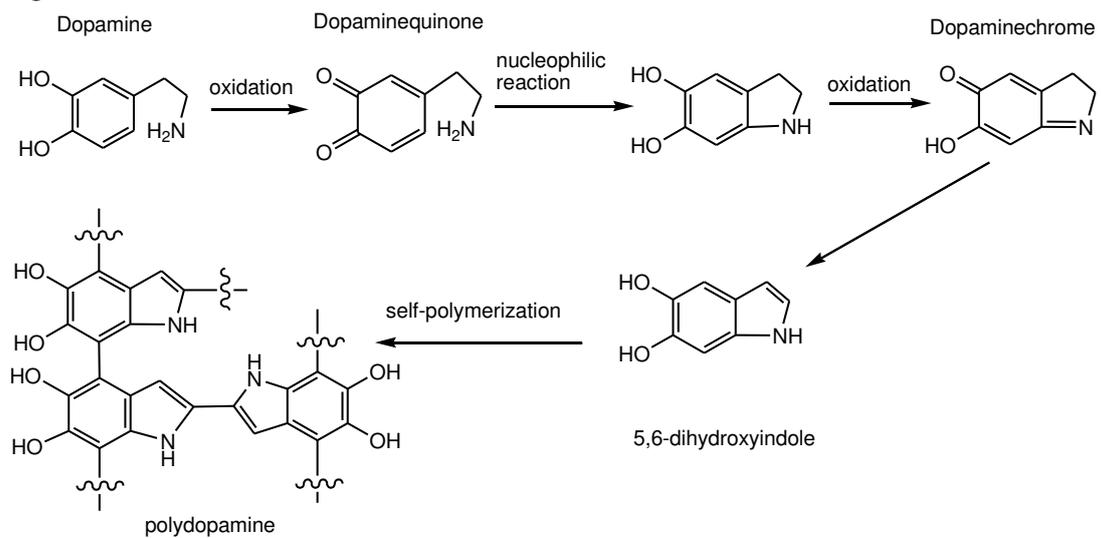
Fig.1 Mechanistic scheme for the formation of polydopamine by self-polymerization of dopamine.
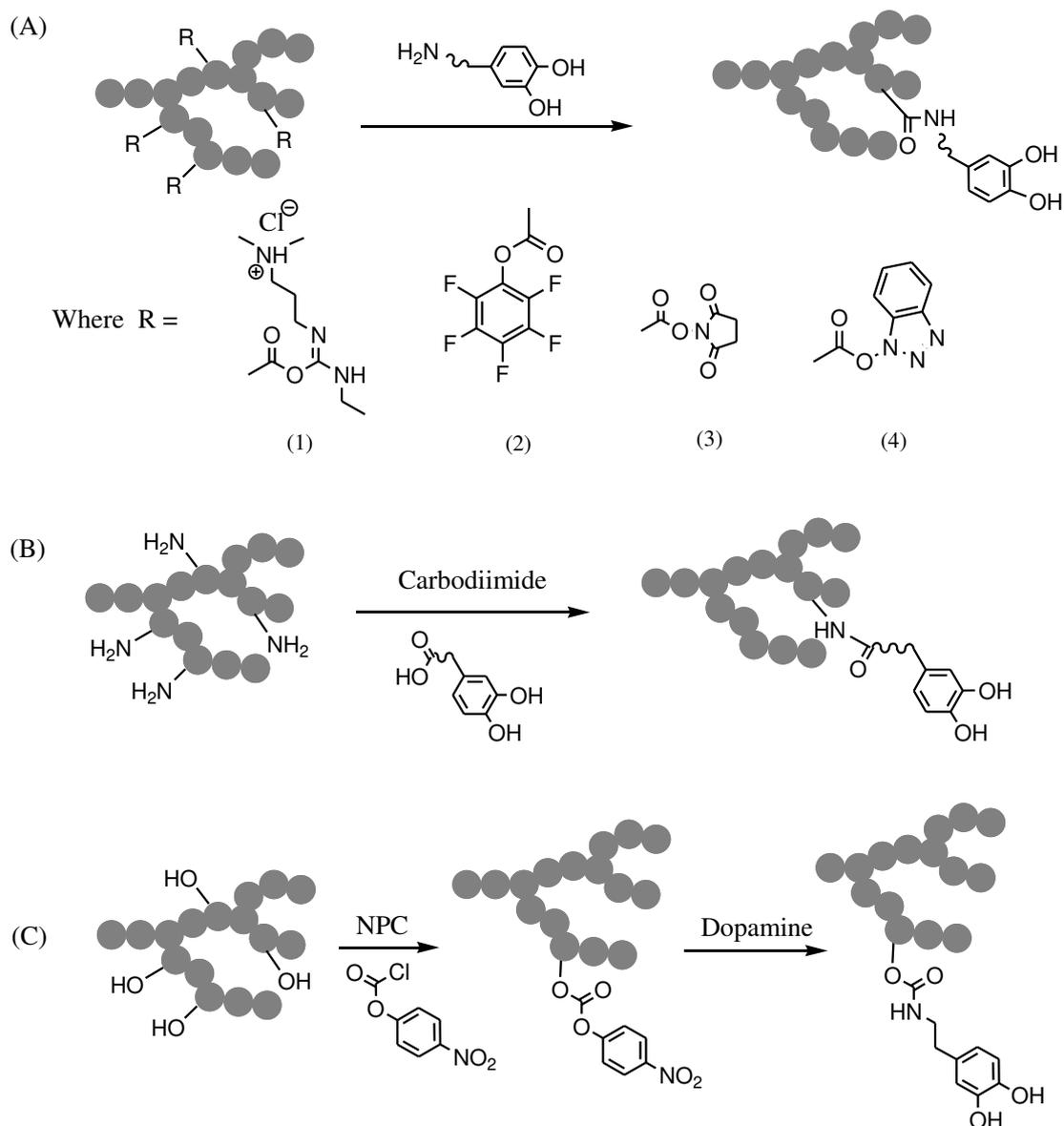
Fig. 2 (A) Strategies for the ligation of catecholamines onto polymers bearing carboxylic acid (activated by carbodiimide chemistry) (1), pentafluorophenyl (2), succinimidyl esters (3), and triazole activated esters (4). (B) Strategy for the ligation of catechol derivatives bearing a carboxylic acid function using carbodiimide chemistry. (C) Ligation of catecholamine onto hydroxyl-functionalized polymers using NPC as an activator.

Fig.3
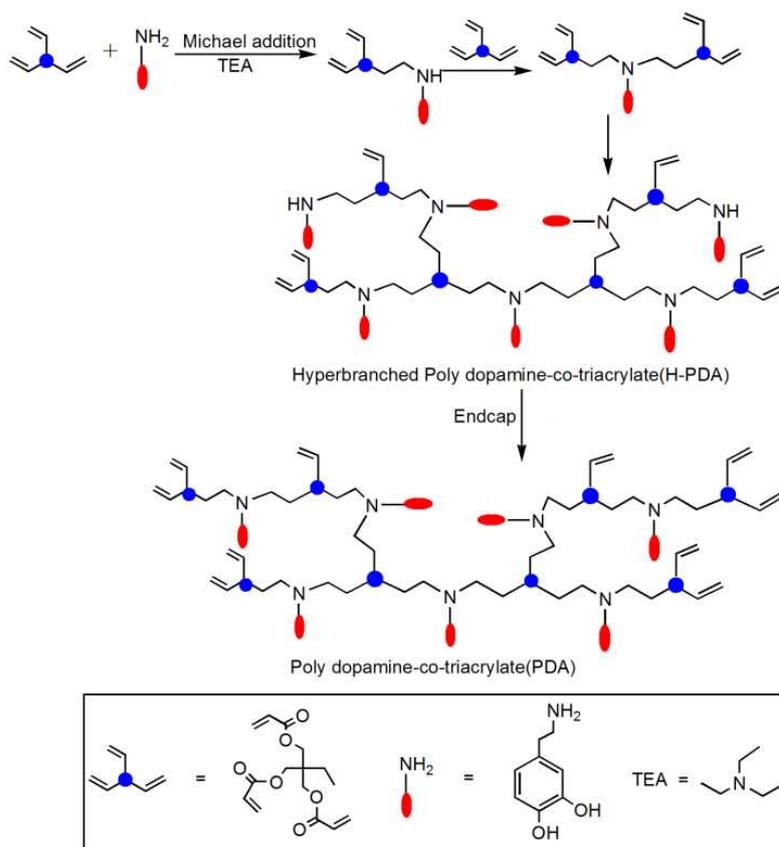
Fig.3 Reaction mechanism of the self-condensation between dopamine and triacrylate monomers through Michael Addition reaction. Reproduced with permission from (20).

Fig.4

(A) Unprotected monomer

Where R = H or CH₃
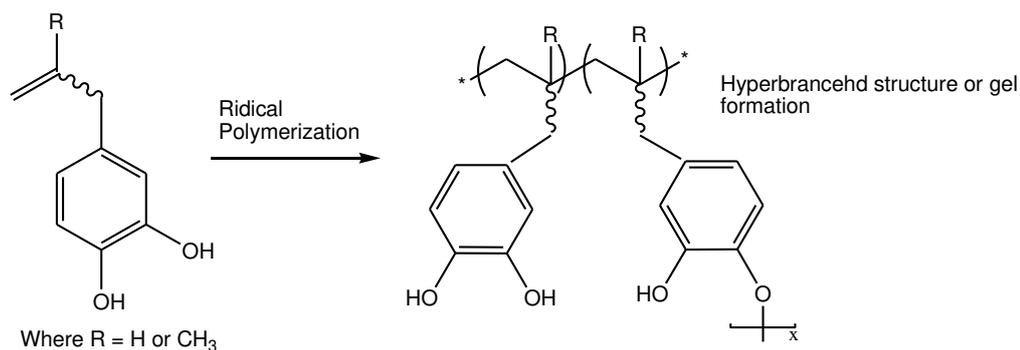
(B)
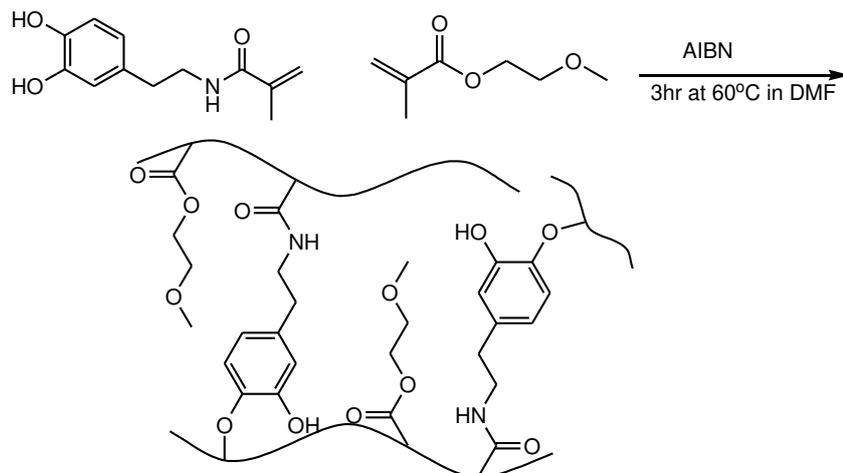
Fig. 4 (A) Polymer architectures obtained from vinyl monomers bearing unprotected catechol unit (B) Synthesis and the proposed resulting architecture of the copolymer p(DMA-co-MEA). Reproduced with permission from(44).

Fig.5
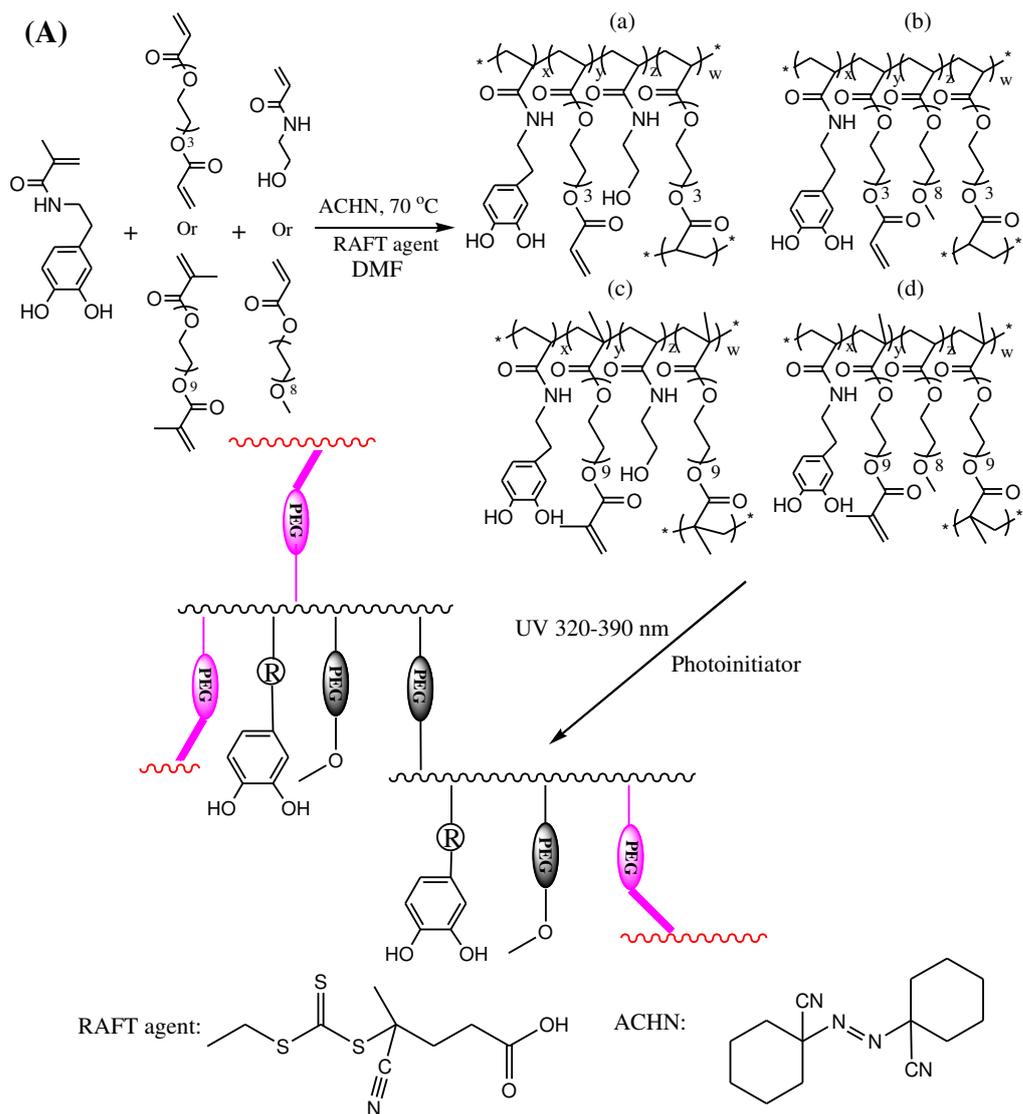
Fig.5 Representation of the synthesis of (A) P(DMA-HEAA-PEGDA) and (B) P(DMA-PEGMEA-PEGDA) (C) P(DMA-HEAA-PEGDMA) and (D) P(DMA-PEGMEA-PEGDMA) via RAFT polymerization and the cross-linking mechanism through radical photo polymerization by UV. Reproduced with permission from (21).

Fig.6
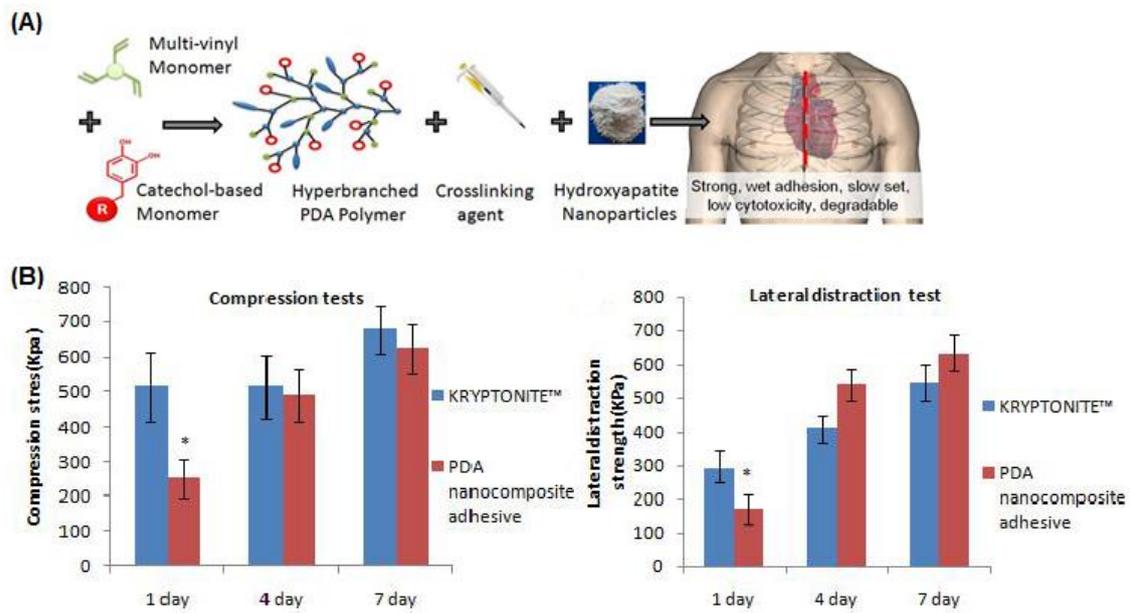
Fig. 6 (A) Strategy of using catechol-modified dendritic PDA polymer nanocomposite (R: −NH$_2$) for sternal closure. (B) Compression and lateral distraction tests on sternal halves bonding with the PDA adhesive after a curing time of 1 day, 4 days or 7 days controlled with KRYPTONITE™. Reproduced with permission from (19).

Fig.7
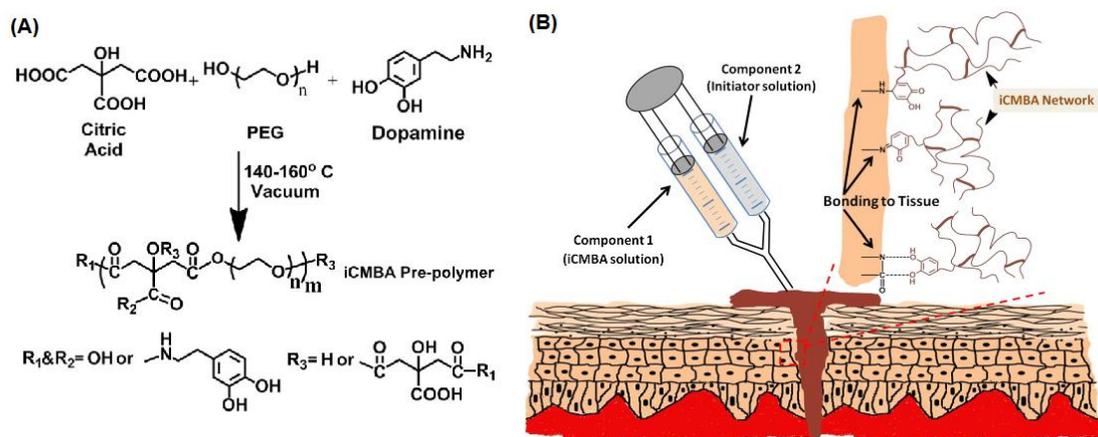
Fig. 7 (A) Schematic representation of iCMBA pre-polymers synthesis through polycondensation reaction. (B) Schematic of iCMBA application for wound closure (65).

Fig.8
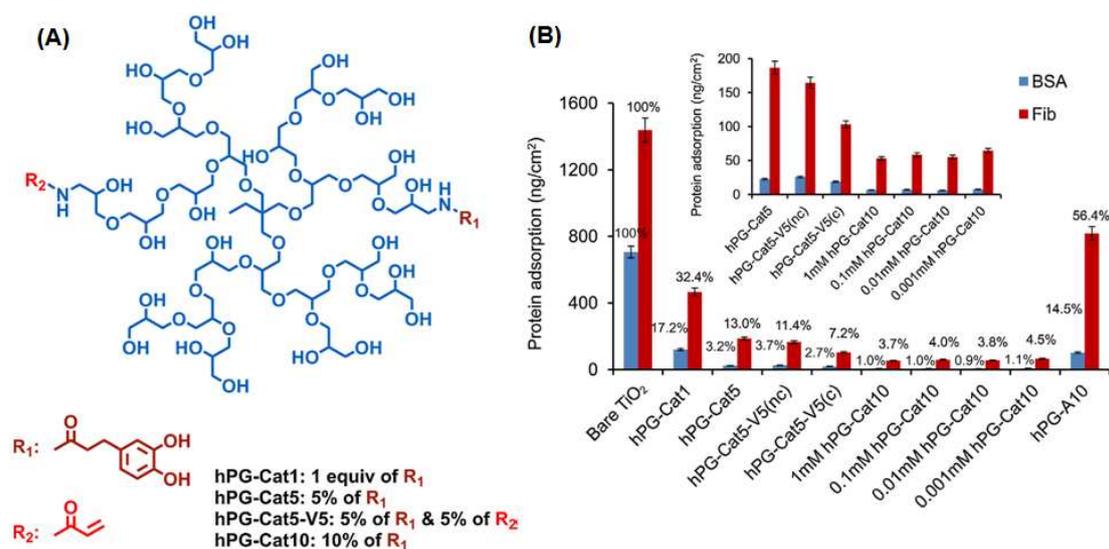
Fig. 8 (A) Chemical structures of the functional hyperbranched polyglycerols (HPGs) to modify TiO$_2$ surfaces. (B) Quantification of protein adsorption of bovine serum albumin(BSA, blue) and fibrinogen (Fib, red) on modified TiO$_2$ surfaces as obtained after Quartz Crystal Microbalance (QCM) measurements. Individual percentage value was calculated by comparison of protein content of bare vs. functionalized surface. The 100% values refer to adsorption of 706.2 ng/cm^2 for BSA and 1438.8 ng/cm^2 for Fib on bare TiO$_2$ surfaces. Reproduced with permission from (77).

Fig.9
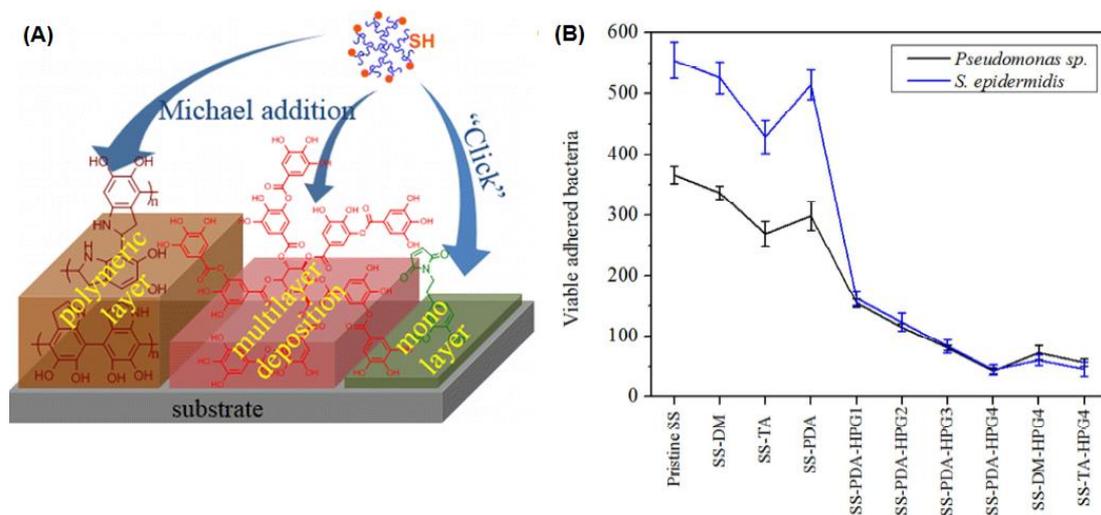
Fig. 9 (A) Various anchoring strategies on stainless-steel surfaces and immobilization of the thiolated hyperbranched polyglycerols. (B) Quantitative amount of the viable bacteria adhered on the sample surfaces, counted based on the fluorescence micrographs at an area of 350×420 μ m^2 (76).