

# Nanoparticle-based Drug Delivery Systems: Promising Approaches Against Infections

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## ABSTRACT

*Despite the fact that many new drugs and technologies have been developed to combat the infectious diseases, these have continued to be global health challenges. The use of conventional antimicrobial agents against these infections is always associated with problems such as the development of multiple drug resistance and adverse side effects. In addition, the inefficient traditional drug delivery system results in inadequate therapeutic index, low bioavailability of drugs and many other limitations. In this regard, antimicrobial nanoparticles and nanosized drug delivery carriers have emerged as potent effective agents against the infections. Nanoparticles have unique properties owing to their ultra small and controllable size such as high surface area, enhanced reactivity, and functionalizable structure. This review focused on different classes of antimicrobial nanoparticles, including metal, metal oxide and others along with their mechanism of action and their potential use against the infections. The review also focused on the development of nanoparticle systems for antimicrobial drug delivery and use of these systems for delivery of various antimicrobial agents, giving an overview about modern nanoparticle based therapeutic strategies against the infections.*

**Key words:** Antimicrobial Nanoparticles, Drug Resistance, Drug Delivery System, Infection, Metal and Metal Oxide, Review

## INTRODUCTION

Infectious diseases, whether intracellular, or extracellular infections, biofilm-mediated, or medical device- associated have always been a global problem in public health causing millions of deaths each year. The breakthrough of miracle drugs, called antibiotics in the 20<sup>th</sup> century resulted a dramatic reduction in death and illness from these infectious diseases. However, changes in the society, environment, technology and evolving microorganisms are contributing to the emergence of new diseases and development of antimicrobial resistance (Cohen 2000). Bacterial resistance to antibiotics can be resolved by the development of

new antibiotics and chemical modification of existing drugs. The development of new antimicrobial drugs does not assure that it will catch up with the microbial pathogen fast enough and there will be no development of resistance in the future. For example, now-a-day's, hospital and noscominal infections by both Gram-positive and Gram-negative bacteria are increasing and continued evolution of antimicrobial resistance with sub-lethal concentration of antibiotic used is causing serious threats to human health. Therefore, there is an acute need for more effective and long-term solutions to this ever-growing problem (Taylor et al. 2002).

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One of the promising efforts to address this challenging and dynamic pattern of infectious diseases is the use of nanotechnology. Nanotechnological applications in medicine have yielded a completely new field of technology that is set to bring momentous advances in the fight against a range of diseases (Ferrari 2005). Nanoparticles (NPs) are defined as the “particulate dispersions, or solid particles with a size in the range of 10-1000 nm”. This small size range gives them specific properties such as a high surface area and an enhanced reactivity (Niemeyer 2001). NPs consisting of metals and metal oxide may be promising antimicrobial agent to which pathogens may not develop resistance. These NPs use various antimicrobial mechanisms against the pathogens; they may disrupt the cell membrane directly, or form free radicals. In comparison to the conventional antibiotics, nanostructured antimicrobial agents help in reducing the toxicity, overcoming resistance and lowering the cost. In addition, nanosized drug carriers are also available, which can efficiently administer the antibiotics by improving the therapeutics and pharmacokinetics of the drug. Nanotechnology also assists in development of fast, accurate and cost effective diagnostics for the detection of pathogenic microbes. This review focuses on introducing the role of nanotechnology, particularly NPs in controlling the infectious diseases and in drug delivery systems.

### **PROBLEMS ASSOCIATED WITH CONVENTIONAL ANTIMICROBIAL THERAPY**

Conventional antimicrobial therapy consists of chemotherapeutic agents, or antibiotics to treat the infectious diseases by either killing of the microbes, or interfering with their growth. With the commercial production of the first antibiotic penicillin in the late 1940s, use of the antibiotics to treat the infectious diseases increased and to-date many new antibiotics have been developed (Taubes 2008), ranging from the topical antibiotic ointments (such as neosporin) to intravenously injected antibiotic solutions. These drugs have proven to be effective in eliminating the microbial infections that arise from minor cuts and scrapes to life threatening infections. An antimicrobial drugs act on the microbes by various mechanisms such

as inhibiting cell wall synthesis (e.g.,  $\beta$ -lactam drug, vancomycin, bacitracin), inhibiting the protein synthesis (chloramphenicol, tetracyclines, aminoglycosides, macrolids), inhibiting the nucleic acid synthesis (fluoroquinolones, rifampicin), inhibiting the metabolic pathways (sulfonamides, trimethoprim), and by interfering with the membrane integrity (polymixin B) (Walker 1996). Being a life saving drug for so many decades, antibiotics do suffer from a range of limitations, which include narrow spectrum of antimicrobial activity, problem regarding the safety and tolerability of the antimicrobial agent, antibiotic mediated enhancement of microbial virulence properties which may also lead to prolongation of host carrier state and may lead to harmful side effect to the host such as toxicity, or any allergic reaction. Inefficient delivery of the drugs has also been one of the major limitations of conventional antimicrobial therapy. For example, conventional drug dosage forms (such as tablets, capsules etc.), when administered orally, or applied topically may be distributed nonspecifically in the body causing systemic side effects, problems of poor uptake and destruction of drugs.

Another major limitation of antimicrobial therapy is the development of bacterial resistance to antibiotics. More than 70% of bacteria causing infections are now resistant to at least one of the drugs most commonly used for the treatment. Some organisms are so reluctant that they can only be treated with the experimental and potentially toxic drugs. These microbes use diverse mechanisms to develop the resistance against the antibiotics such as they may alter the drug target, inactivate enzymes, inhibit efflux transport, or develop alternate metabolic pathways for their growth. Some of the important resistant bacteria along with their resistance mechanisms are listed in Table 1. One of the serious clinical threats in treating the infections via antibiotics emerged with the development of vancomycin-resistant *Enterococcus* (VRE) which showed resistance to many commonly used antibiotics (Gold and Moellering 1996). Another example is that of methicillin resistant *Staphylococcus aureus* (MRSA) strains that have caused great concern due to potential spread of antibiotic resistance. Cohen (2000) reported that more than 40% of *S. aureus* strains collected from the hospitals were methicillin resistant and some of them were

resistant to vancomycin. One of the global and medical challenges in the 21<sup>st</sup> century is the treatment of vancomycin-resistant microbes because vancomycin is the latest generation of antibiotics and assumed most effective for *S. aureus* infection (Chakraborty et al. 2010). Problems with multiple drug resistance are also increasing in noscomial Gram-negative bacteria, which have the capability of developing different mechanisms for antibiotic resistance. In 1970s, drug resistant *Neisseria gonorrhoeae* and *Haemophilus influenzae* were already recognized worldwide (Berkowitz 2005). One of the most recent new wave of “super super bugs ” came with the emergence of mutant NDM-1 which first emerged in New Delhi and has now spread worldwide from Britain to New Zealand. NDM-1 stands for New Delhi metallo beta-lactamase,

which is an enzyme that confers bacterial multiple drug resistance (Sinha 2005). In 2009, *Klebsiella* was the first bacterium identified to produce NDM-1 in a patient with an infection that did not respond to many antibiotics. In addition, current antimicrobial therapy is incapable of treating the chronic infections such as cystic fibrosis and other pulmonary diseases that demand for intravenous administration of high dose antibiotics, which can cause serious side effects due to sub-lethal concentration of antibiotics in the serum (Beaulac et al. 1996). Therefore, the spread of resistance towards many new classes of antibiotics, including cephalosporins in bacteria, fungi and parasites and difficulties in treating the chronic infections accounts for the development of new, safer and effective antimicrobial therapy.

**Table 1** - Drug resistant bacteria along with their mechanism of resistance.

Microorganism	Drug	Mechanism of Resistance
<i>Gonococci</i>	Quinolone	Mutation in target
<i>Enterococcus</i>	Vancomycin	Changes in target
	Sulfonamide	Over production of target site
		Development of alternate growth requirement
<i>Enterobacteriaceae</i> (e.g.: <i>E. coli</i> )	$\beta$ -lactam (carbapenem)	Drug degrading enzyme
<i>Streptococcus pneumoniae</i>	Macrolide	Drug efflux pump, active efflux
<i>Pseudomonas aeruginosa</i>	Multiple drugs	Multiple factors including loss of porin, drug efflux pump, and drug modifying enzyme
<i>Staphylococcus aureus</i>	$\beta$ -lactam (methicillin) Vancomycin	Production of an additional enzyme that avoids binding Cell wall thickening changes in target

## ROLE OF NANOTECHNOLOGY IN THERAPEUTICS AND DRUG DELIVERY

Nanotechnology is an emerging technology that has opened the possibility of controlling and manipulating the structures at molecular level and is expected to have a substantial impact on medical technology, in pharmaceutical sciences and many more. The potential application of NPs in controlling the infection includes fast, accurate and sensitive methods of disease diagnostics, design of antimicrobial drugs from the metals, metal oxides and biological particles to overcome the antibiotic resistant pathogens and in targeted delivery of drugs that not only improves the biodistribution but also the accumulation of drugs in specific body sites which are resistant to conventional treatment.

## Nanoparticles in Therapeutics against Infectious Diseases

Antimicrobial nanoparticles mainly consist of metals, metal oxides, and many biologically derived materials. The effective antimicrobial properties of these materials are mainly due to their nano-size providing them unique chemical and physical properties such as increased surface to volume ratio and high reactivity (Weir et al. 2008). They act as nano-antibiotics and their potential of controlling infectious diseases have been explored and demonstrated by various researchers. Metal and metal oxide NPs offer a means of new line research in combating the infectious diseases due to resistance developed by several pathogenic bacteria against the antibiotics. An advantage of these nano-antibiotics is that naturally occurring microbes have so far not developed resistance against them. They do not pose direct and acute side effects to human cells.

Moreover, they use multiple biological pathways to exert their antimicrobial mechanisms such as disruption of the cell wall, inhibition of DNA, protein, or enzyme synthesis, photo-catalytic reactive oxygen species production damaging cellular and viral components. In addition, the preparations of these NPs are more cost effective than antibiotics synthesis and they are also more stable for long-term storage and unlike antibiotics can withstand harsh processing conditions such as high pH and temperature without being inactivated (Reddy et al. 2007). Some of the important metal and metal oxide NPs that are used in therapeutics are described below:

### Silver

Since time immemorial, silver-based compounds and silver ions are known for their broad spectrum of antimicrobial properties. Silver is used in different forms such as metals, nitrates, and sulfadiazine. By decreasing the particle size to nanometer range, antibacterial activity of silver can be increased (Chopra 2007). Rai and coworkers (2009) reviewed the antimicrobial potential of metallic silver and silver-based compounds along with its mechanism of action, effect of size and shape of silver-based NPs on their antimicrobial potential. Lara et al. (2010) investigated the bactericidal effect of silver NPs against multidrug-resistant bacteria such as *Pseudomonas aeruginosa*, ampicillin-resistant *E. coli* and erythromycin-resistant *Streptococcus pyogenes*. Luciferase assays determined that silver NPs could inactivate a panel of drug-resistant and drug-susceptible bacteria with MBC and MIC concentrations in range of 30 to 100 nm respectively. Through Kirby-Bauer tests, they showed that the bacteriostatic mechanisms of silver NPs were inhibitions of cell wall, protein synthesis and nucleic acid synthesis. Synergistic effects of silver NPs with antibiotics and other agents have also been explored; for example, silver NPs in combination with antibiotics such as penicillin G, amoxicillin, erythromycin, and vancomycin resulted in enhanced antimicrobial effects against various Gram-negative and Gram-positive bacteria (Fayaz et al. 2010). Martinez-Gutierrez et al. (2010) evaluated the antimicrobial activity of both silver and titanium NPs against a panel of selected pathogenic and opportunistic microorganisms.

### Gold

Many studies have explored the antimicrobial properties of gold NP conjugated with antibiotics. Rai et al. (2009) reported one pot synthesis of spherical gold NPs with cefaclor (a second generation antibiotic), the amine group of cefaclor acted both as reducing as well as capping agent for the gold NP synthesis. The combination of both had potent antimicrobial activity against the Gram-negative (*E. coli*) and Gram-positive bacteria (*S. aureus*) with MIC 10 µg/mL and 100 µg/mL for *S. aureus* and *E. coli* respectively. FTIR and AFM studies revealed that the antimicrobial activity was due to the inhibition of peptidoglycan layer by cefaclor and generation of holes in the cell membrane resulting in leakage of cell content by the gold particles. Recently, Fayaz et al. (2011) biologically synthesized the gold NPs using the non-pathogenic fungus *Trichoderma viride* at room temperature where vancomycin was bound to its surface by the ionic interaction. This novel preparation of gold with vancomycin effectively inhibited the growth of vancomycin resistant *S. aureus* at an MIC of 8µg/ml. The TEM micrographs showed the presence of vancomycin bound gold NPs (VBGNP) in abundance on the cell wall surface of vancomycin resistant *S. aureus* (VRSA), which penetrated the bacterial membrane and resulted in cell death.

### Zinc oxide and Magnesium oxide

Zinc oxide (ZnO) NPs have antibacterial activity against many food borne pathogens such as enterotoxigenic *E. coli* (Liu et al. 2009). Lili and coworkers (2011) investigated zinc oxide NPs for the antifungal activity against two postharvest pathogenic fungi (*Botrytis cinerea* and *Penicillium expansum*). ZnO NPs, causing deformation in fungal hyphae, significantly inhibited the growth of *B. cinerea* and in case of *P. expansum*, ZnO NPs prevented the development of conidiophores and conidia eventually leading to the death of fungal hyphae. Their result suggested the use of ZnO NPs as effective fungicide agents in agriculture and food safety application (Lili et al. 2011). Many others suggested that the antimicrobial mechanism of ZnO most likely involved the disruption of the cell membrane lipids and proteins that resulted in the leakage of intracellular contents and eventually the death of cells (Xie et al. 2011). Lipovsky et al. (2009) suggested the generation of hydrogen peroxide and Zn<sup>+2</sup> ions to be the key antimicrobial mechanisms.

Magnesium oxide shows size dependent antimicrobial properties against *E. coli* and *S. aureus* (Makhluf et al. 2005). Similarly, greater ZnO antibacterial activity has been observed as its size decreases to nanometer level in relation to surface area. For example, Raghupathi et al. (2011) used nitrogen gas isotherms and the Brunauer-Emmett-Teller equation and found direct correlation between antibacterial activity, surface area and particle size. They also found that 4-7 nm ZnO colloidal suspension with 90.4 ml/gm (highest surface area) inhibited 95% of MRSA, *E. faecalis*, *Staphylococcus epidermidis* (high biofilm producing strain) and various other clinically relevant pathogens.

### **Titanium Oxide**

Titanium oxide ( $\text{TiO}_2$ ) is commonly used semiconductor photocatalyst but  $\text{TiO}_2$  NPs show photo-catalytic antimicrobial activity. Photo-catalytic  $\text{TiO}_2$  generates free radical oxides and peroxides, which show potent antimicrobial activity with broad reactivity against many infectious microbes (Choi et al. 2007). Kuhn et al. (2003) reported that antimicrobial efficiency of  $\text{TiO}_2$  NPs was determined by cell wall complexity. The results revealed by them showed that the antibacterial efficiency of  $\text{TiO}_2$  was highest for *E. coli*, followed by *P. aeruginosa*, *S. aureus*, *E. faecium* and *C. albicans*.  $\text{TiO}_2$  doped with metal enhances the antibacterial activity of  $\text{TiO}_2$  by improved light absorption and photo catalytic inactivation (Muranyi 2010). Studies have shown that silver coated  $\text{TiO}_2$  material with optimal silver loading enhances the photo-catalytic and bactericidal activities as compared to  $\text{TiO}_2$  alone (Wong et al. 2010).

### **Aluminum Oxide**

Aluminum oxide ( $\text{Al}_2\text{O}_3$ ) NPs are known to have mild inhibitory effect on microbial growth; they disrupt the cell membranes but only at high concentration. Growth inhibitory effect of alumina NPs on *E. coli* has been reported by Sadiq et al. (2009), who showed that by increasing the concentration above 1000  $\mu\text{g/mL}$ , alumina NPs showed a mild growth inhibitory effect, which might be due to surface charge interactions between the particles and cells. Like  $\text{TiO}_2$  NPs,  $\text{Al}_2\text{O}_3$  in conjugation with silver shows enhanced inhibitory effects on the microbes. Bala et al. (2011) synthesized and characterized the titania-silver ( $\text{TiO}_2$ -Ag) and alumina-silver ( $\text{Al}_2\text{O}_3$ -Ag)

composite NPs by wet chemical method and their surfaces were modified by oleic acid to attach the silver NPs. The antibacterial evaluation from disc diffusion assays against *E. coli* DH5a and *S. epidermidis* NCIMB 12721 suggested that these  $\text{TiO}_2$ -Ag and  $\text{Al}_2\text{O}_3$ -Ag composite NPs had enhanced antimicrobial potential.

### **Copper and Copper Oxide**

Copper is a structural constituent of many enzymes in living microorganism. It can generate toxic effects at high concentration when in free ionic form by generating the ROS that disrupts the DNA and amino acid synthesis (Esteban et al. 2009). Ruparelia et al. (2008) showed that copper NPs have greater affinity to carboxyl and amine groups at high density on the surface of *B. subtilis* than that of silver NPs showing superior antibacterial activity. Copper oxide being cheaper than silver, easily miscible with the polymers can be an alternative to silver NPs. Ren et al. (2009) investigated the antimicrobial potential of copper oxide NPs generated by the thermal plasma technology that contained traces of pure Cu and  $\text{Cu}_2\text{O}$  NPs against a range of bacterial pathogens, including methicillin-resistant *S. aureus* (MRSA) and *E. coli*. Their study revealed that the ability of CuO NPs to reduce the bacterial populations to zero was enhanced in the presence of sub-MIC concentrations of silver NPs.

### **Iron Oxide**

It shows antimicrobial activity by generating the  $\text{O}_2$  free radicals that is generated by converting the  $\text{H}_2\text{O}_2$  to more reactive hydroxyl radicals via Fenton reaction (Touati 2000). These free radicals can depolymerize the polysaccharides, break DNA strands, can initiate lipid peroxidation, or inactivate the enzymes (Weinberg 1999). Tran et al. (2010) showed that IO/PVA inhibited the growth of *S. aureus* at concentration of 3 mg/mL at all time points.

### **Nitric Oxide**

Nitric oxide releasing the NPs can be a promising antimicrobial alternative because NO, a diatomic free radical is a molecular modulator for immune responses to infection (Weller 2009). NO and its derivatives, also called reactive nitrogen species, generate broad antimicrobial activity (Fang 2004). Some studies have shown that NO releasing silica NPs effectively killed many Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S.*

*epidermidis* and *S. aureus*) bacteria and fungi (*C. albicans*) within the established biofilms without being toxic to the mammalian cell (Hetrick et al. 2009). NO releasing NPs can be used to treat the infected wounds.

Wang and coworker compared the antimicrobial activities of six metal oxide NPs (NiO, ZnO, Fe<sub>2</sub>O<sub>3</sub>, Co<sub>3</sub>O<sub>4</sub>, CuO, and TiO<sub>2</sub>) in two different modes (aqueous and aerosol). These NPs displayed significant antimicrobial activities due to the combined effect of soluble ion stress and nano related stress (Wang et al. 2010). Recently, Sundaram et al. (2011) subjected five metal oxide NPs, Al<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub>, CeO<sub>2</sub>, ZrO<sub>2</sub> and MgO to evaluate their antimicrobial potential against various ophthalmic pathogens such as *P. aeruginosa*, *Acinetobacter* sp, *Klebsiella pneumoniae*, *E. coli*, *S. viridians* and *S. pyogenes*. The result showed that Fe<sub>3</sub>O<sub>4</sub> had maximum activity (15±0.32 mm dia) against *P. aeruginosa* and the minimum activity (9±0.21 mm dia) was seen by MgO NPs. Gordon et al. (2011) synthesized the composite NPs comprising of iron oxide, zinc oxide and zinc ferrite phases by synthesizing the Zn/Fe oxide composite NPs via basic hydrolysis of Fe<sup>2+</sup> and Zn<sup>2+</sup> ions in aqueous continuous phase containing gelatine. The weight ratio [Zn]/ [Fe] governed the antibacterial activity of these NPs against *S. aureus* and *E. coli*, i.e., the higher the ratio, the higher the antibacterial activity.

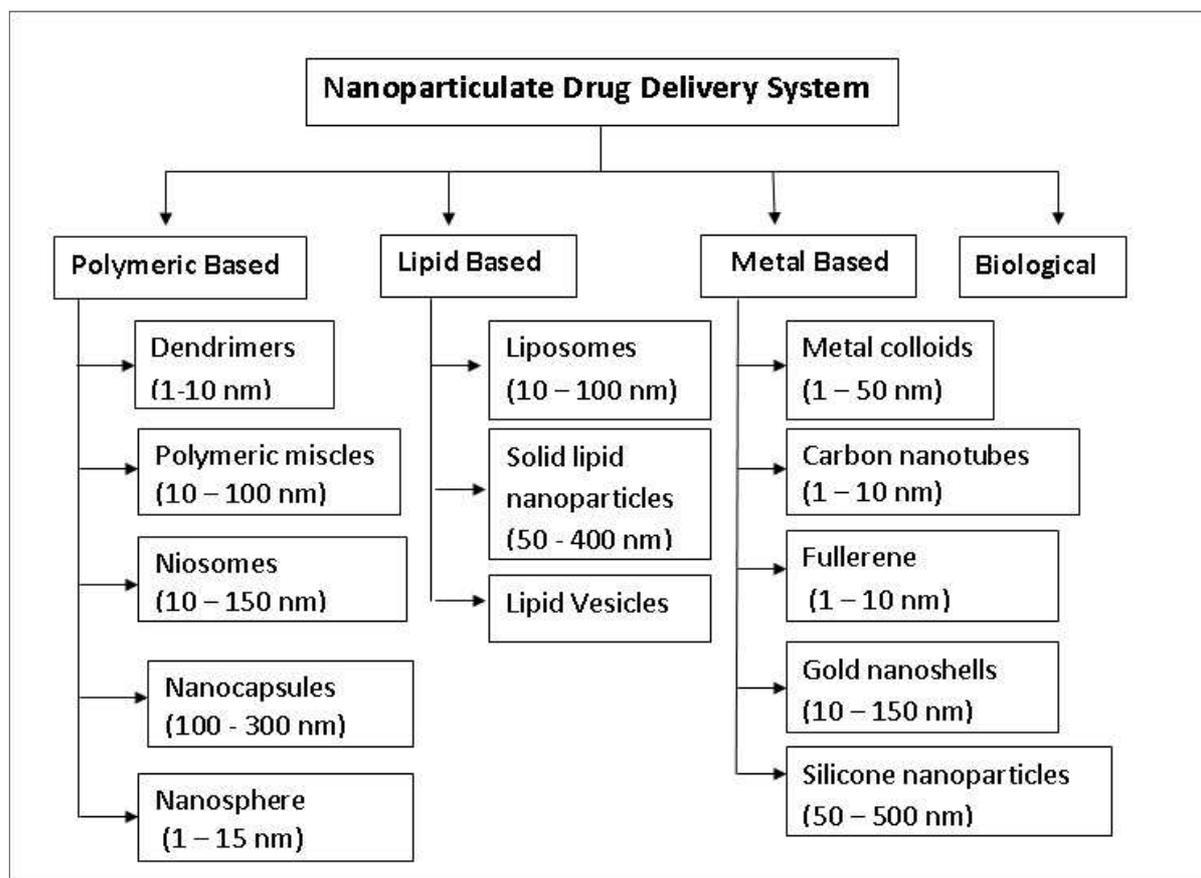
Other than metal and metal oxides, many biologically derived materials also show potent antimicrobial properties. For instance, chitosan (partially deacetylated chitin) is widely used as antimicrobial agent, either pure, or with other polymer and metal ions (Chung et al. 2003). These materials have been engineered for their antimicrobial properties at nano-scale (Rabea et al. 2003). The antimicrobial effect of chitosan depends upon its molecular weight. Honary et al. (2011) studied the effect of the molecular weight of chitosan on the physiochemical and antibacterial properties of Ag-chitosan NPs. The results showed that antibacterial activity of the NPs against *S. aureus* increased with decreasing the particle size due to increase in the surface area and smallest particle size was obtained using high molecular weight chitosan. Many theories have been put forward on the antimicrobial mechanism of chitosan. Qi et al. (2004) suggested that chitosan bound to the negatively charged bacterial surface causing the agglutination and increased the

permeability of cell membrane, which resulted in the leakage of intracellular component. Many others proposed that it inhibited the enzyme activities, RNA and protein synthesis. Chitosan as an antimicrobial agent has many advantages such as broad spectrum of activity, high microbe killing efficiency, high biodegradability and low toxicity (Rice et al. 2010)

### Nanoparticles for Antimicrobial Drug Delivery

Over the last few decades, considerable studies have been done on the development of new drug delivery system to overcome the limitations caused by the conventional dosage/delivery systems. An ideal drug delivery system should pose two important elements: controlled and targeted delivery. In this regard, NPs have emerged as the potential and effective drug delivery systems. Drugs have an optimum concentration within which they are beneficial. Therefore, in designing the NPs, the major goal is to control the particle size and surface properties to achieve the controlled release of the pharmacologically active agent at a specific site at the therapeutically optimal rate within the dose regime. Owing to their ultra small and controllable size, NPs can easily penetrate body cells, and more importantly, they show high reactivity with biological systems, i.e., both host cell and microbes (Zhang et al. 2010). NP mediated drug delivery offers many advantages over the conventional delivery system such as:

- (1) Controlled and sustained release of the drug at the site of infection, thus increasing the therapeutic efficiency of the drug, minimizing the systemic side effect and lowering the frequency of administration.
- (2) Drug can be incorporated into the system without any chemical reaction, thus preserving the drug.
- (3) Drug release and degradation profile can be easily modified by tuning the size of NPs to the size of the drug to achieve zero order, or first order kinetics.
- (4) Enhanced bioavailability of the drug at a specific site in the right proportion for a prolonged period.
- (5) It improves the serum solubility of poorly water soluble drugs and also multiple drugs can be delivered to the same cell for combined synergetic therapy.



**Figure 1** - Types of nanoparticulate drug delivery systems.

### Lipid Based

#### *Liposomal nanoparticles as drug carrier*

Liposomes are phospholipid bilayers with an entrapped aqueous volume. They are classified into multilamellar vesicles (MLVs, diameter >200 nm), unilamellar vesicles (large unilamellar vesicles (diameter 100–400 nm), and small unilamellar vesicles (diameter <100 nm)), based on the number of layers (lamellarity) and diameter. Both synthetic and natural lipids can be used. Phosphatidyl choline, electrically neutral phospholipids containing fatty acyl chains of varying degrees of saturation and length are most widely used in liposomal formulation. Liposomes were used as antimicrobial agents since 1995 when FDA approved Doxil (doxorubicin liposomes) as the first liposomal delivery system to treat the AIDS associated Kaposi's sarcoma (Lian et al. 2001). These are biodegradable, non-toxic and can encapsulate both hydrophobic and hydrophilic drugs in the aqueous core and the phospholipid bilayer respectively without any chemical

modification. In addition, liposomes can be deliberately engineered to possess the distinctive properties such as long systemic circulation time, target cell specificity, pH, reductive environmental and temperature sensitivity, which are achieved by selecting the appropriate lipid composition and surface modification for the liposomes (Lian et al. 2001). Another remarkable feature of liposomes is the lipid bilayer structure that can easily fuse with the bacterial membranes, thereby releasing the drug within the cell membrane, or into the interior of the microorganism.

There are many successful examples of liposomal antimicrobial drug delivery. One such example is polymyxin B loaded liposomal formulation containing 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol showed dramatic improvement over free drug in terms of reduced side effect and enhanced antimicrobial activity. Liposomes are also widely used in the delivery of chemotherapeutic agents. Chan et al. (2009) synthesized core shell NPs consisting of

PLGA (poly lactic-co-glycolic acid) hydrophobic core, soybean lecithin monolayer and PEG shell by modified nano-precipitation method combined with self-assembly. Docetaxal encapsulated nanoparticles showed that the amount of lipid coverage affected drug release kinetics. The data

showed that PLGA-Lecithin-PEG core shell NP could be useful in the controlled release of drugs (Chan et al. 2009). Other successful examples of liposomal drug delivery systems are summarized in Table 2.

**Table 2** - Liposomal drug delivery system.

<b>Liposomal Formulation</b>	<b>Drug Loaded</b>	<b>Microbe Targeted</b>	<b>Activity</b>	<b>References</b>
Stearylamine (SA) & Dicetyl Phosphate	Zidovudine	HIV	Targeting of ZDV to lymphatics is enhanced.	Kaur et al. (2008)
Hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidylglycerol (DSPG)	Amphotericin B	<i>Aspergillus fumigates</i>	Targeted delivery of drug at infection site	Takemoto et al. (2004)
Partially hydrogenated egg phosphatidylcholine (PHEPC), cholesterol, and 1,2-distearoylsn-glycero-3-phosphoethanolamine-N-(polyethylene glycol) (PEGDSPE)	Gentamicin	<i>Klebsiella pneumonia</i>	Drug showed increased survival rate of animal model and increased therapeutic efficacy	Schiffelers et al. (2001)
1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol	polymyxin B	<i>Pseudomonas aeruginosa</i>	Drug showed decreased bacteria count in lung, increased bioavailability and decreased lung injury caused by bacteria	Omri et al. (2002)

## **SOLID LIPID NANOPARTICLES (SLN) AS DRUG DELIVERY CARRIER**

SLN are a new generation of colloidal drug carriers, also called lipospheres. These sub-micron-sized particles in the range of 52-100 nm consist of physiologically biocompatible lipids, which remain solid at body and room temperature and remain dispersed in aqueous solution. SLN are mainly prepared from the lipids, waxes and surfactants for emulsification. Commonly used lipids in SLN formulation include fatty acids, triglycerides, steroids and surfactants. Emulsifiers for the stability of lipid dispersion are sodium cholate and sodium glycocholate. Methods employed to prepare the SLN include high pressure homogenization, emulsifier solvent diffusion, and multiple emulsion solvent injection. SLN have unique properties as potent drug carrier as they combine several advantages and avoid the disadvantages of other colloidal carriers such as lipid immersion, liposomes and polymeric NPs.

The advantage of SLN as drug carrier system is that they are made up of physiologically biocompatible and tolerable lipids, hence they are not toxic to the human body. Drug release can be controlled and targeted as immediate release or sustained release. SLN formulation also protects the sensitive drugs from any photochemical, or oxidative degradation as the drug is immobilized by the solid lipids and drug leakage is reduced when compared to liposomes. Both lipophilic and hydrophilic drugs can be encapsulated and delivered by the SLN with slight modification in SLN formulation. Urban-Morlan et al. (2010) synthesized the solid lipid NP containing cyclosporine by emulsification diffusion method. Differential calorimetric assay revealed that cyclosporin affected the lipid structure and entrapment efficiency was higher with relatively fast release of cyclosporine.

Various examples of SLN based antimicrobial drug delivery targeted against the microorganisms are summarized in Table 3.

**Table 3** - Solid lipid based drug delivery system.

Formulation	Drug loaded	Microbes	Activity	References
Stearic acid	Rifampicin, isoniazid, pyrazinamide	<i>Mycobacterium tuberculosis</i>	Increased residence time, increased drug bioavailability, decreased administration frequency, prolonged drug release, high physical stability, high encapsulation efficiency	Pandey et al. (2006)
Glyceryl tripalmitate and tyloxapol	Clotrimazole	Fungi (e.g. yeast, aspergilli, dermatophytes)	High physical stability, chemical instability when exposed to light	Souto et al. (2004)
Glyceryl behenate and sodium deoxycholate	Ketoconazole	Fungi	High physical stability, chemical instability when exposed to light	Souto et al. (2005)
Glycerol palmitostearate	Econazole nitrate	Fungi	High encapsulation efficiency, enhanced drug penetration	Sanna et al. (2007)
Stearic acid, soy phosphatidylcholine, and sodium taurocholate	Ciprofloxacin Hydrochloride	Gram negative, gram positive and mycoplasma	Prolonged drug release	Jain et al. (2007)
Stearic acid, soy phosphatidylcholine, and sodium taurocholate	Tobramycin	<i>Pseudomonas aeruginosa</i>	Increased drug bioavailability	Cavalli et al. (2002)

### Polymeric-based NPs

Polymeric NPs can be formed as nano-spheres, or nano-capsules depending upon the method of preparation. Nano-capsules are vesicular systems in which drug is confined to a cavity surrounded by a polymeric membrane and nano-spheres are matrix systems in which the drug is physically and uniformly dispersed. In 1976, Langer and Folkman demonstrated the first use of polymeric based delivery of macromolecules. Since then, many synthetic and semi-synthetic, biocompatible and biodegradable polymers have been used extensively in the clinic for controlled drug release. The most commonly and extensively used polymeric NPs include poly-D, L-lactide-co-glycolide, polylactic acid, poly-ε-caprolactone, poly-alkyl-cyanoacrylates, chitosan and gelatin. Polymeric NPs also possess several remarkable properties making them a potential drug delivery vehicle. Firstly, they are structurally stable in the biological fluids under harsh conditions and can be synthesized with desired size distribution. Secondly, by manipulating the polymer length, surfactants and organic solvent during synthesis, size, zeta potential and drug release profile of NP can be precisely tuned. Thirdly, the functional

groups of polymers can be functionalized with desired ligands for the targeted delivery, e.g., lectin conjugated glydyne NP that selectively adhered to the carbohydrate receptors on the surface of microbes were studied for treating *Helicobacter pylori* infection (Umamaheswari et al. 2003). Due to obvious advantages such as improving the therapeutic effect, prolonging the biological activity, controlling the drug release rate and decreasing the administration frequency, a great deal of work has been done on polymeric NPs. For example, polybutylmethacrylate NPs was loaded with rifampicin and it showed antibacterial activity against *S. aureus* and *Mycobacterium avium* due to effective delivery of the drugs to macrophages both *in vitro* and *in vivo*. Cao et al. (2010) used, xyloglucan (polymer) was grafted with doxorubicin (DOX) and galactosamine and was used to target liver hepatocytes. This novel nano DDS showed improved transfection efficiency and hepatocyte specificity, which could be useful for tumor therapy. Other examples of polymeric NPs for antimicrobial drug delivery are shown in Table 4.

**Table 4** - Polymeric based drug delivery systems.

Formulation	Drug	Targeted Microorganism	Activity	References
Poly (D,L-lactide) (PLA) Nanospheres	Arjunglucoside	<i>Leishmania donovani</i>	Toxicity is reduced	Tyagi et al. (2005)
Polyethylene glycol (PEG)-PLA Nanocapsule	Halofantrine	<i>Plasmodium berghei</i>	Prolonged circulation half-life	Mosqueira et al. (2004)
Alginate nanoparticles	Rifampicin, isoniazid, pyrazinamide	<i>Mycobacterium tuberculosis</i>	High drug payload, improved pharmacokinetic, higher therapeutic efficacy	Ahmad et al. (2006)
Poloxamer 188 coated poly(epsilon-caprolactone) (PCL) nanospheres	Amphotericin B.	<i>Candida albicans</i>	Lower <i>in vivo</i> toxicity	Espuelas et al. (2003)
Glycosylated polyacrylate nanoparticles	Beta-lactam/ ciprofloxacin	<i>Staphylococcus aureus</i> , <i>Bacillus anthracis</i>	Improved bioavailability, higher therapeutic efficacy	Turos et al. (2007)
Polyethylene oxide (PEO) modified poly(epsilon-caprolactone) (PCL) Nanoparticles	Saquinavir	HIV	Protect the drug from cytochrome C metabolism and bypass P efflux pump.	Shah et al. (2006)

### ***Dendrimers as a drug carrier***

Dendrimers are macromolecules with highly branched polymers with 3-D structures that provide a high degree of surface functionality and versatility (Nanjwadea et al. 2009). Fritz Vogtle and coworkers first introduced dendrimers in 1978 (Bhuleier et al. 1978). Dendrimers consist of three components: an initiator core, an interior layer composed of repetitive units and an exterior (terminal functionality) layer attached to outermost interior layers. To develop dendrimeric systems for delivering drugs, these are prepared from two synthetic iterative approaches: one divergent and another convergent. In the divergent approach, synthesis is initiated from the core and proceeds outwards to the exterior through repetition of coupling and activation steps. In contrast, In the convergent approach synthesis starts from the periphery and proceeds towards the core (Gillies et al. 2005).

Dendrimers possess several unique properties that make them efficient NP carriers for the antimicrobial drug delivery. The well defined highly branched 3D structure provides a large surface area to size ratio resulting in greater reactivity with microorganisms *in vivo*. The availability of many controlled functional surface groups, polydispersity and their ability to mimic cell membrane adds to their potency as drug carriers. Both hydrophilic and hydrophobic agents can be loaded at the same time either by

encapsulating drug within the dendritic structure, or by interacting with the drugs at their terminal groups by electrostatic, or covalent bonds also due to the availability of functional groups. Dendrimers with specific and high binding affinity to a wide variety of viral and bacterial receptors can be synthesized (Sajja et al. 2009). Surfaces of dendrimers can be functionalized with PEG, which allows the delivery system to circulate in the body for prolonged time and thus maximizing the opportunity of the drug to reach the relevant site. PEGylated dendrimers are difficult to be detected by defense mechanism there by slowing the process of breakdown (Bhadra et al. 2005). PAMAMs were the first and most popularly studied dendrimers, but because of the cytotoxicity caused by the terminal amines, its clinical use as a drug carrier was limited. However, by masking the terminal amine groups by some means like terminating their carboxylic, or hydroxyl group would not only overcome its limitation but also improve the efficiency by solubility enhancement and making it more biocompatible and less toxic (Gillies et al. 2005). A study has indicated that PAMAM dendrimers might be considered as the biocompatible carriers of quinolones (nadifloxin and prulifloxin) under suitable condition (Cheng et al. 2007). Dendrimer use resulted in increased aqueous solubility of these antibiotics. Table 5 summarizes more dendrimeric-based antibacterial drug delivery systems.

**Table 5** - Dendrimer-based drug delivery system.

Dendrimers Formulation	Drug Loaded	Microbes	Activity	Reference	
Polyamidoamine (PAMAM) dendrimers	Nadifloxacin and Prulifloxacin	Various bacteria	Improved water solubility	Cheng et al. (2007)	
	Niclosmide	Tapeworm	Controllable drug release along with improved water solubility.	Devarakonda et al. (2005)	
	Silver salts	Gram-positive bacteria <i>P. Aeruginosa</i>	Prolonged half life circulation, high drug payload	Balogh et al. (2001)	
Pegylated lysine based copolymeric dendrimer	Artemether	sulfamethoxazole	Strept throat, <i>Staphylococcus</i> infection, and flu	Increased antibacterial activity, sustained drug release	Abeylath et al. (2008)
		<i>Plasmodium falciparum</i>	Increased drug stability, enhanced solubility, prolonged drug circulation half-life	Bhadra et al. (2005)	

**Other drug delivery carriers:**

Metal colloids, carbon nanotubes, gold nanoshells and silica are some of the organometallic-based systems that can be efficiently used as drug delivery carriers. Many new drugs have low aqueous solubility and high therapeutic efficacy. One such drug is paclitaxel. Berlin et al. (2010) used PEGylated hydrophilic carbon clusters (<40 nm) as effective drug delivery vehicle for paclitaxel. Mesoporous silica NP (MSNS) has attracted great attention in the last decades as efficient drug delivery carrier as they possess many unique properties such as tunable particle size, morphology and pore size. Unlike other organic carriers, they are free from bioerosion and biochemical attack. In addition, they have high drug loading capacity, sustained release profile and good thermal stability (He and Shi 2011). Yang (2008) used hollow silica NP for drug delivery. Doxorubicin as model drug was loaded into HSNPs and notable sustained drug release from HSNPs was demonstrated.

**CONCLUSION**

Conventional antimicrobial therapies consisting of use of antibiotics and other agents have been saving lives from the infectious diseases for many decades. However, the occurrence of antibiotic resistance acquired by the infectious microbes is causing a serious problem in treating the infectious diseases. The development of new antibiotics and chemically modifying existing drugs could be one

of the approaches against this threat, but this can lead to only limited and temporary success. In this regard, nanomaterials are offering new potential of becoming a new class of antimicrobial agents. Owing to their ultra-small size and high surface to volume ratio, NPs possess unique physicochemical properties. NPs such as metal and metal oxides are used as antimicrobial agents and as carrier for the delivery of antibiotics that help them in overcoming the resistance mechanisms in the target microbes. These nano-materials use multiple synergistic paths on the same platform to enhance the antimicrobial activity and overcome the antibiotic resistance. This review focused on different classes of antimicrobial NPs including metal, metal oxide and others along with their mechanism of action and their potential use against infection. The review also focused on the development of NPs system for the antimicrobial drug delivery and use of these systems for the delivery of various antimicrobial agents.

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Received: April 25, 2012;  
Accepted: June 03, 2013.