Nanoparticles as a Platform for Antimicrobial Drug Delivery

Satish Patel¹, Deependra Singh¹, Shikha Srivastava¹, Manju Singh¹, Kamal Shah²,
Durgesh Nandini Chauhan³, Nagendra S Chauhan^{4,*}

¹University Institute of Pharmacy, Pt. Ravishankar Shukla University, India

²Institute of Pharmaceutical Research, GLA University, Mathura, India

³Columbia Institute of Pharmacy, Raipur (C.G.), India

⁴Drug Testing Laboratory and Research Center (AYUSH Lab), India

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Abstract The hasty developments in nanotechnology will have intense impact on various areas of therapeutic applications like drugs and bioactive delivery, tissue engineering, and other application. This review mainly emphasized on the nanoparticle systems for delivery of antimicrobial drug. Various antimicrobial agents have been used to kill or inhibit the growth of microbes such as bacteria, fungi and viruses. As the pharmacological actions of these drugs have been well established, feeble delivery and degradation could lead to insufficient therapeutic index and cause side effects. Nanoparticles have many advantages like small and controllable size, large surface area to mass ratio, and functionalizable structure. These properties make the nanoparticles, a suitable delivery system of antimicrobials. Along with this, it also overcomes the limitations intra-additional antimicrobial therapeutics. In last few years, development and fabrication of antimicrobial agent in nanoparticle systems has evolved as an innovative and promising alternative that increases therapeutic effectiveness and overcoming the undesirable side effects. In this chapter, we focused on the current progress and challenges in producing nanoparticle system for antimicrobial drugs delivery for the treatment of microbial diseases.

Keywords Nanoparticles, Nanotechnology, Antimicrobial Drug Delivery

used to eradicate the microbes. Despite the fact the therapeutic efficiency of available drugs and treatment has been well proven, incompetent and deprived delivery of antimicrobial agents could consequence in insufficient therapeutic index and causing adverse effects like nausea, vomiting, irritation, scaling and gut microbial flora reduction. Along with developing multidrug resistant microbial strains, however, variations in the society, environment, technology and developing microorganisms are contributing to the emergence of new diseases and development of antimicrobial resistance (1). The continuing presence of antibiotic resistance in pathogenic and opportunistic microorganisms forces the pharmaceutical companies and the researcher community to continuously develop novel antibacterial drug, drug targets and delivery system to improve the activity against multidrug-resistant bacteria. In the current scenario, the progress of molecular nanostructures through precise particle size and shape is of prominent interest in biomedical applications like delivery of antimicrobial agents. Nanoscale materials/polymers have emerged up as novel antimicrobial agents and delivery system because of high surface area to volume ratio and distinctive properties (2; 3). Due to various metallic and polymeric nanoparticles (4) have confirmed antimicrobial activities, the development of novel applications in this field makes them an attractive alternative to antibiotics.

Earlier, before discovery of chemotherapeutics, many herbs and various inorganic antimicrobials such as silver and copper etc. were used to cure microbial infections. In the recent times, the advances in the field of nanoscience and nanotechnology has provide opportunities for the nanosized inorganic and organic particles which are leading applications as improvements in industrial, medicine and therapeutics, synthetic textiles and food packaging products (5; 6). Nano-technological applications in medicine have generated an entirely new field of technology that is set to bring momentous advances in the management of various

1. Introduction

Microbial infections remain foremost causes of morbidity and mortality in hospitals around the world. The innovation of miracle drugs called antibiotics in the 20th century leading a histrionic reduction in death and illness from these infectious diseases. Plentiful antimicrobial agents have been

diseases (7).

In earlier decades, the application of nanotechnology, particularly the use of nanoparticles for antibiotic/drug delivery, has produced noteworthy impact in management of infectious diseases. Various systems for delivery of nanoparticles like gels, liposome, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, have acknowledged momentous attention. Antimicrobial molecules loaded into nano-carriers by different methods like chemical synthesis, cross-linking, physical encapsulation, adsorption, to show an improved pharmacokinetic profile and therapeutic index when related to their free form (8). Innumerable nanoparticle-based drug delivery systems have been approved for clinical use to treat a variety of infectious diseases, and a number of formulations are now under various stages of pre-clinical and clinical tests (9). Due to advancement in fabrication, green synthesis multifunctional nanoparticles, various inventive approaches have emerged, more work on improving on nanoparticle therapeutic efficacy against microbial infection. In this chapter, we discuss about nanoparticle approaches having significant potential to improve upon current treatments. Researches and investigations were made in this arena provide wonderful prospects for alternative and more effective antimicrobial approaches that amend the pharmacokinetics properties of antibiotics and produce novel antibiotics with novel inhibition mechanisms.

2. Nanoparticles

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effect in term of therapeutic and patient protection (10). Various novel drug delivery system like transdermal patches, Microspheres, Nanoparticles, Resealed erythrocytes, Ocusert, Depots, Liposomes, Niosomes, Buccal films etc., offer several advantages over the conventional drug delivery systems (11). Moreover, the development of novel drug delivery systems is going to be the outmost need of pharmaceutical industry especially after enforcement of product patent. Nanoparticles attract an increasing interest in contemporary drug research because they could be used as a very efficient drug delivery system. Nanotechnology is evolving as a rapidly growing field with its application in various fields of science and research for the purpose of producing new substances and molecules at the nanoscale level (12). The word “nano” is used to show one billionth of a meter or 10^{-9} . The term “Nanotechnology” was first used by a Japanese scientist Professor Norio Taniguchi in 1974 to define precision manufacturing of materials at the level of nanometer. Nanotechnology deals with novel technology that provides a platform for development and exploration of biological systems, and offers various stimulus models for bio-assembled

components. Nano-structured materials whichever inorganic or organic exhibited numerous features like optical and catalytic. These properties mainly depend on the size and shape of prepared nanoparticles.

Nanoparticles are defined as particulate dispersions or solid particles or groups of atoms in the size range of 1-100nm. “Nano” is a Greek word identical to dwarf means extremely small. The use of nanoparticles is getting impulse in the present century as they having defined chemical, optical and mechanical properties.

Nanoparticles, first developed around 1970, they were initially devised as carriers for vaccines and anticancer drugs. The drugs may be enclosed inside the sphere of the nanoparticle or linked to the surface. Once they are at the target site, the drug payload may be released from the nanoparticle by diffusion, swelling, erosion or degradation. Active systems are also possible, e.g. drug release in response to the input of external energy such as targeted ultrasound, light or magnetic field. Nanoparticles have been successfully used in nano-chemistry to enhance the immobilization and activity of catalysts, (13) in medical and pharmaceutical nano-engineering for delivery of therapeutic agents, (14) in chronic disease diagnostics, and in sensors (15). Nanoparticles have been also used in clothing and in the food industry to limit bacterial growth (16; 17).

2.1. Properties of Nanoparticles

- Bulk material should have constant physical properties regardless of its size, but at the nanoscale size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant.
- For bulk materials larger than one micrometer (or micron), the percentage of atoms at the surface is insignificant in relation to the number of atoms in the bulk of the material. The interesting and sometimes unexpected properties of nanoparticles are therefore largely due to the large surface area of the material, which dominates the contributions made by the small bulk of the material.
- Nanoparticles of usually yellow gold and gray silicon are red in color; gold nanoparticles melt at much lower temperatures (nearly 300°C for 2.5 nm size) than the gold slabs (1064°C).
- Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or coating in a liquid.
- Nanoparticles also often possess unexpected optical properties as they are small enough to connect the electrons and produce quantum effects. For example

gold nanoparticles appear deep red to black in solution.

- The high surface area to volume ratio of nanoparticles provides a tremendous driving for drug diffusion.
- Moreover, nanoparticles have been found to impart some extra properties to various day to day products. For example the presence of titanium dioxide nanoparticles imparts what we call the self-cleaning effect, and the size being nano-range, the particles cannot be observed. Zinc oxide particles have been found to have superior UV blocking properties compared to its bulk substitute. This is one of the reasons why it is often used in the preparation of sunscreen lotions, and is completely photostable.

2.2. Advantages of Nanoparticles

Nanoparticles can offer significant advantages over the traditional delivery mechanisms in terms of various aspects (18). Nanoparticles have capability of both passive and active drug targeting due to its particle size and surface characteristics. With the use of nanoparticles, there is increase in drug therapeutic efficacy and reduction in side effects due to altering organ distribution of the drug and subsequent clearance of the drug. Nanoparticles also control and sustain the release of the drug. On the basis of choice of

matrix constituents, nanoparticles release and degradation properties can be easily modulated. Nanoparticles also have an advantage of Site-specific targeting. It can be achieved by using targeting ligands to surface of particles. Nanoparticles used for various routes of administration including oral, nasal, parenteral, intraocular etc. Along with these nanoparticles have high stability, capability to transport both hydrophilic and hydrophobic molecules, high ratio of surface area to mass, high reactivity, prolonged systemic circulation, precise drug targeting and concurrent delivery of multiple drugs (18).

2.3. Limitations of Nanoparticles

In spite of these advantages, nanoparticles do have limitations.

- For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size and large surface area readily result in limited drug loading and burst release.

Table 1 state about the different parameters for characterization nanoparticles and instruments used for these characterizations.

Table 1. Different Parameters for characterization of Nanoparticles

Parameters	Instrument used
Particle size & size distribution	Zetasizer, Photon correlation spectroscopy, Mercury porosimetry, Laser diffractometry
Particle Morphology	Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (AFM)
Charge determination	Laser droplet anemometry, Zeta potentiometer
Surface hydrophobicity	Water contact angle measurements, rose bangle (dye) binding, hydrophobic interaction chromatography, X-ray photoelectron spectroscopy
Chemical analysis of surface	Static secondary ion mass spectrometry
Carrier drug interaction	Differential scanning calorimetry
Nanoparticle dispersion stability	Critical flocculation temperature
Release profile	In-vitro release characteristic under physiologic & sink condition
Drug stability	Bioassay of drug extracted from nanoparticle, chemical analysis of drug

Figure 1. Types of nano-particulate delivery systems

3. Nanoparticles as Platform for Antimicrobials Delivery

These characteristic physicochemical properties have advantages in delivering and targeting to the target site, consequently minimizing adverse effect. Additionally, these could move in cells through endocytosis and consequently release the antibacterial agent to eliminate infections. In fact, a number of researches on nanoparticles based antibiotics have been developed and reviewed.

3.1. Metallic Nanoparticles

The continuous growing resistance of microbes to antibiotics causes severe health complications in current years. To confrontation with these problems, modern researcher identified the novel application by combining nanotechnology with intrinsic antimicrobial activity of the metals. Metallic nanoparticles are being utilized in many field of science with engineering comprising medical fields also and are still attract the scientists to invent new dimensions for their respective worth which is generally credited to their corresponding small sizes. In present scenario, the research in nanoparticle field is mainly focused on its synthesis or green synthesis not much on its applications. Research mainly focused on green synthesis

because of disadvantages of physical and chemical methods like considerable environmental defect, laborious and expensive (19). The metallic nanoparticles are most promising because of good antibacterial properties due to their large surface area to volume ratio, which is coming up as the current interest in the researchers due to the growing microbial resistance (20). Various Metals like copper, zinc, titanium, magnesium, gold (21) and metal oxides have been widely studied for their antimicrobial activities. Metal oxide nanoparticles, recognized due to its highly potent antibacterial effect, include iron oxide (Fe_2O_3), titanium oxide (TiO_2), copper oxide (CuO), and zinc oxide (ZnO). These nanoparticles mainly synthesis by either reducing the particle size by mechanical/ ball milling, chemical etching, microwave decomposition, thermal/ laser ablation and particle sputtering by chemical precipitation, microwave hydrothermal method, electrochemical precipitation, hydrothermal synthesis, vapor deposition, solvo-thermal method, atomic and molecular condensation, sol gel process, spray pyrolysis, laser pyrolysis, aerosol pyrolysis or by green synthesis using bacteria, plant extract and fungus (22). In the Table 2, 3 and 4, we briefly discussed about various metallic nanoparticle, their mechanism of action, application and limitation and toxicity.

Table 2. List of metallic nanoparticles

S.N.	Nanoparticles	Method of Preparation	Bacteria & Disease treated	Advantage	Reference
1.	Metal nanoparticles (Ag, Pt)	Ultrasonic irradiation method	<i>Streptococcus aureus</i> and <i>Escherichia coli</i>	Show antimicrobial activity of metals	23
2.	Silver (Ag) nanoparticle	Chemical Synthesis	Gram negative bacterial strains, <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>	Show antimicrobial activity of such hybrids materials	10, 24
3.	Copper nanoparticles	Modified polyol method	<i>Micrococcus luteus</i> , <i>Streptococcus aureus</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , and <i>Pseudomonas aeruginosa</i>	Show antimicrobial activity of metals	25
4.	Cobalt oxide nanoparticles	Simple urea-based Thermal decomposition method	Gram-positive And Gram-negative bacteria	Show antimicrobial activity of metals	26
5.	Quercetin-Acetylcholine-Selenium Nanoparticles	-----	Multidrug-resistant super bugs	Synergistic properties of both drug enhance the antibacterial activity of Selenium Nanoparticles	27
6.	CaO Nanoparticles	Microwave irradiated synthesis	Gram negative and gram positive bacteria and pathogenic yeast	Cheap, Nontoxic and inhibits the biofilm formation	28
7.	Dextran-and polyacrylic acid-coated ceria nanoparticles	-----	<i>Pseudomonas aeruginosa</i>	Enhanced biocompatibility properties, Minimized toxicity, and reduced clearance by the immune system	29
8.	Carboxyl-capped bismuth Nanoparticles	-----	<i>Helicobacter pylori</i>	-----	30
9.	ZnO nanoparticles	Precipitation method	Gram negative and gram positive bacteria	More stable and potent antibacterials against broad spectrum of microorganisms	31
10.	Selenium doped ZnO nanoparticles	Mechano-chemical method	-----	-----	-----
11.	Ampicillin loaded gold nanoparticles	Chemical Synthesis	Gram-negative and Gram-positive bacteria	Formed a potent system with new properties To destroy ampicillin-resistant bacteria	32
12.	Cefaclor loaded gold nanoparticle	One pot synthesis	<i>Escherichia coli</i> and <i>Streptococcus aureus</i>	-----	33
13.	Polyvinylpyrrolidone coated silver Nanoparticles	-----	HIV-I	Effective cyto-protective and post-infected anti-HIV-1 activities toward Hut/CCR5 cells.	34
14.	Metallic nanoparticle (Ag,Cu,W)	Pressurised gyration	<i>Pseudomonas aeruginosa</i>	Enhanced antimicrobial efficiency than pure poly(methyl methacrylate)fibres	35
15.	Silver Nanoparticles with titanium oxides	-----	<i>A.niger</i> , <i>P.spinulosum</i> and <i>S.chartarum</i> , and <i>E.coli</i> and <i>S. epidermidis</i>	Antimicrobial efficacy enhanced by titanium oxides	36
16.	Titanium dioxide nanoparticles	Green synthesis and advanced hydrothermal method	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> , and <i>Aspergillus niger</i>	Enhanced antibacterial activity against Gram-positive bacteria	37

Table 3. List of Metal/Metal oxide nanoparticle with their mechanism of action

S. No.	Metal/ Metal oxide nanoparticle	Mechanism of action	Reference
1.	Silver	Create holes in the cell wall of microbes by increasing the cell membrane permeability and in capacitating the respiratory chain. Inhibit and interrupt protein structure by binding to thiol and amino groups. Photo-catalytic and induce reactive oxygen species. Poisoning respiratory enzymes and components of the microbial electron transport system Binds to surface, altering the membrane function, and Bind to DNA bases and inhibiting replication	38, 39, 40, 41, 42
2.	Titanium dioxide	Photo-catalytic Stimulates reactive oxygen species burst. Reactive oxygen species destruct the cell membrane, DNA, and macromolecules and various functions of the bacterial cell	43, 44
3.	Gold	Destroy bacteria via photo-thermal heating Generate holes in the cell wall resulting in the leakage of cell contents and cell death Bind to the DNA of bacteria and inhibit the uncoiling and transcription of DNA	33, 45
4.	Iron oxide	Depolymerize the polysaccharides, Break DNA strands, can initiate lipid per oxidation or inactivate the enzymes	46
5.	Magnesium oxides	Inducing reactive oxygen species Inhibit essential enzymes of the bacteria	44
6.	Zinc Oxide	Cell wall damage due to ZnO-localized interaction Enhanced membrane permeability Internalization of nanoparticles due to loss of proton motive force and uptake of toxic dissolved zinc ions led to mitochondria weakness, intracellular outflow, and releasing expression of oxidative stress caused eventual cell growth inhibition and cell death Reactive oxygen generation	47, 48, 49
7.	Nitric Oxide	Affecting reactive nitrogen species than reactive oxygen species	50
8.	Copper oxide	Membrane disruption and Reactive oxygen species production Interact with DNA molecules and intercalate with nucleic acid strands. Disrupt biochemical processes.	43
9.	Aluminum oxide	Increases diffusion and accretion inside the microbial cells Create spit formation, increases perforation, and causes membrane disorganization and also causes microbial cell death	51

Table 4. Limitation and toxicity of Metallic nanoparticle

S. No.	Metallic nanoparticle	Limitation/Toxicity	Reference
1.	Silver	Aggregation of particles into large particles due to high surface energy leads to loss of antibacterial activity. Oral toxicity, eye irritation, corrosion, and dermal toxicity	52
2	Silicon oxide	10 nm particle having strong impact on cell viability and genotoxic effects	52
3.	Gold nanoparticles (4-5 nm)	Inflammation, accretion of gold in lungs, and an increased number of macrophages	53

3.2. Polymeric Nanoparticles

Polymeric nanoparticles with biodegradable and biocompatible polymers are good candidates as particulate carrier for antimicrobial agent and drug delivery and there has been considerable interest in the use of nanoparticles as potential delivery systems. Numerous investigations have shown that nanoparticles can not only improve the stability of therapeutic agents against enzymatic degradation, but by modulating polymer characteristics, they can also achieve desired therapeutic levels in target tissues for the required duration for optimal therapeutic efficacy (54, 1). Depending on their composition and intended use, they can be administered orally, parenterally, or locally (54). Different nanoparticles manufacturing methods were described allowing modification of physicochemical characteristics such as size, structure, morphology, surface texture and composition to meet different requirements.

Nanoparticles act on microbes by releasing antibiotics, antimicrobial peptides, and antimicrobial agents or by contact-killing like quaternary ammonium compounds etc. Cationic groups (with long hydrophobic chains) are capable to lysis the membrane to penetrate and burst the bacterial membrane and lead to death (52, 55).

Lots of the nanoparticle therapeutics in research are polymeric nanoparticles, which have been comprehensively explored as platform for drug delivery. Polymeric nanoparticles are fabricated from biocompatible and biodegradable polymers. Polymeric nanoparticles are formulated by a self-assembly process using block-copolymers comprising of two or more polymer chains with different hydrophilicity. Polymeric nanoparticles have been framed to encapsulate either hydrophilic or hydrophobic drug molecules, as well as macromolecules

such as proteins, peptides and nucleic acids (56).

The main issues in this field are the loading efficiency, stability of bioactive agent during preparation and release, release profiles and surface modification. Particles size and surface property (surface charge and hydrophobic or hydrophilic property) are primary factors for the in-vivo fate of nanoparticles. Surface modification of nanoparticles has been achieved mainly by two methods:

- Surface coating with hydrophilic polymers/surfactants
- Development of biodegradable copolymers with charged functional group or hydrophilic segments.

3.2.1. Methods of Preparation of Polymeric Nanoparticles

Method of preparation are mainly depends upon the physico-chemical characteristic of polymers and the drugs. They are classified as-

- Amphiphilic macromolecular cross linking
 - I Heat cross-linking
 - II Chemical cross-linking
- Polymerization methods
 - I Emulsion polymerization
 - II Dispersion polymerization
 - III Interfacial complexation
 - IV Interfacial condensation polymerization
- Polymer precipitation methods
 - I Solvent extraction/ evaporation methods.
 - II Solvent displacement methods
 - III Salting out.

Table 5. Polymer used in nanoparticle preparation with advantages

Polymer	Advantage
Poly(alkyl cyano acrylate)	Improve in-vitro in-vivo and drug stability.
Poly(alkyl cyano acrylate)polyester	Targeting RES for intracellular targeting.
Polyester with adsorbed PEG	Prolong systemic drug effect, avoid uptake by RES.
Poly (methyl meth acrylate)	Enhanced immune response.
Poly (methyl meth acrylate)	Enhanced bioavailability ,protection from GIT
Poly(alkylcyano acrylate)	Improve retention of drug /reduced washout.
Gelatin	Enhanced delivery and significant higher expression level.
Chitosan	Enhanced delivery and significant higher expression level.
PLGA	Enhanced delivery and significant higher expression level.
Poly-alkyl cyano acrylate	Improve absorption /permeation.

Table 6. List of polymeric nanoparticles

S. No.	Nanoparticles System	Method of Preparation	Bacteria & Disease treated	Advantage	Reference
1.	Quaternary ammonium polyethylenimine Nanoparticles	Chemical Synthesis	<i>S.aureus</i> , <i>S.epidermidis</i> , <i>Enterococcus faecalis</i> , <i>P.aeruginosa</i> and <i>E.coli</i>	Long lasting antimicrobial effect against a wide range of bacteria and effect on biocompatibility	57, 58
2.	Ciprofloxacin- loaded poly-isobutyl cyanoacrylate nanoparticles	Emulsion polymerization	<i>Mycobacterium avium</i>	Modifications In the pharmacokinetic properties and augment the activity	59
3.	Ampicillin-loaded polyethyl cyanoacrylate nanoparticles	Emulsion polymerization	<i>E.coli</i> , <i>S.aureus</i> , <i>S.faecalis</i> and <i>S.epidermis</i>	Increases drug encapsulation capacity and a size distribution and exhibit an activity equal or More than the free drug.	60
4.	Silver–carbene complex-loaded L-tyrosine polyphosphate nanoparticles	Water-in-oil-in-water emulsion method	Cystic fibrosis and <i>P.aeruginosa</i>	Sustain the release of the drug	61
5.	Rifampin and azithromycin loaded PLGA nanoparticles	Emulsion techniques	Persistent chlamydial infection	Better invitro efficacy	62
6.	Nisin-loaded solid lipid nanoparticles	Hot high pressure homogenization	<i>Listeria monocytogenes</i> DMST2871a nd <i>Lacto bacillus plantarum</i> TISTR850	Sustain the antibacterial action of nisin	63
7.	Rifampicin- loaded polylactide-co- glycolide nanoparticles	Emulsification/ solvent diffusion method	Gram-positive bacteria and Tuberculosis	-----	64
8.	Kojic acid-chitosan-tri-polyphosphate nanoparticles	-----	<i>S.aureus</i> and <i>P.aeruginosa</i>	-----	65
9.	Florfenicol- loaded solid lipid nanoparticle	Hot homogenisation and ultrasonic technique	<i>S.aureus</i> and <i>E.coli</i>	-----	66
10.	Quaternary ammonium polyethylene imine nanoparticles	-----	<i>S.viridans</i> , <i>Stenotrophomonas maltophilia</i> , <i>E.coli</i> and Peritonitis	-----	67
11.	Caffeic acid phenethyl ester PLGA nanoparticle	-----	<i>P.aeruginosa</i> , <i>E.coli</i> , <i>S.aureus</i> and methicillin- resistant <i>S.aureus</i>	-----	68
12.	Thioridazinein poly(lactic-co-glycolic) acid nanoparticles	-----	<i>M.tuberculosis</i>	Reduced dosing localized targeting and sustained release and reduce systemic toxicity and improve the antibacterial in-vivo activity	69
13.	Chitosan nanoparticles with chlorhexidin	-----	Periodontitis	Enhance the antibacterial activity	70
14.	Retinoic acid and lauric acid loaded solid lipid nanoparticles	-----	<i>Propionibacterium acnes</i> , <i>S.aureus</i> and <i>S.epidermidis</i>	Innovative acne therapy and decrease the side effect	71
15.	Poly(l-glutamic acid)-capped silver nanoparticles with ascorbic acid poly(lactide-co-glycolide) nanospheres	-----	Methicillin-resistant <i>S.aureus</i> and <i>E.coli</i>	New treatment of infections and Use in wound dressings and prophylactic applications	72
16.	Clarithromycin loaded PLGA nanoparticle	Nano-precipitation method		Enhanced physico- Chemical properties and therapeutic efficacy	73
17.	Daptomycin-loaded chitosan nanoparticles	-----	Endophthalmitis	Increasing the effectiveness of Treatment and reducing toxicity associated with systemic administration	74

18.	Clindamycin loaded PLGA hydroxyapatite nanoparticle	Sono chemical homogeneous precipitation and ultrasonic de-agglomeration	Wound healing	Enhance drug absorption and delivery	75
19.	Ciprofloxacin loaded Glycosylated polyacrylate nanoparticles		<i>S. aureus</i> , <i>Bacillus anthracis</i>	Enhanced bioavailability, Increased therapeutic Efficacy	76
20.	Azithromycin loaded PLGA nanoparticle	Nano-precipitation method		Better physico- Chemical properties and therapeutic efficacy	77
21.	Rifampicin, isoniazid, pyrazinamide loaded Alginate nanoparticles		<i>M. tuberculosis</i>	Increase drug load, Pharmacokinetic activity and Therapeutic efficacy	78
22.	Rifampicin loaded PLGA nanoparticle	Emulsification/ solvent diffusion method	Gram-positive and Gram-negative bacteria	Enabling drug penetration to parasites present in macrophages	64
23.	Halofantrine loaded PLA nanoparticle		Malaria	Improved stability, lower toxicity than free form in solution and rapid uptake by tissues	79
24.	Saquinavir loaded Polyethylene oxide Modified poly(epsilon caprolactone) Nanoparticles		HIV	Shield Saquinavir from enzyme cytochrome C Metabolism and avoid P-efflux pump	80
25.	PLGA nanoparticle entrapped eugenol and trans-cinnamaldehyde	Emulsion evaporation method	<i>Salmonella</i> and <i>Listeria</i>	Mask the hydrophobic property	81
26.	Levofloxacin loaded PLGA nanoparticle	Emulsification-solvent-evaporation method	Pulmonary infection	Biphasic extended drug release	82

Table 7. List of Polymers for nanoparticle fabrication

S. No.	Polymer	Composition	Action through	Reference
1.	Poly- ϵ -lysine	cationic homopeptide of L-lysine	Disrupting the cell membrane of bacteria	83
2.	Quaternary ammonium compounds.	Benzalkonium chloride, stearylalkonium chloride, and cetrimonium chloride	Interact with surface of bacteria and denature structural proteins and enzymes	52
3.	Chitosan	N-acetylglucosamine polymer chitin	Interrupted membrane functions like destabilization of membrane protein and membrane lysis, affect respiration and cell division, drug efflux system	84

3.3. Techniques to Determine Antibacterial Activity of Nanoparticles

Various experimental methods and assays are available for measuring the antibacterial efficacy of nanoparticles. Each method is unique and having their advantage and disadvantage. These methods/assays are (85):

- Optical density measurement
- Spread-plate(colony counts on agar)
- Cell counting devices
- Live/dead fluorescent stain MTS/MTT/XTT assays
- Crystal violet staining

4. Conclusions

In summary, it can be concluded that nanotechnology developed as a new approach in pharmaceutical sciences and research grasps great promise for overcoming complications related to delivery of antimicrobial and infection curing approaches. Various antimicrobial substances are unusable due to their instability, physicochemical limitations, enzyme degradation and cytotoxicity. Along with these problems, many microbes and their strains were getting resistant to the available antibiotics become as problem that surges the necessity to develop novel antibacterial substances. These issues were reasons for emergence of nanotechnology that provide many option for antimicrobials. The small size of the nanoparticles is very suitable for delivery of antibacterial substances.

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