Chapter 6

Quantum Dots-Based Nano-Coatings for Inhibition of Microbial Biofilms: A Mini Review

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Additional information is available at the end of the chapter

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Abstract

Infection of implants by microbial biofilm is chiefly caused by *Staphylococci*, *Pseudomonas* and *Candida* species. The growth of microbes by forming biofilms offers them protection from antibiotics, drugs and host defense mechanisms. The eradication of biofilms from implants and medical devices is difficult because of the protection by the biofilm forming pathogenic microbes. Hence, researches are focused on development of antibiofilm materials, which are basically constituted of antimicrobial substances or antimicrobial coatings. Nanomaterial-based coatings offer a promising solution in this regard. Quantum dots (QDs) are the group of semiconductor nanoparticles with high photoluminescent properties compared to conventional organic fluorophores. Thus, drug-conjugated QDs can be a promising alternative for biofilm treatment, and these can serve as excellent alternatives for the mitigation of recalcitrant biomaterial-associated infections caused by resistant strains. Furthermore, their use as antibiofilm coating would avoid the dispersion of antimicrobial agents in the surrounding cells and tissues, thereby minimizing the risks of developing microbial resistivity.

Keywords: quantum dots, microbial biofilms, fluorescence, infections, antibiofilm materials

1. Introduction

Quantum dots (QDs) represent a class of colloidal semiconductor nanocrystals having fluorescent properties that absorb photons at a particular (lower) wavelength and emit at a higher wavelength. These QDs are basically composed of a core and corona layer. The photoluminescence emission wavelength of QDs is directly proportional to its size. The core of the QDs may contain one or more heavy elements such as cadmium, selenium, zinc or tellurium. QDs possess significant superiority over the conventional fluorophores

in terms of physicochemical and fluorescent properties. The distinguishable fluorescent properties, smaller size, photostability, resistivity to metabolic degradation and capability of conjugation to ligands/biomolecules make QDs a superior choice for biological applications compared to conventional fluorophores.

In the last three decades, several microbes (fungi, yeast and bacteria) have emerged as major human pathogens and have been responsible for causing life threatening diseases especially in immunecompromised individuals and patients with serious medical issues [1]. The widespread and prolonged use of antifungal agents and drugs for treating the infection caused by the pathogens has resulted in increasing incidences of multidrug resistance (MDR). Additionally, several mutant strains have developed that show high resistance to the antifungal drugs being used [1]. For example, *Candida albicans*, a dimorphic opportunistic pathogen, occurs as a normal commensal in humans but becomes pathogenic in immunecompromised individuals. The azole resistive clinical isolates of *C. albicans* result in cross-resistance to several unrelated drugs and this arises because of the phenomenon of multidrug resistance (MDR) [2, 3]. Similarly, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the two most pathogenic bacteria known to cause severe infection and biofilm formation [4]. Several mechanisms are responsible for development of MDR, some of which involve an overexpression of drug efflux pumps encoding genes such as *CDR1* and *CDR2* belonging to ATP-binding cassette [2, 5, 6]; overexpression of the drug and *MDR1* belonging to the major facilitator superfamily transporters [3, 6] and overexpression of mutations in *ERG11* and encoding the target enzyme of azoles, lanosterol 14α-demethylase [7]. Hence, microbial infection has become a major problem with concerns focusing on those that have become resistant to antibiotics. Around 2 million people are affected annually with antibiotic-resistant bacteria of which approximately 23,000 people die as per the studies of U.S. Center for Disease Control and Prevention [8].

Microbial communities adhere to a solid surface especially in surface/water interference forming biofilms [9]. Microbes attach to the surface by means of extracellular polymeric substances (EPS), and this acts as their survival means against harsh environmental conditions. Biofilm formation is however associated with surface deterioration and corrosion. In addition, pathogenic microbes form biofilms on medical devices and implants, and this has become a great concern in the arena of healthcare. Biofilm also enhances microbial activity and provides protection against harsh environmental conditions such as drugs, antibiotics and common sanitizers. Because of the emerging conditions of MDR, there is a demand for developing new drugs, antimicrobial agents and modifiers capable of inhibiting microbial growth and biofilm formation. With the necessity of developing antimicrobial agents with diverse functionality and ability to kill both strains of bacteria, nanomaterials have been widely investigated in this regard. Silver nanoparticles [10], copper oxide nanoparticles [11–13], metal oxide nanoparticles [12, 13] and even carbon nanomaterials [14] have been reported for their excellent antimicrobial efficiency. Among these, silver nanoparticles have been extensively used as antimicrobial and antibiofilm agents due to their broad spectrum antimicrobial activity, multiple cellular targets and minimum host toxicity. However, high concentration of silver is toxic to humans and its persistent use causes argyrosis and argia [15, 16]. Hence, the demand is for exploring novel nanomaterials with effective antimicrobial and antibiofilm properties along with biocompatibility. Therefore, the requirement must be

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targeted towards exploring novel biocompatible nanomaterials with effective antibiofilm and optical properties. QDs can be suitable alternatives because of their intriguing optical, fluorescence, high quantum yield, photostability and easy conjugation efficiency. QDs easily attach to microbial surface because of their small size and their dispersion stability is basically governed by colloidal theory [17]. These are excellent candidates in biomedical applications such as imaging, diagnosis and sensing and drug discovery. Developing QDs-based nanocomposites as coating materials on implants and catheters can thus combat pathogenic invasion and biofilm formation. QDs could be engineered with coating agents and conjugated with bioactive ligands or biorecognition elements for targeted treatment, biofilm visualization, and inhibition.

2. Biofilm formation, its mechanism and transmission

Biofilm can be defined as microbial cells enclosed in an exopolysaccharide matrix and adhered to a cell surface. Formation of biofilms by bacteria and fungus is a defense strategy for protection from environment. Microbes secrete extracellular polymeric substances (EPS) that act as a primary scaffold for attachment to solid substrate [18] and its basic constituents are proteins, polysaccharides, nucleic acids with some lipids and humic substances [19]. Three-dimensional study of the EPS layer suggested that it forms a gel-like network wherein microbes are embedded and it also maintains the attachment of bacteria to the solid substrate [20]. Stability to the 3D structure of EPS is rendered by the hydrophobic interactions as well as van der Waals attraction between amino acids/peptides and cations such as Ca^{2+} and Mg^{2+} [21]. Biofilm formation and its structure depend on the environmental conditions to which the bacteria are exposed. When cells are in a nutrient stress condition, an increase in EPS secretion occurs, which promotes hydrophobic interactions to allow attachment to solid substrate [22]. It has been suggested that the presence of a high concentration of EPS negatively affects the diffusion of lipophilic compounds (such as sanitizers, antibiotics and hydrocarbons), across the microbial cell surface [23, 24].

Among bacteria, *P. aeruginosa* is an opportunistic pathogen that causes a number of infections in humans. It develops resistance to antibiotics by forming biofilm matrices that comprise polysaccharide-EPS. It has been noticed that it forms and regulates biofilm via quorum sensing mechanism and therefore most of the researches have focused on disrupting the quorum sensing pathway [25]. Similarly, biofilm formation in *Staphylococcus epidermidis* has also been analyzed using different methods such as microtiter plate, congo red agar plate test and via molecular detection of the ica locus [26–28]. It was found that production of a slimy substance assisted in forming biofilm and was associated with virulence also. The production and formation of biofilm depend on the media constituents; however, the exact mechanism behind the formation of a mature biofilm is still being investigated. However, on the basis of in vitro experimental models, biofilm formation can be segregated into four different stages: (i) attachment of microbial cells to surface, (ii) formation of multi-layer structure via the accumulation and aggregation of cells, (iii) maturation of biofilm and (iv) detachment of cells from biofilm into planktonic state and initiation of a new biofilm cycle [29, 30]. The initial step of attachment is normally driven by hydrophobic, electrostatic and Lifshitze-van der Waals forces, and hence is nonspecific in

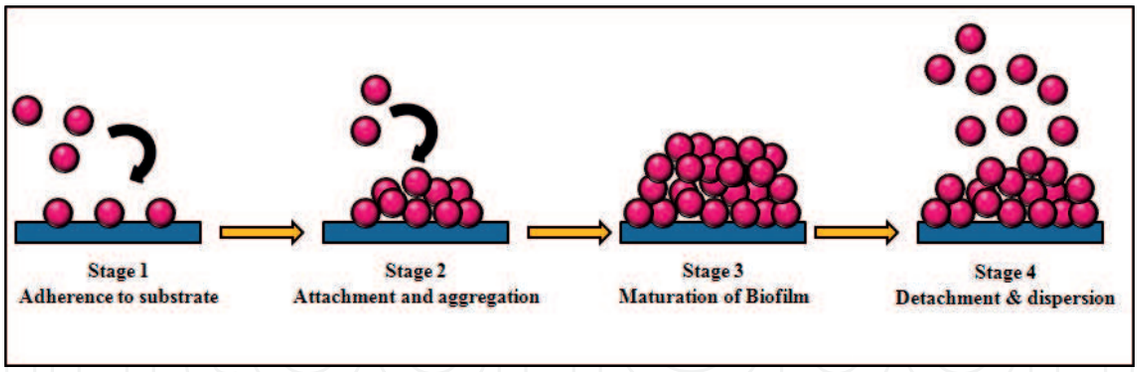

Figure 1. Schematic illustration of the different stages involved in biofilm formation and detachment.

nature. Additionally, certain specific proteins also assist in binding of the microbes to the surfaces [30]. The second step of accumulation is mediated via microbial surface components that recognize adhesive matrix molecules and occurs via an active process. This step involves the establishment of biofilm on the microbial surface. This process is followed by the maturation step. In this step, the characteristic features of the biofilm are formed on basis of specific microbial type. In the final step, where a new phase of invasion is initiated involves the detachment and dispersion of the microbes [31, 32]. **Figure 1** shows the schematic illustration of the different stages in the cycle of biofilm formation and detachment.

P. aeruginosa, *Vibrio cholerae* and some *mycobacterial* species are the common human pathogens that form biofilms and hence have the possibility of infecting humans. There are several mechanisms via which pathogenic microbes in the biofilm can initiate an infection. The seeding dispersal of a large number of pathogenic cells is one of the possible mechanisms that can initiate an infection, as the microbes are not sessile in a biofilm and hence can easily detach and initiate an infection. Secondly, the virulent phenotypes present in a biofilm can expand their colony and initiate infection. This is highly possible as biofilm has a huge heterogeneity in its phenotypical constitution [33, 34]. In addition to these, several other mechanisms have been hypothesized that could possibly allow the survival of a pathogenic organism and its transmission. For example, the detachment of pathogenic microbes from the biofilm, quorum sensing [35], co-aggregation and auto-aggregation [35, 36], modification in biosynthesis of EPS and metabolic pathways and genetic mutations [37] are important issues. However, the complete understanding of the mechanism of biofilm formation and virulence requires complete analysis of the pathogen's life cycle, environmental parameters and the different phenotypes.

3. Role of QDs in inhibiting biofilm formation

Biomedical implants are a necessity in modern health care; biofilm formation on these implants and devices is a major cause of their failure. Mostly *S. epidermidis* and *S. aureus* are observed in contaminated biomedical implants and devices [38]. Biofilms formed on implants and medical devices are difficult to remove as they are protected by exopolymeric matrix secreted by the pathogenic microbe [39]. Although a number of metal and their nanosize

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forms (silver, copper, gold etc.) have been used as antimicrobial agents, there efficiency is diminishing due to MDR. Investigations on the antibacterial and antifungal property of QDs have been conducted, which suggests that they can serve as excellent candidates for biomedical applications because of their solubility and biocompatibility.

Aqueous solubility and compatibility make graphene quantum dots (GQDs) useful in biomedicine. GQDs are reported to be biocompatible at cellular levels investigated via WST-1 assay, LDH production, ROS generation and *in vitro* and *in vivo* distribution [40]. GQDs also possess antibacterial property against *Escherichia coli* and *S. aureus*, and GQDs with low dose of H_2O_2-based band-aids have also been prepared based on the peroxidase-like property of these particles. The designed band-aids showed a good anti-disinfectant property. They analyzed the effect of formed GQDs on biofilm formation and destruction and observed a reduction in biofilm formation by *S. aureus* at 100 μg/mL and 100 mM of GQDs and H_2O_2 concentration, respectively. Furthermore, they also observed that GQDs alone also showed antibiofilm properties [41]. The studies thus suggested that appropriately designed GQDs had the ability to breakdown existing biofilms and simultaneously prevented the formation of new ones. Habiba et al. suggested the antimicrobial property of silver-graphene quantum dots against *P. aeruginosa* and *S. aureus*. They observed a synergistic effect between silver nanoparticles and GQDs with 25 and 50 g/ml of silver-graphene quantum dots inhibiting *S. aureus* and *P. aeruginosa* growth, respectively. Thus, the potential applicability of Ag-GQDs as fabrication and antibacterial coating agents was clearly established [42].

Furthermore, the use of semiconductor QDs will allow visualization of biofilm inhibition due to their fluorescent properties. The current methods being used for biofilm analysis are SEM, AFM, MRI and Raman spectroscopy that require lengthy and costly procedures apart from sample modulation, which sometimes provide partial details of the samples concerned [43, 44]. Other than this, conventional fluorescent dyes conjugated with carbohydrate recognition elements are used for biofilm analysis via confocal laser microscopy [45]. However, the use of a synthetic complex is sometimes toxic to cells thereby preventing in situ analysis. Therefore, QDs can be an exceptional solution for this. Moreover, amphiphilic carbon dots (CDs) have been shown to penetrate the EPS layer of *P. aeruginosa*, allowing direct visualization of its architecture, growth and how external agents affect its inhibition. The hydrocarbon side chains of CDs dock to the EPS network resulting in making the EPS scaffold highly fluorescent [46]. In yet another study, QDs with two varied surface chemistry [−COOH and polyethylene glycol (PEG) modified] were analyzed for their mobility and distribution in *P. aeruginosa* PAO1 biofilms. It was inferred that the QDs did not penetrate the bacterial cell but did colocalize with EPS matrix of the biofilm. While surface functionalization and QDs flow rate did not show any distinctive difference, analysis of center of density suggested that QDs with –COOH surface groups diffused easily compared to PEGlyated QDs. Biofilms treated with PEGlyated QDs had rough polysaccharide layers and cell distribution compared to –COOH functionalized QDs. It was thus concluded that treatment with nanomaterials can result in varying the structural parameters of biofilm [47]. The fluorescent property of QDs would thus allow recognition of biofilm formation at different growth stages and environmental conditions. Additionally, spectroscopic analysis can also be performed, which would allow better understanding of the phenomenon of binding of QDs to EPS. Conjugated QDs have also been used for biofilm imaging analysis. In a study, CdTe

QDs tagged with Concanavalin A for labeling the saccharide molecules on the surface of *C. albicans* was studied. It relied on the ability of Concanavalin A to specifically bind to α-D mannose and glucose residues of saccharides. They observed that almost 93% of cells were labeled with the modified CdTe particles and were highly specific in activity [48]. Similarly, CdSe/ZnS QDs surface capped by 3-mercaptopropionic acid (MPA) and the amino acids (leucine or phenylalanine) were also used for labeling the biofilm produced by *Shewanella.* Amphiphilic core/shell CdSe/ZnS QDs were used for labeling the hydrophobic microdomains of biofilm produced by *Shewanella oneidensis*, a Gram-negative bacteria. It was inferred that CdSe/ZnS@dihydrolipoic acid-Leu or CdSe/ZnS@dihydrolipoic acid-Phe QDs showed increased hydrophobicity in comparison to CdSe-core QDs capped with 3-mercaptopropionic acid (MPA). Thus, the functional group on QD surface and the ligand density played an integral role in interaction with biofilm matrix. While the hydrophilic MPA-capped QDs were homogeneously associated, DHLA-Leu and DHLA-Phe QDs were specifically confined assisting in identifying the hydrophobic microdomains of biofilm. Hence, appropriate conjugation of surface functional groups can significantly dictate their interaction with biofilm [49]. Quite recently, selenium nanoparticles have been reported for their tremendous potential in biofilm inhibition in *C. albicans*. For the study, selenium nanoparticles were synthesized via laser ablation method and were used to analyze biofilm inhibition. They observed a very good attachment of selenium nanoparticles to the *Candida* surface, which was due to electrostatic attraction between the positively charged surface of *Candida* and negatively charged Se nanoparticles. The particles affect the cellular morphology of the fungus by substitution of sulfur groups of amino acids by the Se particles. This consequently altered the protein structure and damaged Candida morphology. Size and crystallinity of particles had a significant effect on biofilm inhibition [50].

Figure 2 presents the mode of action of quantum dots. The application of QDs as antibiofilm agents can inhibit microbial biofilm at two stages. It can act at the initial stage, where its presence would hinder further attachment of microbial cells to the solid substrate thereby preventing the progression to mature biofilm stage and EPS secretion. Secondly, QDs can act on the matured biofilm, where its penetration into the cells would result in killing of the microbes and subsequent dispersion of the formed biofilm.

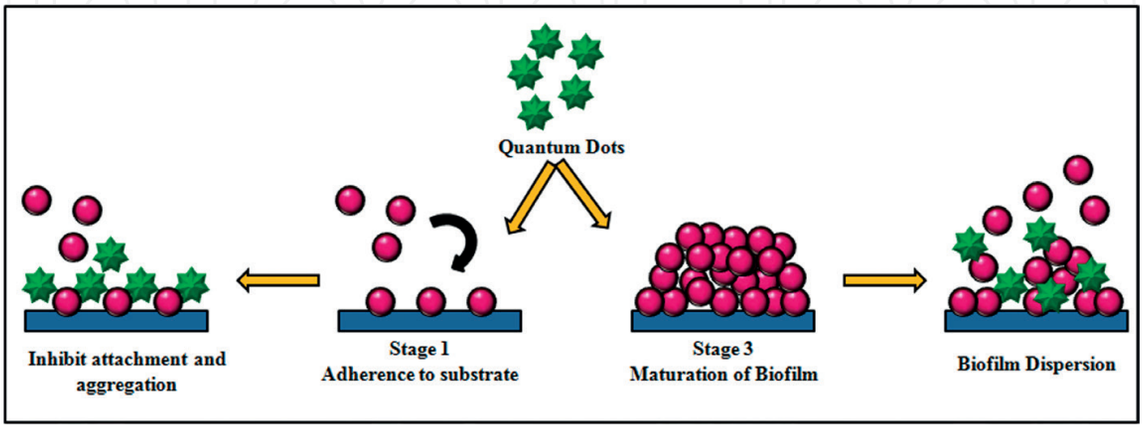

Figure 2. Schematic illustration showing the possible mode of action of antimicrobial quantum dots on biofilm.

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With this, we envision that QD-based antibiofilm coatings can be promising probes in investigating biofilm imaging, treatment and their eradication. Furthermore, their broad spectrum activity and minimal host toxicity are additional advantages in this regard. Hence, the use of semiconductor QDs would not only allow detecting the inhibition process but also favor their visible monitoring.

4. Conclusion and future perspective

There is a steady increase in the use of QDs. Despite the several advantages offered by QDs, with some improvements, these can emerge as excellent probes for biological applications. Focus should be towards improved protocols for functionalizing the surface of QDs simultaneously making sure that its properties remain unaltered and secondly, appropriately modifying the surface of QDs so that they do not aggregate in a protein-rich solution or cystol. These methods along with the said advantages would assist in utilizing QDs for biological and biomedical applications. Furthermore, the QDs can be tagged with antimicrobial drugs or drugs can be encapsulated inside the QD core thereby increasing the potency of drugs even at low concentration. Synergistic effect of silver nanoparticles with antibiotics such as penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin is known. Therefore, studies on the synergism between QDs and drug molecules have to be analyzed in detail. This would also assist in providing insights into the molecular mechanism of action of QDs and any kind of cellular changes occurring in the pathogen upon its interaction with pathogenic microbes. Additionally, QDs labeling would allow a high throughput analysis of biofilm inhibition and disruptions that will have significant effect in healthcare sector to identify and combat biofilm formation and pathogenic infections.

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