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Polymer/nanosilver composite coatings for antibacterial applications

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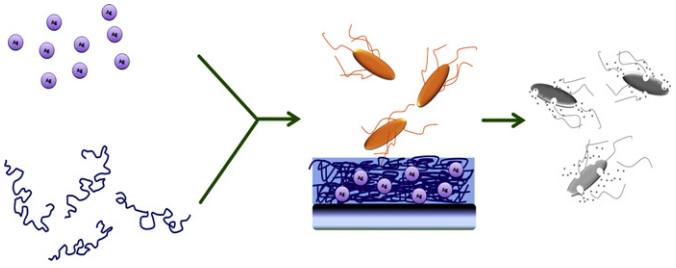
HIGHLIGHTS

- Progress on antibacterial mechanism and cytotoxic effects of nanosilver is presented.
- Antibacterial functions of polymers are described.
- Recent proceedings in fabrication of polymer/nanosilver composite coatings for antibacterial applications are surveyed.
- Future challenges and directions of polymer/nanosilver composite coatings for antibacterial applications are proposed.

GRAPHICAL ABSTRACT



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ABSTRACT

Nanosilver is regarded as a new generation of antibacterial agents and has great potential to be utilized in antibacterial surface coatings for medical devices, food package and industrial pipes. However, disadvantages such as easy aggregation, uncontrollable release of silver ions and potential cytotoxicity greatly hinder its uses. Recently, polymers possessing unique functions have been employed to fabricate nanocomposite coatings with nanosilver for better biocompatibility and enhanced antibacterial activity. This review starts with progress on antibacterial mechanism and cytotoxic effects of nanosilver. Antibacterial functions of polymers are subsequently discussed. Advances of fabrication of polymer/nanosilver composite coatings for antibacterial applications are surveyed. Finally, conclusions and perspectives, in particular future directions of polymer/nanosilver composite coatings for antibacterial applications are proposed. It is expected that this review is able to provide the updated accomplishments of the polymer/nanosilver composite coatings for antibacterial applications while attracting great interest of research and development in this area.

1. Introduction

Bacterial contamination on various surfaces of medical devices, wound dressings, industrial pipes, food packages, and separation membranes is a globally serious concern, posing great threat to their efficiency and lifetime [1–7].Generally, bacteria adhere on these surfaces followed by growth under suitable environmental conditions to form so-called biofilms, which are notoriously difficult to be removed [1,8–10]. The biofilms provide ideal shelters for bacteria inside to metabolize safely with much increased tolerance to antibiotics and host immunological defense, and to infect and/or

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spread to other places for enlarged area [1,9,11]. The only effective way to remove the biofilm-induced infection/contamination is to completely dump the contaminated devices/items with new ones for replacement, which is extremely inconvenient and costly [1,9,12]. Therefore, it is highly desirable to design high-performance antibacterial surfaces that can strongly resist bacterial adhesion and/or kill bacteria for preventing biofilm formation.

Nanomaterials can play an important role in antibacterial applications primarily due to their large surface area and size/shape-dependent physicochemical properties [5,7,13–15]. Among various antibacterial nanomaterials nanosilver is the most promising one, which has exhibited much greater antibacterial effect as compared to bulk silver materials [5,13–20]. In addition, nanosilver has a broad-spectrum antibacterial activity to kill a variety of bacteria existing in everyday life, nosocomial environments, and industrial processes, including those that are antibiotic-resistant [5,13]. Thus, it is very promising to introduce nanosilver on a surface for broad antibacterial applications. However, it is still illusive to fabricate surface coatings with strong antibacterial effects and good biocompatibility/environmental safety by using nanosilver only [21–23]. Aggregation of silver nanoparticles, uncontrollable release of silver ions and promoted adhesion of bacteria greatly reduce antibacterial effects of nanosilver [17,19,23–25]. Polymeric materials with great structure tailorability and flexibility have pronounced potential to inhibit aggregation of nanosilver and form uniform surface coatings on various substrates [19,26]. These materials can also control the release of silver ions for sustained antibacterial effects and reduce cytotoxicity [17,27]. More importantly, they can be designed to resist bacteria adhesion and enhance bactericidal properties [12,28,29]. Thus, it is profitable to combine nanosilver and polymer matrix to form multifunctional composite coatings for antibacterial applications. It is noted that polymer/nanosilver composites with different shapes, in particular with a fiber shape, have been extensively studied [30–33]. The applications of silver polymeric nanocomposites as advanced antimicrobial agents have also been reviewed recently [34]. However, polymer/nanosilver composites for antibacterial surface coating and the fabrication methods are not systematically summarized.

In this review, research progresses on antibacterial mechanism and cytotoxic effects of nanosilver are firstly presented. Polymer functions for antibacterial applications are subsequently described. Then, recent proceedings in the fabrication of polymer/nanosilver composite coatings for antibacterial applications are further surveyed. Finally, conclusions and perspectives, in particular the future directions of polymer/nanosilver composite coatings for antibacterial applications are proposed. It is expected that this review is able to provide the updated advances of the polymer/nanosilver composite coatings for antibacterial applications while attracting great interest of research and development in this area.

2. Antibacterial mechanism of nanosilver

Nanosilver is a cluster of silver atoms with sizes ranging from 1 to 100 nm, which can be synthesized with various approaches using different precursors, reductants and capping agents [35]. As summarized in previous reviews, nanosilvers with different sizes, shapes and surface properties could be produced *via* various approaches such as photo-reduction, chemical reduction, seed-mediated growth, templating synthesis and biosynthesis as well [36–40]. Nanosilver applied in antibacterial tests possesses distinct morphology and physicochemical properties. Therefore, a complicated mechanism with multiple pathways may exist in nanosilver bactericidal effects. In addition, the morphology and physicochemical properties of nanosilver may affect its interaction with bacteria, thus becoming the major factors involved in nanosilver antimicrobial effects. Due to its large surface area-to-volume ratio, nanosilver exhibits great efficiency against a broad spectrum of bacteria and is widely used in clinical applications such as catheter coating, wound dressing and antibacterial hand gels [35]. It is very critical to understand scientific insights of antibacterial effects of nanosilver for designs of composites containing nanosilver as an antibacterial surface coating. In recent years, several reviews have summarized possible antimicrobial mechanisms of the nanosilver [35,41], but the mechanism is still not fully elucidated. In this section three mostly recognized antibacterial mechanisms are discussed. This review mainly focuses on the antibacterial effects of polymer/nanosilver composites. Thus, the antivirus mechanism and the antimicrobial mechanisms for nanosilver-based materials are not included in this survey although anti-virus effects are important parts in antimicrobial activity of the nanosilver.

2.1. Antibacterial effects caused by nanosilver-released silver ions

Metallic silver (Ag(0)) on the surface of nanosilver can be oxidized into Ag_2O in aerobic solutions [20,42,43]. Then the metabolism of bacteria creates an acid environment for the release of silver ions, which has been evidenced in several studies conducted by different laboratories [20,42,43]. It is believed that the silver ions interact with bacterial cell walls, plasma membranes, bacterial DNA and proteins, as well as ribosomes, resulting in bactericidal effects [35,44–47]. Bacterial cell wall is a specific layer of peptidoglycan consisting of sugars and amino acids outside the plasma membrane [48]. Numerous receptors and enzymes responsible for cell respiration locate in the peptidoglycan layer. Since silver ions can bind with negatively charged peptidoglycan, they could easily attach to the thiol group (—SH) of receptors and enzymes along the peptidoglycan membrane resulting in misfolding of proteins, further disabling the bacteria oxygen metabolizing enzymes and leading to bacterial death [49–52]. Interestingly, Gram-positive bacteria are less susceptible to nanosilver than Gram-negative bacteria [46], which may be explained by the much thicker peptidoglycan cell walls of Gram-positive bacteria than those of Gram-negative bacteria. For Gram-positive bacteria the thick peptidoglycan molecules form a dense network-structured cell wall around the bacterial cell membrane, which may prevent penetration of silver ions into inner parts of the cell wall. Therefore, the silver ions only react with outer layers of peptidoglycan and cannot cause significant adverse effects on the bacteria. Negatively charged plasmic DNA inside bacteria is another target of silver ions [46,47]. Silver ions diffuse into the bacterial cells and bind to DNA bases to inhibit the replication and transcription processes, further preventing bacterial production. Zong and coworkers well controlled the synthesis and tests under anaerobic conditions to preclude Ag(0) oxidation and release of Ag ions. It was found that the silver nanoparticles did not show toxic effects on *Escherichia coli*. However, significant antibacterial activity was detected when *E. coli* was treated with the same nanoparticles under aerobic conditions [53]. This work fundamentally confirms that the antibacterial activity is caused by nanosilver-released silver ions, but cannot be used to explain the antibacterial mechanism of nanosilver due to the ambient environment in real applications.

2.2. Intrinsic antibacterial properties of nanosilver

Silver ions released from nanosilver have been proven to be one possible mechanism. However, it is not the only mechanism for antibacterial activity of nanosilver. In a comparative study of nanosilver and silver ions it was observed that silver nanoparticles showed a higher antibacterial potency than silver ions, which suggested that nanosilver might possess intrinsic antibacterial

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capability besides the elution of silver ions [54]. Nanosilver can bind with cell walls as well as plasma membranes of bacteria and penetrate into bacterial cells, causing structural changes, degradation, and finally cell death [55,56]. The nanosilver-released silver ions may change the permeability of cell wall for better penetration of nanosilver into bacterial cells. Interestingly, a recent work reported that common ligands including chloride, sulfide, phosphate, or organic acids in the silver salts-based comparative studies could hinder the bioavailability and mitigate the toxicity of silver ions but not nanosilver at relatively low concentrations [54,57]. The presence of common ligands might cause the higher nanosilver antimicrobial effects observed than their equivalent silver ions concentration in previous reports [54]. In comparison to Zong's work mentioned in Section 2.1, it can be found that whether nanosilver has intrinsic antibacterial properties remains as a question. Delicate control of nanosilver properties and experimental conditions may be needed in future investigations.

2.3. Antibacterial effects caused by reactive oxygen species

The generation of reactive oxygen species (ROS) by nanomaterials is a well-established mechanism for nanotoxicity. A lot of nanomaterials have been demonstrated to induce production of ROS in biological systems and further to result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA [58–64]. Results obtained by using electron spin resonance method coupled with spin trapping and spin labeling show that nanosilver can induce pH-dependent production of hydroxyl radicals and oxygen in the presence of hydrogen peroxide, a biologically relevant product continuously generated in cells [65]. The use of ROS scavenger could significantly decrease ROS levels in bacteria and antibacterial activity of nanosilver [65]. The results clearly indicate that ROS production is involved in the antibacterial activity of nanosilver. Since silver ions can also generate ROS, ROS involving in antibacterial activity of nanosilver may come from both nanosilver and its released silver ions. The excess ROS can break the oxidation/anti-oxidation balance inside bacterial cells, leading to formation of oxidative stress. Subsequently, ROS reacts with biological molecules such as proteins, lipids and DNA to cause significant antibacterial effects. The presence of oxygen is of great importance for ROS generation. Thus, ROS-mediated antibacterial activity could be a possible mechanism in ambient condition.

3. Effects of morphology and surface charge on nanosilver antibacterial activity

Size, shape, surface charge, and aggregation status of nanomaterials significantly affect their interactions with biological systems [34,35,66,67]. As to nanosilver these parameters are of great importance to its antibacterial activity as well [34,35].

Nanosilver with a smaller size possesses higher surface-to-volume ratio, exposing more silver atoms on its surface and further facilitating the release of silver ions [68]. In addition, small nanosilver enters bacteria more easily and its high surface energy can promote the generation of ROS, causing much stronger oxidative stress in bacterial cells than large one [35]. In a recent study silver nanoparticles with sizes of 44, 50, 25, and 35 nm were prepared by using glucose, galactose, maltose and lactose, respectively. The smallest (25 nm) silver particles showed the strongest antimicrobial activity, while the largest particles (50 nm) had the lowest antimicrobial effect [69]. Therefore, nanosilver with smaller size shows stronger antimicrobial activity. Very recently the cytotoxicity was examined using silver nanoparticles with different characteristic sizes (~10, 50, and 100 nm) against several cell lines including MC3T3-E1 and PC12. It was observed that the smallest sized silver nanoparticles (10 nm size) had a greatest ability to induce apoptosis than the other ones (50 and 100 nm) [70]. Thus, although small nanosilver can offer strong antibacterial activity, the potential cytotoxic effects on human and the non-sustainable release profile significantly limit its applications in antibacterial coatings.

Nanosilver with different shapes such as nanosphere, nanorod, nanoplate, nanotriangle and nanowire can be obtained by using different approaches and synthesis conditions [71–73]. They exhibit distinct optical and electrical properties for applications like surface-enhanced Raman scattering and immunosensing [74–77]. Colony forming capabilities of *E. coli* cells treated with spherical, rod-shaped, and truncated triangular silver nanoparticles were compared to explore shape effects on nanosilver antibacterial activity [78]. The strongest antibacterial activity was observed for truncated triangular silver nanoparticles, while rod-shaped nanoparticles displayed inferior performance [78]. The percentage of {1 1 1} facets, which have a high-atom density and high reactivity, in differently shaped silver nanoparticles is proposed to explain the shape-dependent antibacterial effects [78].

Surface charge is another critical parameter that can greatly influence the bioactivity of nanosilver. Silver nanoparticles with various surface charges ranging from highly negative to highly positive have been utilized to study the role of surface charge in antimicrobial activity [79]. It is quite similar to the easy binding of positively-charged silver ions with negatively charged bacterial cell wall. Negatively charged nanosilver presented less toxic effect to *bacillus species* (Gram-positive bacteria), whereas the positively charged nanosilver showed the strongest antibacterial activity. The authors attributed the charge-dependent effect to the interaction of nanosilvers and negatively charged cell wall [79]. The electrostatic repulsion force between negatively charged nanosilver and cell wall blocks the contact of nanosilvers with bacteria, leading to the less toxic effects. However, the interaction force between nanosilver and cell wall changes to attraction when positively charged nanosilver is used, then resulting in a strong antibacterial activity.

It has been observed in several reports that aggregation reduces antimicrobial effects of nanosilver [80–82]. Undoubtedly, aggregation of nanosilver can decrease contact possibility of bacteria and nanoparticles. In addition, aggregation of nanosilver causes great reduction of surface-to-volume ratio, further inhibiting the elution of silver ions and production of ROS. Therefore, highly dispersed nanosilver is favorable for antibacterial applications.

Based on above information, control of size, shape, surface properties, and aggregation degree is crucial for performance of nanosilver-caused antibacterial effects. However, currently it is still very hard to find a synthesis approach that can produce nanosilver with optimized properties. Thus, polymers have been combined with nanosilver to control silver ions release, surface charge, dispersion status and even the shape of nanosilver for achieving desirable antibacterial surface coating materials.

4. Cytotoxicity of nanosilver to mammalian cells

Nanosilver-caused toxicity to mammalian cells has been extensively investigated [42,83–87]. A recent review discusses the transport, activity and fate of silver nanoparticles at cellular and organism levels [88]. Nanosilver is cytotoxic to several different cell lines, including mouse fibroblast (NIH3T3) [89], monocytes (THP1) [90], rat liver cells (BRL 3A) [58], male mouse germline cells (C18-4) [91], human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251) [42]. The developmental toxicity and neurotoxicity of nanosilver are also reported both *in vitro* and *in vivo* [86,92].

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Several mechanisms were proposed to elucidate the cytotoxicity of nanosilver [34,93]. Similarly to its antibacterial effects, the cytotoxicity of nanosilver was related to the release of silver ions, which can target mitochondria to induce the mitochondrial swelling, aberrant metabolism and apoptosis. Silver ions may also bind with intracellular biological groups such as DNA and RNA complex to block the replication and transcription processes, influencing the cell cycle and resulting in genotoxicity. Additionally, cytotoxicity induced by nanosilver- and silver ions-generated ROS are the most extensively investigated mechanism. Exposure to silver nanoparticles causes the production of ROS intracellularly in a concentration-dependent manner [34,93]. If sufficient amount of ROS accumulates in cells, the resulted oxidative stress can lead to the cytotoxic consequences including DNA/protein oxidative damage, apoptosis and necrosis. The alteration of the production of cytokines associated with the inflammatory response is considered to be the mechanism for inflammation-related toxic effects [34,93]. Both stimulatory and suppressive effects on the production of pro-inflammatory factors have been reported [94,95]. Stensberg et al. has speculated that the bi-directional effects of nanosilver are attributed to the exposure dose and cell type applied in different studies [88].

Normally, the cytotoxic level of nanosilver or silver ions is much higher than the antibacterial level. However, long term exposure to low concentrations of nanosilver can induce toxicity to rats [96]. Thus, specific care should be taken before nanosilver is used as an antibacterial agent. Since biocompatible polymeric materials are widely used to reduce toxic effects of nanomaterials, they may also be utilized to fabricate antibacterial surface coatings with good biocompatibility.

5. Role of polymers in antibacterial coatings

Nanosilver faces great challenges for antibacterial surface coatings due to easy aggregation, difficulty to be robustly and controllably immobilized on surfaces, potential toxicity to human beings and the environment, lack of controllability in synthesis and processing, and burst release of silver ions [17,19,23,24]. Polymeric materials are good candidates to form composite coatings with nanosilver due to their great structure tailorability, flexibility, and various methods available for polymer immobilization [19,26,97,98]. Polymer components in antibacterial coatings serve various chemical and physical functions [99–101]. Firstly, they can act as stabilizers for nanosilver synthesis and prevent nanosilver from aggregation in solutions or on surfaces. Secondly, polymers function as linkers for nanosilver, which is directly loaded or *in situ* synthesized in antibacterial composite coatings. Thirdly, polymers can be used as matrix to control silver ion release by changing the interaction between polymers and nanosilver, as well as nanosilver concentration. These functions are closely related to fabrication methods of composite coatings, and thus will be further discussed in an individual section (see Section 6). In this part we will review their biofunctions including anti-adhesive and bactericidal properties, which can synergistically promote antibacterial effects of the composite coatings.

5.1. Polymers with bactericidal effect

It has been extensively reviewed that polymers containing antimicrobial functional groups are employed to enhance the efficacy of some existing antimicrobial agents, minimize the environmental problems with conventional antimicrobial agents and prolong the lifetime of the antimicrobial agents [97]. The combination of bactericidal polymers and nanosilver synergistically enhances bactericidal effects, although bactericidal activity of polymers

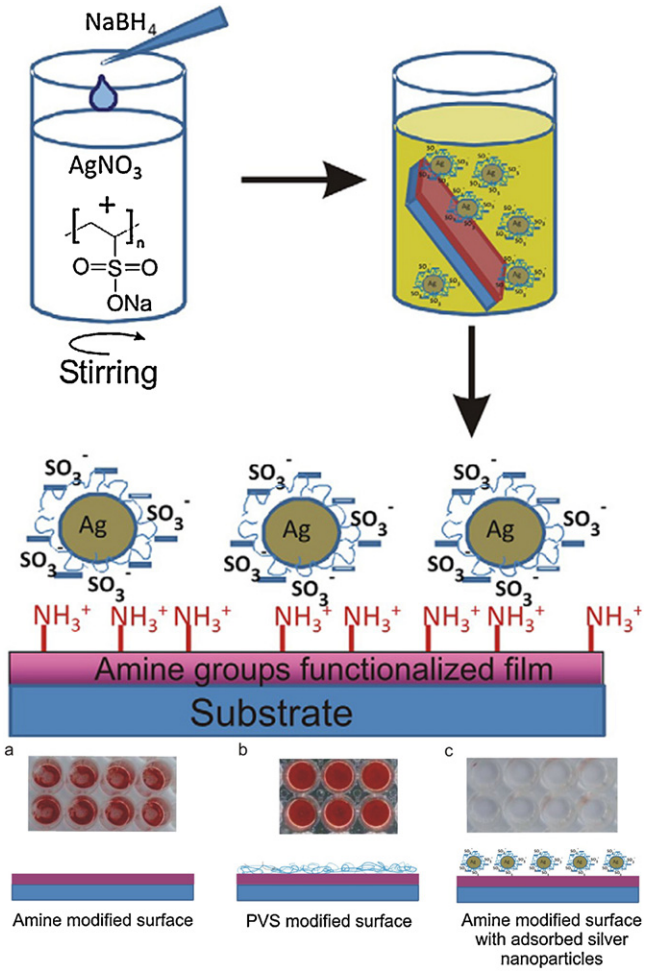

Fig. 1. Schematic representation of the preparation of antibacterial surfaces and detection of *Staphylococcus epidermidis* biofilm formation by safranin staining in wells coated with (a) allylamine plasma polymer film (b) with PVS and (c) with adsorbed silver nanoparticles [120]. Reproduced by permission of Institute of Physics.

generally is much weaker than that of nanosilver [102,103]. On one hand, the polymers could stabilize and disperse nanosilver for enhancing its antibacterial property. On the other hand, with stronger bactericidal property than polymers, nanosilver can play a major role in the short-term antibacterial effect of polymer/nanosilver composite coatings, [23,104] while after its depletion in the form of silver ions the bactericidal polymers can have a dominant effect in the long-lasting or permanent antibacterial coatings [97].

Polymer based on quaternary ammonium compounds (QAC) is one of the main types of bactericidal polymers (see examples in Fig. 1) [1,12,29]. A QAC based polymer normally includes three parts: apolar alkyl chain, spacers and cationic groups. The spacers will ensure the mobility of the cationic groups for antibacterial effects [1,12]. QAC combined with hydrophobic alkyl chain provides a possible "hole-poking" mechanism for antibacterial effects [1,105]. The alkyl chain could greatly influence antibacterial performance by offering high lipophilicity to cause effective damage of structural organization and integrity of cell membranes, followed by cytoplasmic membrane disruption, leakage of cytoplasmic contents, and cell lysis [29,106]. N-hexyl-N′-(4-vinylbenzyl)-4,4′-bipyridinium dinitrate (HVVN), a typical QAC polymer, has been synthesized to form a composite coating with silver nanoparticles

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on PET surfaces. The composite coatings show strong antibacterial activity against *E. coli* and still remain stable after prolonged immersion in phosphate buffer solution and after aging in a weathering chamber [102].

Chitosan is a natural polymer derived from the deacetylation of chitin with both antibacterial property and biocompatibility [107,108]. Several possible mechanisms have been proposed to explain its antibacterial property. The positively charged amine groups could interact with negatively charged bacterial cell membrane and further cause the leakage of intracellular constituents. Chitosan could also bind with DNA after penetration into the nuclei of bacteria, subsequently inhibiting the synthesis of mRNA and proteins [108]. Chitosan/heparin/nanosilver composite coatings have been prepared for antibacterial applications. The composite coatings have strong bactericidal effects on *E. coli* without significant cytotoxicity to mammalian cells. In addition, the strong antibacterial property can last for 1 month [22,103].

Other bactericidal polymers have also been reported such as polyhexamethylene biguanides [12,29], furanone-incorporated polymers [12,109], antibiotics-attached polymers [12,110], and antimicrobial peptides [1,12,28]. Although these polymers have great potential to be combined with nanosilver for the fabrication of polymer/nanosilver composite coatings, they are still adopted very little for this application. Thus, they should present tremendous opportunities for future investigation.

5.2. Polymers with anti-adhesive effect

Another main biofunction that polymers can provide in antibacterial surface coatings is to resist the adhesion of bacteria, which is the first and critical step for biofilm formation [1,9,12]. The integration of nanosilver and anti-adhesive polymers has been demonstrated as one of the most efficient strategies to produce a surface coating with strong antibacterial activity [99,104,111].

Most typical anti-adhesive polymers that have been used for polymer/nanosilver composite coatings should be polyethylene glycol (PEG). Surfaces functionalized with PEG can reduce adhesion of proteins, bacteria and cells due to formation of an interfacial layer to prevent direct contact of surface and proteins [12,112]. The adhesion-resistant ability depends on the chain length, grafting density, and molecular weight of PEG [112,113]. A network coating containing nanosilver, PEI units and hydroxyl groups has been prepared for antibacterial applications. After modification with PEG the coating presents a microbe-repelling property besides silver ion release and contact killing effects, demonstrating the strong anti-adhesive activity of this multifunctional active antimicrobial network coating [104].

Besides PEG, some natural polymers such as dextran and heparin have also been used for polymer/nanosilver composite coatings to resist the adhesion of bacteria [111,114]. Use of dextran and heparin not only introduces anti-adhesive properties to the nanosilver-based composite coatings, but also significantly improves their biocompatibility [111,114]. Both properties are beneficial to antibacterial applications of the coatings.

Some other anti-adhesive polymers have shown great potential for the fabrication of polymer/nanosilver composite coating. One example is poly (2-methyl-2-oxazoline) (PMOXA). PMOXA attached poly-L-lysine (PLL) with the optimal grafting density can eliminate protein adsorption to a level of $<2\ ng/cm^2$, equal to the protein repellent properties of the most effective PEG-based coatings [12,115]. Zwitterionic surfaces formed from sulfobetaine methacrylate and methacryloyl polymers have also been demonstrated to reduce both short-term (1–2 h) and long-term (24–28 h) adhesion and biofilm formation of *E. coli*, *Straphylococcus epidermis* and *Pseudomonas aeruginosa* [12,115].

6. Methods to form polymer/nanosilver composite coatings

Two ways are utilized to incorporate the nanocomposites with well-dispersed nanosilver on surfaces: (1) polymers with nanosilver are fabricated first and then attach to surfaces; (2) polymers are immobilized on surfaces first followed by nanosilver incorporation. In both cases, it is very critical to successfully attach the polymers on a surface. In this section, we will briefly summarize the nanosilver loading approaches, and then present recent progress on fabrication of polymer/nanosilver composite coatings in terms of polymer attachment methods. In particular, layer-by-layer (LbL) approach with unique advantages for the fabrication of antibacterial coatings will be highlighted in detail. Finally, different methods will be summarized and compared with respect to polymer type, coating approaches, Ag NP loading and Ag NP size range.

6.1. Incorporation of nanosilver

A lot of methods have been developed for the incorporation of nanosilver into polymer matrix. Since their principles are similar, they will only be briefly summarized here.

In general, nanosilver is primarily incorporated by direct adsorption or *in situ* synthesis. The direct adsorption of nanosilver is very simple and controllable, but it can easily induce aggregation between silver nanoparticles. For example, in Dacarro et al.'s work, nanosilver was directly adsorbed on covalently attached PEI layer [116]. With the increase of the adsorption time, the color of coating changes from yellow to red and brown black, indicating the successful attachment of silver nanoparticles but with aggregations. In comparison, *in situ* synthesis approach is relatively difficult to be carried out due to the challenge for silver ion loading. However, it is more advantageous than direct adsorption of nanosilver in the formation of uniformly distributed silver nanoparticles in polymer matrixes. Many matrixes such as PBT [117], PVA [101], HVVN [102] and polyelectrolyte multilayers [103,118,119] have been applied for the *in situ* synthesis of silver nanoparticles, and different mechanisms have been used for silver ion loading. For example, Wan et al. have loaded silver ions by using the chemical affinity between sulfur and silver [117]. Yuan et al. have exploited both coordination and electrostatic force to load silver ions [103]. Rubner et al. have used ion-exchange reaction for the loading of silver ions [118,119].

6.2. Surface attachment via physical adsorption

Physical adsorption is the most straightforward approach to modifying surfaces with polymers/nanosilver composite coatings. Various forces such as electrostatic force, hydrogen bonding, and biomolecular recognition can be used to drive the adsorption [120,121]. As a facile and inexpensive approach physical adsorption can be applied to attach various functional polymers/nanoparticles on nearly any surface with suitable functional groups or charges [100,121]. Furthermore, most of them can be performed in aqueous solution at low temperature and ambient pressure, rendering it a green approach [100,120,121].

Electrostatic force is one of the most commonly used interactions for physical adsorption. Travan et al. [100] activated a bisphenol A glycidylmethacrylate (BisGMA)/triethyleneglycol dimethacrylate (TEGDMA) thermosets surface to expose carboxyl groups through hydrolysis. Then silver nanoparticles, synthesized with lactose-modified chitosan as a biocompatible stabilizer, were adsorbed on the activated thermoset by electrostatic force between carboxyl groups and positive chains of the polysaccharide. Vasilev et al. [120] exploited the electrostatic interaction to immobilize polyvinyl sulphonate (PVS)/silver nanoparticle composite on a surface. To efficiently attach negatively charged PVS/silver nanoparticle composites on the surface, plasma polymerization

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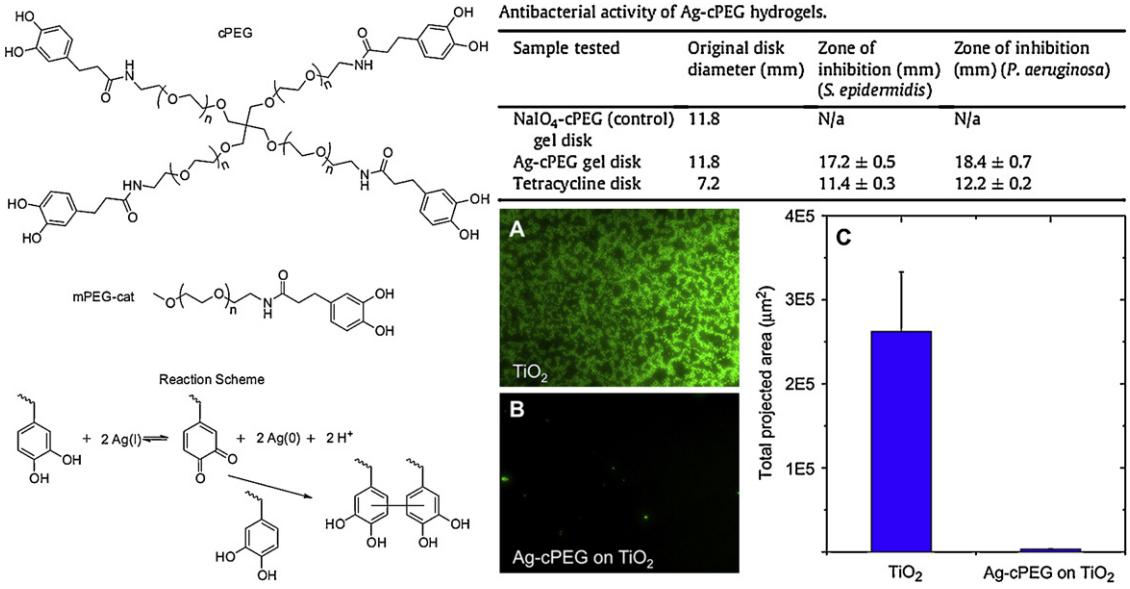


Fig. 2. Molecules synthesized and proposed reaction scheme (Left), antibacterial activity of Ag-cPEG hydrogels (upper right), Bacterial attachment onto Ag-cPEG coatings (A and B), and quantitative *S. epidermidis* cell attachment data obtained from image analysis (C) [99]. Reproduced by permission of Elsevier.

of allylamine was employed to produce an amine-functionalized surface with positive charges for facilitating the electrostatic adsorption (Fig. 1). Both polymer/nanosilver composite coatings discussed above have shown excellent antibacterial properties, demonstrating the efficacy of this electrostatic force driven physical adsorption method. It is worthy of a note that the polyelectrolytes used to not only provide the electrostatic charge, but also stabilize silver nanoparticles for relatively uniform distribution. Furthermore, these polyelectrolytes offer unique functions for practical applications, in which lactose-modified chitosan provides biocompatibility and low cytotoxicity while PVS offers anti-thrombogenic activity.

Besides the electrostatic force, other interactions such as hydrophobic force and hydrogen bonding have been utilized to physically immobilize polymer/nanosilver composites on a surface as well. A novel nanosilver-incorporated antibacterial hydrogel was developed using reactive catechol moieties functionalized water-soluble PEG (Fig. 2). The precursor solution was spin-coated onto a clean TiO_2-coated Si wafer. After gelation the hydrogel coating was attached on the surface *via* physical adsorption, in which catecol moieties play an important role as adopted during the DOPA adhesion on various surfaces by the same mechanism [122–124]. Further, the catechol oxidation and silver ion reduction occurred simultaneously, forming intermolecular crosslinking and nanosilver [99].

6.3. Surface attachment via covalent bonding

Covalent grafting of polymers provides a promising strategy to achieve long-term environmentally stable and well-defined polymer/nanosilver composite coatings [102,117]. Various functional groups can be introduced into the polymeric coatings by organic synthesis approaches for nanosilver incorporation, antibacterial property, and biocompatibility [111,116,117,125]. However, in comparison to the physical adsorption, the covalent attachment cannot be applied universally on various substrates, and thus new chemistry is needed for different substrates. Due to the diversity of chemical reaction usable for polymer attachment, here we only focus on the two most commonly used and important approaches: self-assembly and irradiation.

In Dacarro et al.'s work [116], PEI was linked with silane, and then covalently immobilized on a Si-OH terminated surface (glass, quartz, or silicon with SiO_2 layer) to form a self-assembled monolayer (SAM). This covalently bonded PEI layer was much more stable than physically adsorbed one over a wide pH range, and could be used as an efficient linker for binding of silver nanoparticles (Fig. 3). Wan et al. first self-assembled a monolayer of 2,2′-bithiophene (BT) on the Cu surface. Then, a chemical oxidative graft polymerization of BT on the monolayer was carried out to prepare a homogeneous PBT film. Silver ions were subsequently loaded *via* their interaction with sulfur for reduction into nanosilver [117]. Similarly, in the work of Ferrer et al.[114], a wafer was first functionalized with amine group *via* forming a SAM through silane chemistry, and then dextran with embedded silver nanoparticles was covalently immobilized on the wafer.

Plasma and/or light irradiation is also frequently used for surface activation and polymer attachment. PLLA surface was covalently modified with a nanosilver-incorporated polymer *via* four sequential steps (Fig. 4) [101]. Firstly, oxygen plasma treated PLLA films

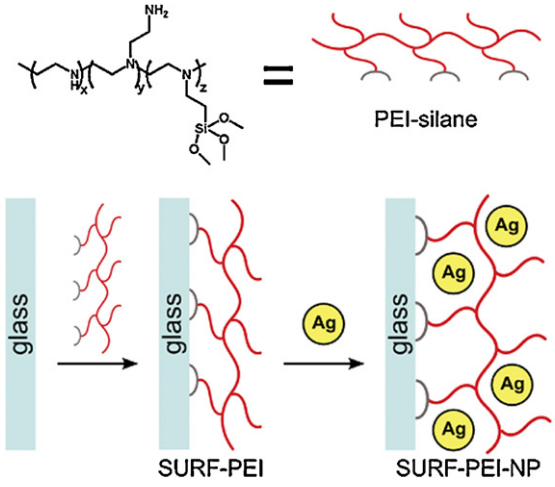


Fig. 3. Schematic representation of PEI-silane structure and two step synthesis of a silver nanoparticle monolayer grafted on PEI SAM. The chemical bond between glass and PEI-silane is Si—O—Si bond [116]. Reproduced by permission of The Royal Society of Chemistry.

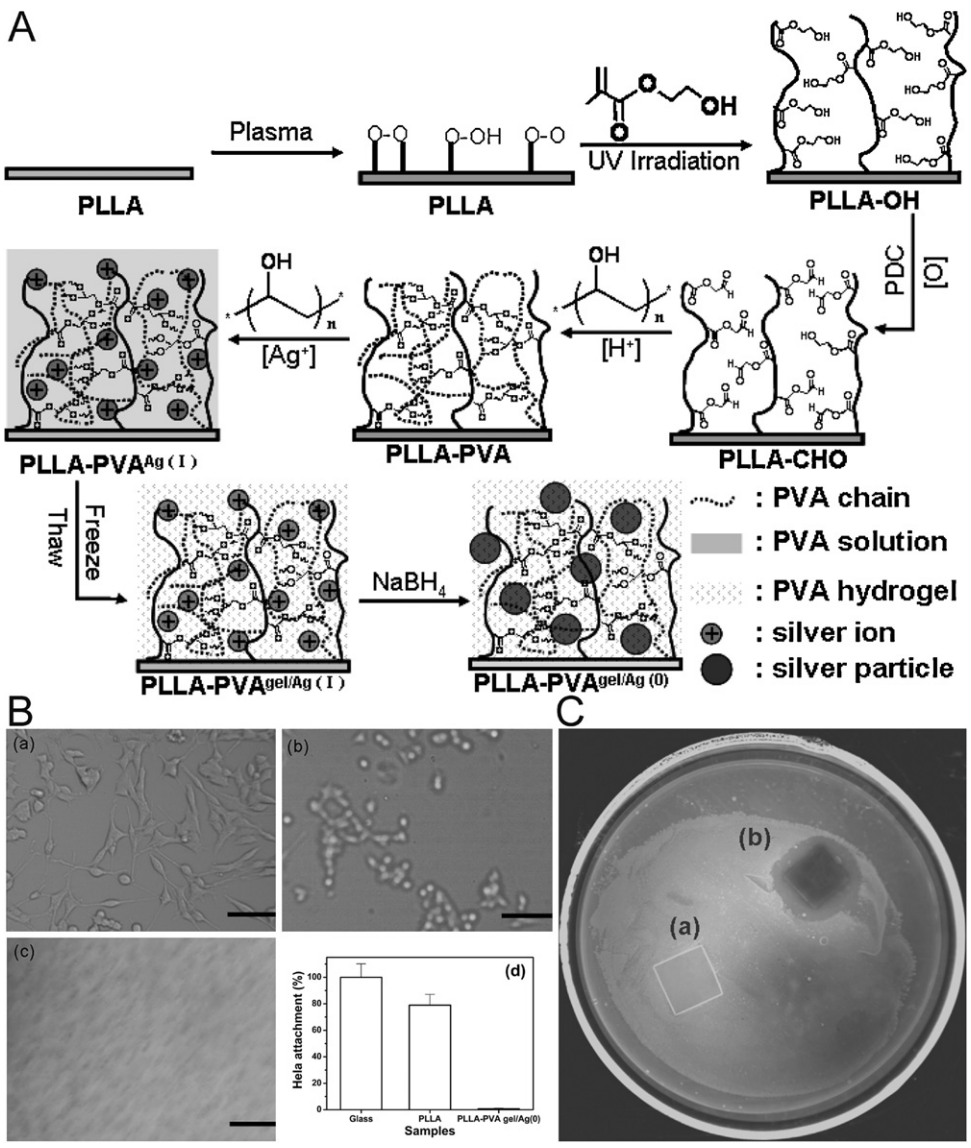


Fig. 4. (A) Process for fabricating PLLA-PVA$^{gel/Ag(0)}$ Film. (B) Optical images of adhered Hela cells on (a) glass, (b) virgin PLLA, and (c) PLLA-PVA$^{gel/Ag(0)}$; (d) is percent Hela adhesion on different substrates relative to that on glass (which served as the control). The scale bar is 100 μm. (C) Antibacterial activities of (a) PLLA-PVA^{gel} and (b) PLLA-PVA$^{gel/Ag(0)}$ [101]. Reproduced by permission of American Chemical Society.

were grafted with polyHEMA *via* UV-initiated polymerization to produce PLLA-OH. Secondly, the PLLA-OH films were oxidized using pyridinium dichromate (PDC) to get aldehyde-functionalized PLLA (PLLA-CHO). Thirdly, PVA was directly immobilized on PLLA-CHO *via* acid-catalyzed acetal formation. Finally, silver ions were loaded into PVA matrix, after which the hydrogel was formed by the "freeze/thaw" method. The silver ions were then reduced to silver nanoparticles to form polymer/nanosilver composite coating, which could show excellent anti-adhesive and antibacterial performance. In the work of Shi et al. [102], PET was firstly pretreated with argon plasma for the formation of surface oxide and peroxide groups, and then a UV-induced surface graft polymerization was carried out to attach HVVN on pretreated PET (Fig. 5). Silver nanoparticles were synthesized *in situ* by UV-irradiation. The antibacterial test showed that HVVN chain exhibited an antibacterial property, and silver nanoparticles greatly enhanced the antibacterial effect. This composite thin film could kill 99.9999% of the bacteria within 5 h, and its antibacterial functionalities were very stable (Fig. 5). Ho et al. [104] first modified PEI with polymerizable double bonds by reacting with methacryloyl chloride to obtain PEI-MA. A network coating was then synthesized using UV-initiated copolymerization of PEI-MA and 2-hydroxyethyl acrylate (HEA) on trimethoxymethacryloxypropyl silane-modified glass slides. Silver nanoparticles were incorporated by silver ion loading and reduction (Fig. 6A). After nanosilver loading and PEG covalent modification, this coating could kill more than 99.9% of the bacteria in the bacteria suspension surrounding it. Furthermore, after the silver was released to a degree that cannot kill the bacteria, the coating still allowed four to eight times less bacteria to adhere than that without PEG (Fig. 6B and C).

6.4. Layer-by-layer self-assembly

LbL self-assembly, based on alternate adsorption of different building blocks primarily driven by the electrostatic force, has been widely used for fabrication of functional ultrathin film coatings [46,111,126–133]. Recently, a lot of works have been reported to use this approach for the fabrication of antibacterial coatings [3,103,114]. The advantages of this technique are as follows [111,126,127,134–136]: (1) various building blocks such as polyelectrolytes, nanoparticles, and biomacromolecules can be

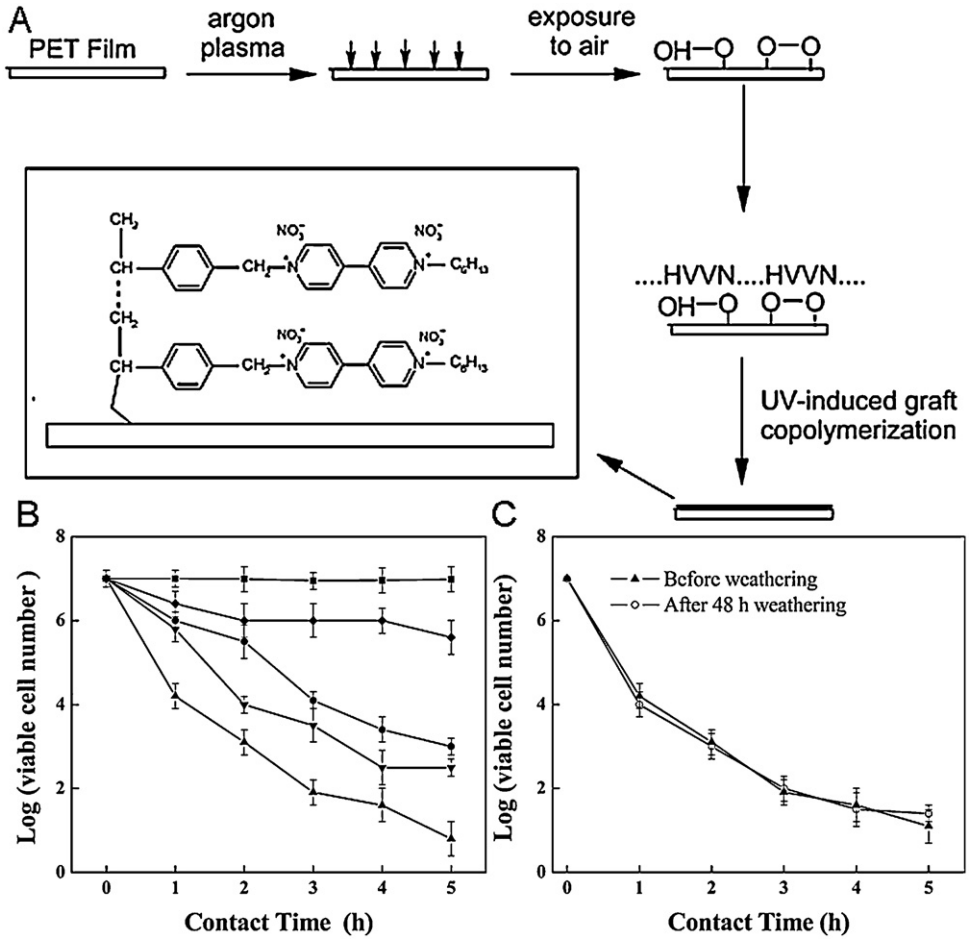
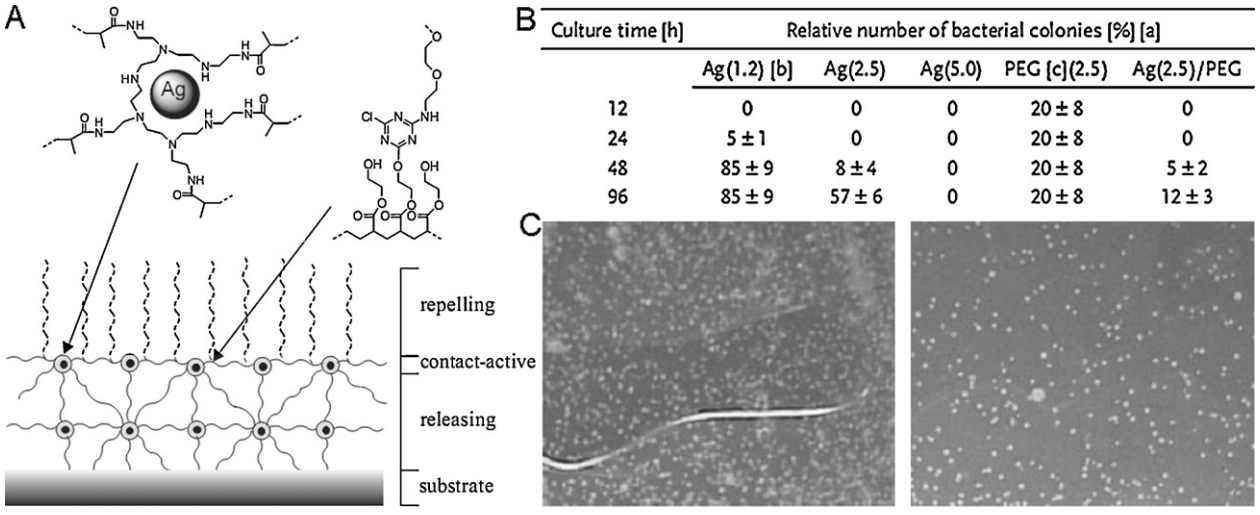


Fig. 5. (A) Scheme of argon plasma pretreatment and the graft copolymerization of HVVN with the PET. (B) Viable *E. coli* cell number as a function of time in contact with the different substrates: pristine PET (■), VBV-PET (♦), HVVN-PET (●), HVVN-PET after reaction in $AgNO_3$ for 30 min (▼), and HVVN-PET after reaction in $AgNO_3$ for 15 min (▲). The cell number was determined by the surface-spread method [102]. Reproduced by permission of American Chemical Society.

used; (2) virtually any substrate with any geometry and chemical composition can be adopted; (3) the nanostructure and chemical composition can be controlled at the molecular level; (4) it is facile, low-cost, and environmentally friendly. Since LbL approach can provide such advantages that are particularly promising for the fabrication of polymer/nanosilver composite coatings, it will be highlighted in detail in this section. The principle of this approach is shown in Fig. 7 [136].



Culture time [h]	Relative number of bacterial colonies [%] [a]				
	Ag(1.2) [b]	Ag(2.5)	Ag(5.0)	PEG [c](2.5)	Ag(2.5)/PEG
12	0	0	0	20 ± 8	0
24	5 ± 1	0	0	20 ± 8	0
48	85 ± 9	8 ± 4	0	20 ± 8	5 ± 2
96	85 ± 9	57 ± 6	0	20 ± 8	12 ± 3

Fig. 6. (A) Architecture of a multiply active antimicrobial PEI network film. (B) Number of *S. aureus* colonies grown on differently modified PEI-MA/HEA networks. All experiments were performed at least in triplicate and the error is the standard deviation. [a] The reference for each sample was number of bacterial colonies grown on the respective unmodified network (typically 5 to 20 × 10^2 colonies/cm^2). [b] The number given in parenthesis is the PEI content of the network given in wt.%. [c] PEGylated PEI-MA/HEA network. (C) Images (0.6 cm × 0.75 cm) of *S. aureus* colonies grown after being attached to a PEI-MA/HEA network with 2.5 wt.% PEI and loaded with silver (left) and to a similar network additionally modified with PEG (right). Cultivation time was 96 h [104]. Reproduced by permission of John Wiley and Sons.

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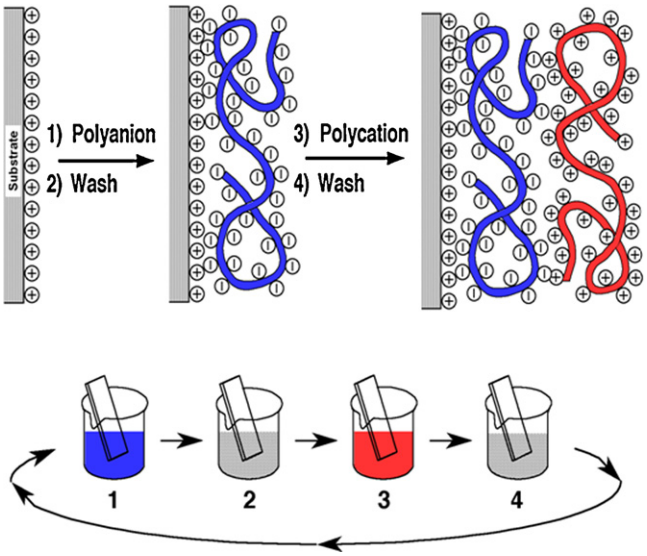

Fig. 7. The principle and process of LbL self-assembly [136]. Reproduced by permission of American Association for the Advancement of Science.

LbL polymeric coatings with nanosilver show greatly enhanced antibacterial performance, and thus have received much attention [2,5,22,103,137]. One of the main challenges is to embed nanosilver into multilayers. The pioneering work using polyelectrolyte multilayers as nanoreactors to synthesize silver nanoparticles was reported by Rubner et al. [118,119]. In this work, poly(allylamine hydrochloride) (PAH)/ poly(acrylic acid) (PAA) film was fabricated with LbL self-assembly. By adjusting assembly pH, the number of free carboxylic acid groups in the film was tuned. The nonionized carboxylic acid groups were then utilized for the loading of silver ions, which were further reduced to form ultrasmall silver nanoparticles in the polymer matrix (Fig. 8). Spatial control of silver nanoparticles could be realized by incorporating non-active multilayer regions. Furthermore, the nanoparticle size and silver concentration could be controlled by the assembly pH and also silver ion exchange and reduction durations.

A two-level antibacterial coating with both release-killing and contact-killing properties was fabricated based on the above work (Fig. 9) [137]. A PAH/SiO_2 nanoparticle multilayer was assembled as the outmost layer on a PAH/PAA LbL film. The SiO_2 nanoparticles were then modified with a bactericidal quaternary ammonium silane, OQAS. Ag^+ was loaded into the PAH/PAA region followed by reduction with dimethylamine borane complex to form releasable silver nanoparticles. This nanocomposite coating showed a very high initial bacteria-killing effect against both *E. coli* and *S. epidermidis* due to the release of silver ions and retained significant antibacterial property after depletion of silver due to the immobilized quaternary ammonium salts. The same research group also developed hydrogen-bonded multilayers with *in situ* synthesized silver nanoparticles both on planar substrates and on magnetic colloidal particles [5]. The antibacterial activity significantly enhanced with the increase of the coating thickness. In addition, the duration of silver release was dependent on the total amount of silver nanoparticles as well as the number of loading and reduction cycles. This study also provides a method to realize the localized antibacterial performances by magnetic directing.

Differently from Rubner's works that used synthetic polyelectrolytes as building blocks, Yuan et al. [103] have employed two biocompatible and biodegradable polysaccharides, chitosan and heparin, to fabricate a multilayer film for silver nanoparticle incorporation. The amine groups of chitosan could coordinate with

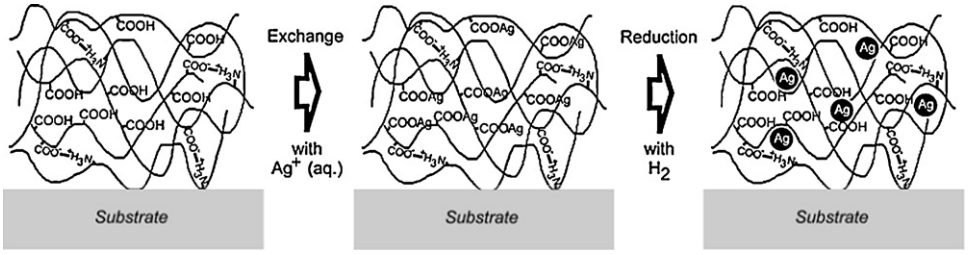

Fig. 8. Schematic of the metal-ion exchange and reduction process flow (not drawn to scale) [119]. Reproduced by permission of American Chemical Society.

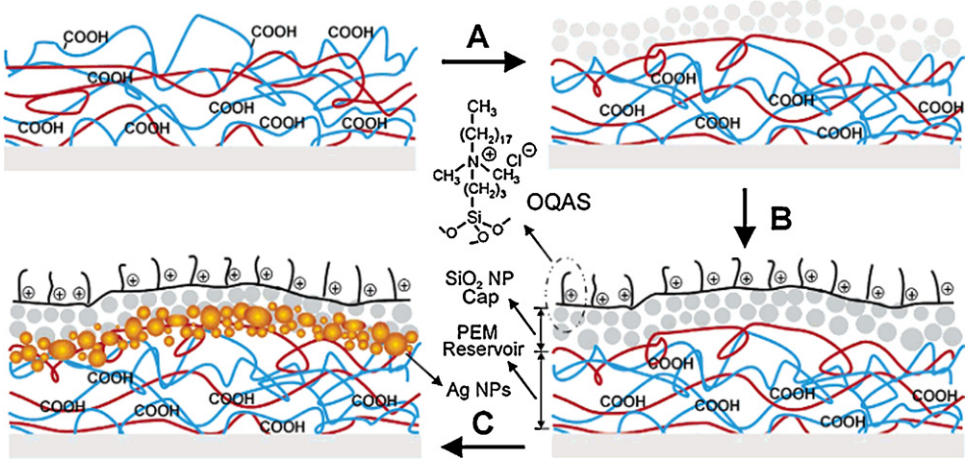

Fig. 9. Scheme showing the design of a two-level dual-functional antibacterial coating with both quaternary ammonium salts and silver. The coating process begins with LbL deposition of a reservoir made of bilayers of PAH and PAA. (A) A cap region made of bilayers of PAH and SiO_2 NPs is added to the top. (B) The SiO_2 NP cap is modified with a quaternary ammonium silane, OQAS. (C) Ag^+ can be loaded inside the coating using the available unreacted carboxylic acid groups in the LbL multilayers. Ag NPs are created *in situ* using the nanoreactor chemistry described previously [137]. Reproduced by permission of American Chemical Society.

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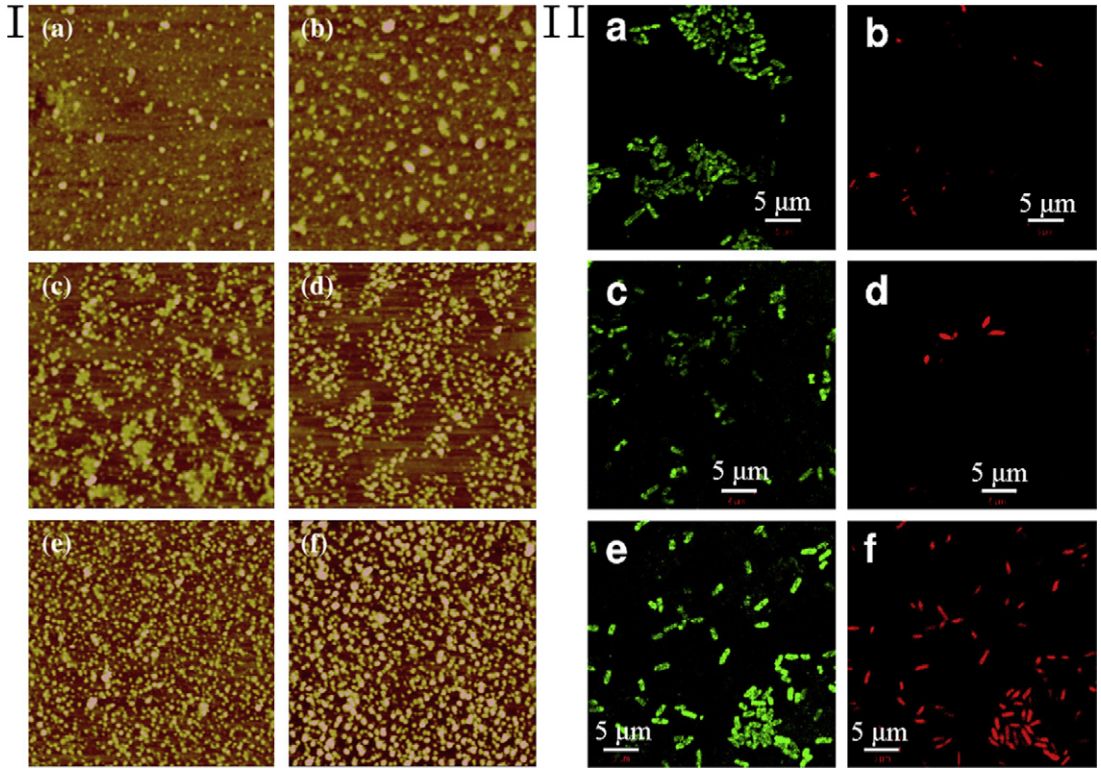

Fig. 10. AFM topography images with high surface density of silver nanoparticle on HA layers of 2 (I(a)), 4 (I(b)), 6 (I(c)), 8 (I(d)), 10 (I(e)) and 12 (I(f)). (2.5 μm × 2.5 μm, maximum *z*-range is 20 nm.), and CSLM images of *E. coli* on bare quartz (II(a), II(b)) and 4 HA-layer surface without (II(c), II(d)) and with (II(e), II(f)) silver nanoarray formation. All cells were visible at an excitation wavelength of 488 nm due to staining with FITC (II(a), II(c), and II(e)), whereas only dead cells were visible at an excitation wavelength of 543 nm due to staining with propidium iodide (II(b), II(d) and II(f)). Scale bar represents 5 μm [138]. Reproduced by permission of Elsevier.

metal ions and carboxyl and sulfate ions could bind metal ions by electrostatic force. Thus, silver ions were successfully loaded in the multilayers for further reduction to form silver nanoparticles. The silver concentration and nanoparticle size were tunable by changing assembly pH and loading pH. The composite thin films exhibited much stronger antibacterial effect than films without the silver nanoparticles. Furthermore, the antibacterial property could last more than 1 month.

Cui et al. [138] reported an *in situ* approach to fabricate a silver nanoarray in LbL assembled hyaluronan (HA)/poly (dimethyldiallylammonium chloride) (PDDA) multilayers (Fig. 10). The array structure relies on bilayer number. The surface density of silver nanoparticles could also be tuned by bilayer number and UV irradiation/drying cycles. Although HA/PDDA provides a better environment for bacteria survival than a bare quartz surface, the nanosilver embedded multilayers kill most of bacteria, demonstrating excellent silver nanoarray-induced antibacterial performance.

To date, most people focus on the antibacterial property of silver nanoparticle incorporated multilayers. However, as discussed previously, high concentration nanosilver can exhibit toxicity to mammalian cells. Agarwal et al. [21] have systematically investigated the surface modification with silver nanoparticle-impregnated PAH/PAA multilayers. They precisely controlled the silver content in the multilayers by changing the PAA pH. By reducing the silver content to a value of ~4 mg/m^2, a film with good attachment, spreading ability of mammalian cells and highly effective antibacterial property against *S. epidermidis* was obtained. In addition, after further lowering the silver content by decreasing the silver ion concentration in loading solutions, the result predicted that there was a value, below which the antibacterial property would disappear, although it was not measured [21].

All of the above works load silver ions and nanoparticles after the fabrication of multilayer films, requiring the presence of free functional groups as nanoreactors. Fu et al. [22] used LbL self-assembly of chitosan–silver ion complex and heparin to directly assemble silver-ion incorporated multilayers on an aminolyzed PET substrate. Silver nanoparticles were then synthesized by reduction in the multilayers. It was shown that their size could be controlled by silver ion concentration and reductant solution pH. The nanosilver loaded multilayers showed an excellent antibacterial activity primarily due to the silver nanoparticles, while exhibiting low cell toxicity and good anticoagulation property attributed to the polysaccharide films.

A novel LbL approach to fabricating nanoparticle multilayers using polymer as both a linker and a reductant have recently been developed by Sureshkumar et al. (Fig. 11) [139]. In brief, the substrate was immersed into dopamine solution in alkalilne pH environment (10 mM Tris, pH 8.5). The dopamine would self-polymerize on the substrate. This polydopamine coated substrate was further immersed into silver ion solution to adsorb and reduce silver ions into silver nanoparticles. These procedures were repeated for several times to get a polymer/nanosilver composite thin film coating. The silver nanoparticle multilayers showed a clear inhibition zone against *E. coli*, indicating its good antibacterial activity. Furthermore, the activity could be enhanced by increasing the deposition step. This approach could be extended to fabrication of multimetallic nanoparticles such as Ag–Au bimetallic nanoparticles (Fig. 11). Although the authors did not examine the applications of these multimetallic nanoparticles, they could probably enhance the antibacterial and catalytic activities of silver nanoparticles.

6.5. Surface attachment via other emerging approaches

Besides the above conventional methods, a lot of new approaches are emerging for high-performance antibacterial

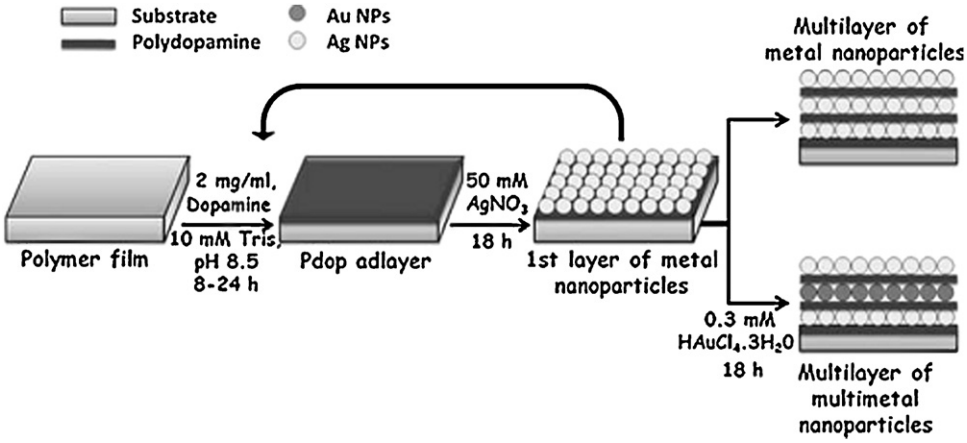

Fig. 11. Schematic illustration of the preparation of multilayered metal NPs on the surface of polymer film using Pdop coating [139]. Reproduced by permission of The Royal Society of Chemistry.

polymer/nanosilver composite coatings. Eby et al. [20] synthesized silver nanoparticles using lysozyme as both a stabilizer and a reductant. The silver nanoparticles and lysozymes formed a complex, which was then electrophorectically deposited on substrates such as stainless surgical blades and syringe needles. The lysozyme not only maintained its structure and property for lysis of *Micrococcus lysodeikticus* cells, but also promoted the uniform coating on stainless steel surface. This coating exhibited antibacterial effects toward many types of bacteria including *Acinetobacter baylyi*, *Bacillus anthracis Sterne*, *Bacillus subtilis*, and *Staphylococcus aureus*.

Sileika et al. [140] employed a simple immersion technique to deposit polydopamine onto polycarbonate substrates *via* self-polymerization of dopamine. Silver nanoparticles were *in situ* reduced and deposited on the polydopamine modified substrates. Another layer of polydopamine was then deposited followed by graft coating with PEG *via* the reaction of thiol group and quinones. The release of silver ions from this coating could be sustained for at least 10 days. This composite thin film coating demonstrated a dual function of bacterial-killing due to the silver nanoparticles and fouling resistance due to PEG against *E. coli*, *S. epidermidis*, and *P. aeruginosa*.

Listcher et al. [23] have studied plasma deposition of a nanosilver incorporated ultrathin polymer coating. This coating showed a controllable burst release of silver ions with the rate dependent on composition of gas mixture. Therefore, the coating exhibited an excellent antibacterial activity toward *P. aeruginosa* and *S. aureus* during the burst release stage, and after that period, it had very good long-term cytocompatibility, thus being very promising for implants or medical devices.

Zaporojtchenko et al. [141] have employed co-sputtering of noble metals and polytetrafluorethylene (PTFE) to produce silver nanoparticle incorporated composite thin film coatings. The Ag/PTFE and Ag–Au/PTFE showed antimicrobial properties against *S. aureus* and *S. epidermidis*. The silver ion release could be controlled by the coating thickness, silver volume fraction and nanoparticle composition. The Ag–Au/polymer had higher antibacterial ability than Ag/polymer nanocomposite.

6.6. Comparison of different fabrication methods

A synoptic table is drawn (Table 1) by us to summarize the approaches discussed above for comparison, which clearly shows that the LbL self-assembled multilayered film offers a promising way to *in situ* produce small silver nanoparticles. In contrast, the *in situ* physical adsorbed 1-layer polymer film has relatively larger silver nanoparticles. Direct adsorption of silver nanoparticles probably provides the widest tuning range of silver nanoparticle size by the pre-synthesis conditions. Nevertheless, real antibacterial applications are very complicated with different requirements for polymer types, processing parameters and nanosilver size. Apparently there is a great need to develop new approaches for

Table 1
Synoptic table of reported approaches to fabricating polymer/nanosilver composite coating in terms of polymer type, method of coating, method of making Ag NP, and size range of anchored Ag NP.

Polymer type	Method of coating	Method of making Ag NP	Size range of anchored Ag NP	References
Lactose-modified chitosan	Electrostatic adsorption	Direct adsorption	Clustered NP, >40 nm	[100]
PVS	Electrostatic adsorption	Direct adsorption	a few nm to above 50 nm	[107]
Catechol-derivatized poly(ethylene glycol)	Physical adsorption by non-electrostatic interactions	*In situ* chemical reduction	~50 nm	[99]
PEI-silane	Covalent bonding	Direct adsorption	~7 nm	[116]
Polybithiophene	Covalent bonding	*In situ* chemical reduction	~15 nm	[117]
PVA	Covalent bonding	*In situ* chemical reduction	unknown	[101]
HVVN polymer	Covalent bonding	*In situ* photochemical reduction	Tunable, ~25 nm after 15 min reduction	[102]
Dextran	Covalent bonding	Direct adsorption	~5 nm	[114]
PEI-HEA copolymer	Covalent bonding	*In situ* chemical reduction	Tunable, 4–50 nm	[104]
PAH/PAA multilayers	LbL self-assembly	*In situ* chemical reduction	Tunable, 2.1–9.3 nm	[119]
PAA/PAAm multilayers	LbL self-assembly	*In situ* chemical reduction	Tunable, 3.69–6.13 nm	[25]
Chitosan/heparin multilayers	LbL self-assembly	*In situ* thermal reduction	Tunable, 6.4–35.0 nm	[103]
HA/PDDA multilayers	LbL self-assembly	*In situ* photochemical reduction	Tunable, 8.1–12.4 nm	[138]
Dopamine	LbL self-assembly	*In situ* chemical reduction	35–50 nm for the first layer	[139]

further enhancing the performance of polymer/nanosilver composite coatings.

7. Conclusions and perspectives

In conclusion, the polymer/nanosilver composite coating provides a promising surface functionalization strategy to combine the properties of polymers and nanosilver synergistically. High antibacterial performance with bactericidal and/or adhesion-resistant properties has been achieved. Composite coating with antibacterial properties and biocompatibility/environmental safety has also been achieved. Although the polymer/nanosilver composite coatings are significantly advanced in past decade, great challenges still remain for fundamental exploration and practical applications.

Various methods to fabricate polymer/nanosilver composite coatings have been developed, but great efforts should be paid to controllability for nanosilver size, shape, distribution and its interaction with polymers. Exploration of an inexpensive and facile fabrication method to fabricate polymer/nanosilver composite coatings with well-tuned nanoparticle size, shape, distribution and interaction with polymers will be very important for its different practical applications.

The polymers used in polymer/nanosilver composite coatings are mostly selected from existing compounds. Rational design of new polymers targeting specific applications for polymer/nanosilver composite coatings is important since it has scientific significance while leading to important applications. An asymmetrically structured polymer demonstrates both antibacterial and human cell growth-promoting abilities by different chemistry from its two side surfaces [142]. A bright direction for such polymer/nanosilver composite is to design asymmetric chemical structures for different functions.

Polymers have great potential to be modified or/and immobilized by various functional groups. The one of the future hot research points could go to functionalize polymers used in composite coatings for multiple functionalities such as bactericidal coatings, anti-adhesive properties, and a multifunctional antibacterial coating integrating release-active, contact-killing, and bacterial resistant properties.

The controlled silver release from polymer/nanosilver composite coating is very essential for the time-dependent antibacterial properties and the long-term antibacterial effect. Efforts on the antibacterial composite coatings with controlled silver release property are urgent for better antibacterial effect and personalized use.

The underlying biological mechanisms of nanosilver antibacterial effect and toxicity against human cells are not fully understood yet. The effect of nanosilver size, shape, and uniformity on nanosilver antibacterial ability is still illusive. In particular, the fundamental insights regarding the interaction of nanosilver with bacteria, the biological effect of nanosilver and polymer/nanosilver composite coatings on human cells as well as the implication on bacteria adhesion and viability need to be further investigated.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.colsurfa.2012.12.029.

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