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Review

Recent progress and perspectives in applications of 2-methacryloyloxyethyl phosphorylcholine polymers in biodevices at small scales

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Abstract

Bioinspired materials have attracted attention in a wide range of fields. Among these materials, a polymer family containing 2-methacryloyloxyethyl phosphorylcholine (MPC), which has a zwitterionic phosphorylcholine headgroup inspired by the structure of the cell membrane, has shown outstanding ability to prevent nonspecific protein adsorption. This property makes MPC polymers excellent materials for the construction of biocompatible surfaces and interfaces with high antibiofouling performance for both macroscopic and microscopic applications. In this review, we summarize recent progress in the design, synthesis, and application of MPC polymers for biodevices with characteristic length scales ranging from millimeters to nanometers, with a focus on their applications in microfluidic devices, biosensors/bioprobes, artificial implants, and drug delivery systems. Finally, future perspectives and challenges in this field are discussed.

Keyword: 2-methacryloyloxyethyl phosphorylcholine, non-specific protein adsorption, antibiofouling, microfluidic devices, biosensors, artificial implants, drug delivery systems

1. Introduction

Biocompatible polymers can be applied in biological systems and perform their desired functions without excessive adverse responses from the system. Natural and synthetic biocompatible polymers have been used for several decades in a broad range of fields such as chemistry, biology, bioengineering, medicine, pharmaceutical science, drug discovery, materials science, and environmental science. Among biocompatible polymers, a polymer family containing 2-methacryloyloxyethyl phosphorylcholine (MPC) has attracted attention for both fundamental studies and applications.[1–6] MPC polymers are synthetic phospholipid polymers with zwitterionic phosphorylcholine (PC) head groups, which can form cell-membrane-like structures on various material surfaces.[4,7,8] This special surface structure has a unique capacity to prevent nonspecific protein adsorption (NPA), and thus biofouling by the adsorption of biomolecules, cells, and other biological entities. This property is useful in applications involving biological entitles (e.g., proteins, other biomolecules, cells), biological samples (e.g., tear, saliva), contact with plasma and whole blood, and implantation in the body or other biological environments. Thus, various MPC polymers with different molecular architectures, such as random, block, graft, and charged structures, have been developed for a wide range of macroscopic and microscopic applications.[9–15]

Meanwhile, there is currently a trend to miniaturize biodevices having biocompatible property and use in biology and biomedicine, because small devices can be portable and simple to operate, provide high-throughput analysis, consume little energy, require less reagent use, and can be delivered or inserted into small target areas.[16–20] The length scales of such biodevices usually range from millimeters to nanometers. However, because of their small sizes, fouling by biological entities (e.g., proteins, cells, other biomolecules) significantly decreases the functional surface area

of the devices, resulting in remarkable changes in their properties and decreasing their performance. In the last decade, various MPC polymers were designed and synthesized to resolve the critical biofouling issue in such small biodevices to have biocompatible property and can be used in a wide application range. In particular, their development for microfluidic devices, biosensors/bioprobes, artificial implants, and drug delivery systems (DDSs) is quite active, because these areas show promise for purposes of bioanalysis, diagnosis, and therapy. Hence, these four types of biodevices having characteristic length scales ranging from millimeters to nanometers were particularly focused in this review. Accordingly, Figure 1 summarizes current applications of MPC polymers in these four types of biodevices at small scales, including sensitivity improvement and cell manipulation in microfluidic devices, qualitative and quantitative analysis by biosensors/bioprobes, drug loading and release by extracellular or intercellular stimulation in DDSs, and the repair, replacement, or restoration of organs/tissues by artificial implants. This review describes recent progress in the design, synthesis, and application of MPC polymers as antibiofouling coatings on the surfaces of these typical small biodevices and their successful application in the related areas. Finally, future directions and remaining challenges in the development of MPC polymers in biodevices at small scales are also discussed. Our article is not intended to be a comprehensive review of the entire field of MPC polymers but rather to motivate the expansion, improvement, and development of MPC polymers by highlighting some representative developments for the focused biodevices at small scales with a wide application range.

2. Microfluidic devices

Microfluidic devices, including lab-on-a-chip or micrototal analysis systems, have been developed

to manipulate subnanoliters of fluids inside and/or around geometries with submillimeter scales for diverse applications in areas such as chemistry, biology, medicine, environmental science and materials science. Applications have been performed in the small spaces of microfluidic devices, where the surface area of the wall is small. Hence, controlling the surface is very important because the surface-area-to-volume ratio increases dramatically as the size of the functional space decreases. The biofouling of the wall is a significant effect that must be prevented, especially in applications involving proteins, cells, and other biological entities, as it can cause irregular fluid flow, clog the channel, or change the properties of functional surfaces, significantly degrading the performance. The use of MPC polymers is a powerful strategy to suppress biofouling and undesirable effects in microfluidic devices. The MPC polymers have been employed in microfluidic devices since the early stage of the development of microfluidic devices.[21–24] They are used mainly for two purposes. One is to prevent biofouling which can reduce clogging and detection noise to enhance the analytical performance, including selectivity and sensitivity during quantitative analysis such as chip-based immunoassays,[25–27] surface plasmon resonance (SPR),[28–33] and separation techniques,[34–37] The other is to realize specific functions such as cell purification,[38,39] cell preservation,[40–42] protein/cell-adhesive behavior,[14,15,43–45] and fluidic manipulation.[46,47]

For early diagnosis of cancer by capturing and detecting circulating tumor cells (CTCs), Xiao et al. immobilized zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) on brominated polyethyleneimine/polyvinyl alcohol (PEI/PVA-Br) nanofibers *via* atomic transfer radical polymerization (ATRP).[48] After that, folic acid (FA) ligands were attached to the PMPC-nanofibers by the redox-sensitive disulfide group (Figure 2A). The PEI/PVA-PMPC-FA nanofibers on the surface of the microfluidic platform potentially prevented NPA and blood cell

adhesion, making it possible to capture cancer cells with overexpressed FA receptors. Tris(2-carboxyethyl)phosphine (TCEP), an effective reducing agent for breaking disulfide bonds, was employed to release the FA-bound FA receptor from the PMPC before staining and quantitative counting under a fluorescence microscope. The developed MPC polymer-based material coupling with the microfluidic method exhibited potential to be applied in clinics to analyze CTCs from the whole blood of cancer patients without complicated sample pretreatment.

MPC polymers have attracted attention for use as coatings on microfluidic surface used in the SPR technique to analyze samples containing biomolecules, cells, and other biological entities. Akkahat et al. used the grafting-to method to immobilize thiol-terminated poly(MPC-*co*-methacrylic acid (MAA)) (referred to as PMAMPC-SH in the reference[28]) brushed on gold (Au)-coated SPR chips for avidin (AVD) determination in blood plasma (Figure 2B).[28] PMAMPC reduced NPA and thus enhanced the sensitivity and specificity of detection by improving the signal-to-noise ratio. The limit of detection (LOD) for AVD analysis was 1.5 nM, which is much lower than that of conventional SPR sensors having surface of a self-assembled monolayer of 11-mercaptoundecanoic acid (150 nM AVD).

In addition to quantitative analysis, MPC polymers have been applied for other specific purposes in microfluidic chips. For example, Otaka synthesized poly(MPC-*co*-*n*-butyl methacrylate (BMA)-*co*-*p*-nitrophenyl-oxycarbonyl poly(ethylene glycol) methacrylate (MEONP)) (referred as to PMBN in the reference[39]) *via* radical polymerization followed by covalent bonding with antibodies against stage-specific embryonic antigen 1 (AbSSEA-1) on the surface of microchannels in microfluidic chips. The PMBN-AbSSEA-1-modified microchannel was used to purify pluripotent stem cells (iPSCs) in routine cell culture.[39] The modified surface affected the difference in mobility between positive and negative SSEA-1 cells. The iPSCs (spiked circles,

positive SSEA-1 cells) moved more slowly because of interactions with AbSSEA-1. By contrast, negative cells (smooth circles) and other impurity molecules moved faster because the PMBN-AbSSEA-1-modified surface prevented NPA (Figure 2C). This approach provides an alternative purification method for separating target molecules from impurities in a stem cell culture solution.

Other interesting research was reported by Xu et al. An MPC polymer-based hydrogel was prepared for cell preservation.[40–42] Poly(MPC-*co*-BMA-*co*-*p*-vinylphenylboronic acid (VPBA)) (referred to as PMBV) was prepared *via* radical polymerization and then cross-linked with high average molecular-weight (high-M_W) PVA to form a polymer network for storing L929 cells in microfluidic channels (Figure 2D). The addition of the hydroxyl groups in a low-M_W sugar solution such as D-fructose or D-galactose to the microchannel can break the boronic linkage and transform the hydrogel into a solution, resulting in cell release, as shown in the orange box in Figure 2D. The prepared hydrogel performed well in the sustainable storage of cells under hypothermic conditions at 4° C for 1 week and at 25° C for at least 4 days. The viability of cells under typical cell culture conditions in the microchannel was better than that of cells on a microplate (Figure 2E). The reasons were that the microchips prevented the evaporation of moisture in the hydrogel while maintaining gas exchange. The chip could reduce cell contamination from the external environment. In addition, the cytotoxicity responses of the cells preserved at 37° C in the developed hydrogel on the chip and in the standard cell culture medium were compared. Figure 2F shows that the response of the cells preserved in the developed hydrogel on the chip to toxins (saponin, triton X-100, and methanol) was similar to that of cells in the standard cell culture medium. This work provides an alternative method of storing and delivering cells for external laboratory analysis while maintaining good cell function.

3. Biosensors and bioprobes

Biosensors and bioprobes are small biodevices to measure targeted molecules and monitor targeted sites, respectively. The detection area of the devices binds to the targets before generating various types of signals (for example, changes in light intensity, light absorbance, potential, or heat) that are directly or indirectly proportional to the presence of the targets. The interferences resulting from the non-specific adsorption of biological entities is a critical issue impeding the use of the biosensors and bioprobes to obtain highly precise and accurate detection. The adsorption may cause severe problems, such as reductions in the surface area and specificity for reactions and decreased stability of functional groups. These problems would result in low signal to noise ratio, insufficient output conversion, and poor analytical performance. MPC polymer coatings have been applied to modify the surface of biosensors/bioprobes to suppress biofouling and prevent undesirable behaviors. Generally, there are two primary applications of surface coatings of MPC polymers: (1) quantitative analysis of biological samples such as tears, serum, and urine,[49–56] and (2) semi-quantitative or qualitative analysis for disease diagnosis.[57–63]

Several publications have reported the advantages of coating a standard electrode with MPC polymers, which can significantly increase binding selectivity and decrease noise during measurements because of their ability to prevent NPA.[51,52,54,55,64] For instance, Li et al. synthesized poly(MPC-*co*-VPBA-*co*-vinylferrocene (VFC)) (referred to as PMVF in the reference[51]) by radical polymerization. The prepared polymer was used to support NPA resistance and intermediary electron transfer. The PMVF solution was mixed with a glucose oxidase (GOx)-PVA solution to form a hydrogel, causing the enzyme to become stably accommodated in the ferrocene units of the hydrogel. Next, a photoreactive azide-unit pendented water-soluble PVA (AWP) solution was dropped on an Au electrode before the PMVF/GOx-PVA hydrogel was spin-coated

layer by layer (LBL) for glucose analysis (Figure 3A). In solution containing glucose, GOx catalyzed the oxidation of glucose leading to the decrease in the reduction current of the modified electrode. This study demonstrated a rapid, simple electrode-preparation approach to motivate the further development of enzyme electronic biosensors using different enzymes for specific analytes.

The versatility of MPC polymers also makes them suitable for the quantitative analysis of various materials. For example, the Mitsubayashi group prepared poly(MPC-*co*-2-ethylhexyl methacrylate (EHMA)) (referred to as PMEH in the reference[50]) *via* free radical polymerization having *α, α′*-azobisisobutyronitrile (AIBN) as an initiator. Then, they prepared a mixture of the polymer solution with GOx. The prepared mixture was dropped on a polydimethylsiloxane (PDMS) contact lens and cured at 80 ℃ to obtain a sensing electrode attached to the contact lens, as shown in Figure 3B.[49,50] The modified contact lens could analyze glucose in a tear (as aforementioned detection principle) without interference of NPA. Another example was reported by Pinyorospathum et al.,[53] who synthesized thiol-terminated PMPC (referred to as PMPC-SH in the reference[53]) by reversible addition-fragmentation chain-transfer (RAFT) polymerization. The PMPC-SH was modified on a screen-printed electrode-based paper having gold nanoparticles (AuNPs) surface on working electrode. The PMPC-SH self-assembled onto the working electrode *via* the interaction of the thiol group with gold. The modified MPC polymer on the paper helps to reduce NPA during the analysis of C-reactive protein (CRP) in a certified serum. The change in current was observed when adding CRP into the solution in the presence of calcium (Ca^{2+}). This is due to the fact that CRP interacted with the PC group of PMPC and persisted on the surface of the electrode. The PMPC modified electrode exhibited selective binding with CRP without interference from bilirubin, myoglobin, or albumin, at a suitable pH and Ca^{2+} concentration. In addition to its biocompatibility, the MPC

polymers itself can facilitate CRP-specific binding in the presence of Ca^{2+}.[4,29,65–68] These results exhibit promise for using the MPC polymers in biosensors for CRP determination.

MPC polymers have attracted attention for use as surface coatings on bioprobes. The MPC-modified surface can resist NPA, enabling efficient semiquantitative or qualitative analysis such as image analysis for disease diagnosis or the observation of an area inside the body without surgery.[57–63] For example, Yudasaka et al. replaced sodium deoxycholate on the surface of single-walled carbon nanotubes (CNTs) by poly(MPC-*co*-BMA) (referred to as PMB) using ultrafiltration.[69] The obtained PMB-coated CNT emits near-infrared (NIR) fluorescence at wavelengths of 1100–1400 nm.[57] Apolipoproteins in blood were adsorbed on the PMB-coated CNTs before specific binding with apolipoprotein receptors on the capillary endothelial cells of brown adipose tissue (BAT), as illustrated schematically in Figure 3C, left. This interaction resulted in a bright bioimage indicating capillary density in the BAT as observed by an NIR camera, as shown in Figure 3C, right. This method provided a more precise image with less light scattering compared to images obtained using organic dyes. However, the adsorption mechanism between PMB and apolipoprotein is still unclear. This work may support the development of methods for the analysis of adipose tissues and other thermogenic tissues, which may provide a new therapeutic target for obesity-associated metabolic disorders. Another use of MPC polymers for qualitative sensing was reported by Ma et al., who synthesized diblock copolymer of poly(MPC-*b*-2-methylthio ethanol methacrylate (MEMA)) (referred to as PMM in the reference[61]) *via* RAFT polymerization. After that, a fluorophore that emits light by two-photon induction (TP) was bridged with prednisolone (Pred), an atherosclerosis theragnostic, *via* reactive oxygen species (ROS) responsive linkage (referred to as TPP in the reference[61]). Finally, TPP was loaded into core-shell PMM *via* self-assembled micelles of PMM (referred to as TPP@PMM).[61] The prepared

micelles were biocompatible, with little NPA; thus, they circulated stably in the blood to deliver the dual-encapsulated fluorophore and Pred to an inflammatory atherosclerosis site. The two molecules were linked by β-cyclodextrin (CD), which is sensitive to ROS. Therefore, in the target area, the TPP@PMM micelles dissociated because of high ROS expression and high lipid levels; consequently, the CD bond was broken, and the drug was released (Figure 3D). The two-photon aggregation-induced emission (AIE) of the active fluorophore successfully generated fluorescence emission in the infected tissue for image analysis. The practical application of this method was demonstrated by in vivo use on atherosclerosis-prone apolipoprotein E-deficient mice (referred to as $ApoE^{-/-}$ in the reference[61]) for potential atherosclerosis theragnosis.

4. Artificial implants

Artificial implants are small biodevices to repair, replace, or restore various body parts such as the hip and other joints, ocular lens, heart, breast, and teeth. Because implanted devices must be attached to or inserted into the body, they will inevitably come into contact with biological entities such as proteins and cells. Implantation usually causes nonspecific adsorption of proteins and cells, resulting in undesirable responses such as thrombus formation and capsular formation on the surface of the implants, which can cause infection and, in the worst cases, death. Thus, the surfaces of artificial implants should be modified to give them antibiofouling properties and thereby biocompatibility. Coating with MPC polymers is among the best strategies for this purpose. Moreover, the use of MPC polymers provides the additional benefit of enhancing the lubricant property of the devices because it has hydrated layers at the PC group.[4]

Several implanted devices for heart disease treatment have been developed, for example, valves,[70–72] catheters,[73–76] and stents[77–80]. In this type of treatment, it is essential to reduce the

adhesion of blood cells, which can induce thrombus formation and blood clogging. Copolymers of MPC and many kinds of other monomers *via* ATRP,[81] free radical polymerization,[70,77,78,82], and condensation reaction[83,84] etc., have been employed to obtain different structural architectures before coating on the cardiovascular devices allowing the devices have antifouling surface. Dip-coat approach with/without surface activation,[77,82,83,85] or further polymerization[79,86,87] are the common methods used for the surface coating. Liu et al. prepared random copolymers of poly(MPC-*co*-lauryl methacrylate (LMA)-*co*-N-(3-aminopropyl) methacrylamide hydrochloride (APMA)) (referred to as PM(PCLA) in the reference[70]) by free radical polymerization. The introduction of APMA increased the crosslinking strength with glutaraldehyde that treated on the surface of porcine pericardium (PP), a heart valve leaflet (Figure 4A, top). The average molecular weight (M_W) of the polymers was adjusted, and the devices coated with PP-PM(PCLA)3 (M_W 116,868 g mol^{-1}) exhibited remarkably reduced blood coagulation, as demonstrated by Figure 4A, which shows thrombus formation on the valve (Figure 4A, middle) and a scanning electron microscopy (SEM) image of platelet/blood cell adhesion on the surface of the material after 2 h circulation (Figure 4A, bottom).

MPC polymers may also be applicable in artificial implants used in the beauty industry such as silicone for breast. PDMS is a common material of breast silicone that is initiated before covalent bonding with PMPC *via* photo- or heat-induced radical polymerization.[88–91] Ham et al. grafted nanolayer of PMPC on PDMS silicone by simply dipping the silicone in a mixture of MPC and ethylene glycol dimethacrylate, and irradiating the silicone with UV light. The covalently grafted PMPC silicones were implanted in a Yorkshire pig for 6 months and showed excellent anti-inflammation and anti-fibrous capsule behavior, as displayed in Figure 4B.[90] Kang et al. introduced heat-induced polymerization as an alternative to UV-induced polymerization.[91] They immersed a

silicone breast in an initiator mixture solution of benzoyl peroxide and dipentaerythritol penta-/hexa-acrylate in dichloromethane/acetone for 16 h at 70 °C. The results revealed that the modified silicone by heat-induced polymerization resulted in 45% less capsular formation, while the modified silicone produced by UV-induced polymerization gave ~25% less capsular formation, when compared both modified silicones with unmodified silicone. The heat-induced polymerization gave a thicker nanolayer PMPC-grafted surface; therefore, a better inhibition of capsular formation was obtained. However, both coating approaches reduced the incidence of infection by ~20%.

In addition to the suppression of fouling, MPC polymers also play an additional role in increasing lubrication and softness, which enhances the performance of materials used in orthopedics[92–98] and ophthalmology.[99–107]. Most of the grating methods used for coating MPC polymers on orthopedic devices is photo-induced radical polymerization followed by few reports of thermal-induced radical polymerization[94,96] or dip-coat method[108] For instance, Liu et al. synthesized poly(MPC-*co*-dopamine methacrylamide (DMA)) (referred to as DMA-MPC in the reference[108]) using free radical polymerization and coated the copolymer on titanium alloy (Ti6Al4V) by simply immersing in the copolymer solution for 24 hr. The DMA-MPC copolymer successfully coated onto the Ti6A14V substrate by an ion-dipole interaction. After that the alloy was used as articular cartilage. Tribological tests revealed that the coefficient of friction (COF) decreased from 0.124 for the unmodified surface to 0.051 for the modified surface because the hydrated PC layers acted as a lubricant. Figure 4C shows the surface modification procedure and highlights the two advantages of the DMA-MPC-modified surface: 1) bacterial inhibition, which reduces infection, and 2) lubricant formation, which improves the wear performance. In ophthalmology, the synthesis of MPC polymers *via* free radical polymerization, ATRP, or RAFT have been attempted before

merging into interpenetration networks (IPN) such as poly(MPC-*co*-bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate),[99] 2-hydroxyethyl methacrylate hydrogel,[104] collagen networks,[100,105,109,110] silicone hydrogel,[103,106,111,112] to create small optical devices. In addition, MPC polymers can be grafted on small optical devices by spin coating,[113] plasma technology[107], and salinization[114] etc. The development not only provides antifouling property, but also provides lubricant and soft properties of intraocular lenses (IOLs), contact lenses (CLs), and corneal etc. For example, Tan et al. synthesized poly(MPC-*co*-MAA) (referred to as P(MPC-MAA) in the reference[107]) *via* free radical polymerization before coating the polymers on an IOL *via* air plasma treatment. Six weeks after cataract surgery, the modified lens exhibited remarkable suppression of anterior capsule opacification and inflammation while maintaining diopter, resolution, transmission, and bending and stretching properties. This work proved that the use of P(MPC-MAA) in IOLs could potentially provide better reconstruction and restoration of vision. Another example in the ophthalmologic field, where MPC polymers are widely applied as surface coatings, is the CLs. The Ishihara research group reported synthesis of silicone hydrogel CLs by radical polymerization. The hydrogel was dipped into poly(methacrylic acid) solution to generate IPN before immerging into mixture solution of polyaminoamide-epichlorohydrin (PAE) and poly(MPC-*co*-2-aminoethyl methacrylate (AEMA)) (referred to as PMA in the reference[106]). This step allowed PAE and PMA bound the substrate *via* amide-bond.[103,106] The prepared CLs strongly resisted the nonspecific adsorption of lipids and proteins. In addition, the softer surface and lower COF of the lens made it more comfortable to wear. Figures 4D and 4E show the antifouling and lens friction properties of the modified CLs, respectively. The results showed that the interaction force with human serum albumin (HSA), and COF values of the modified surface were significantly lower than the bare surface (Figure 4E). The prepared MPC polymers as

aforementioned examples have shown promise for increasing moisture at the surfaces of lenses and joints. Thus, the lubrication and softness are the properties that play a significant role in orthopedics and ophthalmology.

5. Drug delivery systems

DDSs are engineered small devices to carry, deliver, and release therapeutic agents to specific sites inside the body. The NPA may induce failures in the delivery of therapeutic agents to desired target sites, leading to drug degradation, cell toxicity, and unexpected side reactions. To resolve the problem, copolymers composed of MPC enabling to suppress NPA and other moieties allowing encapsulation, delivery and controlled release of therapeutic agents have been developed to form many kinds of drug carrier structures such as nanoparticles (NPs),[115–121] dendrimers,[122,123] micelles,[124–129] polymersomes,[130–132] and liposomes[9,132,133] at micrometer to nanometer scales. The characteristics of the MPC moiety in MPC copolymers to suppress NPA can plays a critical role in the improvement of the biocompatibility of the DDS by increasing blood circulation time, enhancing specific binding to the targeted cells, avoiding immune recognition and elimination, and reducing cell toxicity. In addition, the capability of the MPC moiety to enhance lubrication is also a favorable property in the development of DDSs. Meanwhile, MPC-copolymer-based drug carriers with responsive groups can afford controlled drug release and binding with the target sites under an extracellular or intracellular stimulus such as pH,[134–137] temperature,[138] an enzymatic reaction,[122] a redox reaction,[124,127,139–142] a competitive metal formation,[143] light,[129,144,145] or oscillation.[146]

Cai et al. reported the preparation of poly(MPC-*b*-ε-caprolactone (CL)) (referred to as PCL-ss-PMPC in the reference[124], where -ss- denotes the disulfide bonds), *via* ring-opening polymerization

(ROP) and ATRP. Then, they encapsulated doxorubicin (DOX), an anticancer drug into the PCL-ss-PMPC micelles by dialysis method. The PMPC part allowed the PCL-ss-PMPC micelles circulating for a long time in blood and accumulating in cancer part before rapidly internalizing into tumor cells because of their biomimetic shells. The prepared micelles had the disulfide bonds as the reduction responsive linkage. Therefore, the remarkable difference in redox potential between the intracellular tumor cells and the extracellular environment after the addition of dithiothreitol, a reducing substance, triggered disulfide bond dissociation in the PCL-ss-PMPC micelles, resulting in DOX release, as shown in Figure 5A.[124] Treatment of tumors in rats using these micelles showed promising results, as the tumor volume decreased significantly. This innovative strategy could be used to create other biopolymeric drug carriers for effective cancer therapy.

DDSs using MPC copolymers with pH-sensitive units have been widely developed. For example, Ohara et al. prepared cationic copolymer of poly(MPC-*b*-3-(methacrylamidopropyl) trimethylammonium chloride (MATAC)) (referred to as $P_{20}M_{167}$ in the reference[137]) and anionic copolymer of poly(MPC-*b*-sodium 6-acrylamidohexanoate (AaH)) (referred to as $P_{20}M_{190}$ in the reference[137]) *via* RAFT radical polymerization. Polyion complex (PIC) vesicles were prepared by electrostatic interactions between the cationic ($P_{20}M_{167}$) and anionic ($P_{20}A_{190}$) copolymers, making it possible to encapsulate Texas red-labeled dextran (TD 70), a hydrophilic nonionic molecule, which was used as a model small molecule. The hydrophilic PC group of PIC vesicles played a role in NPA resistance and excellent biocompatibility allowing the PIC vesicles entering into the targeted cell by endocytosis. After that, the PIC vesicles were dissociated under acidic conditions inside the lysosome because negative charges of PAaH was neutralized resulting in charge imbalance. While, $P_{20}M_{167}$ contributed to lysosome breakage, which released the TD70 molecules

to the cytoplasm (Figure 5B, bottom).[137] Fluorescence images of TD70 in L292 cells revealed successful drug release, opening a path to further developments in the introduction of drugs into the cytoplasm without cytotoxicity.

The employment of MPC polymers in DDSs coupled with other trigger strategies for drug release are also of interest, although there are few publications. For example, Chen et al. prepared a diblock copolymer of poly(MPC-*b*-serinyl acrylate (serA)) (referred to as PMPC-*b*-PserA in the reference[115]) by RAFT having 4,4'-azobis(4-cyanovaleric acid) (ACVA) as an initiator and mixed it with $FeCl_3$ for self-assembly into nanoscale coordination polymers (NCPs) *via* metal complex formation of ferric ion (Fe^{3+}) and PserA. Next, curcumin, an anticancer drug, was loaded by an oil-in-water emulsion method.[115] The zwitterionic PC of PMPC-*b*-PserA/NCPs prolonged drug circulation time and decrease drug toxicity because of its hydrophilicity. To release the drugs, deferoxamine (DFO), an iron-chelating agent, was employed to capture Fe^{3+} from the PMPC-*b*-PserA/NCPs (Figure 5C).[143] The results showed promise for the efficient drug delivery using PMPC-*b*-PserA/NCPs and release of anticancer drugs using competitive metal complex formation of two metal chelates (PserA and DFO). Scalcedo et al. modified PMPC on the surface of PEI-grafted core–shell Fe_3O_4@SiO_2 mesoporous NPs (referred to as PEI/MSNPs) using glutaraldehyde as a crosslinking reagent to obtain PMPC/PEI/MSNPs. The prepared MSNPs were employed in ovarian chemotherapy to store TWIST-siRNA (a sensing molecule) and daunorubicin (an antitumor antibiotic). The particle size of the PMPC/PEI/MSNPs reminded stable for 72 h compared with the uncoated PEI/MSNPs after incubation in bovine serum albumin (BSA) and fetal bovine serum (FBS) plasma proteins. The results proved the NPA resistant property which allowed the PMPC/PEI/MSNPs to survive from opsonization in the bloodstream and to be internalized by the cancer cell. After that, an external magnetic field was introduced to oscillate

the magnetic MSNPs, resulting in heat generation, which facilitated the release of the encapsulated molecules from the silica pores (Figure 5D).[146] This method achieved in coating the PMPC on PEI/MSNPs to co-deliver sensing molecules and drugs for dual-function therapy, which may motivate future research on other multifunctional MPC polymer coupled drug carriers to obtain multiple effects in therapy. Although these two articles demonstrated effective drug delivery to the targeted cell by association of MPC polymers with interesting drug releasing strategies, the risk due to the disposal pathway of the metal residues after dissociation should be addressed. Zhang et al. conjugated 1,2-ethaneditiol-modified MPC (HS-MPC) on the surface of phosphoramidate (PAD) dendrimers by thiol-Michael addition click reaction (referred to as PAD-MPC in the reference[122]). The zwitterionic surface of dendrimers forms hydrated layers which can reduce NPA and extend the blood circulation time for increasing tumor targeting. The modified dendrimers were designed to store DOX. The P–O ester bond in PAD-MPC was effectively hydrolyzed with the assistance of the phospholipase C (referred to as PLC) enzyme as a catalyst. Because breast cancer cells overproduce PLC, the drugs were released at the target cells.[122] The dendrimers showed high cytotoxicity against tumors, as demonstrated by several results. Thus, the MPC polymer-modified dendrimers can be applied as a drug carrier using an enzyme as a stimulator in drug-release strategy. The final example of MPC polymers in DDSs was coupled with light sensitive moieties and implemented by Zhao et al.[145] They combined CD-modified PMPC (referred to as CD-PMPC in the reference[145]) with azobenzene-modified mesoporous silica NPs (referred to as bMSNPs-AZO in the same reference) by supramolecular interaction to capture the anti-inflammatory drug diclofenac sodium (DS). The azobenzene in the synthesized NPs was partial *trans*-to-*cis* isomerized under visible light, resulting in drug release (Figure 5E, top). Apart from biocompatible property of PMPC, after light exposure, the robust hydration layer of the $N^+(CH_3)_3$

and PO_4^- groups of CD-PMPC improved lubrication (Figure 5E, bottom), which was indicated from the decreasing of COF value in a tribological test. This property is the recent finding of PMPC ability that have employed in DDSs and can be useful in osteoarthritis therapy. Because this method uses visible light, which can reduce the damage to cells and penetrate cells more deeply than ultraviolet light,[129,144,147] it may result in safer treatment.

6. Future perspectives

The selected progress highlighted in this review has proved that MPC polymers can offer excellent functions and performance in applications in biodevices at small scales. Based on the current progress, brilliant future perspectives of this field in both fundamental study and practical applications can be depicted as shown in Figure 6, while many challenges towards these future perspectives need to be conquered as described in the following.

i) The extension of MPC functionality by not only enhancing reported properties such as antibiofouling, lubrication, and direct penetration into cell membrane without toxicity, but also developing other new properties, is expected to be important in some emerging fields using small biodevices such as nanorobotics, nano energy, space science, and quantum biology. The development of nanorobots for transporting, manipulating, transducing, actuating, and sensing molecules or subcellular entities in the body is one of the growing fields, recently.[148–150] To reach the goal, there are needs to suppress NPA for prolonging the resident time of the nanorobots and to have energy sources for driving and controlling the nanorobots inside the body. Surface modification of the nanorobots using new MPC copolymers with additional functional moieties enabling to induce energy conversion by taking advantage of the in vivo biological environment could play an essential role in this field. Such MPC polymers could not

only guarantee the biocompatibility and working efficiency of the nanorobots in the body but also offer mechanisms to supply nano energy for tiny nanorobots by converting chemical energy inside body into electric energy. In addition, the biocompatible and water-rich properties of miniaturized MPC hydrogels with other moieties to preserve nutrients without generating toxicity or to degrade its-self into fertilizer may be an alternative hydro-absorbent to grow plants for astronauts during space missions, which is necessary especially when the space mission requires long period of time to other planetary bodies.[151] Last, the use of well-defined nanoscale MPC surfaces to eliminate quantum coherence resulting from nonspecific interactions between single molecules and the quantum material-based biosensors would be helpful to elucidate quantum coherences of certain biological interactions of interest in some physiological processes,[152–155] finally contributing to the development of the emerging field of quantum biology.[156]

ii) As the further miniaturization to the nanometer scale is a trend in the development of biodevices, the surface modification of emerging nanoscale biodevices such as nanoneedles,[157–159] nanowires[160–162] and nanofluidic devices,[163–172] provides new opportunities for the use of MPC-based materials. As nanodevices have ultrahigh surface-to-volume ratios, it is not easy to modify and functionalize the surface. In addition, the MPC polymers available for use in microdevices or open nanostructured surfaces may no longer be satisfactory for these nanodevices. The reason is that the dimensions of the polymer typically approach the length scales of these nanodevices, making it extremely difficult to handle polymers inside the nanospace. Hence, in such case polymers with well-regulated short chain lengths are required. Proof-of-concept of this strategy has been done by Shinomiya et al.[164] In their work, well-tailored thermoresponsive polymer brushes with well-regulated short chains were successfully

self-assembled in tiny nanofluidic channels, enabling the active regulation of femtoliter-scale fluids. According to the principle, this strategy will be also effective for MPC polymers. Another alternative strategy is to consider other forms of MPC-based materials. For example, the direct use of MPC-derived monomers with special structures and functions may make it possible to avoid this issue,[173] but comprehensive studies are necessary to maintain the high performance exhibited by the polymers.

iii) The use of zwitterionic MPC polymers in biological applications has increased significantly because of their outstanding biocompatibility and biofouling resistance. However, it is necessary to understand the mechanism of NPA resistance by the PC group to promote the design of functional MPC polymers. The structure of water layer around the PC groups has been considered to play a key role of MPC polymers in suppression of NPA. Hence, the investigation of the structure and behaviors of water in MPC polymers and their surfaces has been investigated by using techniques such as differential scanning calorimetry,[174,175] attenuated total reflection infrared spectroscopy,[176,177] and thermogravimetric analysis.[178] The use of these approaches can provide information of water layer from bulk, to micrometer, or even nanometer scales, but still face great difficulty to further extend to a single molecule or atomic level to fully understand the details of the role of the water molecule in the MPC polymers. Combination of these conventional techniques with small nanodevices allowing the confinement of single molecules would provide new approaches to reach this goal.[163,164,170,179–183] Some preliminary efforts in this direction has been done by Xu et al. They reported the in-situ probing of the behavior of water confined in a nanofluidic device.[183] The further application of the in-situ probing technique to nanochannels with well-defined assembly of single MPC molecules would provide new insights into the mechanism of MPC polymer to suppress NPA.

iv) The description of available polymers, including MPC polymers, is based mainly on average information such as average M_W, average degree of polymerization, and the abundance of polymer sequences, which may vary depending on the synthesis pot. To fully explore the potential of MPC polymers, it is essential to develop methods that allow precise synthesis of MPC polymers with desired sequence and properties that have not yet been obtained. The development of techniques enabling the manipulation of single monomer molecules in the liquid phase is necessary but still highly challenging. Nanodevices having nanoconfinement effects of single molecules would be potential tools to overcome the challenge.[179,184,185] Novel mechanisms allowing to freely manipulate and arrange MPC monomers in a precise sequence could be expected by further coupling such nanodevices with other manipulation mechanisms such as optics, magnetics, electrostatics, fluidics in the future.

7. Conclusions

The significant development of MPC polymers, which have been successfully used in biodevices at small scales ranging from millimeters to nanometers, has been demonstrated in a broad range of applications. Because of their outstanding antibiofouling properties, MPC polymers are potential materials for use in small biodevices in contact with biomolecules, cells, and other biological entities. Moreover, the copolymerization of MPC with other monomers affords a variety of functions for specific purposes in microfluidic devices, biosensors/bioprobes, artificial implants, and DDSs. Therefore, MPC polymers are a powerful material with many benefits, as summarized in this review. The challenges in deeper understanding the properties and extending the applications of MPC polymers are given and waiting for researchers to explore.

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Figures

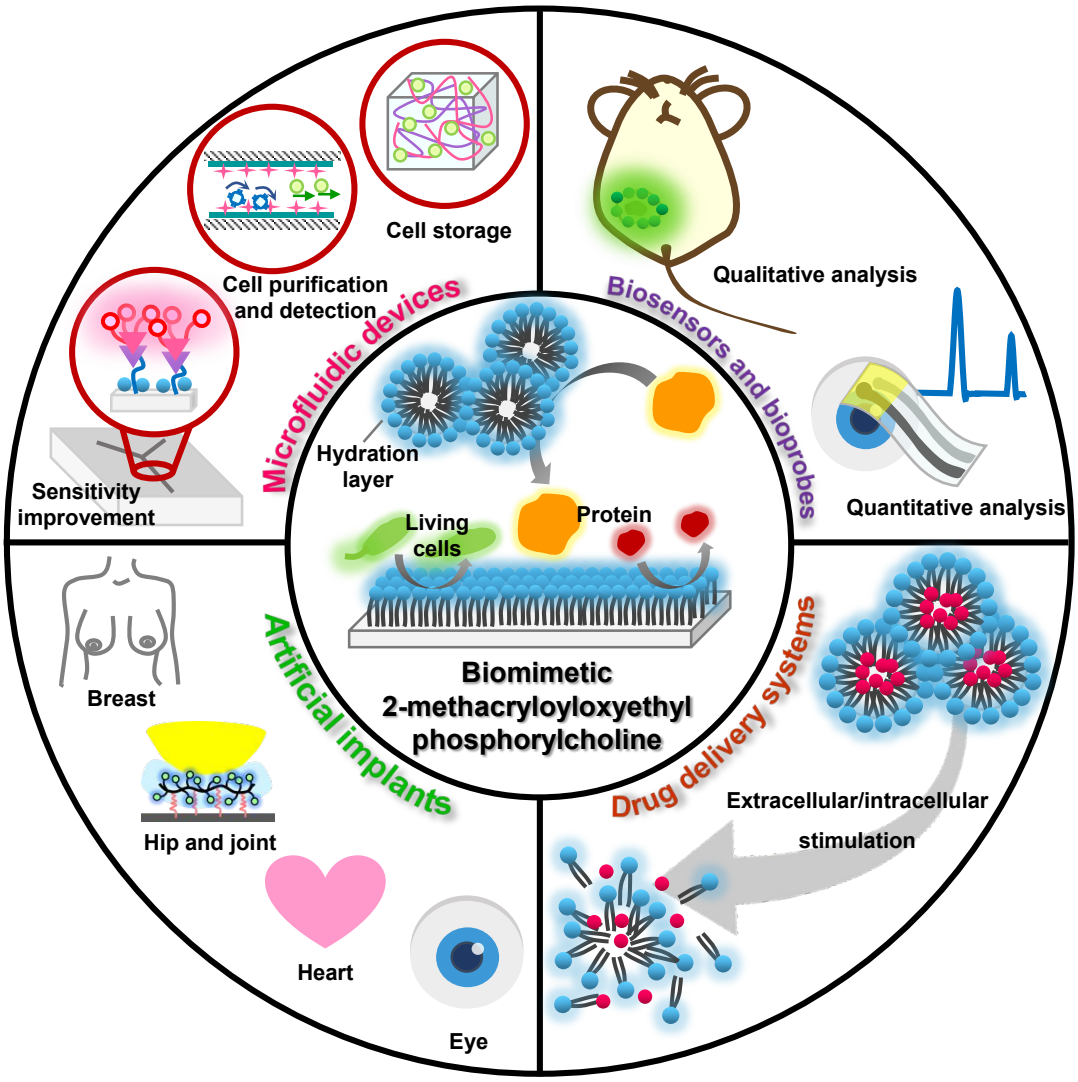

Figure 1 Overview of applications of MPC-based materials in biodevices at small scales.

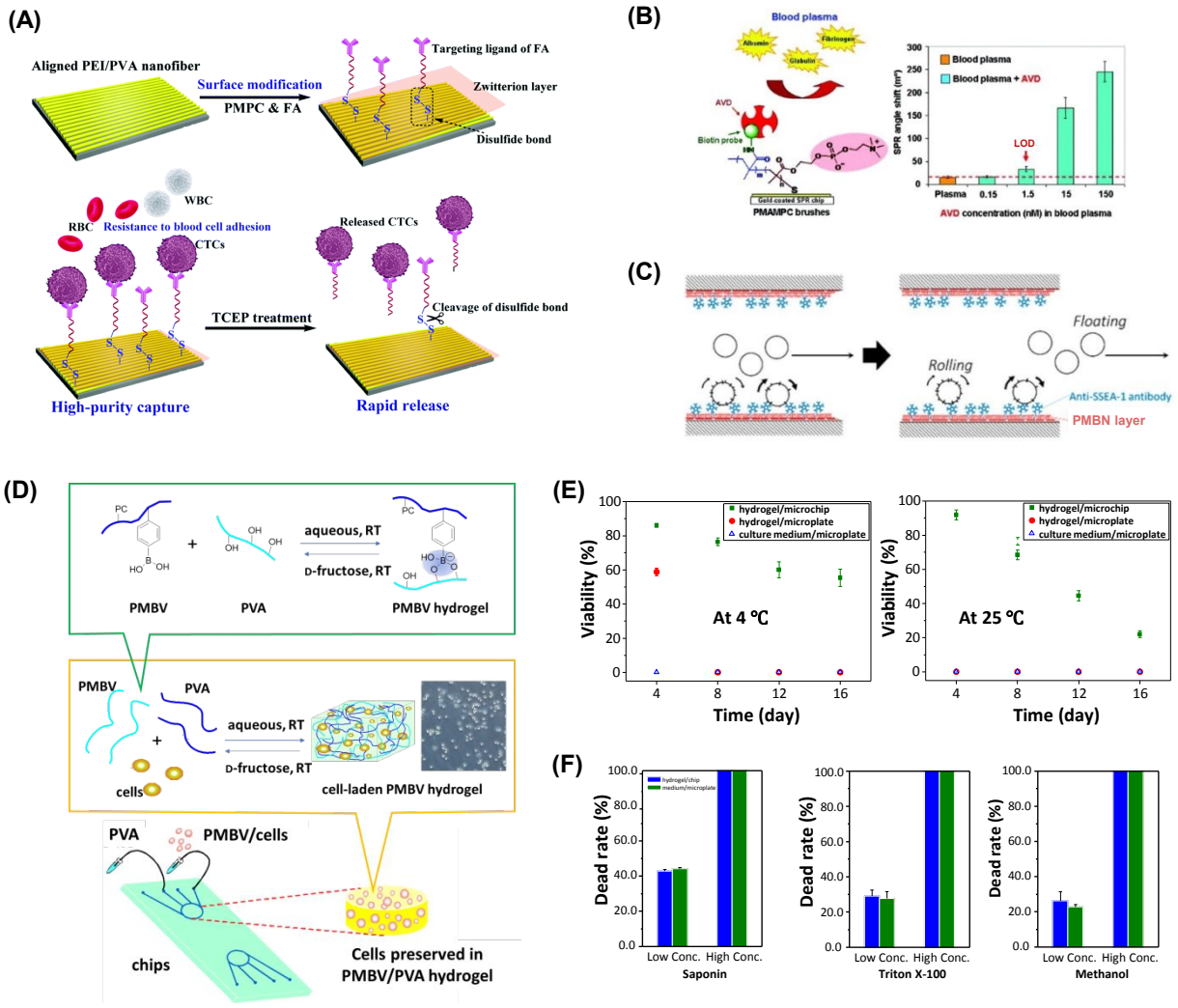

Figure 2 Representative applications of MPC polymers in microfluidic devices: (A) schematic of nanofibrous PEI/PVA alignment for capture and release of CTCs (reprinted with permission from ref. 48. Copyright © 2018, Royal Society of Chemistry), (B) schematic of PMAMPC brush immobilized on gold-coated SPR chips for AVD determination in blood plasma to increase detection sensitivity with LOD at 1.5 nM (reproduced with permission from ref. 28. Copyright © 2012, American Chemical Society), (C) removal of iPSCs (spiked circles) from other cells (smooth circles) in anti-SSEA-1/PMBN modified microchip (reproduced with permission from ref. 38. Copyright © 2017, American Chemical Society), (D) introduction of PMBV and PVA solution into microchannel to form hydrogel for spontaneous cell packaging and storage and the

deformation of the developed hydrogel by D-fructose (reproduced with permission from ref. 40. Copyright © 2010, John Wiley and Sons, and ref. 42. Copyright © 2015, American Chemical Society), (E) variability of cells stored in synthesized hydrogel in microplate/microchannel at 4 °C and 25 °C (reproduced with permission from ref. 42. Copyright © 2015, American Chemical Society), and (F) cytotoxicity responses to saponin, triton X-100, and methanol of cells preserved in the hydrogel on microfluidic chip compared with that of cells in standard culture medium (reproduced with permission from ref. 40. Copyright © 2010, John Wiley and Sons).

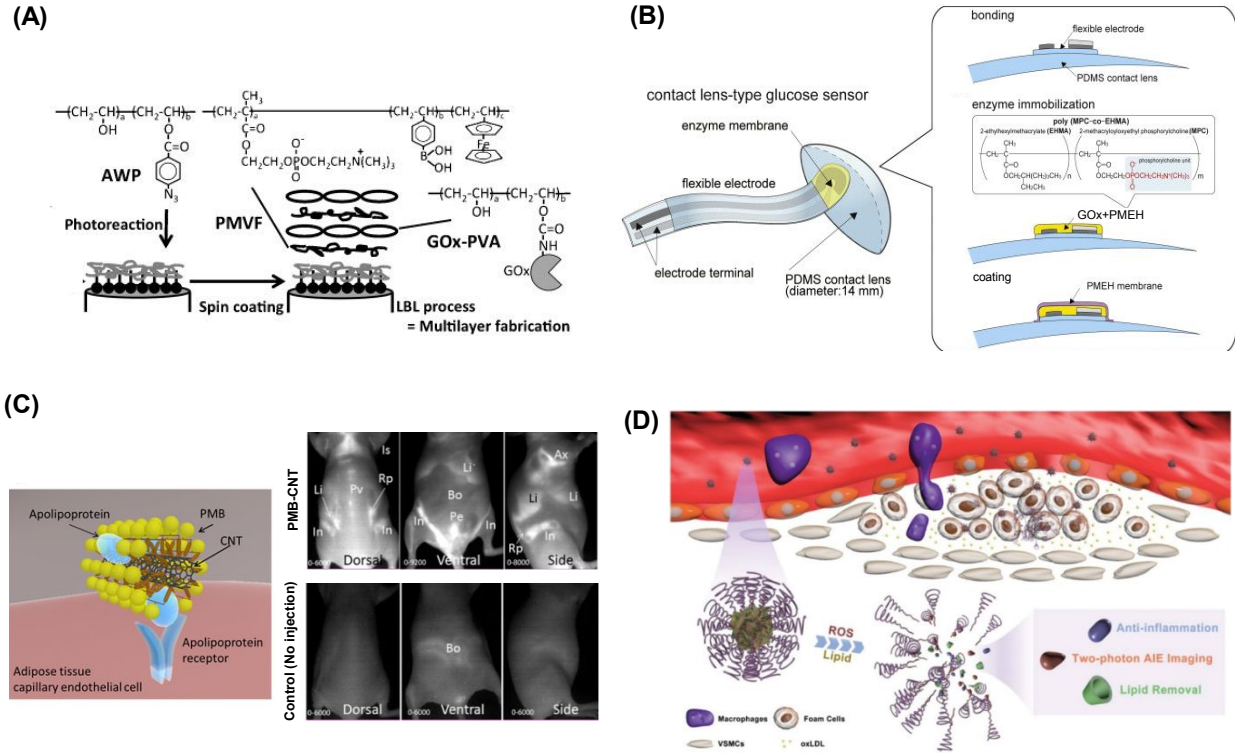

Figure 3 Representative applications of MPC polymers in biosensors and bioprobes: (A) LBL modification of PMVF/(GOx)-PVA hydrogel on surface of gold electrode (reprinted with permission from ref. 51. Copyright © 2012, Elsevier), (B) glucose biosensor attached to PDMS contact lens using a mixture of PMEH and GOx enzyme (reprinted with permission from ref. 50. Copyright © 2011, Elsevier), (C) schematic illustration of binding between PMB-coated CNTs and apolipoprotein complex with receptor on adipose tissue (left) and NIR images of a mouse with (right, top) and without (right, bottom) the injection of PMB-coated CNTs (reprinted with permission from ref. 57. Copyright © 2017, Springer Nature), and (D) drug release and AIE imaging of TPP@PMM micelles for atherosclerosis theragnosis (reproduced with permission from ref. 61. Copyright © 2020, John Wiley and Sons).

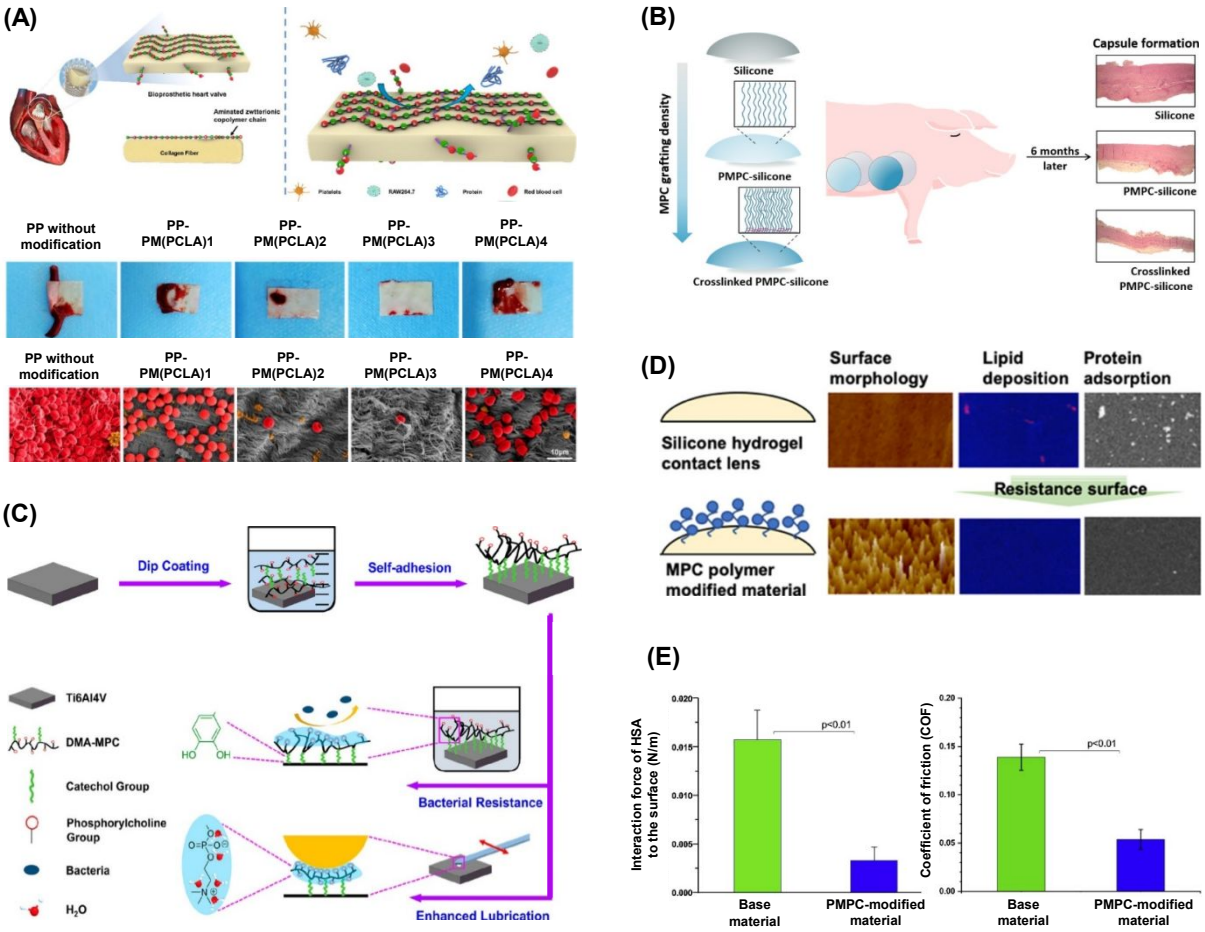

Figure 4 Representative applications of MPC polymers in artificial implants: (A) schematic illustration of NPA resistance on MPC-modified surface of valve leaflets (top), illustrations of thrombus formation on the developed valves (middle), and SEM images of platelet and red blood cell adhesion on the surface of the developed valves (bottom) (reprinted with permission from ref. 70. Copyright © 2021, Elsevier), (B) capsule formation 6 months after silicone implantation in Yorkshire pig (reproduced with permission from ref. 90. Copyright © 2020, American Chemical Society), (C) surface modification of Ti using DMA-MPC copolymer to resist bacterial adhesion and increase lubrication (reproduced with permission from ref. 108. Copyright © 2019, American Chemical Society), (D) comparisons of lipid and protein adsorption on hydrogel contact lens

with/without PMAE modification (reproduced with permission from ref. 106. Copyright © 2021, American Chemical Society), and (E) interaction force of HSA on contact lens (left) and coefficient of friction of contact lens with/without PMAE modification (right) (reprinted with permission from ref. 103. Copyright © 2021, Elsevier).

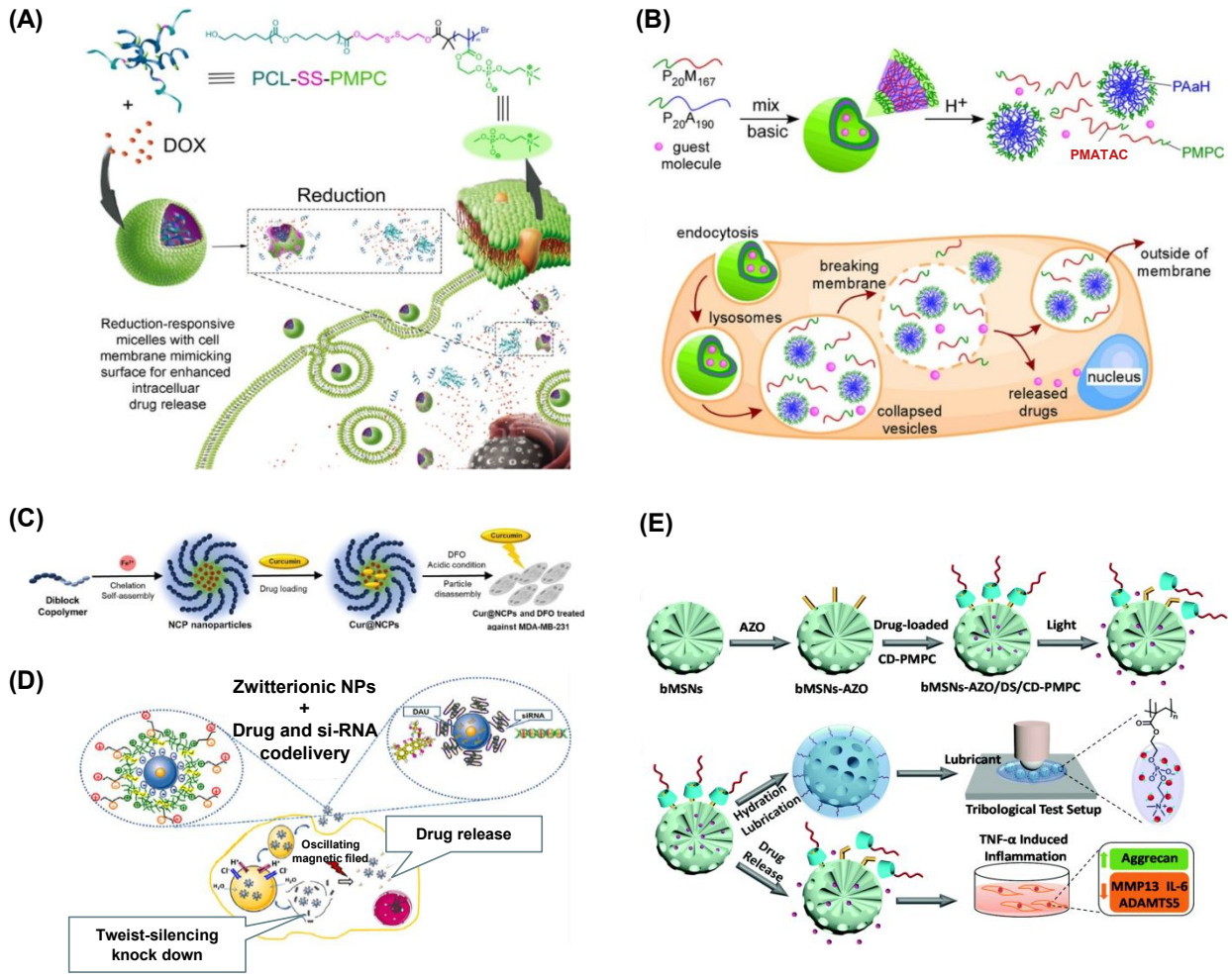

Figure 5 Representative applications of MPC polymers containing different responsive groups in DDSs: (A) redox-responsive PCL-ss-PMPC polymeric micelles (reprinted with permission from ref. 124. Copyright © 2018, Elsevier), (B) pH-responsive PIC vesicles (reproduced with permission from ref. 137. Copyright © 2019, American Chemical Society), (C) competitive-metal-complex-formation-responsive Fe^{3+}-curcumin/PMPC-*b*-PserA/NCPs (reproduced with permission from ref. 143. Copyright © 2021, American Chemical Society), (D) extracellular-oscillation-responsive PMPC/PEI/MSNPs (reprinted with permission from ref. 146. Copyright © 2018, Elsevier), and (E) visible-light-responsive bMSNPs-AZO/DS/CD-PMPC (top) and

lubrication generated by prepared NPs (bottom) (reprinted with permission from ref. 145. Copyright © 2021, Royal Society of Chemistry).

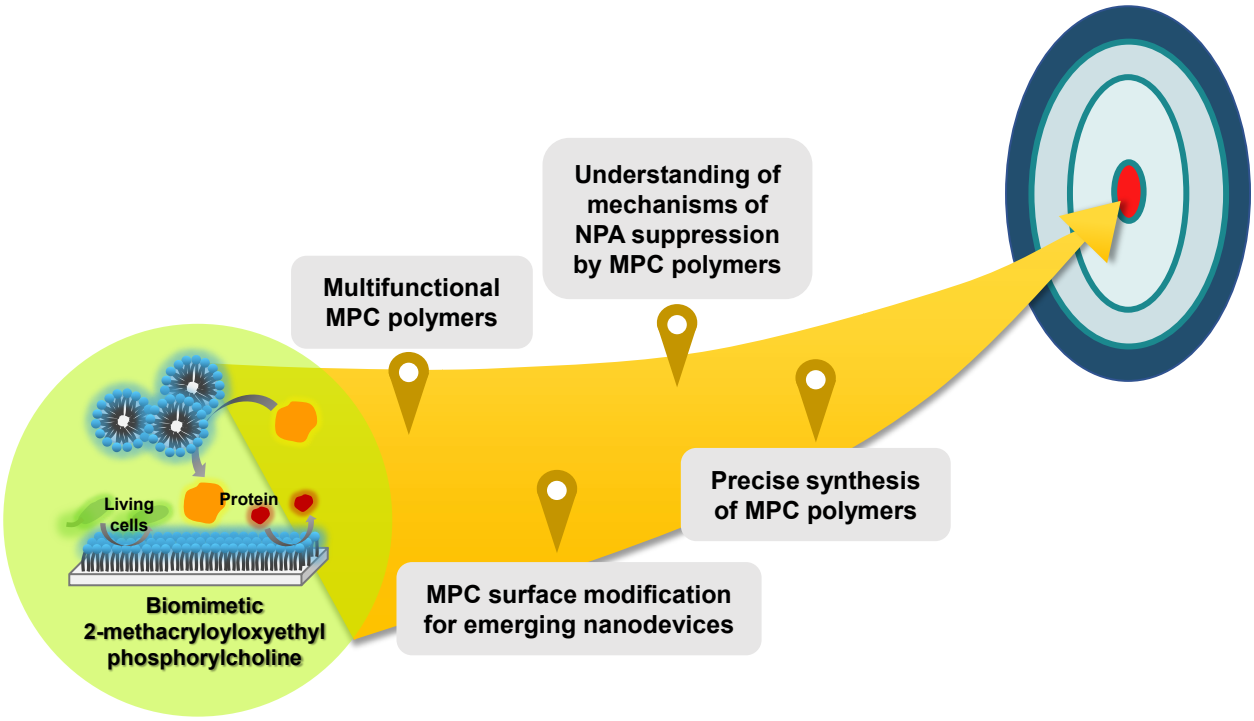

Figure 6 Future perspectives for MPC-based materials in biodevices at small scales.