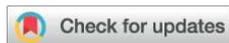


REVIEW

Roles of polymer brushes in biological applications

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Abstract: Polymer brushes are macromolecular structures with polymer chains tethered to a surface resembling a brush. They have shown variety of uses in biological applications. Because of the nature of crafted polymers, the functionalized surfaces exhibit unique functions such as low friction, altered adhesion, protein binding and selective adsorption. Functionalization can be controlled by changing parameters such as grafting densities, chemical configurations, shapes and thickness. In this review, a particular emphasis has been provided for studies related to biological applications of polymer brushes based on their ultra-low friction, hydrophilic elongated surfaces, and binding properties. It provides useful information for researches and labs working on finding better solutions for drug delivery, arthritis, artificial joints, antibiofouling coatings and protein immobilization and purification.

Keywords: grafting density, drug delivery, anti-biofouling, ultra-low friction, protein immobilization

1 Introduction

Polymer brushes are comprised of polymer chains which connect on one end to a surface and extend approximately normal to the surface, giving them the appearance of a brush. One of their main properties is called grafting density, which is the number of polymers attached to the surface in a given area. Grafting density controls the morphology of polymer brushes. Low graft density results in a mushroom morphology for each polymer while high grafting density results in an upright morphology [1]. Their unique properties are partially dependent on grafting density; thus polymer brushes are so appealing due to the ability to control grafting density.

Polymer brushes were first explained theoretically in the 1970s studying polymer chains with a polar head adsorbing onto a surface [2], followed by experimental fabrication in the 1980s [3–6]. However, while a new and innovative surface modification technique, not many useful applications polymer brushes were initially found. Thus, most early studies focused on effect of grafting density on polymer brush height, developing theory which matches experimental findings, and simulation and modeling of polymer brushes [1, 3–5, 7, 8]. In 2003 it was discovered that electrically charged polymer brushes result in each polymer pushing away from its neighbors, increasing the overall height of the polymer brush [9]. This resulted in coefficient of friction (COF) as low as 0.0006 or even lower. Once the attractive effect of charged polymer brushes on COF were discovered, the majority of research has focused on the modification of the tribological properties of polymer brushes. Due to their excellent tribological properties, three dimensional structures, hydrophilicity, and water-swelling properties, they became a prime study subject for biological applications. [Table 1](#) presents the most related publications on the low frictional properties of polymer brushes since 2003, along with major findings.

2 Synthesis route for surface functionalization

The structure of polymer brushes is made of closely packed monolayers of macromolecules. These monolayers can be utilized to produce under control multiple nanostructures to form a surface. As a result, these nanostructures are becoming a significant platform for the material science and engineering due to the fact that they can be used to construct surfaces previously impossible to fabricate. The fabrication of a surface using the polymer brushes is accomplished by grafting chemically.

There are currently two principal strategies to fabricate a surface by grafting the polymer brushes on a desired substrate. These two principal strategies are named the “grafting-onto” and

“grafting-from” as indicated by Figure 1 [23]. The Grafting-onto approach engages the processes of physisorption and chemisorption. This approach consists of grafting pre-synthesized polymer chains that have already desired length. A polymer is a chain made of single elements called monomers which are linked. For this method to work, each of the polymers must have a chain-end within functional groups. The polymer chain-end is required to have either a high affinity to the substrate or its complementary elements. The complementary elements can be coated on the substrate to serve as a bonding to the polymer brushes if needed [23]. The grafting-onto strategy is difficult to control when a specific result is desired. This is due to the polymers coiling preventing to increase the grafting density. As a result, this method is less used to fabricate the polymer brushes.

The polymer brushes grafting-from method also uses the processes of physisorption and chemisorption. Contrary to the grafting-onto strategy, this approach consists of attaching monomers instead of polymers. As a result, the fabrication density of the polymer brushes can be easily controlled to achieve a desired result. Based on this, the grafting-from strategy is

Table 1 Publications on the tribological properties of polymer brushes

Polymer brush	Focus of study	Major findings	Published	Reference
PMMA- <i>b</i> -PSGMA	Effect of charged polymers on polymer brushes	Charged polymer brushes → COF~0.001	2003	[9]
PMMA	In-depth study of tribological properties	COF _{PMMA brush} < COF _{PMMA film} , tribological properties rely on solution	2005	[10]
MPC	Effect of high-density polymer brush on COF various environments	Extremely low COF can be achieved at high density even in humid air	2007	[11]
pMPC	Polymer brush comparison to synovial joints	Lubrication of polymer brush comparable to synovial joint	2009	[12]
PMMA, PS, PNIPAM	Effect of stretching chains of polymer brushes	Stretched chains have better tribological properties than unstretched	2009	[13]
PMPC, PHEMA, PMMA	Nanoscale characterization of polymer brushes	Friction resistance highly correlated to water absorptivity of polymer/hydrated layer	2009	[14]
PMIS, PHMA	Effect of using poly(ionic liquid) brush	Poly(ionic liquid) brush held much lower COF for many more cycles than regular polymer brush	2010	[15]
PS	Effect of solvent quality on lubrication of polymer brush	Degree of polymer brush height can be controlled by solvent quality	2011	[16]
MPC	High pressure polymer brushes using grafting-from technique	COF remained as low as 0.001 even at a pressure of 7.5 MPa	2011	[17]
MTAC, SPMK	Studied oppositely charged polymer brush interaction	Nanoscale adhesion was accomplished using polymer brushes with opposite charges	2011	[18]
PMMA	Studied effect of fluid viscosity on lubrication of polymer brushes	High-viscosity solvents resulted in hydrodynamic lubrication with COF depending on shear velocity	2012	[19]
PFA-C ₈ , PMMA, PDHMA, PVA, PEGMA, PDMAEMA, PMANa, PMTAC, PSPMK, PDMAB, PMAPS, PMPC	In-depth wettability study of polymer brushes	Surface energy and wettability was heavily affected depending on whether ionic liquid or nonionic liquid was used	2012	[20]
P18MA, P12MA, P6MA	Studies polymer brushes in oil	COF was greatly reduced at pressures as high as 450 MPa	2012	[21]
PMTAC	Studied the formation of a boundary lubrication layer of polymer brushes	Increasing velocity greatly increased gap thickness and reduced COF	2014	[22]

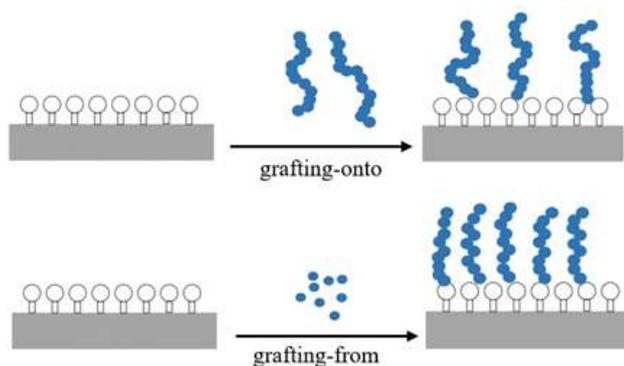


Figure 1 Grafting-onto and Grafting-from strategies (redrawn from [23])

also called the bottom-up approach since the polymer chains are grown from single elements or monomers. The polymer chains are cultivated via a surface-initiated polymerization (SIP) according to Mocny and Klok [23].

To fabricate the polymer brushes, there are a variety of devices used in the process. Figure 2 shows one of such devices [24]. It consists of a chamber containing a chemical solution made of a monomer, $CuCl$, $CuCl_2$, $BiPy$, and a solvent at the bottom. The upper section of the chamber has a nitrogen blanket. A micropump is also part of the device. The surface of the substrate on which the polymer brushes are to be grafted is submerged into the chemical solution. The longer the substrate stays submerged in the solution, the longer the polymer brushes get. The chemical solution is drained out with the micropump to stop the growth of the polymer brushes. The chemical draining also allows a gradient based molecular size as indicated by the side view.

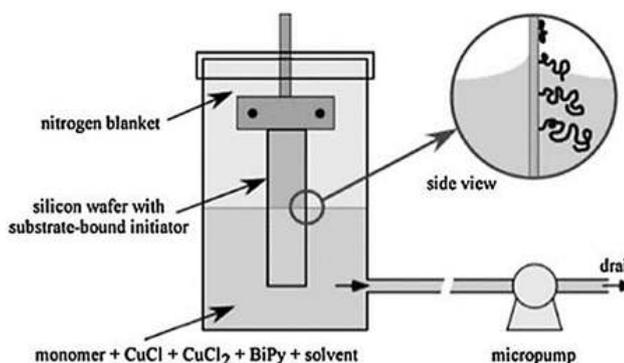


Figure 2 Device for creating surface-grafted polymer (used with permission [24])

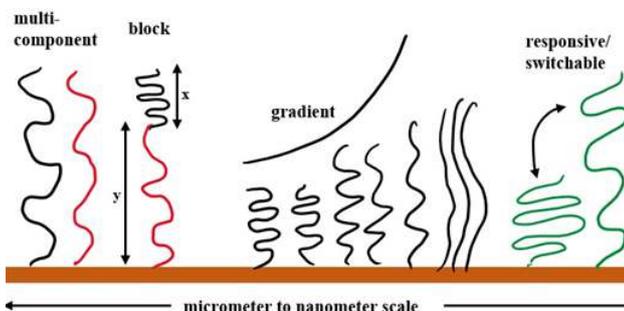


Figure 3 Polymer brush configurations (redrawn from [24])

Polymer brushes can be grafted with different configurations (Figure 3). These configurations are the multi-component, block, gradient, and responsive or switchable. The multi-component consists of alternating chemically different polymers. The block configuration involves the grafting of a polymer brush on top of a different polymer brush. The gradient configuration

simply changes the polymer brush length or molecular size. The responsive or switchable entails different regimes of polymer brushes also on the same surface of the substrate.

3 Characteristics and bio-based applications of polymer brush

Many of the characteristics of polymer brushes have been studied recently and thus the polymer brushes have found their resourcefulness into many applications. One of the important properties of polymer brushes is that they produce very low friction coefficients in aqueous medium. This property can be utilized to mimic synovial joints found in mammals [25]. When compared to other polymers, the polymer brushes possess unimolecular as well as intramolecularly assembled nanostructures with varying properties. These nanostructures of appropriate size range could be used to avoid fast systemic clearance and hence polymer brushes have drastically gained interest for drug delivery [26]. The polymer brush coatings can be looked as tethered polymer with hydrophilic long chains dangling in the surrounding. These highly hydrated layers on the surface increases osmotic pressure when a bacterium is nearby which results into the repulsion of bacteria from the surface. Thus, the polymer brush coatings act like a bacteria barrier and has found useful applications as antibiofilm [27]. The three-dimensional and water-swollen structure of polymer brushes provide sufficient accessible volume to bind many protein monolayers. These properties make them attractive for protein immobilization and purification applications. These high increase in binding capacity can be used to enhance the sensitivity and efficiency of analytical devices [28]. This section presents some of the prime biological applications of polymer brushes.

3.1 Lubrication of synovial joints

The polymer brush is essential in the bio-lubrication of synovial joint. Synovial joints connect bones and support the movement in mammals. These joints have contacting cartilage which lubricated with fluid called synovial fluid. Synovial joint shows low coefficient friction of unfavorable tribological conditions. It also resists wear. At a pressure larger than 5MPa, the coefficient of friction is lower than 0.002. The reason behind their superior tribological performance lays in the molecular structure of the cartilage surface. The surface of the synovial joint cartilage has a polymer brush like structure. This structure combined with the synovial fluids, provides the high wear resistance and the low coefficient of friction in the joint.

There is significant potential in bio-mimic design of synovial joints [29]. The lubricated polymer brush presented a novel lubricating method, the hydration lubrication [30, 31]. The low friction at high pressure is also attractive to many different engineering applications. It also offers a potential solution to lubricate the replaced synovial joint [29].

Polymer brushes can greatly enhance the fluidic lubrication despite its poor performance in dry sliding condition [32]. The Kobayashi *et. al.* compared the coefficient of friction for multiple hydrophilic polymer brushes [32]. Among them, the lowest coefficient of friction in dry nitrogen is around 0.1 of the Poly(OEGMA) brush. The dry sliding poly(SPMK), despite its ultralow friction when lubricated in water (around 0.02), displayed the highest friction in dry nitrogen (0.4 approximately). This finding indicated that, like the cartilage in synovial joint, the key to the low friction in polymer brush is the fluid-polymer interaction. In addition, this low friction state cannot be achieved when lubricating water contains 1000mM NaCl. Further proves that the importance of fluid-polymer interaction.

In order to further discuss the lubricating with fluid, the concept of Stribeck curve have to be introduced. The Stribeck curve indicated that the coefficient of friction of a fluidic lubricated system is controlled by the Sommerfeld number, which is proportional to the entrainment speed, viscosity of fluid and the inverse of load. At the high Sommerfeld number, fluidic film separated surfaces, result friction from hydrodynamic drag. At low Sommerfeld number, the fluidic film is thinner than the surface roughness which leads to contact and high friction. In Bielecki *et. al.*, the Stribeck curve of polymer brushes and bear surfaces lubricated by oil is presented [33]. All the curves collapse into two separate behaviors, the bear surfaces and the polymer brushes. It appears that the polymer brush extended the hydrodynamic lubrication regime thus lowering the coefficient of friction [33]. This extension of hydrodynamic regime can be attributed to the hydration effect of poly(dodecyl methacrylate) due to its rich branches [34].

The branched and linear polymer brush shows different tribological performances. In both the case of aqueous lubrication and oil lubrication, the branched polymer chain (Figure 4) shows a superior tribological performance. In the studies of water lubrications, the branched

poly(SPMK) shows better performance [32], while in the oil lubricated polymer brush branched poly(dodecyl methacrylate) has the lowest friction [33, 35]. It is also worth noting that the polymer brushes in synovial joints are branched. This may indicate this branched structure can employ the “squeeze film” effect of the polymer brush.

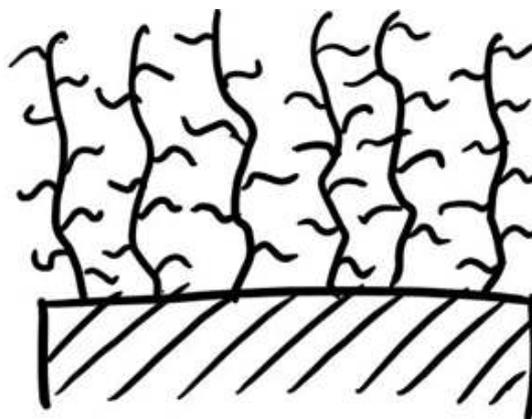


Figure 4 The schematic representation of a branched polymer chain

The polymer brush's tribological property can be further improved with electrochemical forces. Both branched hydrophilic polymer brush and oil compatible polymer brush can only achieve the coefficient of 0.01, one order of magnitude lower than synovial joints. However, the charged polymer brush such as polyzwitterionic polymer brush present the best tribological properties that raveled synovial joints [31]. In aqueous solutions, the charged polymer chain can interact with each other and further reduce the friction. Raviv *et. al.* compares the coefficient of friction of three charged polymer configuration with the polymer chain volume fraction [31]. They conclude that the charged polymer chain can achieve far lower friction compare to the uncharged. The charged polymer brush created a hydration layer, surrounded by the swollen polymer chain [31, 36]. This separation created by the electric force reduced the friction down to 0.001.

A molecular dynamics simulation was constructed by using nanoscale polymer model of a polymer brush system to better understand the lubrication of articular cartilage [37]. They analyzed the frictional properties by using chondroitin 6-sulphate molecules grafted on resilient surface as the polymer brush and water with sodium ions as the synovial liquid. This study concluded that the large deformation of the polymers and the deviation of the synovial fluids from the Couette flow leads to drastic reduction in friction and that the longer the chains of polymer, larger the friction reduction. Hairy polyelectrolyte brushes fabricated from poly (3-sulfopropyl methacrylate potassium salt) (PSPMK) grafted in poly (N-isopropylacrylamide) (PNIPAAm) microgels were demonstrated to be used as intelligent synovial fluid system [38]. Under soft friction pairs, coefficient of friction as low as 0.005-0.015 were obtained. They also demonstrated temperature sensitive drug release capabilities.

3.2 Drug delivery

Due to their versatile properties, polymers are used broadly for drug deliveries. The unimolecular and also intermolecularly assembled nanostructures with varied properties in the polymer brushes helps in drug delivery. And hence, the drug delivery via polymer brush-based scaffolds have attracted a lot of attention recently [39]. Drugs are integrated with the polymer brushes with adaptable structures and features by physical encapsulation or chemical conjugations to build the drug delivery systems. These types of systems are called as brush polymer–drug conjugate (BPDC) systems. To tackle the deadly disease cancer, the delivery of anticancer drugs using polymer brush systems have invited a lot of attention. It is very important to maintain specific considerations and control the dimensions of the scaffolds used for drug delivery in range of 10-200 nm to restrict the clearance and to help tumor targeting via the EPR effect [40].

Doxorubicin (DOX) is widely used medicine in chemotherapy for treatment of cancer. The drug delivery time and dosage are of particular importance for DOX. There have been a lot of studies where polymer brush-based mechanisms have been successfully tested for delivery of DOX as well as other drugs in the desired content and region. Table 2 contains the list of recent works where polymer brush-based systems are used for drug delivery in detail. In one

of the study, the drug delivery system was conjugated with polylactide based biodegradable polymer brush for testing for chemotherapy drug release [41]. When comparing cytotoxicity of the BPDC based drug release and the free DOX, the researchers found that the BPDC was more therapeutically effective towards MCF-7 cells when the concentrations were 5 and 10 $\mu\text{g mL}^{-1}$. The drug release was time and pH responsive as well.

Table 2 Polymer brush-based drug delivery systems

Drug	Polymer brush technique	Usage	Reference
Doxorubicin (DOX)	Poly(lactide (PLA)-based biodegradable scaffolds	Cancer treatment	[41]
Doxorubicin (DOX)	Poly (2-hydroxyethyl methacrylate) (PHEMA) and PCL-b-PEG block copolymers	Cancer treatment	[42]
Doxorubicin (DOX)	Densely grafted PCL-b-PEO onto a functionalized polymethacrylate (PGA)	Cancer treatment	[43]
Camptothecin (CT), Doxorubicin (DOX)	bivalent-brush polymers; prepared by graft-through ROMP of drug-loaded PEG based macromonomers	Cancer treatment	[44]
Doxorubicin (DOX)	Core-Clickable PEG-Branch-Azide Bivalent-Bottle-Brush Polymers by ROMP	Cancer treatment	[45]
Paclitaxel (PTXL)	A degradable BPDC synthesized through azide-alkyne click reaction of acetylene-functionalized PLA with azide-functionalized PTXL and poly(ethylene glycol) (PEG)	Cancer treatment	[46]
Paclitaxel (PTXL)	Diblock BPDC of Poly (ethylene glycol) (PEG)-based macromonomer	Cancer treatment	[47]
Ibuprofen (IBU), poorly water-soluble drugs	Poly (methyl methacrylate-co-methacrylic acid)-b-poly(poly(ethylene glycol) methyl ether mono-methacrylate) [P(MMA-co-MAA)-b-PPEGMA] synthesized by ATRP technique	Painkillers	[48]
Aspirin (ASA)	PSPMK brushes grafted PNIPAAm microgels	Reduce fever, muscle aches	[38]

3.3 Anti-biofouling

One of the biggest barriers in tissue engineering are the non-specific bacteria adhesion and protein adsorption. Understanding the fundamentals of nature's non-fouling conditions for these proteins and bacteria have given rise to environment friendly ultra-low fouling initiatives [49,50]. The two strategies developed for this purpose are; contact killing and use of an anti-fouling material [51–53]. Due to the higher grafting density as well as the molecular weight, the surface modified with the polymer brush exhibited a better performance than the self-assembled monolayers (SAMs) surfaces [54,55]. Recently, the zwitterionic polymer has attracted a lot of attention as a replacement of PEGylation, due to their chemical diversity [56–59]. Another method to integrate anti-biofouling properties in these films is ester hydrolysis [58,60].

Grafting polymer brushes is an effective strategy to prevent biofouling. This is attributed to the chemical strength of the surface modified via polymer brushes [61–65]. However, despite the resistance exhibited by these components, drawbacks like the short working period and single anti-fouling mechanism, need to be overcome. One way to prevent this is using multiple component surfaces. Combining the structural and surface chemistry of these materials is vital for developing its anti-biofouling properties [66]. For instance, in recent study, a NIPAM polymer brush was made inspired by the feet of the Gecko. It showed a significant decline in green algae adhesion [67]. Table 3 lists a collection of recent studies that proves antibiofouling nature of polymer brushes and their various applications.

Table 3 Polymer brush systems used for anti-biofouling applications

Polymer brush system	Properties/Applications	References
3-(trimethoxysilyl) propyldimethyloctadecylammonium chloride coating of silicone rubber	Antimicrobial surface coatings (gram-positive and gram-negative)	[51]
Cross-linked hyperbranched fluoropolymer (HBFP) and poly(ethylene glycol) (PEG) coatings on 3-APS glass slides	Green fouling resistance, marine antifouling	[52]
zwitterionic poly(carboxybetaine methacrylate) (pCBMA) on glass surface	Resistance to bacterial biofilm formation (<i>P. aeruginosa</i> and <i>P. putida</i>)	[54]
Hydrogels carboxybetaine derivatives	pH controlled antibacterial (<i>E.Coli.</i>), strong mechanical properties	[58]
[2-(methacryloyloxy)ethyl] trimethylammonium chloride and 3-sulfopropyl methacrylate potassium salt	Non fouling properties due to oppositely charged monomers being polymerized together	[59]
PDMAEMA, PSPMA, PHEMA-co-PEG10MA, and PSBMA polymer brushes	Low marine biofouling	[62]
poly(3-sulfopropylmethacrylate) grafted on sylgard-184 silicone elastomer and resorcinol formaldehyde	Inhibition of settlements of microalgae and facilitation of cell release due to the microspines	[66]
PAA gel micro-brushes	Underwater superoleophobic properties, antifouling properties against algae	[67]

Table 4 Polymer brush for protein immobilization applications, their binding methods and uses

Polymer brush	Binding method	Applications/uses	Reference
Repetitive iminodiacetic acid chains polymer brush	Selective binding of histidine-tagged recombinant proteins	Biosensors, drug delivery, proteomics	[71]
Mixed polymer brushes of poly(ethylene oxide) (PEO), and poly(acrylic acid) (PAA)	Selective protein adsorption from a mixture of lysozyme (Lyz), human serum albumin (HSA), and human fibrinogen (Fb)	Responsive bio-interfaces in the fields of nanomedicines, biosensors, smart medicines	[70]
Poly(2-hydroxyethyl methacrylate) (PHEMA) brushes in porous alumina	Protein adsorption, 150 mg of protein/ cm ³ (bovine serum albumin)	Purification of His-tag proteins	[68]
Coating of poly(acrylic acid) (PAA) plus activation of the free -COOH groups	Reaction with amine groups, covalent immobilization, selective binding	Drug testing, medical diagnostics, proteomics	[69]
Poly(oligo(ethylene glycol) methacrylate) (POEGMA) brushes	Direct protein coupling (streptavidin)	Recognition of specific macromolecules for medical diagnostics, biofunctionalization	[72]

3.4 Protein immobilization and purification

Polymer brushes can bind to many monolayers of protein because of their three-dimensional structures. Thus, polymer brushes provide great attraction for protein immobilization and purification. This would enhance the sensitivity and efficiency of many analytical devices like protein microarrays, membrane absorbers and matrix-assisted laser desorption ionization (MALDI) plates used for protein capture. Variety of studies where polymer brushes are used for immobilizing protein have been published. One of the method uses poly(2-hydroxyethyl methacrylate) (PHEMA) brushes in porous alumina made by ATRP to bind proteins [68]. The rapid protein binding and high efficiency of these membranes could be useful in purification of protein. Dai et. al. [69] used poly(acrylic acid) (PAA)/protonated poly(allylamine) (PAH) coatings for covalent immobilization of microarrays of antibodies. This process demonstrates selective binding of proteins to bio-specific molecules as it resists nonspecific adsorption and allow for covalent immobilization. The PAA polymer brushes are highly studied for protein immobilization because in aqueous conditions they could swell three to four times and facilitate binding of larger biomolecules. Mixed polymer brushes composed of PEO and PAA were

developed to test the selective protein adsorption from a mixture of lysozyme (Lyz), human serum albumin (HSA), and human fibrinogen (Fb) [70]. They demonstrated that by controlling the ionic strength, the electrostatic interactions can be controlled, and thus selective adsorption can be achieved. These kinds of materials can be used as biosensors, and smart medicines. Table 3 compiles the studies done on polymer brushes and their applications related to protein immobilization in the recent years. Table 4 contains a list of highly cited papers relevant to this section and their probable applications.

4 Summary

This work reviewed the different synthesis routes of polymer brush, their resourceful characteristics, and applications in the biological and biomedical field. Polymer brushes can be modified according to grafting density and monomers, giving flexibility in properties and applications. The characteristics of polymer brushes were discussed according to their different applications: as lubricants, for drug delivery, anti-biofouling, and protein immobilization and purification.

4.1 Ultra-low friction

It was found that polymer brushes function similar to that of the synovial joint in the human knee, resulting in hydration lubrication. In artificial joints, polymer brushes are currently being researched as one alternative, showing significant friction reduction compared to current materials.

4.2 Drug delivery

The unimolecular and intramolecularly arranged nanostructures of polymer brushes can be utilized to avoid fast systemic clearance which enhances their drug delivery applications. PBDC systems are already successfully tested for cancer treatments, painkillers, and pain relievers. Drugs systems are built by physical encapsulation or chemical conjugations of drugs integrated with polymer brushes.

4.3 Anti-biofouling

Various opportunities exist for the polymer brush in anti-biofouling due to the higher grafting densities and molecular weights. The highly hydrophilic long chains of polymer brushes can be used to repel bacteria and other biofouling elements. Fundamental understanding of the structural and surface chemistry of these materials is vital for developing its anti-biofouling properties.

4.4 Protein immobilization and purification

The 3D and water-swollen structure of polymer brushes intensifies the binding protein monolayers. These properties enable them to be used for protein immobilization and purification. They can be used to manufacture smart medicines and biosensors.

5 Recommendations

(1) Currently, the applications of polymer brushes are limited to small scale uses and research. This is especially true in lubrication in artificial joints as further research is needed to evaluate its feasibility.

(2) The main limiting factor of brushes in industry applications is the issue of high load and limited wear life since high loads and stresses accelerate the degradation of polymer brushes. Because of this, large scale industrial applications have yet to be put into practice.

(3) Newer research is being done on developing “smart” polymer brushes. The research should focus on using polymer brushes to build micro and nano structure and modifying them to be able to respond to very specific stimuli. Their chemical as well physical properties can be immensely improved with change in the length scale of the polymer.

(4) The coefficient of friction of the polymer chains can be improved by upto one order of magnitude by electrochemical forces.

(5) Focus on PAA polymer brushes is needed for protein immobilization. They swell up to three to four times in aqueous medium, they are of great asset in the field.

(6) Poly(SMPK) brushes in aqueous solutions displayed good results against wear resistance for around 500 cycles. Their modifications should be looked thoroughly for long lasting wear resistive polymer brushes.

Conflict of interests

There are no conflicts to declare.

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