Chapter 17
Recent Trends in Antimicrobial or Biofilms with Advanced Specificity at Gene Level Treatment

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Abstract Antimicrobials are lifesaving molecules helpful in eliminating different kinds of infections in the past 100 years and are still having prominent role in the medical practice. The broad-spectrum antibiotics are important even though they can cause a lot of side effects. The future of antimicrobials lies on the specific targeting without eliminating the beneficial flora and fauna of the body. The next-generation antibiotics and biofilms show both the specificity and the broad-spectrum antimicrobial activity without affecting the good bacteria of the gut. Nucleic acid- and peptide-based antibiotics are considered as the future antibiotics or biofilms with advanced specificity at gene level.

Keywords Disinfection · Photo catalysis · Fullerenes · Transduction · Reactive oxygen species

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R. Prasad et al. (eds.), *Nanostructures for Antimicrobial and Antibiofilm Applications*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-40337-9_17

17.1 Antimicrobial Nanotechnology

Nanoparticles play a new role in fields like cosmetics, medicine, engineering, and technology. Silver nanoparticle-based drug products have an antimicrobial property with promising outcomes in the new pharmaceutical manufacturing (Aziz et al. 2015, 2016). Some studies show that liver cancer patients are successfully treated with silver nanoparticles proving their anti-carcinogenic activity; they cause programmed cell death to carcinogenic liver cells (Aziz et al. 2019). Silver nanoparticles did not show any toxic outcomes in humans, unlike animal studies, and there is inadequate information about the toxic mechanisms of silver nanoparticles in animal studies (Ahmadian et al. 2018).

Recently many infections of *Staphylococcus aureus* were identified in patients using biofilms; this bacterial infection is proved to be cured by silver nanoparticles in the experimental studies. The functional genes of *Staphylococcus* bacteria respond to silver ions breaking the cell wall followed by the death of bacteria; only those genes which code for polysaccharides respond to silver ions but not the genes encoding a protein, DNA, and sugars. That is why the latest medical devices are coated with silver nanoparticles to avoid the *Staphylococcus* infection in treated patients. Biofilms coated with silver nanoparticles have different morphology and appearance compared to standard biofilms which can be clearly identified using the scanning electron microscope (Singh et al. 2018).

Food technology is also widely implementing the use of antimicrobial nanoparticles to prevent the spread of foodborne pathogens like salmonella, which previously caused many deaths due to infections in humans and cattle (Prasad et al. 2017a). Some specific salmonella species like enteritidis cannot be easily eliminated from the human body due to their resistance to antibiotics. Peroxidase enzymes could lyse these bacterial cell walls without the antibiotics by increasing the reactive oxygen levels to destroy the vacuoles in the bacteria, so recently nanoparticle-based enzymes were produced to carry out this process. Iron oxide nanoparticles carrying the peroxidase enzyme to the bacterial cell wall can eliminate the bacteria like *Salmonella enteritidis* from the mammalian body; these iron oxide nanoparticles will deliver peroxidase enzymes to the bacterial cell wall thereby lysing the vacuoles to release lysozymes which will destroy the cell organelles thereby causing cell apoptosis (Shi et al. 2018).

Surface modification (Fig. 17.1) is the most widely implemented technique to develop nanotechnology-based medical devices; titanium nanoparticles are coated on implants and biofilms for antimicrobial activity against *Staphylococcus* and *Pseudomonas* species. The degree of roughness on the implant surface is modified to create more surface area to carry the antimicrobial drugs. These implants are bacterial resistant and will not involve in the development of any infection or lesion on the body surface. Dental implants are administered to patients with mandibular or dental fractures or sinuses; these commonly produce infection or lesions due to the presence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other streptococcal species growing in the human saliva (Di Salle et al. 2018).

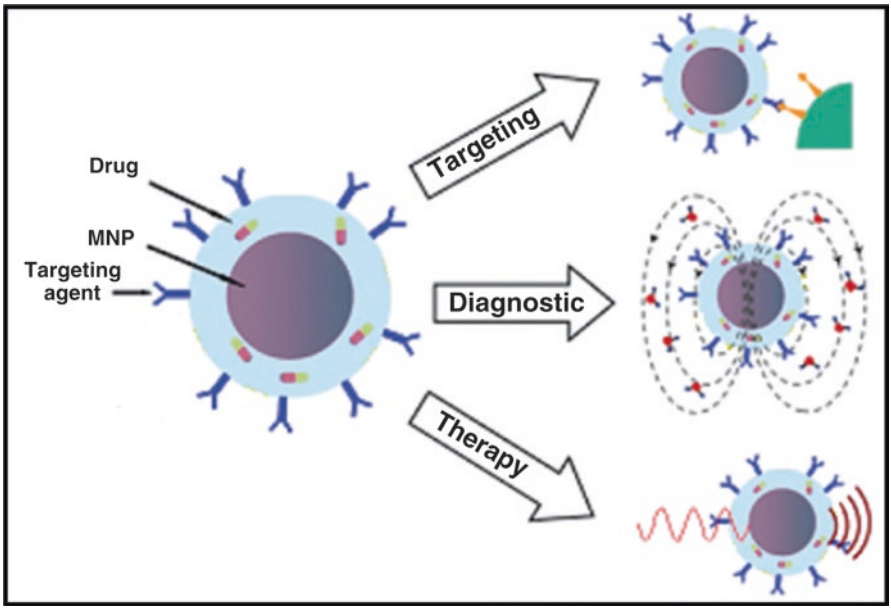

Fig. 17.1 Surface modification of nanoparticles used in antimicrobial therapy

17.2 Bacterial Resistance and Genome Sequencing

Deaths due to antibiotic resistant Gram-negative bacteria are proliferating, and treatment involves enormous medical costs. Novel therapeutics are focused on developing many antimicrobials to overcome these barriers; many investigational drugs are being developed and examined in humans during clinical practice to combat the antibacterial resistance (Avery and Nicolau 2018). The standard classes of multidrug-resistant Gram-negative bacteria are Enterobacteriaceae, Pseudomonadaceae, and Moraxellaceae family; primary pediatric infections are caused by Gram-negative bacteria like *Pseudomonas* and *Acinetobacter* species. The treatment considerations for antibiotic resistance population is different compared to the actual population (Hsu and Tamma 2014).

The novel antimicrobial therapy regimens are totally focused on combing the traditional medications with the novel antibiotics to safely reduce the toxic outcomes and resistance to the body. The traditional antibiotics have higher tolerance compared to novel antibiotics like beta-lactams, quinolones, cephalosporins, aminoglycosides, and beta-lactamase. For instance, combination therapy to overcome the Gram-negative bacterial resistance includes avibactam, cefotaxime, and phleomycin as infusion which are available to the public recently. According to some data published by the Infectious Diseases Society of America, there are about ten investigational antimicrobials against bacteria resistant to antibiotics that can be released into the market in 2020 (Bassetti et al. 2018).

Whole genome sequencing (Fig. 17.2) is a novel approach to combat the antibiotic resistance developed by bacteria for successful determination of the resistance expressing genes in the bacterial gene pool. This approach is a part of bioinformatics to identify the determinants of bacterial resistance and the relationship with the clones. The genome sequencing of *Clostridium difficile*, a known pathogen of several outbreaks of nosocomial infections facilitated to identify genes associated with pathogenesis. This became successful in identifying the genes encoding the bacterial resistance and the susceptibility of species to the various antibiotics like clindamycin, vancomycin, erythromycin, and tetracyclines. Point mutations at these homologous genes will prevent the antibacterial drug action; the multidrug resistance developed by these bacteria is mainly due to the expression of genes like *ermG*, *mefA*, and *msrD*. Many studies show how these Gram-negative bacteria share the above-mentioned genes to neighboring bacteria, especially in the gut to prevent the mechanism of antibiotics (Isidro et al. 2018).

This genetic approach will help to identify the mechanism of resistance, also the bacterial lineage in the spread of infection, which will help in targeting the bacterial genes directly without expressing the genes that promote multidrug resistance. Many opportunistic infection outbreaks in hospitalized patients are mainly caused by the *Pseudomonas aeruginosa* species, which is believed to possess spreading clones with advanced drug resistance mechanisms to drugs like carbapenem and other beta-lactamases. Whole genome sequencing helps to locate the multi-loci sequence and phylogeny analysis or evolutionary relationship of the bacterial strain

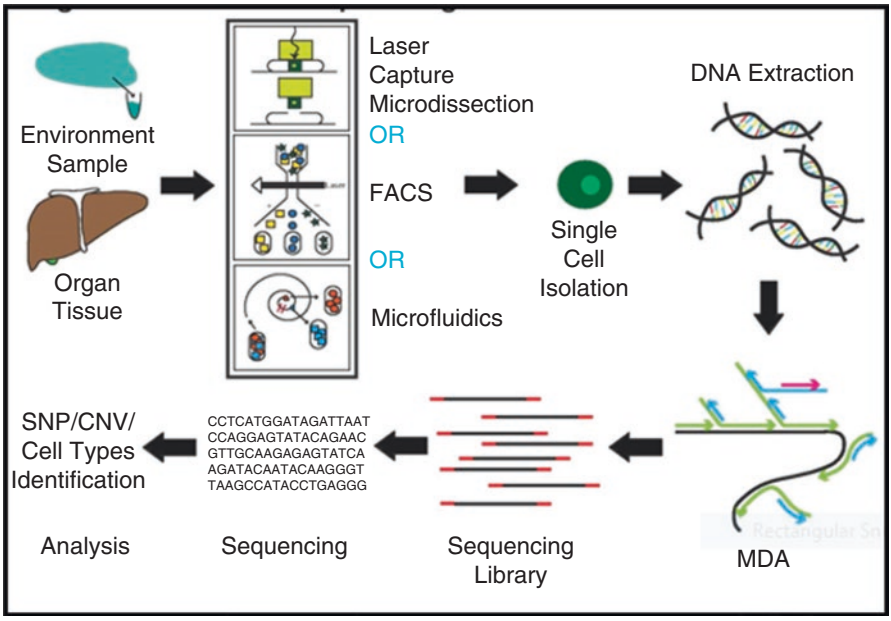

Fig. 17.2 Single cell bacterial genome sequencing

or species. The identified multidrug-resistant genes in *Pseudomonas* species are *GyrA*, *ParC*, *OprD*, *Arm*, and *Rmt* (Telling et al. 2018).

Global dissemination of hospital-acquired infections are prevalent due to an increased hospital stay of the patients for better treatment. Another set of opportunistic pathogens like *Enterococcus faecium* shows vancomycin resistance and reduced susceptibility to daptomycin treatment. The prevalence of this nosocomial infection is about 35.5% of the total hospital-acquired infections, and daptomycin is a commonly prescribed antibiotic in the USA for staphylococcal and enterococcal infections. The alterations in the genetic level to develop multidrug resistance are identified in these bacteria by gene sequencing and multi-locus typing. The data obtained by whole genome sequencing reveals mutations in *LiaR*, *LiaS*, and *Cls* genes; point mutations at any of these genes will express multidrug resistance. Comparative genome analysis of different potential harmful bacteria will help to identify the bacterial colonization and their susceptibility to antimicrobial drugs. The evolving changes in the process of developing antimicrobial resistance can be clearly depicted by this genetic analysis (Wang et al. 2018).

17.3 Biofilm Formation

Biofilms are communities of bacterial and fungal microbes that form protective matrix via adherening with the any surface. A biofilm are described as colonies of bacteria embedded in a thick, slimy barrier of sugars and proteins which can protect colonies from external factors. The surfaces of medical devices are vulnerable to the formation of biofilms, for example, contact lenses and orthopedic implants. They are significant contributors to diseases that are characterized by an underlying bacterial infection like osteomyelitis, periodontal disease, cystic fibrosis, and chronic acne, and biofilms are also found in wounds and are suspected of delaying healing in some.

Planktonic bacteria grow in microcolonies in 24 h of culturing. They can rapidly recover from their mechanical disruption and reform a mature biofilm of fewer than 1–2 days. A unique property of polymicrobial colonies is that they have many protective effects that different species of bacteria can provide to each other individually.

In their favorable conditions, antimicrobial resistant bacteria can be shielded with protective enzymes or antimicrobial binding proteins. As a result, it transfers virulent gene and proteins to the neighboring bacteria and facilitates the antimicrobial resistance. In many hospitalized patients who are unconscious or unable to take food orally and who are treated using the catheters in the veins especially in the arms, legs, groin, and chest may acquire additional blood-borne infections by forming biofilms (Fig. 17.3). In the USA, more than four million catheters are inserted into patients to treat various cardiovascular ailments, in which nearly 10% of the treated population will show biofilm formation and infection susceptibility. The formation of biofilm inside the human body is a very complicated process and involves

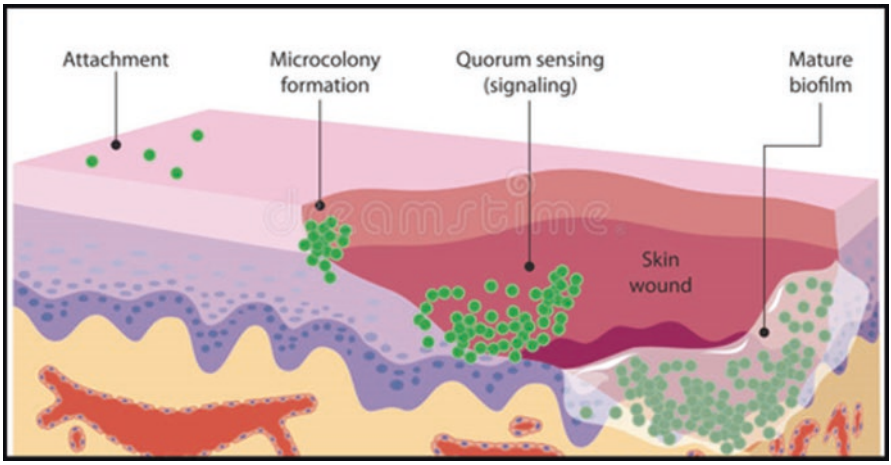

Fig. 17.3 Formation of biofilm after skin injury

different stages like immobilization and surface adherence along with intercellular interactions and microbial colony formation. The adherence of circulating microbes to the surface of the catheters is assisted by electrostatic interactions and forces between the catheter substrate and microbial cell wall leading to biofilm formation (Yousif et al. 2015).

These microbial colonies on the biofilm surface are different from the other microbes and have very complex physiology, and mechanism, and based on this, the biofilm-forming strains of bacteria have more virulence compared to the non-biofilm-forming strains. For example, infection due to *Candida albicans* is widespread worldwide with a prevalence level of 5–70% in the ICU-admitted patients receiving invasive antimicrobial or chemotherapy procedures for immunosuppressive disorders, and this increases the period of hospital stay (3–30 days) and medical expenses (40,000 USD) which proved to be a financial burden. The estimated mortality rate due to these infections is about 75% per annum globally. The pathogenicity of the candida biofilms is high and have greater virulence compared to the non-biofilm-forming strains; these biofilms are very resistant to antifungal agents and can lead to severe outcomes like bloodstream infection or candidemia if left unnoticed (Treviño-Rangel et al. 2018).

Sometimes antimicrobial biofilms will serve as a reservoir for the antibiotic resistance genes, thereby making it difficult for traditional antimicrobials to show their therapeutic effect at minimum sufficient concentrations. This is because of the extensive use of antibiotics and their accumulation in the environment as agricultural wastes as well as toxins in human body organs like kidney and liver; in addition, bacteria develop resistance by altering their genetic integrity suitable to face the antibiotic activity. These antibiotic resistance genes are created because of the extensive use of antibiotics, and the diseases caused by these pathogens are very hard to treat; nowadays, these communicable diseases are getting common

throughout hospital and dining facilities. These unwanted antibiotic-resistant genes are in present in bacterial chromosomal DNA and plasmids. These genes are carried into the atmosphere by natural or manmade vectors and spread the infection along with water and air pollution (Guo et al. 2018).

The spread of infection causing antibiotic-resistant bacteria is mainly through food, water, and air pollution caused by the antibiotic resistance genes. *Salmonella typhi* is a typical example to mention about the functioning of these resistant genes, adaption to aerobic external environment from the anaerobic host environment maintaining the same pathogenicity until it is carried to another host body. This adaptivity, virulence, and biofilm forming capability are made possible by the small RNA molecules developed inside the host environment because of some mutations during the bacterial life cycle. These mutations are because of the availability of high concentrations of antibiotics in the blood in proportion to the bacterial population. These bacteria are classified into different groups based on the type of environment they choose to grow. For example, a group of bacteria called as *Salmonella* grows on chicken broth, sugar substances and dairy products. The upregulation of the biofilm-forming genes is noticed in the growth medium where there is an aerobic atmosphere. Biofilm formation by these bacteria is mainly seen on glass, steel, and plastic materials that come in contact, and maintenance of proper sanitary conditions is required to prevent possible infection by these organisms (Lamas et al. 2018).

17.4 New Trends in Biofilm Formation

The environment in which the pathogens and commensals interact play an essential role in the physiology and composition of the biofilms. The polymicrobial population embedded in the extracellular matrix (Fig. 17.4) forms the biofilm, which can generate many infections. Dental caries is a typical example for the biofilm formed on the teeth by the interaction between food and the microbial population in the oral cavity. These oral biofilms are the reservoirs for many harmful bacteria that nourish on the human food and develop their virulence accordingly; constant changing of diet or following of a fixed diet schedule combined with good oral hygiene will reduce the chances of oral cavities and infections.

The virulence potential of these microbiotas totally depends on the type of food they grow on like sugars, proteins, and fats. The microbial community is classified into the film-forming bacteria and infection-causing bacteria based on which they are involved in causing infection after forming the biofilms or vice versa. Many pharmaceutical oral products will only temporarily eliminate these populations but will not focus on disrupting their further chances to regrow forming new biofilms. New trends in treating such virulent bacteria should focus on understanding the physiology of matrix formation and developing an approach to prevent the formation of biofilms (Bowen et al. 2018).

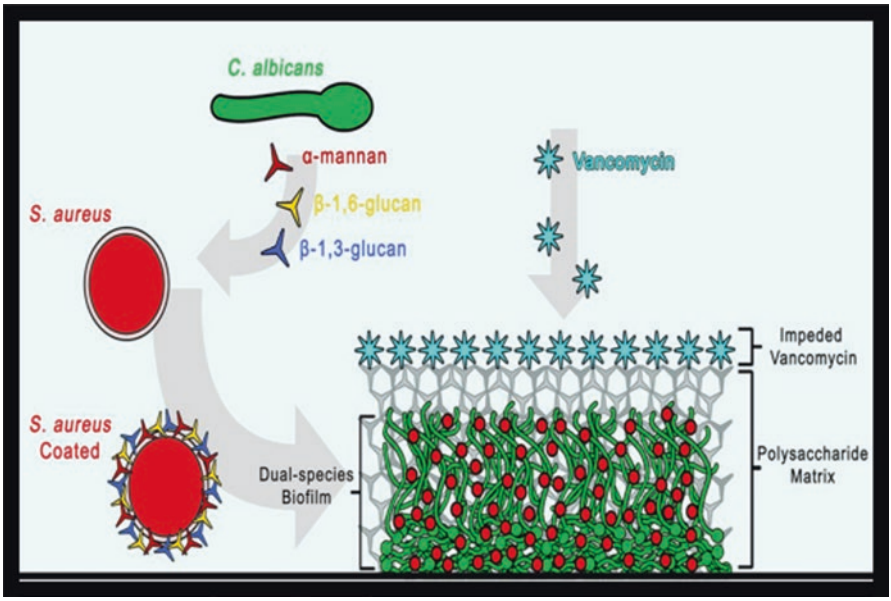

Fig. 17.4 Polysaccharide matrix during biofilm formation

17.5 Antimicrobial Drug Delivery

The small, colloidal polymeric nanoparticles are used as excellent vehicles to agents such as biomolecules and drugs. These nanoparticles, when tagged with imaging agents, offer various additional opportunities to exploit optical imaging in cancer diagnosis and guided hyperthermia therapy (Mahapatro and Singh 2011).

Biodegradable polymers PLGA and several different polymers, both synthetic and natural, have been utilized in formulating biodegradable nanoparticles (Prasad et al. 2017b). These polymers have been tested for toxicity and safety in extensive animal studies and are currently being used in humans for resorbable sutures, bone implants and screws, and contraceptive implants. These polymers are also used as graft materials for artificial organs and recently as supporting scaffolds in tissue engineering research (Panyam and Labhasetwar 2003). The commonly used material for surface modification is poly(ethylene glycol) (PEG), which is a hydrophilic, non-ionic polymer that has excellent biocompatibility. PEG attachment to the particle surface can reduce protein and enzyme adsorption on the surface and will reduce polymer degradation. The degree of protein adsorption can be reduced by modifying the density and molecular weight of polymer on the surface (Xie et al. 2017).

Drug loading into the NPs is achieved by two methods: first, by incorporating the drug at the time of NP production and, second, by adsorbing the drug after the formation of NPs by incubating them in the drug solution. In addition to the adsorption and incorporation, a new method of drug loading for the water-soluble drugs is

chemical conjugation. The widely used surface-coating materials are polyethylene glycol, polyethylene oxide, poloxamers, and lauryl ethers (Soppimath et al. 2001). Synthesis and encapsulation of drugs in polymeric nanoparticles are extensively used for the nanoencapsulation of various useful bioactive molecules and medicinal drugs to develop nanomedicines. Cancer-related drugs paclitaxel, doxorubicin, cisplatin, triptorelin, dexamethasone, xanthine, etc. have been successfully encapsulated on PLGA nanoparticles (Kumari et al. 2010).

Surface functionalization of polystyrene NPs by adsorption of tunable PPE surfactants significantly reduces unspecific protein binding. PPE chemistry allows a straightforward adjustment of hydrophilicity in a homopolymer or the controlled synthesis of amphiphilic block copolymers. Structurally versatile poly(phosphoester) can be used for non-covalent surface modification of model nanocarriers providing an easier approach than covalent linkage (Muller et al. 2017). Three different methods like chemical coupling, surface activation, and coupling reaction were investigated for nanoparticle surface modification and co-incorporation of surface-modifying agents into nanoparticles. Since, the unmodified nanoparticles are anionic in nature, and mixing of these surface-modifying agents with the nanoparticle suspension could result in their ionic bonding with DMAB which optimally enhances arterial U-86 levels compared to other modifications and the unmodified nanoparticles (Song et al. 1998).

Nanoparticles have many applications in both microbiology and drug delivery using the nanoparticles (Table 17.1).Tumor uptake of PEG5000-TA-coated AuNPs could have been a result of the AuNPs' prolonged resident time in the blood and their ability to extravagate from tumor blood vessels. AuNPs coated with PEG5000-TA had the highest colloidal stability, as they did not form aggregates in PBS containing 10 mM DTT or 10% FBS as readily as AuNPs coated with PEG-SH. AuNPs in 20 nm also appeared to be excreted from the body, and 20 nm gold particles are coated with titanium terminated PEG5000 which potential drug delivery vehicles and diagnostic imaging agents (Zhang et al. 2009). SiO_2 NPs are essential materials, and the advantages of using it include low cost of production

Table 17.1 Applications of nanoparticles in microbiology and nanotechnology

Nanoparticle		Applications
Ag	⇒	Home appliances as antimicrobial agents
	⇒	Clothing for odor resistance
TiO_2	⇒	Paints and coating for antimicrobial properties
	⇒	Cosmetics as a UV absorber
Carbon	⇒	Consumer electronics
Nanotubes (CNT)	⇒	Sports equipment for light weight and durability
Fe_2O_3	⇒	Contrast agent for targeted tumor imaging
Fullerenes	⇒	Drug delivery
Fe	⇒	Environmental remediation
Au	⇒	Medical diagnostics

and having high-performance features. This is applied to manufacture materials such as chemical sensors, polishing material, food industry, and cosmetic materials (Telling et al. 2018). Nanobiopesticides like silica nanocomposites (NCs) have shown that nanosilica coated with gold, which is attached to breast carcinoma cells and exposed to the near-infrared light in vitro, show remarkable potential in killing the cancer cells (Esposito et al. 2004; Gref et al. 2000).

Polymeric NPs can be further endowed to target specific organs and tissues, overcoming certain biological barriers such as the blood-brain barrier. The lactic acid (LA) homopolymer (PLA) and its glycolic acid (GA) copolymer [poly(D,L-lactide-glycolide) (PLGA)] are among the most frequently used polymers for the carriers because of their biocompatibility, biodegradability, and drug release from the PLGA NPs which can be easily manipulated adjusting the ratio of LA to GA (Zhou et al. 2010). The linoleic acid–avidin conjugate yielded nanoparticles with enhanced ability to increase ligand density on anti-CD4-targeted nanoparticles formulated with the linoleic acid–avidin conjugate which resulted in a 5% increase in binding to CD4+ T cells. The novel avidin–linoleic acid conjugate facilitates enhanced ligand density on PLGA nanoparticles, resulting in functional enhancement of cellular targeting (Park et al. 2011).

Functionalized SiO_2 NPs with polyaniline as coupling agents were synthesized and the surface of SiO_2 NPs was treated with them. The surface of SiO_2 NPs modified by organic DAs to improve dispersion of them in nonpolar and weak polar organic solvents such as chloroform and acetone. FT-IR spectral measurements allowed us to conclude that the modified SiO_2 NPs have formed, and there is also an intermolecular interaction between the DAs and SiO_2 NPs (Mallakpour and Marefatpour 2015). To increase the therapeutic potential, targeted delivery system CAT has been developed involving direct modification or polyethylene glycol conjugation (Ahmadizadegan 2017; Saraf et al. 2013). For surface morphology, the mannose coupling is an attractive approach for targeting of CAT to macrophages, and it has a significant potential to detoxify ROS. Therefore this approach could be further explored for the treatment of liver disorders due to ROS (Ahmadizadegan 2017; Saraf et al. 2013).

17.6 Green Nanotechnology for Antimicrobial Delivery

The application and usage of antimicrobial drugs are needed to be treated safe, which is evident that usage of nanotechnology application can be safer in the delivery of the harmful drugs (Al Thaher et al. 2017). Nanoparticles have optimal bioavailability with the rapid onset of therapeutic activity (Uppal et al. 2018). The bioavailability confers the stability and non-reactiveness with the metabolism (Howick et al. 2018). The nano-pharmaceuticals have great potential in drug carrier which provide a platform to curb multidrug resistance, toxicity, target specificity, solubility, and low bioavailability (Uddin 2016). Some green chemistry polymers derived from natural polyphenols like tea can act as nanocarriers to deliver drugs at the gene level (Mahata et al. 2018).

The nanoparticles which are applied for antiseptic and disinfectant in chronic skin such as micellar nanoparticles (Jahromi et al. 2018). They are usually formulated as nanoemulsions as they have functional drug carrying capacity (<=20%) for a wide range of water solubility of antimicrobial drugs that have barriers with the systemic administration (Hörmann and Zimmer 2016). MNPs are evident that they are characterized to be the best vehicles with great potency of skin penetration with minimal adverse effects (Senapati et al. 2018). These are stable at room temperature for more than 5 years (Amodwala et al. 2017). These nanoparticles take support from skin framework and enhances the drug delivery in the stratum corneum with high therapeutic levels of drugs like acyclovir in the blood; when accompanied with nanocarriers, many antimicrobial drugs can be delivered to the bacteria at the gene level (Loh 2016) (Fig. 17.5).

The antibiotics are readily obtained in the form of multiphasic composition with supporting solvent, oil, and other surfactants (Prud'homme et al. 2017). The multiphasic composition is processed with ultra-sonicator and homogenizes with emulsifier and electric overload (Swager et al. 2018). The composition and stability in the antimicrobial nanoparticles can be analyzed by permeation technique or the HPLC (Moronshing and Subramaniam 2018). Polysporin is the best formulation with high stability and analyzed with various experiments (Nani et al. 2018).

The mode of drug delivery through MNPs are limited via transdermal delivery (Zou et al. 2016). Thus, MNPs are evident to have potential modes of delivery such as nasal, vaginal, rectal, and other parenteral routes (Carvalho et al. 2018). The other way of application of MNP technology is a nonconventional mode of delivery such as the behavior of nicotine transdermal patch and raloxifene estrogen patch which is termed as pseudo-patc or a patchless strip (Sharma and Chandra 2017).

Delivery of various pharmaceuticals such as antimicrobials at gene level are facilitated by supercritical fluids (SCF). They are highlighting the processing and the potentiality of the chemical industry for the sustainability and addressing the potential asstets for future (Fages et al. 2004). Pharmaceutical waste is measured by

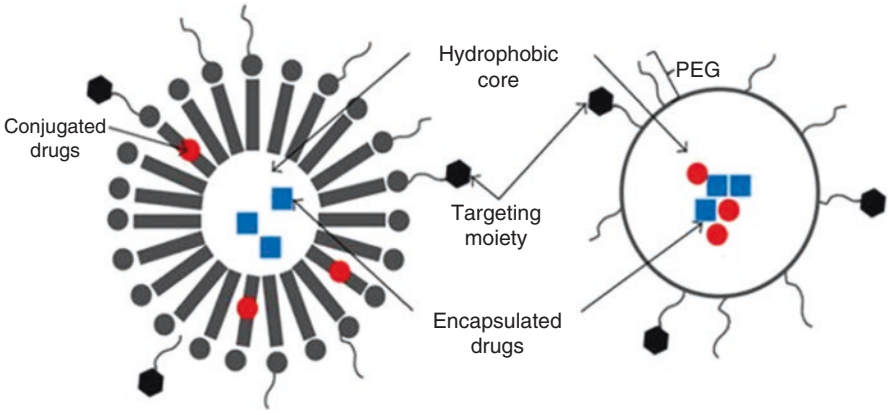

Fig. 17.5 Antimicrobial drug delivery using the micellar nanoparticles (Loh 2016)

E-factor (Kg waste per Kg product) with the help of chemical price-volume relation (Dias-Ferreira et al. 2016). As per some statistics in oil refiners, there is only 10% waste, but it is greater than 25% in pharmaceutical industries (Nickum 2018). The super critical fluids can protect environment by treating pharmaceutical waste.The purification of solid wastes with the supercritical fluids will avoid reliable incondensable waste products, thereby saving the environment (Lemasson et al. 2016). The treatment with supercritical fluids gets highlighted and various technologies are in good progress with ample research and publications (da Costa Lopes et al. 2016). The main objective of SCF is applicable in fields like micro-encapsulated particles and aerogels constituting silica particles (Bu et al. 2016). There are different techniques like impregnation and supercritical extraction through gaseous and supercritical fluids (Padrela et al. 2018).

The physical properties of SCF can be similar to any fluid which has critical pressure and temperature that can change physical state (Gorbaty and Bondarenko 2017). For example, CO_2 can behave as an SCF at a temperature of 31.1° and atmospheric pressure of 73 whereas water gains SCF properties at a temperature of 374.1° and pressure of 218.3pressure (Gandhi et al. 2017). The SCF effects on solubility and viscocity depend on temperature, and exceptions like porosity make SCF a unique from other solvents (Kumar et al. 2017). The physical properties are widely exploited in the SCF (Aliev and Abdulagatov 2017). The phase equilibrium of solid substance is more significant compared to gaseous solvents like air and it is measured by EOS (Eckert et al. 2017). The typical application of SCF extraction was processing of coffee using SCF (Hrnčič 2018).

Valencia is a plant product which have pharmaceutical and nutraceutical characters, which is also considered as SCF plant. For the extraction, aerogels are made with solvent exchange and pressurization. SCFs are widely used in material synthesis (Aliev and Abdulagatov 2017). There are different coating methods which are used globally with various coating designs (Song 2017). The various types of coating methods like basic dimensional analysis between water and Sc-CO_2 use chitosan as an encapsulant in chitosan-DMSO-CO_2 system encapsulated TiO_2 (Hao et al. 2017). Application of SCF are in impregnation of NSAIDs, polymeric matrix development and extraction of green biomass by counter current immiscible fluid extraction (Chen et al. 2019).

Super critical extraction has diverse applications in extraction of cannabinoids in medical use for controlled delivery using sorptive process and waste management and SCF in cosmetics by algae tissue engineering. Such applications are TiO_2 and Cao encapsulations in chitosan for self-heating applications (Freund et al. 2018). Pressure and temperature are the key determinants for SCF, and for rocket fuel, the warm water is not SC, so pressure and temperature make it SCF, and pre-polymer is used for encapsulation. Chinese SCF plant was cheaper compared to valencia big plants (Jovel et al. 2017). *Elsholtzia ciliata* is a bacteria whose extract acts as a supercritical fluid used in the antimicrobial delivery for infections like fever, colds, and gastric and renal disorders; this supercritical extract has both antimicrobial and antioxidant activity (Ma et al. 2018).

Bacterial colonization in body tissues create infections by forming biofilms; scaffolds that are synthetically made have porous properties that give them the ability to regenerate dead tissues by carrying antimicrobials like vancomycin that are processed using supercritical carbon dioxide foam (Garcia-Gonzalez 2018). Antimicrobial extracts of paraguariensis leaves and fruits are made using supercritical carbon dioxide, and compressed propane gas showed to reduce the minimum inhibitory concentrations of *Escherichia coli*- and *Staphylococcus aureus*-related infections (Fernandes et al. 2017). The supercritical oil extracts from citrus seeds and peels are proved to have antimicrobial properties when modified with supercritical carbon dioxide for antimicrobial by-products (Ndayishimiye et al. 2018). Herbal extracts have always proved to have antimicrobial properties as well as antioxidant activity; supercritical extracts obtained from these herbs are used in the preservation of food (Vieitez et al. 2018). The expression of the antimicrobial peptide genes will initiate the pathogenesis of periodontal diseases; the higher the expression of these genes, the more chronic the disease will be (Jourdain 2018).

The goal of drug delivery is to find a useful alternative for traditional oral drug regimens, which are worsening the viral infection to chronic disease due to lack of medication adherence and bioavailability in the patients. The multidrug resistance of bacteria is the main problem addressed by nanotechnology in drug delivery (Table 17.2). The controlled level of infection can be maintained for an extended period using the nano-formulations that can achieve targeted drug delivery to deeper tissues. The adolescent patients have increased the scope of complete recovery from the infection using nanomedicines compared to older patients. Patient medication adherence challenges and side effects can be minimized to a greater extent by adding these formulations to the drug regimen.

Nanoparticle formulation can be prepared using nanocarrier like gold or a polymer which is attached to the different combinational drug molecules on the surface of the nanoparticle. This nanoparticle formulation is administered in subcutaneous route to the HIV patient for prolonged bioavailability and extended drug release into the lymph tissues where the viral fragments are mainly located for future relapse of

Table 17.2 Drug resistance in treating biofilms

Gene	Function	Drug
P. falciparum chloroquine-resistance transporter (Pfcrt)	Reduces chloroquine levels in the digestive vacuole.	Chloroquine
P. falciparum multidrug resistance 1 (Pfmdr1)	Member of the ABC family of transporters. Associated with increased chloroquine resistance in the presence of Pfcrt	Chloroquine, Mefloquine
P. falciparum multidrug resistance protein (Pfmrp)	Transporter protein located in the parasite plasma membrane that regulates the movement of toxic metabolic products.	Quinoline
Target enzymes dhfr, dhps	4 mutations in dhfr and 2 mutations in dhps are associated with clinical resistance to antifolate combination therapies.	Sulfadoxine Pyrimethamine

infection cycle (Aziz et al. 2018). The formulation is made with cheap and reliable excipients and adjuvants to market it as a cost-effective medication for HIV (Cheng et al. 2018). Through this strategy, a new method of diagnosing and treating the virus in the lymph nodes can be possible even if the plasma viral load is zero (Bowen et al. 2018).

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