# Chapter 16
# Mesoporous Silica Nanomaterials as Antibacterial and Antibiofilm Agents

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## Contents



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**Abstract** Antimicrobial agents are vital to fight infectious diseases which are pooling up day by day. The treatment of microbial infections is increasingly getting convoluted by the ability of microorganisms to develop resistance towards a wide range of antimicrobial agents. Resistance is most often an evolutionary process taking place either through lateral gene transfer or during antibiotic therapy, thereby contributing to the emergence of diseases that were under good control for many years.

Further, drug resistance enforces high-dose administration of antibiotics leading to adverse side effects and intolerable toxicity. This has prompted the search for alternative strategies to treat microbial infections either by controlling their growth or by preventing the formation of bacterial biofilms. Recently tremendous developments in the field of nanotechnology have been recorded with nanoscale materials emerging as novel antimicrobial agents.

Nanotechnology is an interdisciplinary area of science with promising interests across the globe steering into nanoindustrial revolution with innumerable applications. The enormous diversity of the nanoparticles that exhibit new and enhanced size-dependent properties compared to their bulk material are being exploited as antimicrobials for treating infectious diseases. Numerous nanodevices like carbon nanotubes, quantum dots, and polymeric micelles have been reported as potential antibacterial candidates. In the present scenario, mesoporous silica nanoparticles (MSNs) are emerging for their widespread applications as antibacterial and antibiofilm agents. MSNs are constituted of an amorphous silica matrix with ordered porous molecular sieves characterized by periodic arrangements of uniformly sized mesopores (diameter between 2 and 50 nm). MSNs with uniform and tailorable pore dimensions with high surface areas are currently being employed in a number of applications such as wastewater remediation, indoor air cleaning, bio-catalysis, drug delivery, $CO_2$ capture, bioanalytical sample preparation, pervaporation membrane improvement, etc. MSNs with their unique properties like chemical stability, surface functionality, and biocompatibility are used in quorum quenching as well as prospective antibacterial agents. The present book chapter deals with MSNs and their applications as possible antibacterial and antibiofilm agents.

**Keywords** Mesoporous silica nanoparticles · MSNs · Antibacterial · Antibiofilm · Biocompatibility

## 16.1 Introduction

Antimicrobial agents are vital to fight infectious diseases which are pooling up day by day. The treatment of microbial contaminations is progressively getting convoluted by the ability of microorganisms to develop resistance towards a wide range of antimicrobial agents (Aziz et al. 2016). Further drug resistance enforces enhanced-dose administration of antibiotics rendering contrary side effects. It leads to the

search for novel approaches to treat microbial infections either by controlling their growth or by preventing the formation of bacterial biofilms. Recently tremendous developments in the field of nanotechnology have been recorded employing nano-sized materials as newer emerging antibacterial agents (Aziz et al. 2016).

Nanoscience is an area of science with full of promising interests across the globe steering into nanoindustrial revolution with innumerable applications in catalysis, cosmetics, diagnostics, and targeted drug delivery systems (Juan et al. 2015; Prasad et al. 2016, 2017). The enormous diversity of the nanoparticles with their novel and improved size-dependent possessions compared to their bulk material is being exploited for treating infectious diseases. Numerous nanodevices like carbon nanotubes, quantum dots, and polymeric micelles have been reported as potential antibacterial candidates (Albanese et al. 2012; Lakshmi et al. 2017). However, recent trends involved molecular manufacturing of nanomaterials studied under molecular nanotechnology.

Molecular nanotechnology involves theoretical manipulation of single molecules to produce the desired structure or an atom in a finely controlled way, using the principles of mechanosynthesis operating on a nanoscale. Particle size, porosity, and surface properties of nanomaterials can be certainly monitored to match the physicochemical characteristics of guest components with intended applications (Bayir et al. 2018). Further by conjugating the functional groups, stimuli-sensitive molecules and targeting molecules to both the inner and outer surfaces of the silica pores lead to the improvement of disparity and loading and subsequent release of transporters to targeted places (Chan et al. 2016).

Nanoporous materials can be made up of an amorphous or crystalline framework of cage type or cylindrical structures with void spaces. According to IUPAC, based on pore size, nanoporous materials are of three types, namely, macroporous (pore sizes between 50 and 1000 nm), microporous (0.2–5 nm), and mesoporous (pore size ranging between 2 and 50 nm). Porous polymeric beads that allow easy access to the internal pores at relative ease are the macroporous materials. Carbons and amorphous glasses, zeolites, and metal-organic frameworks (MOFs) with high thermal stability and catalytic activity are examples of microporous materials which are employed in cracking processes and also be served as ion exchange media, gas separation, and drying agents. MOFs are currently considered as the fast-growing classes of microporous solids. Comparatively mesoporous materials with an intermediate pore size such as porous inorganic solids with the controllable large internal surface area are currently exploited at an atomic, molecular, and nanometer scales leading to alternate disease treatment strategies (Chen et al. 1993).

Mesoporous silica nanoparticles (MSNs) with their well-known applications as antibacterial and antibiofilm agents are constituted of a porous amorphous silica matrix with uniformly sized mesopores arranged periodically in the form of a molecular sieve (diameter between 2 and 50 nm). MSNs with their unique properties like chemical stability, surface functionality, and biocompatibility are used in quorum quenching as well as prospective antibacterial agents (An et al. 2016). The present book chapter deals with MSNs and their applications as possible antibacterial and antibiofilm agents.

## 16.2 Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica is a very popular inorganic nanomaterial made up of two most copious (silicon and oxygen) elements in the environment, existing as silicon dioxide ($SiO_2$). Silica molecule exists in a complex of interconnected silicon atoms in a tetrahedral arrangement linked covalently with four oxygen atoms. Based on extensive physicochemical, ecotoxicological safety, and epidemiology data, it is evident that there were no ecological or health hazards allied with these materials. Further US FDA has regarded silica as a material that is "generally recognized as safe" and has been approved by the EU for their usage in cosmetics and food additives (Bobo et al. 2016).

The discovery of silica nanoparticles dates back to late 1970s. Silica nanoparticles with 4.6–30 nm pores are arranged in an hexagonal array termed SBA (Santa Barbara Amorphous material) produced by the California University, Santa Barbara (Sakai-Kato et al. 2011). Later MSNs were synthesized independently by Mobil Corporation laboratory, Japan, in 1997 under the trade name MCM (Mobil crystalline materials) or Mobil composition of matter (WU et al. 2016). Table 16.1 shows some of the morphologies of mesoporous silica (MS) and their associated materials (Bagwe et al. 2006).

MSU-n (Michigan State University silica), KIT-1 (Korean Institute of technology silica), and FSM-16 (folded sheet-derived mesoporous silica), HMM-33 (Hiroshima Mesoporous Material-33), TUD-1 (Technical Delft University), and COK-12 (Centrum voor Oppervlaktechemie en Katalyse/Centre for Research Chemistry and Catalysis) are synthesized newly with varied sizes and pore symmetry (Fruijtier-Pölloth 2012). Tozuka et al. (2005) have demonstrated the usage of quaternary ammonium surfactants with layered polysilicate kanemite as a template for FSM-16, which is used in pharmaceutical applications besides as an adsorbent and catalyst.

Currently MSNs with a wide range of pore geometries (hexagonal, cubic, cylindrical) and particle morphologies (discs, spheres, rods) have been synthesized and exploited in the field of medical sciences (Fig. 16.1). MSNs have a honeycomb-like structure with narrow pore size distributions and high surface areas (>500 $m^2/g$).

**Table 16.1** List of mesoporous silica nanoparticles

| S. no | MSN type | Pore symmetry | Pore volume ($cm^3/g$) | Pore size (nm) |
|---|---|---|---|---|
| 1 | SBA-11 | 3D cubic | 0.68 | 2.1–3.6 |
| 2 | SBA-12 | 3D hexagonal | 0.83 | 3.1 |
| 3 | SBA-15 | 2D hexagonal | 1.17 | 6–0 |
| 4 | SBA-16 | Cubic | 0.91 | 5–15 |
| 5 | MCM-41 | 2D hexagonal | >1.0 | 1.5–8 |
| 6 | MCM-48 | 3D cubic | >1.0 | 2–5 |
| 7 | MCM-50 | Lamellar | >1.0 | 2–5 |
| 8 | KIT-5 | Cubic | 0.45 | 9.3 |
| 9 | COK-12 | Hexagonal | 0.45 | 5.8 |

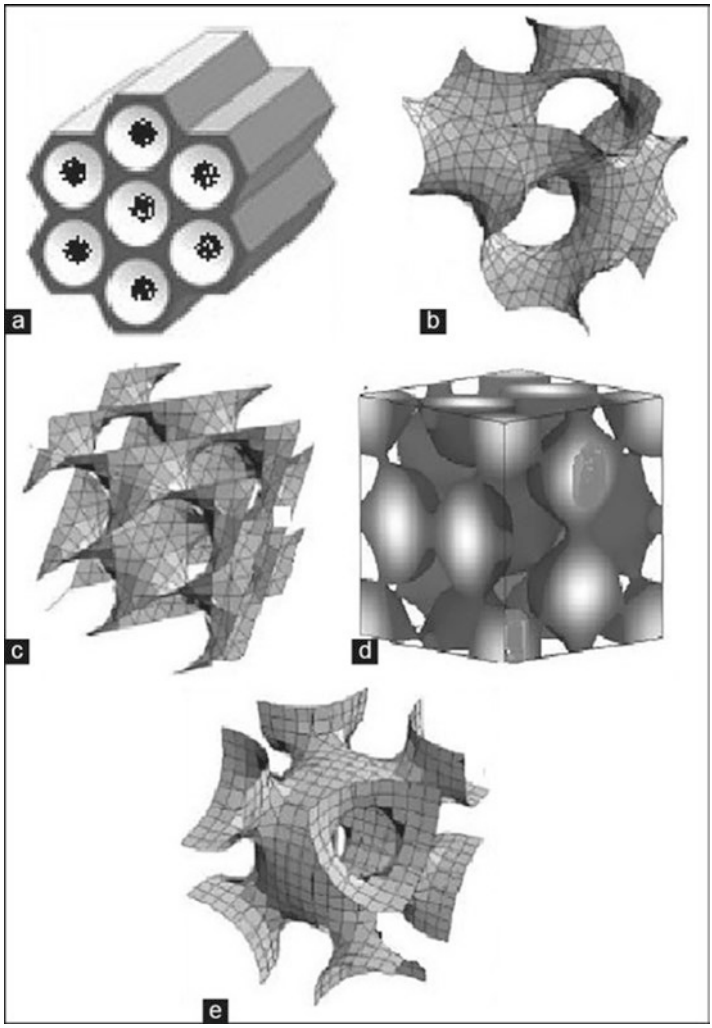


**Fig. 16.1** Shapes of MSNs. (**a**) Hexagonal 2D, (**b**) cubic bicontinuous, (**c**) bicontinuous cubic, (**d**) cage type, (**e**) cage type, respectively

The strong Si-O bonds render them stable against external mechanical stress and degradation thereby making them unique and significant in the field of biotechnology. Mesoporous materials have many advantages such as:

- Tunable pore diameter
- The unique, customizable mesoporous structure
- Low cytotoxicity
- Better binding ability with organic ligands
- Enhanced surface properties to bond with therapeutic molecules

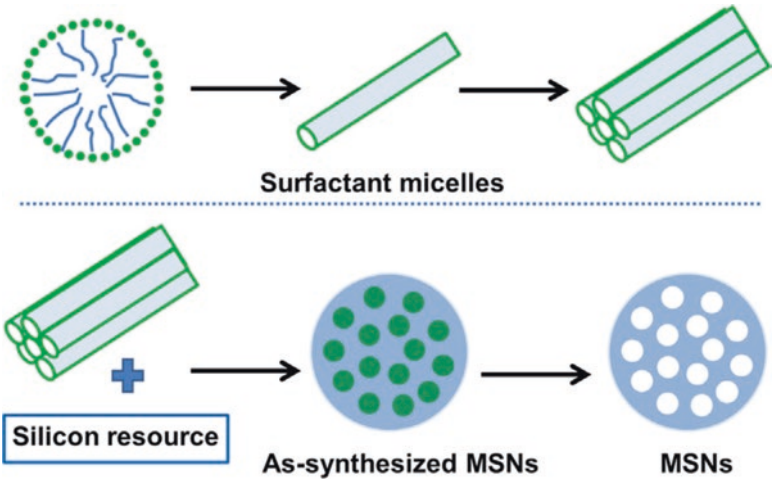


**Fig. 16.2** Schematic representation of MSNs synthesis

- Uniform adsorption and subsequent drug delivery
- Biocompatibility with large pore volume to surface area
- Ecofriendly and regarded as safe

Owing to the above advantages, MSNs were exploited over a wide array of applications in industrial, therapeutic, food, and cosmetic industry. Today, MSNs have been used as adsorbents, drug delivery vehicles, biosensor, bioimaging and biosignal probes, and other critical diagnostic applications (Hom et al. 2010; Grumezescu et al. 2013).

## 16.3 Synthesis of MSNs

The synthesis of silica nanoparticles can be carried out by a wide range of approaches which can be by physical techniques (e.g., sputtering, sonochemical, and microwave-assisted), mechanical methods (e.g., ball milling and attrition), and chemical routes (precipitation, micelles, solvothermal, and vapor phase synthesis). The mesoporous particle synthesis can be done by a spray drying method or simple sol-gel method with slight modifications in their procedures (Ashraf et al. 2015).

Currently, MSNs are synthesized (Fig. 16.2) with a template made of micellar rods reacting with tetraethyl orthosilicate (TEOS), which results in nanosized spheres or rods consisting of a regular arrangement of pores. Presently TEOS is replaced by a better precursor MPTMS (3-mercaptopropyl trimethoxysilane) which ensures uniform sphere formation and also reduces the chance of aggregation. Further, the rate of aggregation can be completely reduced either by capping or plating of the MSNs with gold nanoparticles (Paul et al. 2017; Cicily 2017).

**Table 16.2** List of chemical constituents used in the synthesis of MSNs

| Substrate | Function |
|---|---|
| N-dodecanonyl-β-alanine | Surfactant with an amino acid residue |
| CTAB | Increase water solubility of hydrophobic ligand |
| PEG | Improve biocompatibility and functional characteristics of silica matrix |
| Tween 80 | Surfactant |
| PVA | Settle down gel in THEOS-containing solution |
| PEO | Induce hydration PEO/sol ratio regulates size |
| Sodium hydroxide | Catalyst |
| Hydrogen fluoride | Catalyst |
| Hydrogen chloride | Catalyst |
| Nonionic triblock copolymer | Structure-directing agent |
| Trihydroxysilylpropylmethyl phosphate | Prevent-interplace aggregation |
| Ammonium nitrate | Surfactant removal |
| Methanol | Solvent in TMOS |
| Ethanol | Solvent in TEOS |

*CTAB* N-cetyl trimethyl ammonium bromide, *PEG* Polyethylene glycol, *PVA* Polyvinyl alcohol, *PEO* Polyethylene oxide, *TMOS* Tetramethoxysilane, *TEOS* Tetraethyl orthosilicate, *MSN* Mesoporous silica nanoparticles, *THEOS* Tetrakis (2-hydroxyethyl) orthosilicate, *SBA* Santa barbara amorphous

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The following are the various chemical constituents employed in the formation of mesoporous silica nanoparticles (Table 16.2).

The mechanism of MSN synthesis is a complex multistep protocol that involves extreme conditions like high temperature, pH, and use of highly toxic precursors. Till date, three simultaneous technologies for the synthesis of MSNs, such as the invention of "Stober" synthesis for monodisperse nanoparticles (in 1968), as well as the other two methods including MCM-41 (in 1992) and SBA-15 (in 1998) have been equally exploited. These three protocols collectively received more attention, confirming their widespread usage in the synthesis of MSNs employed in biomedical research for drug delivery and toxicity studies. The versatile applications of MSNs can be attributed to their unique mesoporous ordered structures with large pore volumes and high internal surface areas (Moller et al. 2007).

## 16.4 Characterization of MSNs

Characterization of synthesized MSNs was carried out by microscopic (Fig. 16.3) and spectral analysis. MSNs were studied through transmission electron microscopy (TEM) with bright field imaging operating at 200 kV. TEM is useful to determine the pore characteristics as well as the shape and dimension of the particles. Micrograph Digital TM software is used to measure pore size and the particle

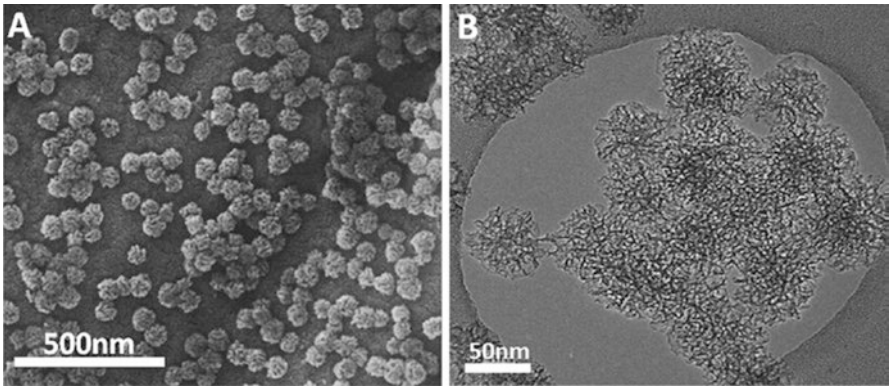


**Fig. 16.3** (**a**) MSN SEM image and (**b**) transmission electron microscopic image of MSNs (https://doi.org/10.1155/2014/176015)

characteristics, whereas channel diameters were studied by line plot display (Chan et al. 2016). Scanning electron microscopy reveals the topography of the MSNs where the particle morphology and pore directions were filmed. Recent studies through SEM analysis showed bacterial cell elongation to nearly twice to tenfold increase in the presence of MSN particles supporting the hypothesis of cell division impairment by mesoporous silica nanoparticles in bacterial population possibly by interacting with FtsZ (Jorge et al. 2016). Crystallographic symmetry of MSNs by XRD analysis is not very clear and ambiguous due to similar short-range peaks which might overlap and appear at low angles (Huang et al. 2013). Further the MSNs were also analyzed by FTIR spectroscopy using KBr pellets which are used to identify organic and inorganic materials and their bonding patterns by measuring the absorption peaks of infrared radiations (Cicily 2017).

## 16.5 MSNs as Antibacterial Agents

Antibacterial agents are chemical constituents which can selectively kill or control the growth of bacterial population, without affecting the surrounding tissue. In general, the agents employed to retard the growth of the bacterial strains are referred to as bacteriostatic, while those which kill the organism are called bactericidal drugs. Antibacterial agents are principal constituents essential to combat infectious diseases. Currently numerous synthetic and semisynthetic chemical substances like β-lactams, aminoglycosides, tetracyclines, sulfa drugs, etc. are employed to treat a wide variety of bacterial diseases. However despite the incidence of a wide series of antimicrobials to fight infections, there is still a tremendous need for the potential novel antibiotics, since most of the antibiotics rendered are ineffective and will have to be used in higher doses due to the emergence of resistance in bacteria.

Resistance in bacteria is inheritable and is acquired either through vertical or lateral gene transfer and which might be chromosomal or extra chromosomal (plasmids). Today the emergence of superbugs such as MRSA (methicillin-resistant *Staphylococcus aureus*), MDR-TB (multidrug-resistant TB), of late VRSA (vancomycin-resistant *Staphylococcus aureus)*, etc. in the medical world is due to the resistance conferred by the bacteria through use and abuse of antibiotic therapy (Worthington et al. 2012). It has been recently noted that half a million of new incidences of MDR TB are recorded annually (Webster and Seil 2012). Further development of new degradative enzymes such as β-lactamases (NDM-1) in certain bacterial strains has led to the failure of an entire set of β-lactam antibiotics which constitute a major share of antibacterial agents (Xia et al. 2009; Ventola et al. 2015). Therefore drug resistance not only enforces the usage of high doses of synergistic drugs but also ends up with adverse side effects.

Drug resistance has impelled the search for development of substitute strategies to treat microbial infections. Among others, nanoscale materials have been synthesized as novel antimicrobial agents with numerous classes of nanosized carriers for treating infectious diseases (Allahverdiyev et al. 2011). Nanomaterials offer enhanced properties to traditional organic antibacterial agents and can control the resistance property of bacterial superbugs. Nanomaterials exert antimicrobial activity by accumulating on the cell membranes, affecting their permeability and transport mechanisms thereby leading to cell leakage and eventual cell death (Aziz et al. 2014, 2015, 2016, 2019). Further nanoparticles in the presence of oxygen trigger the generation of ROS (reactive oxygen species) such as $OH^-$, $O_2^-$, and $H_2O_2$, disrupting the normal metabolic functions of microbes leading to cell death (Hudson et al. 2008). Figure 16.4 depicts the toxic effects of nanoparticles on bacterial structures such as capsule (polysaccharide), cell wall (peptidoglycans), cell membranes, ribosomes (protein synthesis), nucleic acid synthesis (DNA damage), etc. (Kar 2016).

Two major studies, namely, Sahoo et al. (2015) and Tarn et al. (2013), have suggested the exploitation of silica nanoparticles as potential antimicrobials with selective toxicity against bacteria. Later silica-coated silicon nanotubes and silver-doped silica nanoparticles with their biocompatibility and chemical and high thermal stability have proved to display exceptional antimicrobial activity against bacterial populations. The ability of MSNs to encapsulate with inorganic materials (silver, gold, palladium, or iron oxide) creating nanocrystals with a yolk/shell architecture gives them additional functionality in binary system against resistant bacterial strains (Cicily 2017). Trewyn et al. (2007) have synthesized MSNs coated with bactericidal cationic surfactants to treat bacterial diseases, while Juan et al. (2015) used metal nanoparticle coatings on MSNs for microbial infections. The silver nanoparticles encapsulated with MSNs (Ag@MESs) in a core shell structure is used as the best source of antimicrobial silver ions where hydrophobic silver nanocrystals are dispersed uniformly without aggregation by the mesoporous silica shell lattice structures (Sen Karaman et al. 2016).

Mesoporous silica nanostructures are considered as one of the forerunners among nanoparticles to be exploited as antibacterial agents which substitute the broad

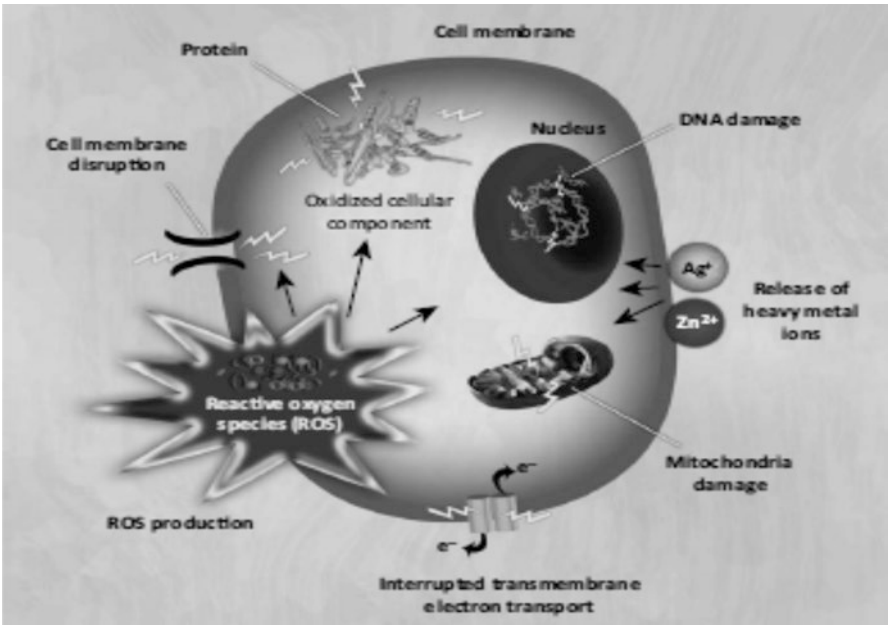


**Fig. 16.4** Toxicity mechanisms of antibacterial nanoparticles (NPs)

usage and amassing of metal nanoparticles in the environment. Literature on MSNs in a wide variety of sizes, shapes, and versatile applications showed explosive usage in biomedical research. Also, their characteristic high surface area ($\geq$1000 $m^2/g$) to volume ratio and adaptable surface functionalization with controlled release of incorporated agents makes them efficient lead molecules to combat antibacterial resistance and to subsequent eradication of biofilm formations (Cheng et al. 2016). Engaging mesoporous silica nanostructures as antibacterial agents is eco-friendly and environmentally safe, since they are easily biodegraded into undisruptive products in the presence of water. Recent studies on mesoporous silica particles are mainly on the drug loading and drug delivery mechanisms owing to their biocompatibility and low cytotoxicity. MSNs with polymer coatings of proteins, DNA, RNA, antibiotics, and other biomolecules are a great choice as carrier vehicles in therapeutic nanomedicine (Wang et al. 2010).

### *16.5.1 Silver Ion ($Ag^+$) and Chitosan-Doped Mesoporous Silica Nanoparticles*

Synthesis of multifunctional MSNs was carried out by dispersing MSNs doped with silver ions using chitosan. Chitosan is used for surface modifications, to prevent the leakage of silver ions, and to increase the dispersibility of MSNs. The antimicrobial

effectiveness was found to show a profound effect on the tested pathogens twice when compared to the normal Ag NPs (Sen Karaman et al. 2016).

### *16.5.2 Surface Modifications of MSNs to Enhance Antimicrobial Activity*

It has been identified that nude MSNs showed mild activity or no activity against microbial strains as such their surface functionalization has been improved by grafting methods to develop ordered secondary structures with new exciting antibacterial and antifungal properties. Polypeptide polymer-grafted mesoporous silica nanoparticles displayed excellent antimicrobial activity against clinical pathogens.Poly-L-lysine which was covalently attached to the surfaces of MSNs using polyvinyl benzyl tributyl phosphonium chloride is responsible for effective destruction of the peptidoglycan in the cell wall resulting in bacterial cell lysis.

Wang et al. (2015) were successful to synthesize MSNs (2.5 nm) with high surface area and maximum loading ability for antibiotics like doxorubicin or gefitinib. Jorge et al. (2016) have developed the surfactant template method to optimize the parameters controlling pore size, particle dimension, and surface modifications. XRD analysis along with FTIR spectra reveals the presence of the characteristic functional groups adsorbed to the surface of MSNs (Paul et al. 2017).

Recently essential oils (EO) encapsulated into MSN matrices were intensively exploited in antimicrobial applications and considered as ideal substances to stabilize volatile compounds and to guarantee their systematic release (Zhao et al. 2017). Encapsulation of EOs into the MSNs enhances their half-life, prolonging their circulation time followed by controlled delivery. Sousa et al. (2014) have synthesized silica mesoporous nanostructures loaded with EOs using multiple emulsion processes which are effective against different clinical bacterial pathogens. However there was no systematic evidence addressing how surface modifications could control the antibacterial activities of MSNs, but nonetheless previous studies favored surface modifications of MSNs for enhanced antimicrobial activity (Ispas et al. 2009).

### *16.5.3 Mode of Action of MSNs*

The mesoporous silica nanoparticles with controllable structural parameters besides huge surface area and high porosity are the ideal antibacterial agents. The mode of action of MSNs on bacteria is by damaging the cell membrane integrity through hydrogen bonding between bacterial lipopolysaccharides and surface hydroxyl groups of MSNs and also by adsorption of membrane lipid molecules onto the MSNs surface. The exact mechanism was attributed to the electrostatic interaction

between the cationic head groups of the hollow MSNs with the phosphate groups of the microbial cell walls, thereby leading to the outflow of electrolytes causing bacterial lysis (Sharmila et al. 2016). Besides membrane damage, membrane gelation and fluidization with MSN attachment are some of the possible destruction mechanisms. Conversely MSN concentration gets lowered rendering them less effective in the presence of bacterial debris, causing precipitation of MSNs, which can be prevented by constant shaking in a shaking incubator.

### *16.5.4 Biocompatibility of Mesoporous Silica Nanoparticles*

MSN biocompatibility as drugs or drug vehicles is mainly based on their cellular uptake and cytotoxic properties, which can be studied using fluorescence and confocal microscopy. Karin Möller and Thomas Bein (2017) have demonstrated that the biocompatibility of MSNs depends on the particle shape, size, surface chemistry, and the presence of functional ligands. Saladino (2016) synthesized a series of antibiotic-loaded MSNs with specific toxicity to kill bacterial populations. Recently MSNs were surface coated by vancomycin (MSNs⊂Van) for selective detection and killing of clinically pathogenic bacteria (Chun Xu et al. 2018).

## 16.6 Antibacterial Tests

Advances in molecular biology combined with biochemical, serological, staining, and microscopic techniques have led to the successful identification and culturing of microorganisms. Bacteria may be exposed to nanometer-sized particles of sediment in their natural environment without adverse effects. However, the synthetic nanoparticles interact with bacteria acting as antimicrobials. To understand the impact of nanomaterials on the physiology and metabolism of the microorganisms, in vivo measurements of bacterial communities can be made where they are susceptible to nanomaterial exposure. For example, the normal flora of the skin may be exposed to large quantities of nanomaterials that are incorporated into topical preparations including sunscreen and cosmetics (Kar 2016). However, measuring whole communities of bacteria is problematic and cumbersome. Further, most environmental bacteria are not easily cultured in the laboratory, and culture-independent techniques, including DNA sequence-based identification, are semiquantitative. As such accurate in vivo measurements are difficult to achieve. The great diversity of bacterial communities, both spatially and temporally, might further make data misrepresentative in small-scale studies. The alternate approach is to study nanoparticle interactions with a well-characterized model system that is easily manipulated in the laboratory and has an international standard that can be made consistent between research groups. Different antibacterial tests can be carried out under in vitro conditions such as the following.

### *16.6.1 Agar Diffusion Method*

Agar cup plate method or Kirby-Bauer disk diffusion method is the most common preliminary test to study the antibacterial activity under in vitro conditions. The freshly revived bacterial cultures (18 h old) were inoculated in a nutrient medium and were transferred into Petri plates. Petri plates thus prepared were incubated at 30 °C for 16–18 h and examined for antibacterial activity by measuring the zones of inhibition (Kavanagh 1992).

### *16.6.2 Determination of MIC by Dilution Broth Method*

Minimum inhibitory concentration or MIC was determined either by macrodilution or microdilution broth method using McFarland nephelometer standards. Multifunctional microplate reader is used to determine the bacterial viability (Tecan Infinite M200) at 600 nm OD (Obeidat et al. 2012).

### *16.6.3 Bacterial Testing of the Growth Curve*

Bacterial growth rate was determined by incubating the cultures in a shaking incubator at 200 rpm at 37 °C and later the percentage of growth inhibition was calculated by % inhibition = (OD of untreated – OD of MSN treated) OD of untreated ×100 (Balouiri et al. 2016).

## 16.7 MSNs as Antibiofilm Agents

The major drawback of antimicrobial agents is their failure to fight against resistant microbial strains that can produce biofilms. Biofilms are formed by a complex microbial community glued to a solid surface, emancipating an extracellular polymeric matrix (EPM) that covers and protects the bacterial cell community (Fig. 16.5). Of late it has been identified that many microbes frequently form biofilms around commonly used medical devices resulting in appalling diseases. Common clinical pathogens like *S. aureus, E. coli, P. aeruginosa,* etc. are found to form biofilms on catheters, medical shunts, prosthesis, breast implants, orthopedic devices, surgical equipment, etc. causing chronic sinusitis, burn wounds, urinary tract infections, biliary tract infections, prostatitis, and other trauma infections. Similarly *E. faecalis, Proteus mirabilis, K. pneumoniae, S. mutans* were also reported to form biofilms on medical devices leading to serious nosocomial infections (Percival et al. 2008).

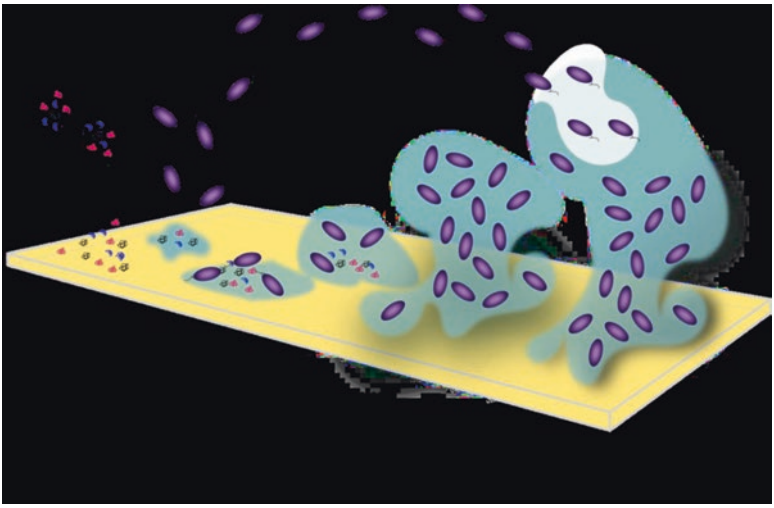

**Fig. 16.5** Biofilm growth cycle

Previously control of bacterial contamination and biofilm formation was carried out either by physical (UV) or chemical (flushing, chlorination) disinfection. Nowadays, surface functionalization with broad-spectrum antimicrobial coatings is effective in killing or controlling the bacterial infections (Renwick et al. 2016). The need for novel drugs which can prevent bacterial colonization and biofilm formation without promoting resistance has led to the following developments:

- Micro-topographic surfaces: Nano-engineered materials with surface topography were developed to prevent bacterial adhesion and biofilm formation. Anti-adhesive coatings using hydrophilic polymers and their derivatives (hyaluronic acid, polyethylene glycol, heparin, etc.) gained much attention recently for the development of bacterial repellent and anti-adhesive surfaces (Reema et al. 2018).
- Antimicrobials with covalently immobilized surfaces such as cationic QACs (quaternary ammonium compounds) and phosphonium moieties were identified as contact-killing surfaces. However their antimicrobial activity diminishes in the presence of bacterial debris (Portin 2012).
- Biocide releasing antimicrobials: Metal nanoparticles (NPs) with surface leaching antibiotics have been designed for a specific delivery of the bactericidal agents into the targeted zones. But leaching materials short lifetime is the major limitation of these antibacterial/antibiofilm agents (Ventola 2015).

Despite of the above innovative strategies, there is still a need to develop antibiofilm agents considering drug resistance and combination therapies. Recent strategies include the use of surface modified medical devices with designs of antibiofilm coatings developed either by graft polymerization, layer-by-layer (LbL) assembly, self-assembled monolayers, or surface covalent modifications. Of all the above methods, LbL deposition of surface coatings with bactericidal and anti-adhesive

properties without the need for chemical modifications and cross-linking agents has proved successful (Song et al. 2017).

### *16.7.1 MSNs for Controlling Bacterial Biofilms*

Recently, mesoporous silica nanoparticles with their unique physicochemical characteristics such as easy functionalization, thermal stability, excellent biocompatibility, and low cytotoxicity compared to their solid/nonporous counterparts have gained much attention (Spataru et al. 2016). Single or mixed populations of Gram-positive bacteria (e.g., *S. aureus, Bacillus* spp., *Streptococcus* spp.) and Gram-negative bacteria (e.g., *E. coli, Serratia* sp., *Pseudomonas* spp.) usually result in biofilm formation leading to persistent microbial infections that are resistant to antibiotic therapy. Antibiotics which were earlier efficient against bacterial species may not be currently effective against biofilm embedded bacteria (Merezeanu et al. 2016). Nanomaterials served as a potential platform to solve the limitations of traditional therapies in preventing biofilm formations or in treating the preexisting biofilm infections. Various metals, metal oxides, hybrid polymer, and biopolymer silica nanomaterials have been recommended as next-generation antimicrobials with maximum activity against biofilm-resistant bacterial populations (Zhang et al. 2012).

Biofilm eradication needs competent penetration and accumulation of the nanoparticles into the biofilm complex. The interactions between MSNs and biofilms are complex, and upon attachment, the silica nanoparticles (<10 nm) diffuse easily through pores in the biofilm structure affecting the membrane integrity. They also inactivate the surface proteins developing into spatiotemporal aggregation patterns among bacterial population resulting in cell lysis and eventual biofilm destruction. MSN deposition within the biofilms and their subsequent action depend on the heterogeneity of the charges and electrostatic interactions across the entire biofilm structure. The cationic quantum dots were able to pass the matrix barrier and accumulate inside bacteria, whereas hydrophilic groups affect mainly the EPM surrounding the cells (Lee et al. 2016). The penetration of MSNs into the bacterial biofilm matrix depends on the size of the EPM pores, high repulsive forces between oppositely charged NPs and biofilm matrix components, hydrophobicity of the surrounding environment, and existence of chemical gradients within the EPM (extracellular polymeric matrix). Further MSN surface capping with small ligands or polymers (polysaccharides, PEG, glycolipids) enhances stability and surface functionality (Ammer et al. 2016).

The ability of mesoporous nanomaterials to penetrate the EPM makes them efficient against resistant bacterial clones within the biofilm depths (Malone et al. 2017). MSN coatings on medical devices recently proved successful in reducing bacterial colonization and biofilm formation. Techniques such as UV irradiation, ultrasound sonochemistry, and LbL assembly are used to develop MSNs incorporated with functional materials or coatings (Li et al. 2012). Recent reports of

antibacterial MSNs with cationic biopolymer loadings such as aminocellulose or thiolated chitosan have proved more successful than the biopolymer itself in destroying planktonic bacteria affecting the cell membrane integrity (Li and Wang 2013). Further essential oils (EOs) are definite candidates to decrease the selection of resistant bacterial species, but are rendered inefficient due to their high hydrophobicity and volatility. To protect and preserve the effects of these active substances (EOs), the microencapsulation technique has been developed by loading these bioactive volatile substances into mesoporous silica nanoparticles, thereby converting them into strong chemosterilant compounds (Zhang et al. 2016).

Amino-decorated $SiO_2$ NPs were synthesized which can easily penetrate and eradicate pathogenic biofilms (*P. aeruginosa* and *E. coli)* through regulated release of bactericidal components (Merezeanu et al. 2016). The antibiotic-encapsulated MSNs (vancomycin, kanamycin) were synthesized for effective biofilm degradation of *S. aureus* (Qi et al. 2013). Further synchronized application of matrix-degrading enzymes like lysosomes with mesoporous nanomaterials has also been proposed as an alternative strategy to facilitate the easy penetration of MSNs to eliminate biofilms (Gupta and Variyar 2016).

### *16.7.2 Mechanisms of MSNs Against Bacteria*

The mechanisms of MSNs toxicity towards bacterial biofilms are vague and have to be understood completely. Primarily the nanosilica materials adhere to the membranes of bacteria in the biofilm cloud through electrostatic interactions and disrupt the integrity of the bacterial membrane network and the entire biofilm complex eventually. The oxidative stress induction generally triggers nanotoxicity through free radical formation. Once inside the cells, the metallic MSNs, either by themselves or by the released ions, will interact with proteins or DNA or RNA molecules, affecting the vital metabolic activities in the microbes. The silica nanomaterials with preferential binding sites to phosphorus- and sulfur-containing proteins and enzymes modify their activity by generating ROS (reactive oxygen species) inducing cell death ultimately. Furthermore, mesoporous silica nanoparticles with their high surface-area-to-volume ratio help to maximize the bioavailability of the loaded antimicrobials during their exposure to microbes (Balaure et al. 2017).

### *16.7.3 Lysosome-Coated MSNs*

Lysosome-coated MSNs are currently employed as potential antibiofilm agents due to their competent antimicrobial activity. They exhibit minimum cytotoxicity and almost insignificant hemolytic side effects under both in vitro and in vivo conditions (Fig. 16.6). Lysozyme (Lys), a natural enzyme found abundantly in mammalian secretions (tears, saliva, etc.), displays remarkable antibacterial activity by destroying the 1,4- β-linkages between N-acetyl muramic acid and *N*-acetyl- D-

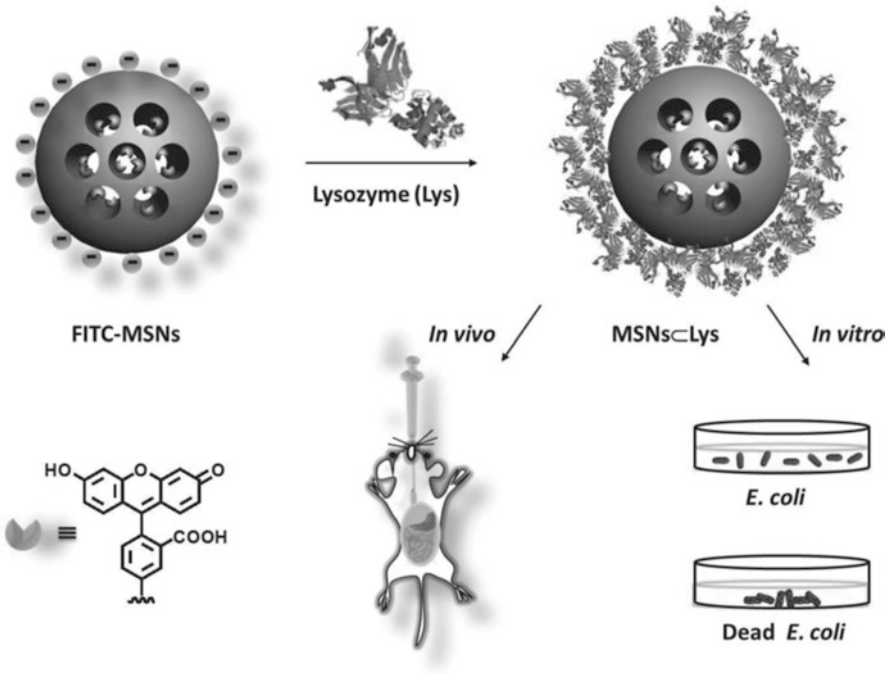


**Fig. 16.6** Schematic representation of antibacterial activity of lysozyme-coated MSNs

glucosamine (NAM–NAG) residues of cell wall peptidoglycan (Song et al. 2017). However, due to their instability and weak binding affinity with peptidoglycan, this ubiquitous enzyme rendered useless for antibacterial defense.

MSNs with their wide range applications in biomedical sciences demonstrated stability and enhanced biological activity with an enzyme or protein conjugate surface immobilization. MSNs coated with lysosomes display enhanced stability of Lys with selective toxicity, thereby reducing the risk of development of resistance compared to conventional antibiotics. MSNs⊂Lys corona increases the membrane perturbation properties by enhancing the local concentration of Lys on the surface cell walls which is responsible for peptidoglycan hydrolysis.

## 16.8 Antibiofilm Tests

### *16.8.1 Initial Bacterial Adhesion*

Initial bacterial adhesion test was performed using non-treated silicone and acylase-coated sheets and observed with bright field microscopy. To allow bacterial adhesion, the bacterial samples inoculated in TSB (tryptic soy broth) were incubated for 3 h at 37 °C (Malone et al. 2017).

### 16.8.2 Single Species Biofilm Inhibition

The biofilm inhibition activity or the total biomass reduction was evaluated using crystal violet (CV) assay. Quantification was carried out both in static and dynamic conditions, against the bacterial population. The total biomass was estimated by the amount of CV bound to each sample by measuring the absorbance at 595 nm (Gurunathan et al. 2014).

### 16.8.3 Mixed-Species Biofilm Inhibition

The biofilm inhibition potential for mixed species biofilms was studied using a combination of the two enzymes (acylase and amylase) into a hybrid multifunctional coating system, and the CV assay was used to measure the total biofilm mass (Gurunathan et al. 2014).

### 16.8.4 Bacterial Viability in the Biofilms

Single- and multiple-species biofilms were cultured with acylase on hybrid silicone samples using a mixture of two dyes, namely green fluorescent Syto 9 and red-fluorescent propidium iodide (1:1), and were subjected to analysis for bacterial viability with Live/Dead® BacLight™ kit (Coenye and Nelis 2010).

### 16.8.5 Biocompatibility Tests

The biocompatibility of the silicone samples coated with enzymes (acylase/amylase and both) was studied using human foreskin fibroblasts cell lines and cell viability was determined using alamarBlue® assay (Gurunathan et al. 2014).

### 16.8.6 MSN Effect on the Protein Leakage in Bacteria

Effect of MSNs on protein leakage was studied by suspending the bacterial cultures in phosphate-buffered saline (PBS) and incubated for 4 h at 37 °C in a shaking incubator (200 rpm). After incubation, the cultures were centrifuged and the supernatant was checked for the amount of protein leakage by Folin-Lowry method.

### *16.8.7 Membrane Fluidity Assay*

Membrane fluidity assay is carried out using a fluorescent probe DPH (1,6-dipheny l-1,3,5-hexatriene). Bacterial cultures with MSNs were suspended in PSB and incubated for 90 min at 37 °C. After incubation, the cultures are centrifuged and resuspended in 5 μM DPH solution and incubated in dark for 1 h at 37 °C. The cells were washed thoroughly to eliminate excess DPH and were finally suspended in PBS. Bacterial sample without MSNs was used as a control, and sodium dodecyl sulfate (SDS) known for membrane damage is taken as a positive control. Fluorescence spectrophotometry was used to measure the fluorescence and the polarization index was later calculated (Sen Karaman et al. 2016).

SEM analysis reveals bacterial cell membrane damage and intracellular protein leakage reflects a significant degree of antimicrobial activity. According to Coenye and Nelis (2010), SEM observation has revealed the alteration of the majority of bacterial cells into elongated filamentous cells when treated with MSNs which was predicted to be one of the defensive mechanisms of microbes against antibiotics and harsh environmental conditions.

### *16.8.8 TCP Assay*

Tissue culture plate (TCP) method was used to determine the biofilm activity based on the incorporation of the crystal violet by sessile cells through colorimetric measurements. Biofilm activity and the inhibition percentage can be calculated by [1 − (A595 of cells treated with MSNs/A595 of non-treated control cells)] × 100 (Kong et al. 2011), and the colony-forming unit was calculated by multiplying viable colonies with the dilution factor and expressed as CFU $mL^{-1}$ (Chun Xu et al. 2018).

## 16.9 Conclusions

Recent developments in nanotechnology have led to the synthesis of efficient nanomaterials loaded with available antimicrobials with improved functionality. The nanomaterials exhibit unique properties, owing to their large surface area/volume and differ from those of their free molecules and bulk compositions. MSNs with their unique properties of size, shape, pore physiology, and surface chemistry are considered as excellent antibacterial and antibiofilm agents. The interaction of antimicrobials with the MSNs damages the bacterial cell membrane resulting in intracellular protein leakage. Enhanced antibacterial and antibiofilm effects were noted when MSNs were used synergistically with other prevalent antibiotics, enzymes, and other bioactive molecules. MSNs have proved to be efficient drug vehicles in

delivering unstable, hydrophobic, volatile essential oils as potential antimicrobial compounds. They significantly improved the compounds' antimicrobial activity, thereby decreasing the opportunity for natural drug resistance to arise. Further the delivery platform could also be potentially extended to conventional biocides and other traditional antimicrobial agents with directed and controlled release of drugs to the target microbes.

Hence, this book chapter provides a novel approach into the antimicrobial effectiveness of MSNs, which holds promise for the advancement of future generation antibiotics with non-toxicity and supple design options. Currently antibiotic modifications at nanoscale can be considered as uncomplicated methods to progress the management of severe infections and are still practical alternatives to reduce the resource and time-consuming selection procedures for new drugs.

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