Chapter 9
Nanoparticles for Biofilm Control

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Abstract Microorganisms of planktonic types have emerged into biofilm structures by acquiring the ability to attach to the surfaces. The extracellular polymeric substances may play a vital role in anchoring the biofilm onto the surface and also protect it from various antibiotics making it highly resistant. This type of survival is procured by species of bacteria, fungi and protists. These biofilms pose numerous hazards to the human health and environment. Over 80% of the diseases are caused by the biofilms which include colorectal cancer, oral infections, periodontitis, cystic fibrosis and many others. Different strategies have been developed to eliminate the biofilms like the use of nano-sized particles. These nanoparticles provide antimicrobial properties and can also be used as a delivery system of the antibiotics with high stability and good biocompatibility. The high surface-area-to-volume ratio makes the nanoparticles to have high contact surface to the bacterial cell membrane and hence plays an efficient therapeutic way in treating the biofilms. In this review, we discuss the various diseases caused by the biofilm and different antibiofilm strategies using the nanomaterials. There is no doubt that the upcoming antibiofilm strategy which uses nanoscience can gain an ultimately new hope in advancements of coping with bacterial infections and resistance.

Keywords Biofilms · Antibiofilm · Pathogenesis · Nanoscience · Biocompatibility

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9.1 Introduction

Biofilm is an organized arrangement of microbial cells which are irreversibly attached to a surface contained in a matrix made of self-produced extracellular polymeric substances. It is responsible for many diseases infecting human health and sometimes has a positive influence like the mutualistic bacteria, namely, *Staphylococcus epidermidis*, which can hold back the formation of colony by pathogenic bacteria through triggering the host immune system and thereby preventing the attachment of microbes (Donlan 2002). Cystic fibrosis (CF), an inherited genetic disorder, is the most common human disease infecting the lungs seen in Western Europe. Patients with cystic fibrosis experience persistent infection caused by *P. aeruginosa*. So when this *P. aeruginosa* bacterium invades the CF lung, it starts to acclimatize with the CF lung and survives for decades. The reason is the excess production of matrix polysaccharide alginate which makes up the mucoid biofilm that resists antibiotics, elements of natural and acquired immunity, and thus resists phagocytosis. This whole process again develops noticeable antibody responses in the form of granulocytes and gives rise to chronic inflammation resulting in harsh lung tissue damage in the CF patients. The other negative effects of biofilms include dental caries or cavities which are caused by overproduction of organic acids mainly when sugary drinks are consumed or while frequent snacking. These acids breakdown the teeth enamel and lead to dental caries. It is approximated that 65 out of 100 infections are related to bacterial biofilms (Lewis 2001). They are the device- and non-device-linked infections. Data estimated for the device-related infections are 2% each for breast implants and joint prostheses; 4% each for mechanical heart valves, defibrillators and pacemakers; 10% for ventricular shunts; and 40% for ventricular-assisted. Non-device-related biofilm infections include periodontitis, osteomyelitis and many to list out. It is important to have oral hygiene since a person is susceptible to suffer from periodontitis which infects the gums and damages the soft tissues (Kokare et al. 2007). Osteomyelitis is a disease in bones caused by bacteria or the fungal cells. When the bacteria enter the bloodstream and infect the growth plate of the bone which is the metaphysic portion of the bone, the white blood cells gather at the site and try to phagocytose or kill the pathogen by releasing enzymes. So, these enzymes may break the bone and form pus spreading throughout the blood vessels. This leads to the dysfunctioning of the affected bone areas (Ziran 2007).

The antibiotics which are available to date have shown low efficacy in treating the biofilms associated with infections because of their high values of minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) leading to in vivo toxicity. Sometimes, biofilms prevent the phagocytosis of the invading bacteria by impairing the phagocytes and complement system. Hence, it is important to focus on the MBCs, MICs, mechanism of action and chemical structures of the antibiofilm substances which include chelating agents, peptide antibiotics, etc. Different strategies can be implemented to combat with the biofilms like replacing the infected foreign bodies such as stents, implants with the sterile ones, blocking the quorum sensing pathway or by altering the c-di-GMP. LP 3134, LP 3145, LP 4010

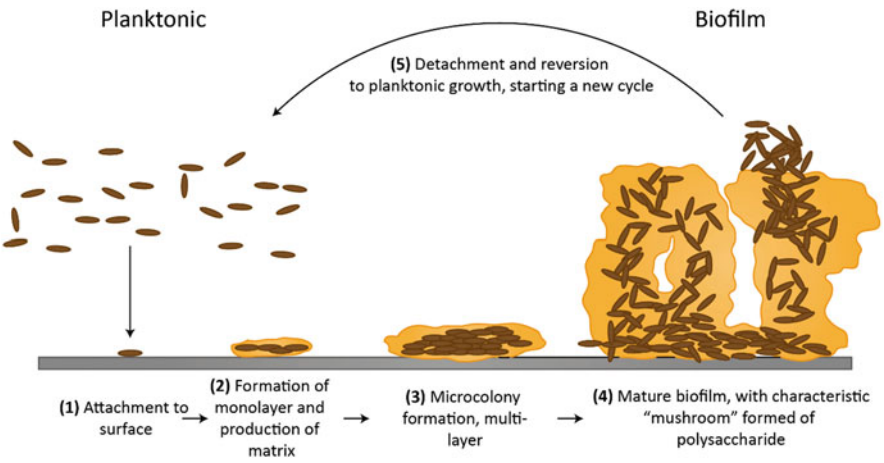

Fig. 9.1 Stages of biofilm formation. (Adapted from Vasudevan 2014)

and LP 1062 can inhibit the formation of biofilm in *P. aeruginosa* and *Acinetobacter baumannii* (Ranita Roy et al. 2018). Nanoscale materials are widely applied in the field of medicine because of their high reactivities with the large surface-area-to-volume ratio. In fact, the physicochemical properties are controllable when it comes to the nanoparticles. The other most important factor why nanotechnology has been more adapted is because of its low toxicity to the host and thus can gain a positive hope over the conventional treatments of biofilms (Ramasamy and Lee 2016). These nanoparticles (NPs) are able to find a way out to prevent the drug resistance mechanisms and other important processes. The combinations of plant-based antimicrobials with the nanoparticles are also studied (Baptista et al. 2018).

In this chapter, we are going to discuss the different stages leading to the formation of biofilms (Fig. 9.1). It is also important to study the types of pathogens involved in biofilm synthesis and the pathogenesis related to the biofilm in humans. As these biofilms give rise to dangerous diseases leading to chronic infections, there is a necessary need to combat the microbes, and also depending on the applications of nanoscience, we will be reviewing various strategies incorporated till now in treating the biofilms.

9.2 Biofilms

In 1947, Antonie van Leeuwenhoek examined the aggregates of "animalcules" scrapped from surfaces of human tooth under the microscope. Almost 100 years later, microbiologists studied the formation of biofilms and also concluded that bacteria grow differently when they attach to a specific surface in immobilized populations. Studies also show that the bacteria eliminated from the native

ecosystem grow predominantly as planktonic cells (Costerton 1999). Biofilms are the organized structures comprising of microorganisms where they stick to each other producing extracellular polymers to cohesion. Biofilms are formed due to various parameters like nutritional cues; identification of specific or non-specific binding sites on a surface etiofilms can bind to the surfaces like the tooth, rock or any single species or a diverse group of microbes (Karatan and Watnick 2009; Hoffman et al. 2005). This shift of survival from a planktonic growth to biofilm keeps them safe from toxic factors like antibiotic desiccation and host body's immune system (Tortora et al. 2015).

9.2.1 Bacterial Biofilms

In order to survive, the wild bacterial strains rely on fimbriae which protrude from the thick layer of exopolysaccharides (EPS). Fimbriae facilitate specific adhesion to the surfaces, and non-specific adhesion to inert surfaces is provided by EPS. Fimbriae interaction with the surfaces is not strong as it can be removed easily by simple sonication. Firm adhesion of the bacterial strains needs the elastic polymers of the EPS for effective non-specific interaction in aquatic ecosystem (Costerton 1999). The bacteria release protons and signalling molecules radially diffusing away from the cell. We observe a sharp increase in the concentration of the diffusing molecules finding itself near a surface or interface which would let the cell recognize that it is near the surface because diffusion became limited on that side. Thus, once the bacterial cell has sensed a surface, they start to form colonies in monolayer fashion. and active adhesion starts leading to biofilm formation. The cells aggregate to form microcolonies at a specific location. Now in order to make this reversible attachment to irreversible attachment, the bacteria should synthesize new exopolysaccharide to cement other bacterial cells in developing biofilm. In this process, the attached cells upregulate the genes required for EPS synthesis itself (Costerton 1999).

The basic structural unit of biofilm is the microcolony. It consists of different types of species. Depending on the species, microcolony (mushroom-like shape) may have composed of 10–20% cells and remaining 75–90% EPS matrix (Costerton 1999). Regarding biofilm formation potentials of pure species bacteria, it is interesting that the quantity of biofilms produced is not only different between the genera but also vary among the species of same genus (Maddela and Meng 2020); this could be attributed to multiple factors, such as metabolic properties, quorum sensing properties (Maddela et al. 2019), functional groups of exopolysaccharides (Maddela et al. 2018), etc. In general, cells attach to the surfaces which are rougher and hydrophobic in nature. The presence of fimbriae, flagella and EPS helps an organism when a mixed community is involved (Table 9.1).

Table 9.1 Variables essential in cell adhesion and biofilm synthesis

Properties of the substratum	Properties of the bulk fluid	Properties of the cells
Texture or roughness	Flow velocity	Cell surface hydrophobicity
Hydrophobicity	pH	Fimbriae
	Cations	Extracellular polymeric substance
	Presence of antimicrobial agents	Showing antimicrobial activity

Adapted from Donlan (2002)

Table 9.2 Fungal biofilms resistant to antifungal agents

Type of fungi producing biofilm	Resistance to antifungal agent
Candida albicans and *Candida parapsilosis*	Fluconazole, amphotericin-B, nystatin, voriconazole
Aspergillus fumigates	Itraconazole, caspofungin
Cryptococcal	Fluconazole and voriconazole
Tichosporonasahii	Amphotericin-B, caspofungin, voriconazole and fluconazole
Pneumocystis carinii	Azole and amphotericin-B

Adapted from Fanning and Mitchell (2012)

9.2.2 Fungal Biofilm

The important fungal species which produce biofilms are *Aspergillus*, *Candida*, *Cryptococcus*, *Trichosporon*, *Coccidioides* and *Pneumonia* (Table 9.2). Factors involving the fungal biofilm resistivity are structural complexity, existence of extracellular matrix (ECM), metabolic heterogeneity intrinsic to biofilms and upregulation of efflux pump genes (Fanning and Mitchell 2012). The biofilms of *C. albicans* are composed of yeast form and hyphal cells which are important for biofilm formation. Steps involving biofilm formation are attachment to the substrate and multiplication of yeast cells on the surface followed by triggering of hyphal formation (Finkel and Mitchell 2011). As the biofilm matures, the cohesivity appears due to ECM aggregation (Al-Fattani and Douglas 2006). Other species of *Candida* like *C. tropicalis*, *C. glabrata*, though contain ECM, fail to produce true hyphae (Silva et al. 2011).

Biofilms of the cells of *Aspergillus* called conidia bind to the substrate and mycelia forms with biofilm maturation. Hyphae can be differently organized in two forms of *A. fumigatus* biofilm infection. For example, hyphae form into a intertwined ball in *Aspergilloma* and in *aspergillosis* show hyphae in separated form (Loussert et al. 2010). There are species which do not produce hyphae as part of their biofilm. Some of the species are *Cryptococcus neoformans* and *Pneumocystis jirovecii* (Cushion et al. 2009).

9.3 Biofilm-Related Pathogenesis

Back in the 1970s, Nils Høiby perceived the connection between the causes of relentless infection and the clusters of bacteria in cystic fibrosis patients (Høiby 2017). It was then noted that biofilms are involved in clinical infections (Costerton et al. 1999; Hall-Stoodley and Stoodley 2009). Bacteria in biofilm mode of survival protect itself by staying in the dormant state from the immune system, thereby causing local tissue damage. In the later stages, it leads to acute infection (Table 9.3 gives an overview of the biofilm-related diseases in humans) (Vestby et al. 2020).

9.3.1 Native Valve Endocarditis

Native valve endocarditis is caused when the vascular endothelium of the four valves, namely, mitral, aortic, tricuspid and pulmonic valves, interacts with the microbes travelling in the blood stream. The species responsible for NVE are *Pneumococci*, *Candida*, *Aspergillus* and some Gram-negative bacteria. The route of infection of these organisms is in blood stream via the oropharynx, gastrointestinal tract and genitourinary tract. Since the microbes bind very poorly to the

Table 9.3 Biofilm-associated diseases

Body system	Affected organs	Disease
Auditory	Middle ear	Otitis media
Cardiovascular	Cardiac valves	Infective endocarditis
	Arteries	Atherosclerosis
Digestive	Salivary glands	Sialolithiasis (salivary duct stones)
	Gall bladder	Recalcitrant typhoid fever and predisposition to hepatobiliary cancers
	Gastrointestinal tract, especially the small and large intestine	Inflammatory bowel disease and colorectal cancer
Integumentary	Skin and underlying tissue	Wound infections
Reproductive	Vagina	Bacterial vaginosis
	Uterus and fallopian tubes	Chronic endometritis
	Mammary glands (breasts)	Mastitis
Respiratory	Nasal cavity and paranasal sinuses	Chronic rhinosinusitis
	Throat, i.e. pharynx with tonsils and adenoids and larynx with vocal cords	Pharyngitis and laryngitis
	Upper and lower airways	Pertussis (whooping cough) and other border tell infections, cystic fibrosis
Urinary	Prostate gland	Chronic bacterial prostatitis
	Urethra, bladder, ureters, kidneys	Urinary tract infections

Adapted from Vestby et al. (2020)

endothelium, nonbacterial thrombotic endocarditis (NBTE) is established when the endothelium is disrupted. This accumulates platelets, fibrin and red blood cells. Fibronectin is released by the endothelium cells with the result of vascular injury. This fibronectin can adhere to collagen, human cells and also the bacteria which leads to biofilm formation. Multiple medications are followed specific to the species involved like the administration of penicillin for streptococcal endocarditis and fluconazole for *Candida* endocarditis (Donlan and Costerton 2002; Stickler 1996.).

9.3.2 Otitis Media

This is a painful ear infection specific in the middle ear located behind the eardrum. The organisms causing otitis media are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. Since only low amounts of antibiotics are penetrated in the middle ear, effective drugs are better used to treat otitis media like amoxicillin, cefaclor and erythromycin (Donlan and Costerton 2002; Wells et al. 1995).

9.3.3 Chronic Bacterial Prostatitis

The infection is seen in the prostate gland which moved from the urethra (Domingue and Hellstrom 1998). Once the bacteria occupy the prostate duct, proliferation occurs very rapidly forming spores of microcolonies and thus forming the biofilms in the dust system. Microbes infecting chronic bacterial prostatitis are *E.coli*, *P. aeruginosa* and species of *Proteus*, *Serratia*, etc. (Donlan and Costerton 2002).

9.3.4 Cystic Fibrosis

This is a type of lower respiratory tract infection. Cystic fibrosis is the absence of cystic fibrosis transmembrane conductance regulatory protein (CFTR). The thickening of the respiratory epithelium is due to the elevated absorption of electrolytes. *Staphylococcus aureus*, *H. influenzae* and *P. aeruginosa* are the microbes involved. The infection can be delayed for several years if treated in the early stages with ciprofloxacin and colistin (Donlan and Costerton 2002).

9.3.5 Periodontitis

This disease is the infection in teeth tissues, gums and periodontal tissues. Subgingival crevice is the first site for infection (Govan and Deretic 1996). The bacteria start colonizing the surfaces of the tooth and mucus and also regulate calcium flux releasing the toxins. Once the bacterial plaque becomes significant with minerals of calcium and phosphate ions (calculus or tartar), the defensive mechanism of the saliva can no longer support the enamel of the tooth and thus cause periodontal diseases (Overman 2000). The suggested treatment is through the elimination of biofilms from the subgingival areas along with addition of antimicrobial substances (Donlan and Costerton 2002).

9.4 Antibiofilm Strategies

With respect to the previous studies, there is an easy and effective way to eliminate premature biofilms with the use of antibiotic than the mature biofilms (Ranita Roy et al. 2018). Despite of it, undetectable nature of the premature biofilms in the body leads to development of clinical conditions which involves most of the mature biofilms (Hoiby et al. 2011; Cramton et al. 1999; Götz 2002; McKenney et al. 1998). Implementation of combinational therapy is more appreciable than the antibiotic monotherapy (Aaron et al. 2002). The biofilm-grown bacteria are more resistant to planktonic bacteria. The other strategy to eliminate biofilm is by finding antifouling or antimicrobial surfaces (Brandl et al. 2008). Nanoparticles made of silver and many other metal nanoparticles display antimicrobial properties which seem to be an effective approach to remove the biofilms (Hoyle and Costerton 1991; Moreau-Marquis et al. 2008; Prasad et al. 2020). The antibiofilm molecules block the signalling pathways in almost all types of bacteria; these molecules can be an enzyme, a peptise, an antibiotic, polyphenols, etc. (Parsek and Singh 2003). Membrane technology has been developed for wastewater treatment. But the formation of biofilm on the membrane is deteriorating the life of the membrane and reducing the water flux. This is the critical problem in the membrane technology development (Ding et al. 2019; Xu and Liu 2011).

The metabolic uncouplers are introduced to disrupt oxidative phosphorylation suppressing the microbial attachment and also reducing the extracellular polymeric substance (EPS) secretions (Chen et al. 2002; Jiang and Liu 2012). The study aimed at inducing the uncoupler, 3,3′,4′,5′ tetrachlorosalicylanilide (TCS), to reduce the EPS and aerobic granulation formation. The optimal level of TCS concentration effectively inhibits the cell binding to the membrane. Bacterial motility is also an important factor in determining the initial cell attachment (O'Toole and Kolter 1998). When the concentration of TCS was increased to 100 μg/L, it showed that the reduced motility ultimately resulted in decreased cell attachment (Feng et al. 2020). The effective way to target the destruction of biofilm is quorum sensing

(Sambanthamoorthy et al. 2014; Kareem et al. 2017; Yu et al. 2018). Cells communicate through different signalling molecules but the way by which the expression of virulence genes is controlled by quorum sensing. The molecules or the compounds which interrupt these communications are called quorum quenchers. These quenchers suppress the virulence gene expression which make the proteases, siderophores, toxic compounds and biofilm formation (Antunes et al. 2010; Ali et al. 2020).

Virstatin was employed which cuts the pili binding by *Acinetobacter baumannii* in order to avoid biofilm production (Chabane et al. 2014). Nanoparticles always showed a better path to inhibit the microbes and so put forth (Ansari et al. 2014). It has been experimented that silver nanoparticles inhibited the growth and occupancy of *E. coli* and *Klebsiella pneumoniae* and also eliminated the exopolysaccharides formation. An inhibitor of multidrug resistant of *A. baumannii* biofilm, 5-episinnuleptolide, attenuated the genes expressing the EPS-producing enzymes which completely vanished in exposure to these compounds (Tseng et al. 2016). Sometimes, the binding of bacteria to the surfaces also depends on the physical properties. Therefore, an effective approach to inhibit the biofilm formation is by changing the surface of several nanostructures of multiwalled carbon nanotubes (Malek et al. 2016).

Bacterial biofilms are a huge threat to the humankind when discussing its growth in water distribution pipelines. These pipes are mostly made of iron stainless steel and galvanized steel or copper-based materials, so biofilms growing on these metals corrode the equipments used in the industry and thus deteriorate the quality of water leading to infectious diseases. The bacteria multiplied in number on stainless steel and titanium. The growth is decreased on copper and nickel substrates as a result of oxidative stress and protein dysfunction. The growth of bacteria in the initial stages is much low on copper, Cu and nickel and Ni substrates when compared to stainless steel (SS) and titanium (Ti); it may be because of varied interactions of microbes with various materials. For example, observe a green coloured material on the copper surface; the possibility is that the surface gave copper ions by getting oxidized. This ceases cellular protein or enzyme activity resulting in the prevention of bacterial attachment to Cu substrate (Santo et al. 2011). In his actual work, the bacterial growth restored after a period of incubation; this occurred as the cells experienced extreme membrane damage, though the DNA is not injured as it is protected by the periplasm (Grosse et al. 2014). Studies showed that the *E.coli* was chiefly destroyed through membrane damage, and also they are wide open to toxic portion of cu (II) which upregulates the genes responsible for ROS (reactive oxygen species) elimination (Wang et al. 2020).

In the recent years, "green antimicrobials" derived from green medicinal plants have been a promising replacements to the conventional ones to eradicate biofilms. These include essential oils which are of high essence due to its cheaper cost, biocompatibility and the ability to fight the bacteria without impelling drug resistance. To critical mechanism of its bactericidal effects is that they can separate the lipid layer from the cell membrane, which increases the permeability of the membrane troubling the cell structures (Wang et al. 2019). This is due to the hydrophobic

nature leading them to indissoluble and unsteady in aqueous media limiting its application in therapeutics. Studies have displayed that enveloping essential oils into a surface-active colloidal transport channel enhances their stability in aqueous medium and also the antibiofilm activity in the food and beverages (Arfat et al. 2014; Chen and Zhong 2015; Landis et al. 2017). Therefore, according to Zhaojie Wang et al. (2018), prepared regulatable thymol (essential oil made of oxygenated compound, phenol) contains chitosan micelles for treating bacterial biofilms. Here, the chitosan is a well-known polycationic polysaccharide made of dispersed structures of beta-(1-4)-linked D-glucosamine and N=acetyl-D-glucosamine with the best biocompatibility and antimicrobial properties. The micelles were produced through spontaneous assembly by amphipathic copolymer comprising of toluidine blue O (TBO)-implanted chitosan (CHI-TBO) and poly(propylene sulphide) (PPS). And now the chitosan, external region of the micelle, easily sticks to the oppositely charged that are the negatively charged biofilms. The ROS (reactive oxygen species) generator is the TBO which is associated with chitosan acting as a photosensitizer destroying various bacteria. This ROS can alter the hydrophobic sulphide to invariable oxidized hydrophilic sulfoxide which is much needed to kill the bacteria. So, ROS is generated from the TBO from thymol-loaded TBO-CHI-PPS micelles (T-TCP) with a simultaneous release of thymol from it (Wang et al. 2018).

9.5 Nanoscience

Nowadays, the nanoparticles are widely used in the fields of biomedical and physiology. Nanoparticle, the name itself, suggests it to be a tiny particle of nanoscale having the size of 1–100 nm. These nanoparticles also have a specific wavelength which is less than that of light. This property allows them to deploy in cosmetics, packaging and coatings. The physical, optical properties, etc. of nanoparticles make them play a unique role in the daily life when compared to the bulk materials. Sometimes nanoparticles of the desired shape and size can be obtained by controlling the parameters like salt concentration, pH value, temperature, aeration, etc. The most common shapes produced are spherical, triangular and hexagonal. Usually, nanoparticles work best when the size is less than the critical value, i.e. 10–20 nm (Singh et al. 2016). Metal nanoparticles are purely made of the metal precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these nanoparticles possess unique optoelectrical properties. The alkali and noble metal nanoparticles whose absorption band is in the visible region of the electromagnetic solar spectrum are Cu, Ag and Au. The facet-, size- and shape-controlled synthesis of metal nanoparticles is important in present-day cutting-edge materials (Dreaden et al. 2012). Metal nanoparticles with the advanced optical properties find applications in many research fields.

9.5.1 Classification of Silver Nanoparticles

Classification of nanoparticles is based on their morphology, size and chemical properties. Some of the well-known classes of NPs are listed below.

9.5.1.1 Carbon-Based NPs

Fullerenes and carbon nanotubes (CNTs) represent two major classes of carbon-based NPs. Fullerenes contain nanomaterial that are made of globular hollow cage such as allotropic forms of carbon. They have created noteworthy commercial interest due to their electrical conductivity, high strength, structure, electron affinity and versatility (Aliana Astefanei 2015). These materials possess arranged pentagonal and hexagonal carbon units, while each carbon is sp^2 hybridized, shows some of the well-known fullerenes consisting of C60 and C70 with the diameter of 7.114 and 7.648 nm, respectively. CNTs are elongated, tubular structures, 1–2 nm in diameter (El-Sherbiny et al. 2013). These are structurally resembling to graphite sheet rolling upon itself. The rolled sheets can be single, double or multiwalled, and therefore they are named as single-walled (SWNTs), double-walled (DWNTs) or multiwalled carbon nanotubes (MWNTs), respectively. Deposition of carbon precursors especially the atomic carbons, vaporized from graphite by laser or by electric arc onto metal particles, is widely required for their synthesis. Lately, they have been synthesized via chemical vapour deposition (CVD) technique (Elliott et al. 2013). Due to their unique physical, chemical and mechanical characteristics, these materials are not only used in pristine form but also in nanocomposites for many commercial applications such as fillers (Saeed and Khan 2014, 2016), as support medium for different inorganic and organic catalysts (Mabena et al. 2011), and for environmental remediation, these can be used as efficient gas adsorbents (Ngoy et al. 2014).

9.5.1.2 Metal NPs

Metal NPs are purely made of metal precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these NPs possess unique optoelectrical properties. NPs of the alkali and noble metals, i.e. the broad absorption band of Cu, Ag and Au, lie in the visible zone of the electromagnetic solar spectrum.

The facet-, size- and shape-controlled synthesis of metal NPs is important in present-day cutting-edge materials (Dreaden et al. 2012). Due to their advanced optical properties, metal NPs find applications in many research areas. Gold NP coating is widely used for the sampling of SEM, to enhance the electronic stream, which helps in obtaining high-quality SEM images.

9.5.1.3 Ceramic NPs

Ceramic NPs are inorganic nonmetallic solids, synthesized via heat and successive cooling. They can exist in the form of amorphous, polycrystalline, dense, porous or hollow structures (Sigmund et al. 2006). With their use in applications such as catalysis, photocatalysis, photodegradation of dyes and imaging applications, nanoparticles are getting great attention of researchers (Thomas et al. 2015).

9.5.1.4 Semiconductor NPs

Semiconductor NPs possess characteristics of metals and nonmetals and therefore found various applications in the literature due to this property (Ali et al. 2017; Khan et al. 2017).

Semiconductor NPs possess wide band gaps and therefore showed significant alteration in their properties with band gap tuning. Therefore, they play a very important role in photocatalysis, photo-optics and electronic devices (Sun et al. 2000). Because of their suitable band gap and band edge positions, a variety of semiconductor NPs are found exceptionally efficient in water-splitting applications (Hisatomi et al. 2014).

9.5.1.5 Polymeric NPs (PNPs)

Polymeric nanoparticles are generally organic based and are mostly found in nanospheres or nanocapsular shaped (Mansha et al. 2017; Prasad et al. 2017). The overall mass of the matrix particles is generally solid, and the other molecules attach to the outer boundary of the spherical surface using the phenomenon called adsorption. In the following case, the solid mass is completely encapsulated within the particle (Rao and Geckeler 2011). The PNPs can readily functionalize and thus find bundles of applications in the literature.

9.5.1.6 Lipid-Based NPs

The lipid nanoparticles contain lipid moieties and have effective applications in biomedicine. Generally, a lipid NP is characteristically spherical with diameter ranging from 10 to 1000 nm. In a similar way to polymeric NPs, lipid NPs also possess a solid core built of lipid and a matrix containing soluble lipophilic molecules. Surfactants or emulsifiers stabilized the external core of these NPs (Rawat et al. 2011). Lipid nanotechnology (Mashaghi et al. 2013) is a special field, focusing on the designing and synthesis of lipid NPs for various applications in drug delivery and as drug carriers (Puri et al. 2009) and RNA release in cancer therapy.

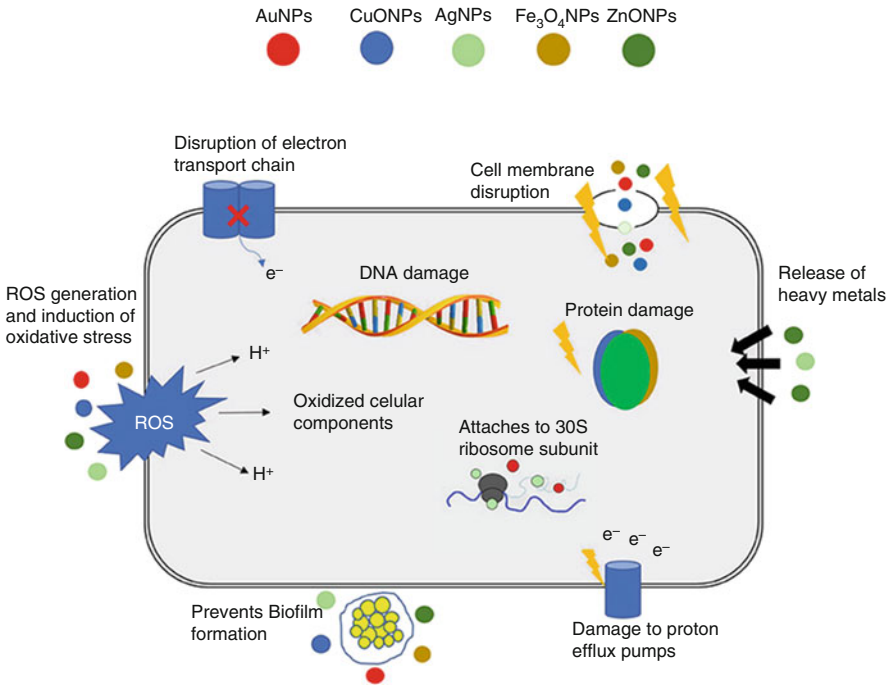

Fig. 9.2 Different mechanisms of action of NPs in bacterial cells. The combination in a single nanomaterial of a multitude of cellular effects may have a tremendous in fighting MDR bacteria. DNA, deoxyribonucleic acid; ROS, reactive oxygen species; AuNPs, gold NPs; CuONPs, copper oxide NPs; Ag NPs, silver NPs; Fe_3O_4 NPs, iron oxide NPs; ZnONPs, zinc oxide NPs. (Adapted from Pedro Bapista et al. 2018)

9.5.2 Synthesis of Nanoparticles

Nanoparticles can be synthesized in two following approaches: (1) top-down approach and (2) bottom-up approach. In simple words, the way in which smaller particles assemble into complex particles operated either by physical or chemical forces is called bottom-up approach, while the process in which bulk material is turned into simply smaller particles preferably nano-scaled materials is called top-down approach. Nanoparticles can be synthesized using three different methods. They are:

(1) Physical method: nanoparticles are synthesized by physical means such as by mechanical means and vaporization.

(2) Chemical method: nanoparticles are synthesized using chemicals via sol-gel process, aerosol process, etc. This method is the widely used and accepted method.

(3) Biological method: other name for this method is the green synthesis because it makes use of plant extracts or parts of the leaves, root, flower and fruits and biological species like fungi, yeast, algae and bacteria (Prasad 2014, 2016, 2017; Prasad et al. 2016, 2018a,b; Thangadurai et al. 2020; Srivastava et al. 2021).

There are multiple ways by which nanoparticles exhibit antimicrobial activity; they are (a) interacting directly with the bacterial cell wall, (b) prevention of biofilm formation, (c) evoking the natural and acquired immune responses, (d) production of reactive oxygen species (ROS) and (e) triggering of intracellular effects (Fig. 9.2) (Prasad and Swamy 2013; Joshi et al. 2018; Inamuddin et al. 2021). Since they do not follow similar mechanism of action of standard antibiotic drugs, it can be widely used against resistant bacteria (Singh et al. 2014; Aderibigbe 2017; AlMatar et al. 2017; Hemeg 2017; Natan and Banin 2017; Rai et al. 2017; Slavin et al. 2017; Zaidi et al. 2017; Bassegoda et al. 2018; Katva et al. 2018; Siddiqi et al. 2018). Gómez-Gómez et al. (2020) used metalloid based NP like tellurium nanoparticles (TeNPs) to investigate its effect on *Staphylococcus aureus* and *Escherichia coli*. These nanoparticles inhibited biofilm formation with reducing nearly 90% of biofilm volume; another exciting findings revealed structure change from sphere to rod-shaped as a consequence of the nanoparticle-biofilm interaction. While the increasing, other co-polymers (for instance polylactic-co-glycolic acid, PLGA) other polymer has emerged to be used in the food and drug administration; PLGA shows significant uses like better compatibility, good stability while preparation (Danhier et al. 2012; Sharma et al. 2016; Swider et al. 2018). So, enclosure of antibiotics into these PLGA nanoparticles helps in safe transport and release at the infection site which in general get degraded by enzymes (Huang et al. 2020). But also the relative low drug packing capability and premature or initial burst release limited the use of PLGA-based nanomaterials in in vivo studies. Therefore, quantum dots appeared as an efficient way to combine with polymer-based nanoparticles for added advantage (Huang et al. 2020).

Carbon quantum dots (CQDs) showed an outstanding drug packing capacity because it possesses a large surface area and stable π-π stacking, water repelling and electrostatic interactions or physisorption (Liu et al. 2012; Wang et al. 2017b). The method used for incorporating the CDQs into the PLGA nanoparticles is microvotex-based microfluid which accurately controls the CQD-PLGA hybrid nanoparticle formation with a fine antimicrobial efficacy to fight with *P. aeruginosa* biofilms (Huang et al. 2020). The enclosure efficacy and the packing capacity of the CQDs can be changed by altering the mass ratio of PLGA to CQDs which helps us facilitate a sufficient space for photothermal effect optimization and reducing the toxic effects triggered by the CQDs. The photothermal effect of both CQDs with and without the PLGA nanoparticles was studied by inducing laser of 808 nm with different power densities. The consequences are the increase in temperature from 37 degrees Celsius to 43 degree Celsius which is seen only in the PLGA with CQDs (Huang et al. 2020). Another interesting finding was that the CQD-encapsulated PLGA nanoparticles are able to transform NIR light into thermal energy which lead us to enhance the photothermal effects. In this study, they used azithromycin (AZI) as an antibiotic and loaded into CQD-PLGA hybrid nanoparticles which eliminated more bacteria of *P. aeruginosa* than the ones with the only AZI. This may be due to increased concentration of antibiotic at the reach of the biofilm site (Huang et al. 2020).

9.6 Knowledge Gaps and Future Directions

The purpose of using nanoparticles in preference to antibiotics is because nanoparticles can inhibit microbial drug resistance effectively in specific cases (Wang et al. 2017a). The highly preventable measures of biofilms are accomplished by smaller size with high surface-area-to-mass ratio. The shape of the nanoparticle also has a noticeable effect on biofilm elimination, for example, rod-shaped nanoparticles show a high impact over the spherical-shaped nanoparticles (Slomberg et al. 2013). With high available research studies, developing the effects of nanoparticles is the starting step for any researcher to try his best (Wang et al. 2017a). In spite of it, a research study reported that there was a spread of multiple drug resistance (MDR) not just in the same species of bacteria but also across the genera when it was the positive hope in promoting conjugative transfer of RP4, PK2 and PCF10 plasmids by aluminium nanoparticles (Qiu et al. 2012). The underlying factors may be the range of damage caused to the cell membranes by the aluminium NPs, the amounts of aluminium NPs and the breeding cells, parameters like temperature and pH and selective expression of particular genes (trfAp, trfA and trbB) which is crucial in transferring and replicating RP4 plasmids. The negative effects are also considered to avoid the MDR which may lead to health hazards.

There are limitations regarding the use of NPs in inhibiting the biofilms. As there are various bacterial strains, with different action times, it's difficult to examine the comparative studies of the antibacterial mechanisms. The complexity of the cell membrane structures can be seen as a critical drawback in in vitro studies. Size can become a limitation in transporting all NPs into the bacterial porins which is generally <600 Da. Further research focusing on the intracellular inhibitory mechanisms is left unattended. Huge attention is made towards the NPs which induced oxidative stress, synthesis of proteins and metabolism of bacterial cells. In the view of increasing resistance of the biofilms, nanoparticles are considered to having the greater potential to resolve with low toxic effects (Wang et al. 2017a). However, key factors like NP resistance and surface associations between NP biofilms and hosts need to be sorted out to guarantee fortunate clinical applications (Ramasamy and Lee 2016).

9.7 Conclusions

As of the resistance posed by the biofilms against the conventional antibiotics, there evolved multiple pathogenesis in humans which lead to chronic infections over decades. It has been evident that the therapeutic use of nanoparticles had tremendous antibiofilm effects as far studied. The influence of nanoparticles on bacterial cell membrane permeability, generation of reactive oxygen species and cellular metabolism and reproduction are of high priority. The bacterial attachment and EPS secretions can be reduced by using metabolic uncouplers like 3,3′,4′,5′

tetrachlorosalicylanilide (TCS). Among numerous types of nano-based materials used and studied in antibiofilm strategy, using silver nanoparticles is one of the best possible way in eliminating the microbes. Quorum quenchers can be used to suppress the expression of virulence genes like proteases, siderophore, etc. which is a way to block quorum sensing characteristic. Other compounds like virstatin and 5-episinnuleptolide are also found to be the key inhibitors of some of the bacterial species.

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