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Universal Polymer Coatings and Their Representative Biomedical Applications

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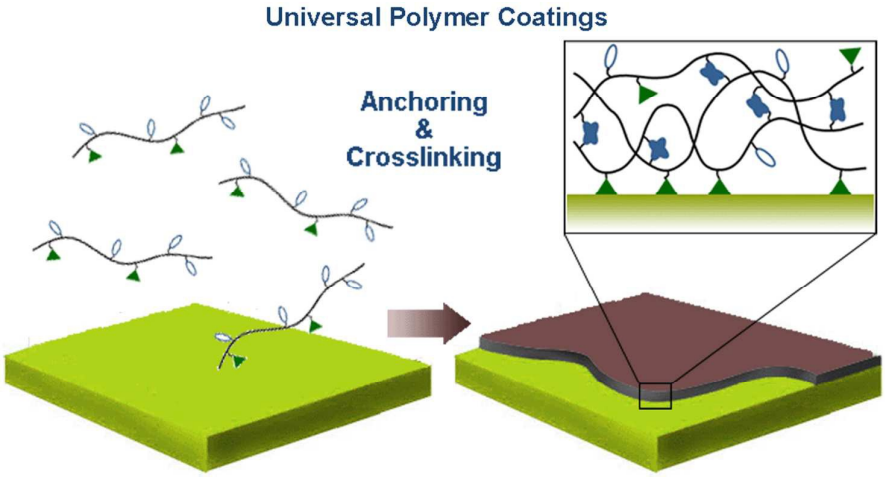
Universal polymer coatings have excellent potential for biomedical applications, because of their substrate-independent properties and versatile surface functionalizations. The goal of this review is to summarize the state-of-art research on universal polymer coatings and their biomedical applications, as well as to present their common features including some general rules for their further development.



1. Introduction

Polymer coatings on solid materials play an increasingly important role in physical, chemical, and biomedical science.[1, 2] Thiol and siloxane chemistry are commonly used to modify noble metal and hydroxylated surfaces, respectively.[3, 4] Besides the widely used self-assembled monolayer (SAM) and chemical surface immobilization that are induced by these and other anchor groups, Langmuir-Blodgett deposition,[5] layer-by-layer assembly,[6] irradiation,[7] and electrostatic or hydrophobic adsorption[2] are well established. However, most of these technologies require specific chemical or physical substrate properties, and thus have failed to become universal coatings.

Universal coatings are the coatings that can modify a wide range of material surfaces and are stable under the applied conditions. Ideally, these coatings are substrate-independent, regardless the chemical composition and physical characteristics (e.g. topology, stiffness) of the substrates. To develop such coatings, the anchoring interactions between the polymers and various substrates must be well designed. Chemical functionalities for the specific covalent binding between the polymeric coating and the surface must be avoided in order to modify different types of substrates, because no anchor can be active on all of the different surface compositions. Although, some of the irradiation technologies can activate many kinds of surfaces, the efficiency and the density of the active sites are relatively low on some surfaces. Therefore, they should be enhanced by some compensatory methods, e.g., polymerization, to obtain dense surface coatings.[8, 9] On the other hand, noncovalent interactions like electrostatic interaction, hydrogen bonding, hydrophobic

attraction, and van der Waals interaction, occur on nearly all types of interfaces. Thus multiple noncovalent interactions can be recognized as the driving forces for constructing polymer coatings on different surface types. Admittedly, most of the noncovalent interactions between interfaces are not strong enough to tether polymer coatings for practical applications. Therefore additional intra-layer interactions, i.e., physical and chemical crosslinking can be used to enhance the stability of the coating.

Crosslinking can either be initiated in situ while anchoring the coating, or in a step-wise fashion after formation of precast layers (**Figure 1**). In the in situ case, one-pot coating is easy and rapid. However, spontaneous crosslinking may cause the polymeric modifiers to aggregate, which makes the surface morphology less controllable. In the latter case using precast layers, further crosslinking procedures like heating or irradiation are required. This step, however, must be well designed to avoid decreasing the performance of the coatings.

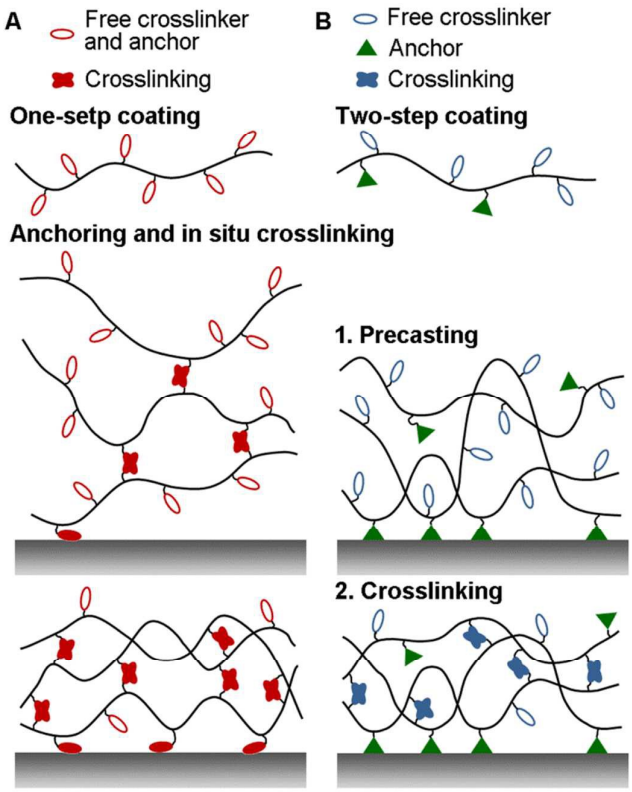


Figure 1. Universal coatings can be stabilized on different kinds of surfaces by interior crosslinking, which can be achieved either (A) by in situ crosslinking together with anchoring or (B) by step-wise crosslinking after formation of a precast layer.

A secondary functionalization of these universal coatings is normally required to achieve specific surface characteristics. Thus, there must be enough active groups remaining in the coatings for further modification. The most important surface coatings in biomedical applications include bioinert, biospecific, and antibacterial coatings. A bioinert surface on the one hand requires dense and stable coatings to prevent protein adsorption on the molecular level and to further repel cell adhesion.[2] These coatings must be hydrophilic and electrically neutral and contain hydrogen bond accepting groups but no hydrogen bond donating groups.[10, 11] Biospecific surfaces on the other hand, which contain cell recognition motives, are another

approach to modulate cell interaction on the surface of a biomedical device.[1] A relatively low density of functionalization is sufficient to trigger cell adhesion. In the case of arginylglycylaspartic acids (RGDs), a minimum density as low as 1 fmol per cm^2 was reported for cell spreading and 10 fmol per cm^2 for forming focal contacts and stress fibers on a surface.[12] Inspired by a cell membrane that contains bioactive carbohydrates and proteins in the bioinert background of a phospholipid bilayer, biospecific molecules can be combined with bioinert coatings to increase the efficacy of the biological communication.[1, 2] As a result, implanted surfaces would only integrate with, for example, endothelial cells, and prevent leukocyte and other cells. When constructing such designed coatings, it is important to achieve multifunctional coatings. Moreover, bioinert materials are often combined with antibacterial agents to repel bacteria adhesion and improve the biocompatibility of the coatings.[13] Besides these functional coatings mentioned above, multiple functional surfaces, e.g., infection-resistant, anticoagulated, self-cleaning surfaces, can be developed by immobilizing different functional molecules[14, 15] on the reactive universal coatings.

In this review, we summarize the characteristics and common features of current universal polymer coating systems, which include surface irradiation, layer-by-layer (LbL) assembly, spin coating, chemical vapor deposition (CVD), laser deposition, blood proteins, mussel-inspired coatings, and plant phenols (**Table 1**). These systems are typed by their anchoring interactions, i.e., chemisorption, physisorption, and multiple interactions, for clearly showing their similarities and differences. We will therefore draw conclusions on the general rules for developing such coatings in the

future. Also, some recent developments based on universal coatings in the area of biomedical applications will be described.

Table 1. Summary of the universal coating systems

Type	Preparation	Anchoring interaction*	Advantage	Disadvantage
Surface irradiation	gas phase	covalent bond	covalently anchored; highly pure	specific equipment; potential damages to the substrates; limited by substrate shape
Layer-by-layer (LbL) assembly	solution phase	electrostatic attraction	shape independent; dip-coating	time-consuming; unstable in strong electrolyte conditions
Spin coating	solution phase	hydrophobic interactions	well-modulated thickness	weak anchoring; limited by the shape
Chemical vapor deposition (CVD)	gas phase	hydrophobic interactions	highly pure	specific equipment; weak interactions; limited by substrate shape
Laser deposition	Gas or solution phase	hydrophobic interactions	comprehensive material source; direct-writing	specific equipment; limited by substrate scale and shape
Blood proteins	solution phase	multiple interactions	shape independent; dip-coating;	degradable
Mussel-inspired coatings	solution phase	multiple interactions	shape independent; dip-coating;	surface roughness; dark colour
Plant phenols	solution phase	multiple interactions	shape independent; dip-coating; cheap resource	surface roughness

* Only main anchoring interactions for each type coatings are shown.

2. Irradiative Chemisorption

High energy ionizing radiation can directly generate initiation sites by liberating electrons from atoms or molecules near the material surfaces. These positively

charged initiation sites can immediately react with other molecules to generate functional groups for further surface modifications. Different radiation methods, including plasma, ultraviolet (UV), gamma ray, microwave, laser, electron beam, etc., have been employed to active correspondingly material surfaces.[16]

Plasma exposure is the most common radiation method. However, plasma, which can easily activate organic surfaces, does not work equally well with inorganic surfaces.[8] Thus, plasma polymerization of monomers with vinyl groups has become a general way to functionalize different solid surfaces as alternative to simple irradiation.[8, 17, 18]. As a result, the sparse active sites on the organic surfaces can be connected by highly crosslinked polymer films, which results in stable coatings on substrates via polyvalent anchoring. As a result, highly crosslinked polymer films can be stably deposited on substrates via polyvalent anchoring.[17] Various chemical surface functionalities like anhydride-,[8] amino-,[17] epoxide-,[19] and perfluoroalkyl- groups,[20] can be achieved by employing differents monomers (**Figure 2**).

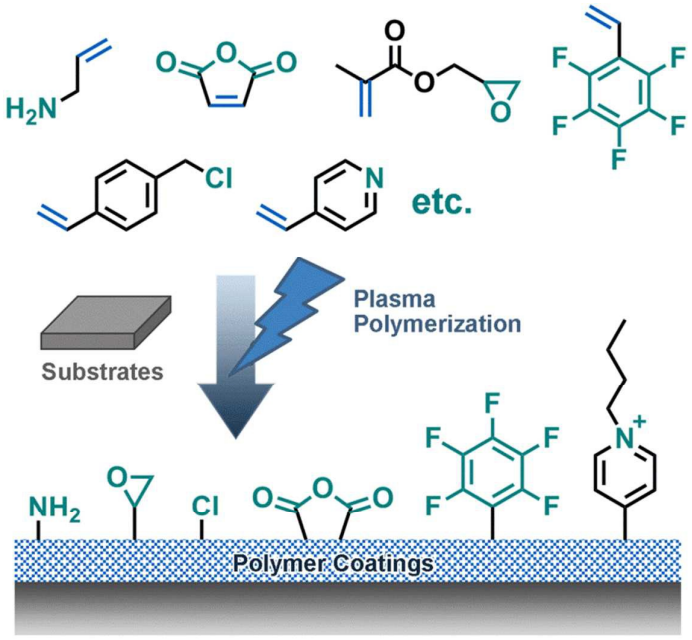


Figure 2. Various functional universal coatings can be achieved by plasma polymerization with different monomers.

Long-term irradiation may change the properties of the functional groups of the monomers and degrade the newly formed polymers. Pulsed plasma with short on-periods and long off-times was proven to deposit polymer films with a higher degree of molecular specificity than traditional continuous wave plasma.[8] The active sites in gas phase and at the growing film surface could be generated in the short plasma duty cycle on-period (microseconds), which initiated polymerization during the longer plasma off-period (milliseconds).[21]

Alternatively, polymeric targets, such as polytetrafluoroethylene (PTFE), polyimide, and polyolefin, have been sputtered to form coatings by radio frequency (RF) magnetron sputtering.[22] Powerful magnets cause the emission of volatile fragments from the polymeric targets. These fragments take part in the plasma

polymerization process and line up on the substrates to form thin films. Since the polymeric targets are provided in a solid state, fewer safety precautions are required than handling the gas of monomers in plasma polymerization.[23] To achieve the secondary modification, amino-rich thin films were prepared by sputtering Nylon 6,6 target in a mixture of N_2/H_2 or N_2/Ar. As a result, a high NH_2/C ratio in the coatings was achieved.[23]

The amino groups presented in the plasma polymerized polyallylamine coatings and RF magnetron sputtered nylon coatings are suitable for immobilization of atom transfer radical polymerization (ATRP) initiators via amide linkages.[9, 17] Bioinert polymer brushes of poly(oligoethylene glycol methacrylate) or poly(carboxybetaine acrylamide) can be subsequently initiated from the functional surfaces, which has resulted in dramatically decreased protein adsorption on the solid surfaces.[9]

The plasmachemical functionalization of surfaces with poly(4-vinyl pyridine) coatings yielded bactericidal activity towards *Staphylococcus aureus* (Gram positive) and *Klebsiella pneumoniae* (Gram negative), after quaternization of the pyridine moieties with bromobutane.[24]

Patterned functional surfaces were developed by depositing two separate functional nanolayers, including an active bottom layer of poly(glycidyl methacrylate) and a passive release top layer of poly(pentafluorostyrene) on the substrates. A selective lift-off of the top layer by a prepatterned adhesive template resulted in the exposure of the underlying active layer.[25]

Surface irradiation methods are easily controlled methods for film growth on

different substrates. In many cases, solvent is not required and the coating processes are suitable for large-scale film deposition. Moreover, the covalently anchored coatings can keep stable under different solvent conditions. However, the irradiation may change the property of the substrates, especially the ultrathin substrate layers, and it can be limited by the shape of the substrates. Additionally, the irradiation and deposition requires the sophisticated equipments, which limits the applications in industry. Thus, physisorbed universal coatings can be considered as alternatives.

3. Physisorption

Typical physisorption of surface coatings include electrostatic attraction, van der Waals force, and hydrophobic interaction. Based on these universal interactions, some technologies, including layer-by-layer (LbL) assembly, spin coating, and chemical vapor deposition (CVD), have been developed to achieve some universal coating systems.

3.1 Electrostatic Attraction

Polyelectrolytes are good candidates to anchor the substrate surface via electrostatic attraction. However, monolayer brushes of block copolymers, which are immobilized through the polyionic block onto the surface and prevent further adsorption via the other flexible block,[26] cannot be efficiently adsorbed on uncharged surfaces and are sensitive to salt concentration. Instead, the layer-by-layer (LbL) assembly technique is more universal. It does not significantly dependent on the nature, size, and topology

of the substrate,[27] due to the intra-coating electrostatic interaction. Some LbL assembly systems indeed successfully fabricate multicomponent thin films on a wide range of surfaces by consecutive adsorption of polyanions and polycations. The electrostatic attraction between oppositely charged and flexible polymers has the least steric demand of all the chemical bonds building and stabilizing fuzzy layered LbL assembled multilayers.

An alternate electrostatic assembly of cationic poly(allylamine hydrochloride) (PAH) and anionic poly(sodium 4-styrenesulfonate) (PSS) has been deposited on a variety of material surfaces, including glass, gold, mica, silicon, and other polymers. The properties of the different underlying surfaces were completely converted to the surface properties of the polyelectrolyte coatings.[28] This chemically active scaffold can be further utilized to fabricate protein microarrays. Mouse IgG has been immobilized on PAH-capped polyelectrolyte coatings. The rest of the surface was then blocked with bovine serum albumin (BSA). The nearly identical specific signal intensities of anti-mouse IgG with low nonspecific binding can be observed on the tested dissimilar substrates.[28]

The LbL assembly is, however, a time-consuming process, especially for fabrication of thick films.[29] Large dimensional building blocks with fast adsorption kinetics can realize a rapid fabrication and have been built with mesoporous silica ($MSiO_2$) nanoparticles were employed with cationic poly(diallyldimethylammonium chloride) (PDDA) to assemble a substrate-independent thick coating with only three coating cycles.[30] This coating exhibited both antireflection and antifogging properties,

because the rough surface morphology and nanopores in the $MSiO_2$ nanoparticles resulted in superhydrophilic surface performance. A maximum transmittance of 99.9% was achieved in the visible spectral range, under optimal conditions.

A one-pot electrostatic attraction based coating was achieved by the aggregation of polyallylamine and orthophosphate anion, which can be fabricated within 60 min.[31] Orthophosphate anions efficiently crosslinked the coatings by both electrostatic interaction and hydrogen bonding. The presence of amino groups in the coatings led to further functionalization. Biotin immobilized coatings recognized streptavidin.

Electrostatic attraction is a relatively strong non-specific interaction, which has induced a set of universal coatings. However, strong electrolyte solutions, e.g. strong acid or base, can interrupt this attraction and decompose the coatings.[32, 33]

3.2 van der Waals Forces and Hydrophobic Interactions

The relatively weak van der Waals and hydrophobic interactions can also be used to anchor universal coatings, if the intra-coating crosslinking is well designed.

A mixture of hydrophilic amine- and epoxy-terminated four-arm polyethylene glycols (PEGs) was spin-coated on a flat substrate. After chemically crosslinking these macromonomers under gentle heating, a hydrogel-like coating with tunable film thicknesses of 4-200 nm was fabricated on a broad variety of solid substrates. Because of its controllable swelling behavior, this coating was able to adsorb a high density of citrate-stabilized gold nanoparticles (AuNP) from aqueous solution and resulted in PEG/AuNP composite films.[34]

In a similar approach, hydrophobic benzocyclobutene-functionalized random copolymers of styrene and methyl methacrylate [P(S-r-BCB-r-MMA)] were spin coated on a wide variety of metal, metal oxide, semiconductor, and polymeric surfaces to produce thin films.[35] The styrene moieties of the copolymers induced balanced interfacial interactions on the surfaces.[36] After heating under 200-250°C, the reactive benzocyclobutene (BCB) moieties resulted in the crosslinking reactions. These crosslinked films were resistant to solvents and formed a robust coating on the substrates. In the other case, a hybrid polymer composed of poly(methylsilsesquioxane) (PMSSQ) block and poly(pentafluorophenyl acrylate) (PFPA) blocks has been employed to coat different materials.[37] PMSSQ blocks initiated crosslinking after spin coating, while the PFPA blocks enabled a variable secondary functionalization of the coatings.

In the case of crosslinkable PEGs that mentioned above, the coating mainly interacted with substrates by weak van der Waals forces. Keeping this kind of hydrophilic coating stable in water solution for long term is a big challenge, because water can shear off the whole coating. Therefore, it is preferable to use hydrophobic coatings like the P(S-r-BCB-r-MMA) and PMSSQ-PFPA cases above. Nonpolar substances tend to aggregate or adsorb on solid surfaces in aqueous solution and repel water molecules. Since water is the most common and secure solvent in our daily life, the hydrophobic interactions have successfully generated a set of universal coatings.

Chemical vapor deposition (CVD), which is often used in the semiconductor industry to produce thin films, can also fabricate hydrophobic coatings of

poly(*p*-xylylenes) and derivatives for a wide range of substrates including PTFE (**Figure 3**).[38] In the CVD polymerization process, diradicals of [2.2]paracyclophane or its derivatives have been obtained during vaporization under heating and vacuum. The diradicals are then deposited on the substrate during polymerization. It has been reported that these CVD polymers strongly anchor on substrate surfaces and are insoluble in common organic solvents.[39] It is reasonable to speculate that the chain transfer in such radical-rich polymerizations may have resulted in chemical crosslinking, which highly stabilized the deposited coatings as well as intermolecular hydrophobic interactions and π-stacking. The copolymers of [2.2]paracyclophane and its functionalized derivatives have generated multifunctionalized CVD coatings, which can be widely used in biomedical applications. Using a vacuum deposition overcomes the limitations caused by solvents and additives in dip coating procedures,[39] so that highly pure coatings can be obtained. However for production every CVD step requires expensive equipment, such as high vacuum conditions.

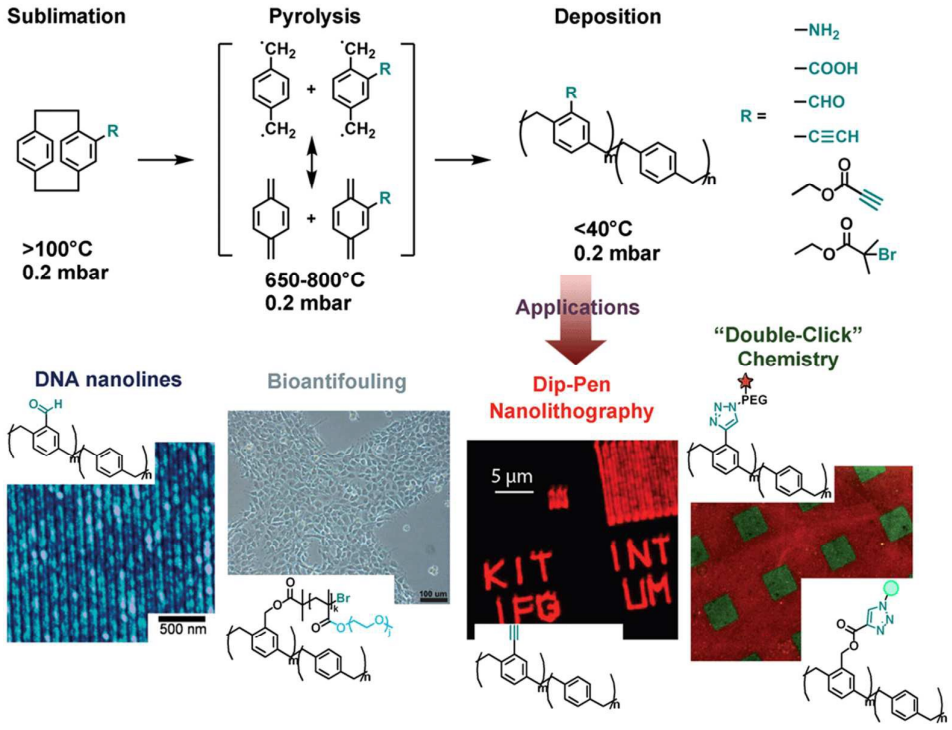


Figure 3. Chemical vapor deposition (CVD) polymerization with various monomers to achieve multifunctional universal coatings. Reprinted from Ref. [40-43] with kind permission of Wiley and The American Chemical Society.

Surface active CVD coatings are good platforms for immobilizing biomolecules. The anhydride-rich coating of poly(p-xylylene-2,3-dicarboxylic anhydride) can immobilize amino-terminated biotin ligands which selectively bind to streptavidin. The biotin-conjugated human anti-α_5-integrins were then immobilized on the streptavidin and specifically interacted with endothelial cells.[44] Surfaces that "click" have been developed by alkyne-containing vapor deposited polymer coatings. The polymers with monoalkyne grafted [2.2]paracyclophane have generated excellent adhesion and stability, even at 680°C and in many organic solvents. On the other hand, enough alkynes were exposed on the surfaces to react with azide-containing biotin-based ligands[45] or support the dip-pen nanolithography by "click chemistry".[42]

In a further development, a bioorthogonal immobilization of biotins and streptavidins was carried out with a copper-free click reaction on the CVD coatings.[43] The synthesized [2.2]paracyclophane-4-methyl propiolate, which contained an electron-withdrawing group in proximity of the alkyne, was identified for copper-free click reaction with azide groups. Moreover, this [2.2]paracyclophane derivative was compatible with the processing conditions during CVD polymerization without decomposition or side reactions. With alkynyl moieties for copper-catalyzed "click" reactions, a two-step cascade of bioorthogonal reaction sequentially immobilized different biomolecules on separate areas of the same surface.[43] Additionally, aldehyde functionalized CVD coatings could link to 5' amine modified complementary DNA sequences by forming imine bonds. Thus, poly(4-formyl-*p*-xylylene-co-*p*-xylylene) was deposited on different substrates to serve as a "replica" to collect DNA microarrays from microcontact printing.[40]

Besides the immobilization of biomolecules, initiators for atom transfer radical polymerization (ATRP) can be directly immobilized to the CVD monomers and be polymerized and deposited on the different kinds of substrates including stainless steel, glass, silicon, poly(dimethylsiloxane), poly(methyl methacrylate), poly(tetrafluoroethylene), and polystyrene.[41] This polymeric initiator coating initiated ATRP of oligo(ethylene glycol) methyl ether methacrylate to produce a bioinert polymeric coating as thick as 300 nm. Both protein adsorption and cell adhesion were significantly inhibited on this bioinert coating.

A physical vapour deposition technique namely laser processing of polymers also

has the potency to modify different material surfaces.[46] Lasers can irradiate and vaporize almost every conceivable target material by either photolytic or pyrolytic processes. These materials, including synthetic polymers and natural biopolymers, can be then deposited on substrates.[47] By depositing blood proteins[48] or mussel inspired polymers,[49] the anchoring interactions of the coatings can be enhanced (for details see Section 4). Interestingly, some of the laser deposition techniques, such as matrix-assisted pulsed laser evaporation and laser guidance approaches, can serve as direct-write techniques to deposit patterns on substrates.[50]

Overall, versatile physisorption based universal coatings have been developed that on the one hand overcome many problems in irradiated chemisorptions, on the other hand suffer stability problems under some application conditions. The inherently weak anchoring interactions of the physisorbed surface coatings, however, can become thermally unstable. These coatings may also be displaced by other solutes in solution. Therefore, these coatings must be carefully utilized in appropriate conditions, i.e., avoid strong electrolyte solutions for electrostatic attraction base coatings, avoid long-term submersion in non-polar solvents or flow environments for hydrophobic interactions based coatings.

4. Bioinspired Surface Coatings

Nature due to evolutionary processes has developed ways to excellently and precisely solve problems from which many artificial systems are suffering. Learning from nature is an endless source of inspiration. In the present section, the universal coatings

that have been inspired or directly collected from natural biological systems of blood proteins, mussel foot proteins, and plant phenols will be described and discussed. These bioinspired surface coatings bind to substrate surfaces by combined multiple interactions, besides simple chemisorption or physisorption, to enhance the stability of the coatings under different conditions.

4.1 Blood Proteins as Adhesive Coatings

It is well known that blood proteins nonspecifically adsorb on blood contact surfaces within seconds via multiple interactions such as van der Waals force, ionic or electrostatic attraction, hydrogen bonds, and hydrophobicity.[2] An approach involving blood proteins to modify both flat and nonwoven substrates has been reported.[51] A set of proteins, including α-lactalbumin, lysozyme, fibrinogen, and soy globulins (glycinin and β-conglycinin), were denatured at their isoelectric point (pI). Under these conditions, a maximum amount of proteins could be adsorbed onto the substrates, because the electrostatic repulsion among protein molecules was limited.[52] Denaturation helped the hydrophobic domains of the proteins be adsorbed on the substrates with the result that the hydrophilic amino and hydroxyl groups could be exposed on the surface for secondary modification. To stabilize the coatings, the adsorbed protein layers were crosslinked with glutaraldehyde in the presence of sodium borohydride. The ATRP initiator molecules could then be immobilized on the amino and hydroxyl groups, from which poly(2-hydroxyethyl methacrylate) (PHEMA) polymer brushes were grown. By combining the fluorinating moieties, these

amphiphilic polymer brushes efficiently prevented further nonspecific protein adsorption.[53] Although the protein based coatings above were only reported for modifying polyolefin surfaces, it is possible to apply these coatings on a wide range of material surfaces because of the nonspecific adsorption of proteins quite general on solid surfaces. In the other case, phase-transited lysozyme was employed to coat a broad range of substrates based on the same concept.[54] However, the main problem for this coating system may be long-term stability, since protein layers can be degradable in physiological environments.

4.2 Mussel Foot Proteins as Adhesive Coatings

Dopamine

Mussels adhere to virtually all types of material surfaces with byssus as the holdfast. The byssus contains 25-30 different kinds of mussel foot proteins (mfps), which are the keys for fast solidification and strong adhesion.[55] Inspired by the most two abundant functional groups of catechol and amine in mfps, dopamine has been recognized as a new and efficient precursor for developing active universal coatings with just a simple immersion (**Figure 4**).[56] To initiate the coating process, the catechol in dopamine must first be oxidized to quinone in alkaline solution or in the presence of oxidant.[30, 56] Although the mechanism for further polymerization of dopamine is still being debated,[57, 58] it is widely agreed that dopamine forms oligomers up to the tetramer level[59] which then aggregate to form coatings via hydrogen bonding and π-stacking.[60] Many mechanistic details of surface anchoring have already been

revealed. Either a charge-transfer complex can form between the catechol and metal oxide surface[61] or a hydrogen bond between the catechol and a mica or silica surface.[62, 63] Covalent bonds on nucleophile containing surfaces have also been explored.[64] The hydrophobic interaction, π-stacking, and van der Waals' force between the catechol and inert polymer surfaces have been discussed as well.[65, 66] On the other hand, amino group can evict hydrated cations from the oxide surface to allow catechol binding to underlying substrates.[67] In addition, a lateral crosslinking by both covalent and noncovalent bonding further enhances the stability of the polydopamine coatings.

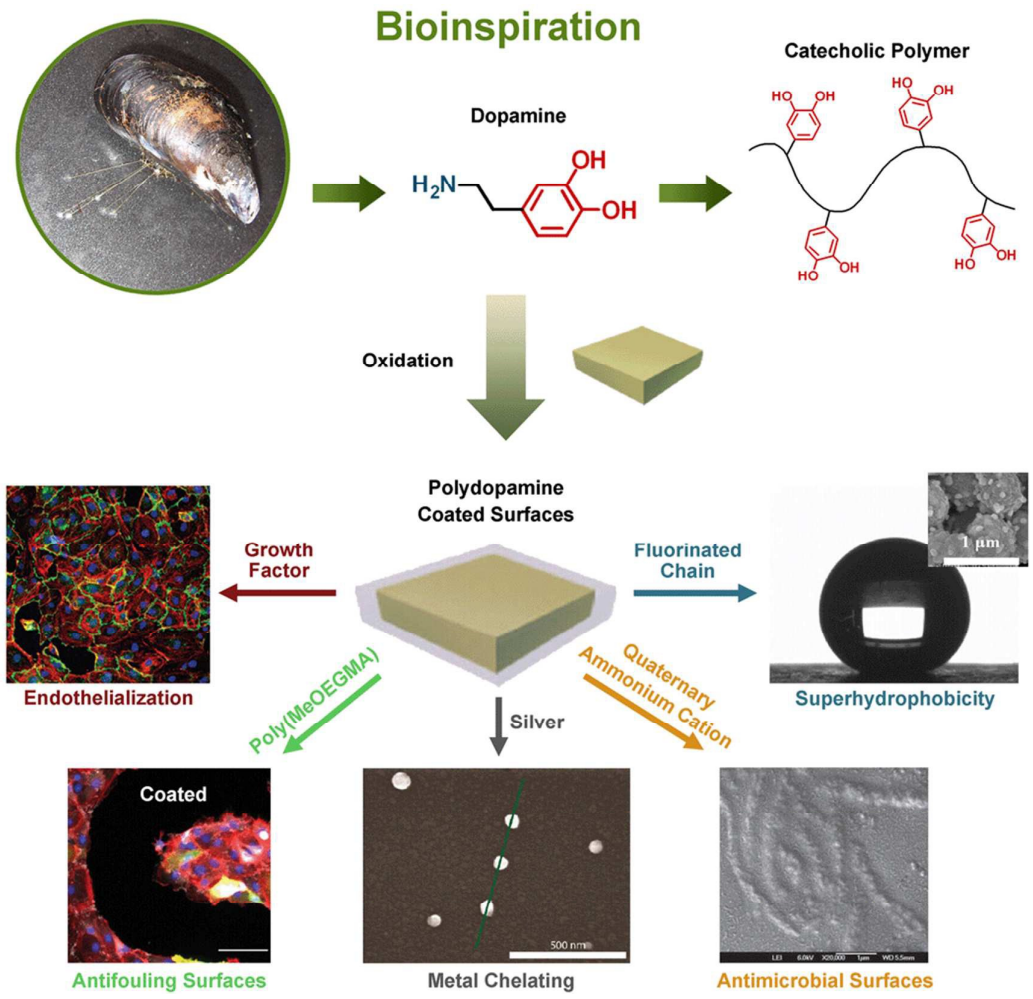


Figure 4. Mussel-inspired polydopamine as universal mltifunctional coatings. The structures of Mfp-1 and Mfp-5 were extracted from Ref. [55]. Modified from Ref. [68-72] with kind permission of Wiley and The American Chemical Society.

Native polydopamine coatings already show low cytotoxicity and can promote the adhesion of osteoblasts[73] and endothelial cells,[74] because the critical surface tension of polydopamine (39.2 dynes/cm) is in the suitable range for cell adhesion (35-40 dynes/cm).[75] Furthermore, a number of secondary modifications can be applied by immobilizing different functional molecules to polydopamine coatings via the

residual free amines and catechols.[15] Bioinert polymer layers have been created by both "grafting to" and "grafting from" approaches, as well as by LbL assembly on polydopamine coatings to achieve substrate-independent surface modification.[69, 76, 77] Biospecific molecules, such as vascular endothelial growth factor,[68] adhesion peptides,[78] and glycosaminoglycan,[79] have been easily immobilized onto polydopamine coatings with an one-step immersion, and have resulted in specific cell adhesion. The metal chelating ability of the catechol groups in the coatings can cause in situ deposition of silver nanoparticles.[70] The silver nanoparticles or the grafted quaternary ammonium groups[71] on the coatings have exhibited strong and broad-spectrum antimicrobial activities. Moreover, the combination of bioinert layers with antibacterial moieties produced the dual fouling resistance and antibacterial properties of the coatings, which significantly improved the antibacterial performance of the surfaces.[70, 71] The deposited silver nanoparticles on polydopamine coated microparticles resulted in a hierarchical structure similar to the micromorphology of lotus leaf. These composite particles became extremely water repellent after fluorination.[72] Although synthetic polydopamine coatings were just introduced in 2007 by the Messesmith group,[56] it has already become one of the most widely applied universal coating due to its facile procedure and chemical versatility.

Dopamine Derivatives

Several dopamine derivatives that form different functionalized coatings have also been identified. 3,4-Dihydroxyphenylalanine (DOPA) contains one more carboxylic

group than dopamine. During the coating formation, the deprotonated carboxyl groups may repel the noncovalently bonded polyDOPA aggregates by electrostatic repulsion, thus more covalently bonded DOPA molecules can be incorporated into the coatings. As a result, the polyDOPA coating showed better stability in strongly acidic and alkaline solutions.[80] A smoother coating can be developed by norepinephrine.[81] Norepinephrine represents the intermediate of 3,4-dihydroxybenzaldehyde (DHBA), which deactivates the amino group of norepinephrine by forming DHBA-norepinephrine. The deactivated amino group results in less crosslinking and obviously suppresses the aggregation of the coating. Polynorepinephrine can be used, e.g., as an NO-loading scaffold in biomedical applications. NO can be stored as diazeniumdiolates which react with aliphatic secondary amino groups in the coatings. In addition, the extra hydroxyl group allows an efficient ring-opening polymerization of biodegradable monomers like ε-caprolactone.[82] The presence of the electron-withdrawing nitro group in the *p*-position lowers the pK of the nitrocatechol. This enhances the acidity and hydrogen bond donor character of catechol and increases its stability against oxidation.[83] The other significant feature is that the *o*-nitrophenyl ethyl moiety can be photocleavable.[84] Furthermore, chloro-catechol prevents microbial fouling due to its toxicity. The appropriate polymer-bound chloro-catechol groups showed effective antibacterial activity and were not toxic for the attached cells.[85] Functional molecules can also be immobilized onto the amine group of dopamine to obtain synthetic derivatives. A lysine-dopamine coating improved cell adhesion, promoted cell growth, accelerated endothelialization on the

substrate surface, and provided plasma clot lysis activity.[86] The copolymerization of dopamine and ATRP initiator bearing dopamine (1:2) resulted in a colorless coating. Surface-initiated ATRP of 2-hydroxyethyl methacrylate (HEMA) can be performed from this coating.[87] A fluorinated dopamine derivative was developed by conjugating perfluorinated chain to the carboxyl group of DOPA.[88] The remaining amine and catechol groups resulted in a structurally rough film with the static water contact angles larger than 150° as a superhydrophobic surface.

Catecholic Polymers

Polymers with the appropriate amount of catechol groups can be directly coated onto material surfaces as functional universal coatings. Catechol-grafted PEGs with 4-5 catechol side groups per polymer chain were employed for the PEGylation on many different substrates.[89] Catechol-grafted poly(ethoxyethyl glycidyl ether-co-allyl glycidyl ether) with around 70 catechol side groups per polymer chain was also successfully coated on many types of substrates including PTFE.[90] This polymeric coating prevented cell attachment without further modification. After the coating was immobilized with 3-mercaptopropionic acid in a thiol-ene reaction, it exhibited excellent cell adhesion. Thus, it is possible to design and adjust cell adhesion with this universal coating.

Systematic studies, on how the grafting amount of catechol groups affects the coatings on different types of surfaces also have also been reported.[91, 92] The thickness and stability of the polymer coatings can be controlled by catechol groups which work

as both anchors and crosslinkers. In the case of metal oxide surfaces, although even one catechol group can tether the polymer chain, multiple catechol units are required in the anchor group to prevent the oxidative detachment.[93, 94] In the case of inert polymeric substrates, such as PTFE, polystyrene, and polyolefin, the interaction between the catechol group and these surfaces is relatively weak.[65, 95] Besides weak anchoring, the other role of catechol as a crosslinker is important to stabilize laterally the coatings on inert substrates.[92] Therefore, a relatively large amount of catechol groups is required to achieve universal coatings. For the design of bioinert surface coatings, however, an overrepresentation of catechol groups leads to protein adsorption and cell adhesion. Only a well-balanced amount of catechol groups can supply coatings with both good stability and bioinertness.[92]

Although catechol is a powerful anchor for surface coating, its effectiveness has been somewhat over praised in some previous publications. Actually, even multiple catechol functionalized polymers hardly reached a very high surface coverage on inert surfaces.[91, 92] In some publications, effective coatings on inert surfaces were obtained by polymers that conjugated with a few catechol groups and the success was announced to fully due to catechol adhesion. We do not doubt these coatings, but we should mention that the hydrophobic effect of the polymer itself has often been ignored, which definitely enhanced the interface interactions besides catechol anchoring. Control experiments should be well designed to explore the further role of catechols in these cases.

Mussel-Inspired Dendritic Polymers

The adhesion and solidification of mussel byssus only needs approximately 3-10 min.[96] A dopamine coating takes much longer to form a thick and dense film.[56] Therefore, a dendritic polymer that better mimicked the mfps with respect to their multivalent adhesion was identified to accelerate the surface coating (**Figure 5**).[97] This heteromultivalent catechol and amine functionalized dendritic polymer (MI-dPG) mimicked not only the functional groups of mfps but also their molecular weight and molecular structure. The molecular weight of MI-dPG was about 10 kDa, which was in the same range as the most adhesive mfp-5 (ca. 9 kDa).[98] MI-dPG, due to its dendritic structure, exhibited a relatively distinct "interior", and exposed functional groups on its surface like folded proteins.[99] It formed a considerably stable coating on virtually all types of material surfaces within 10 min or a micrometer scale coating within hours. Functional molecules, like collagen A and rhodamine B, can be postfunctionalized or prefunctionalized to the MI-dPG coatings. Furthermore, the controllable surface roughness resulted in superhydrophilic and superhydrophobic surfaces.[97] Additionally, based on the MI-dPG coatings, bioinert hierarchical polymer multilayer coatings were constructed, which showed excellent protein resistance properties and long-term stability.[100]

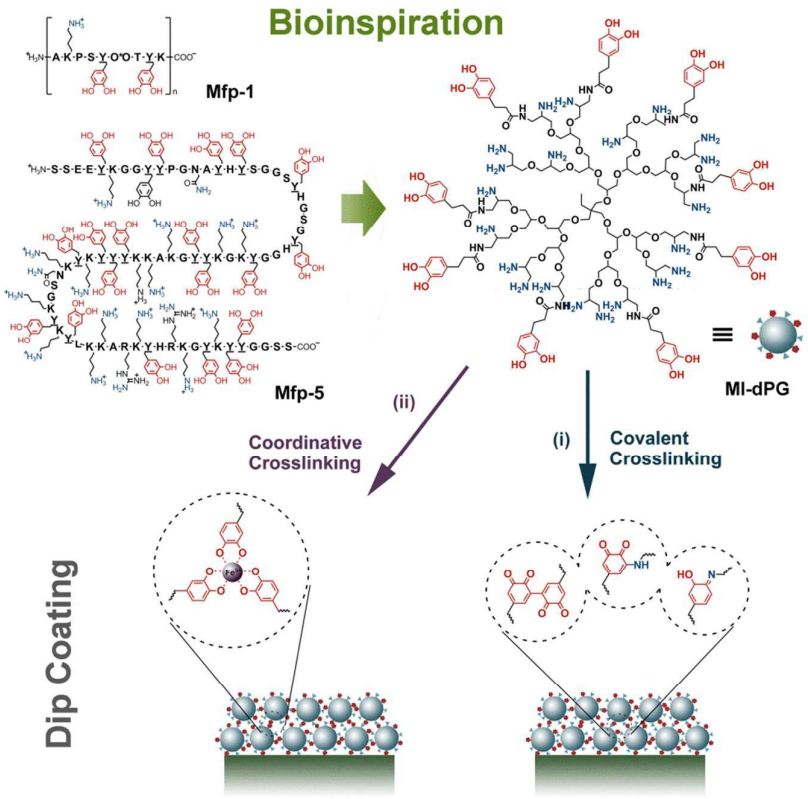


Figure 5. Mussel-inspired dendritic polyglycerol (MI-dPG) that mimicked the mfps by the functional groups, molecular weight, and molecular structure to result rapid covalent (postulated structure) and coordinative crosslinking for universal surface coatings. Reprinted from Ref. [97] with kind permission of Wiley.

Besides catechol induced surface adhesion, mussels limit the auto-oxidation of catechols on the surface of byssal plaques to enhance the adhesion by the thiol-rich mfp-6.[101] Other hydrophobic amino acid residues, mainly in mfp-3 "slow", can retard oxidation of catechols by shielding them from the solvent and, more importantly, compensate the adhesion by hydrophobic interactions.[102] The adhesion of mussel byssus, however, is more complicated than a simple catechol-mediated recipe.

4.3 Plant Phenols as Adhesive Coatings

Tea cups are often stained by tea water. Inspired by this phenomenon, a number of phenolic biomolecules that are present in tea, red wine, chocolate, and many other plants have been identified for versatile universal coatings. These biomolecules possess abundant and dense catechol (1,2-dihydroxyphenyl) and gallol (1,2,3-trihydroxyphenyl) functional groups and thus exhibit strong solid-liquid interfacial properties. A plant polyphenol of tannic acid (TA) and a simple phenolic mimic of pyrogallol were deposited from buffered saline (0.6m NaCl, pH 7.8) to form polydopamine-like films.[103] These phenolic films retained most of the advantages of polydopamine films as multifunctional universal coatings, but they were low cost and colorless. In addition, these coatings could scavenge radical and non-radical reactive oxygen species. In a subsequent work, a library of about 20 kinds of natural and synthetic phenolic molecules was screened.[104] Among them, eight catechol-, gallol-, and resorcinol-rich molecules were identified to form excellent universal coatings. Besides TA and pyrogallol, the other six precursors were epigallocatechin gallate (EGCG), epigallocatechin (EGC), catechin (Ctn), catechol (Ctl), hydroxyhydroquinone (HHQ), and Morin (**Figure 6A**). Moreover, 5-pyrogallol 2-aminoethane, which contains both pyrogallol group and primary amine, has been shown to form coatings with enhanced stability and coating ability,[105] because the presence of amine group enhances the crosslinking. As the polymerization and deposition of dopamine could be accelerated by an oxidant,[30] the laccase-catalyzed polymerization of plant phenols also resulted in a rapid coating formation.[106] In fact,

the oxidation and enzyme catalyzation can accelerate the formation of both polydopamine and phenol coatings.

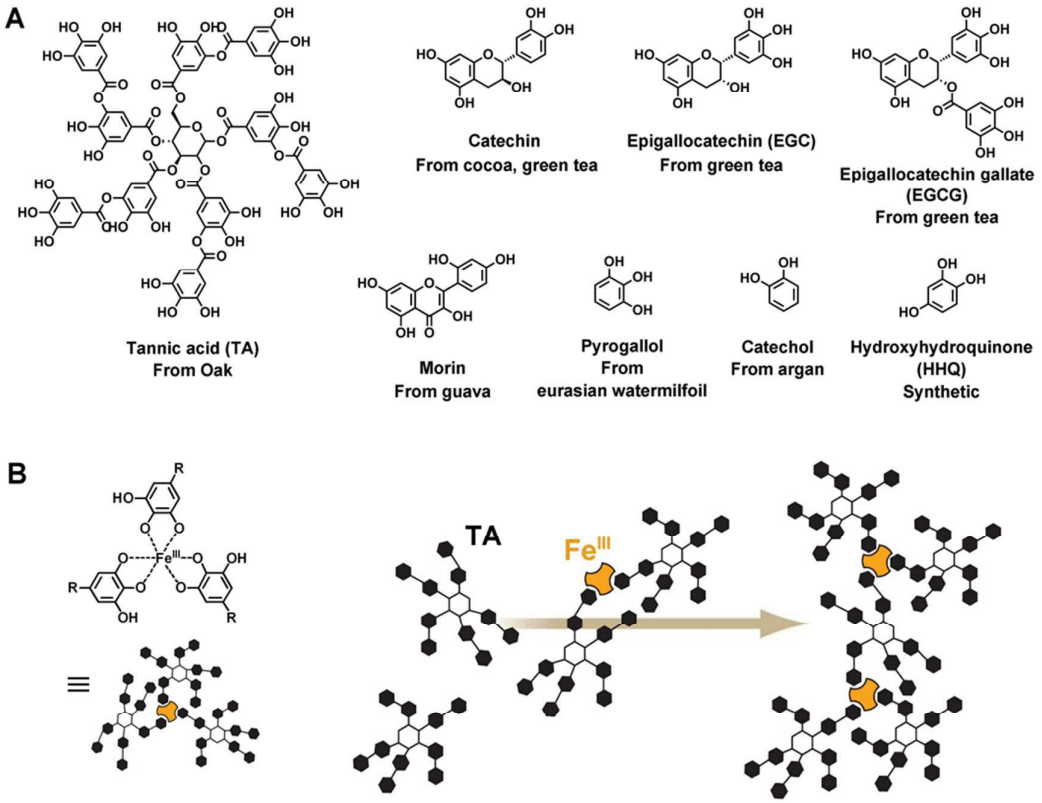


Figure 6. (A) Chemical structures of the natural and synthetic phenols that were identified to form universal coatings [104]. (B) Scheme of the assembly of iron-based coordination complexes. Reprinted from Ref. [107] with kind permission of AAAS.

Besides polydopamine type crosslinking, another self-assembly process based on polyphenols for surface modification was explored. Phenolic moieties are weakly acidic and can donate an electron or electron pair to chelate metal ions.[107] Thus, polyphenols like TA can be crosslinked by coordination with iron, e.g. Fe(III) (**Figure 6B**), then deposited and bound to substrates to form versatile coatings with negligible cytotoxicity.[108] This coordinative crosslinking is pH responsive. At low pH, the

hydroxyl groups are protonated, which leads to a destabilization of the crosslinking and disassembly of the coatings.[109] In the case of a coordination between TA and Fe(III), only mono-phenol complexes formed at pH < 2.0, with the result that the coating disassembled. Even at 3 < pH < 6, when bis-complexes existed, the coatings could not be kept stable. Only when tris-complexes formed at pH > 7, the coatings showed good long-term stability. A library of functional TA-metal networks showed that this pH sensitivity was controllable by changing the metal species and feed concentrations.[110] Moreover, varying the feed concentration of the lanthanide metals allowed control over the fluorescence intensity of the coatings. Similarly, catecholic polymers have also been reported that generate coatings by ion based coordinative crosslinking.[97] Therefore, this new type of coatings is a potential candidate for biomedical applications.

In summary, all three types of bioinspired universal coating systems, i.e., blood proteins, mussel foot proteins, and plant phenols, have been successfully applied on almost all kinds of material surfaces, even regardless of the shape of the substrates. Their combined multiple anchoring interactions and the high degree of intra-coating crosslinking resulted in a set of highly stable coatings. However, our natural systems, e.g., mussel byssus, can even adjust the balance of each interaction to reach optimal adhesion on different substrates.[55] There is still a long way to go in chemistry and materials science to really mimic natural systems to generate the best universal coating.

5. Conclusion and Perspective

An ancient Chinese proverb says “A single chopstick can be gently broken, a pillar of ten chopsticks firmly holds dough”. Both lateral crosslinking and the polymerization of all monovalent anchorings (one single chopstick) combine the binding forces on the substrate surface together to reach the multi-/polyvalent anchoring (pillar of ten chopsticks). Thus, the coating can be indeed stabilized to reach a universal coating, even if the force of the individual monovalent anchoring is relatively small. Therefore, the common features of the presented universal coatings can be summarized, and the general rules for developing new universal coatings can be proposed that: (1) There must be some interaction between the coating materials and the substrate surfaces, even though the interaction might be relatively weak; (2) Lateral crosslinking, either covalent or noncovalent, must be present; (3) The coating should be prepared with the available functions or it can be further functionalized. Stronger interfacial interaction and a higher degree of crosslinking can result in more stable coatings, especially on chemically inert surfaces, such as Teflon.

Among the large family of surface modification systems, however, still only a few universal coatings can be successfully used for practical applications. It is necessary to further establish a mechanistic understanding of the stabilization of universal coatings and the theoretical guidelines for developing such coatings. Therefore, future research can be focused on exploring the mechanisms of the adsorption of polymers onto different surfaces, quantitatively studying the crosslinking’s contribution in stabilizing coatings, and establishing a set of theories to guide the development of

universal coatings. Although homogeneous coatings were obtained by all of the approaches mentioned above, most of the coatings were only studied on a lab scale. The quantitative analysis of the uniformity of coatings on large scale is still lacking, which is also important for practical applications.

Overall, it remains a big challenge to further develop universal coatings to become a real long-term stable tool in our daily lives, however, universal polymer coatings have already added a new page to materials surface modification.

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