We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 5

Nanoparticle based Drug Delivery Systems for Treatment of Infectious Diseases

Mojtaba Salouti and Azam Ahangari

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58423

1. Introduction

The chemotherapy of infections caused by bacteria that inhabit intracellularly presents a number of uncommon challenges. Many bacteria have found the way to produce a "silent" infection inside the cells and to avoid from their bactericidal mechanisms. However many methods for diagnosing and treating these and other bacterial infections presently exist, there is an essential need for new and improved approaches for bacterial destruction. Although the therapeutic efficacy of drugs has been well recognized, inefficient delivery could result in insufficient therapeutic index. It is now clear that a nanotechnology-driven approach using nanoparticles to selectively target and destroy pathogenic bacteria can be successfully implemented. Nanotechnology is one approach to overcome challenges of conventional drug delivery systems based on the development and fabrication of nanostructures. Some challenges associated with the technology are as it relates to drug effectiveness, toxicity, stability, pharmacokinetics and drug regulatory control. Localized diseases such as infection and inflammation not only have perforated vasculature but also overexpress some epitopes or receptors that can be used as targets. Thus, nanomedicines can also be actively targeted to these locations. Various types of nanoparticulate systems have been tried as potential drug delivery systems, containing biodegradable polymeric nanoparticles, polymeric micelles, nanocapsules, nanogels, fullerenes, solid lipid nanoparticles (SLN), nanoliposomes, dendrimers, metal nanoparticles and quantum dots. Nanoparticles have been found useful in the development of systemic, oral, pulmonary, transdermal and other administration routes to study drug targeting, the enhancement of drug bioavailability and protection of drug bioactivity and stability. In recent years, encapsulation of antimicrobial drugs in nanoparticle systems has emerged as an innovative and promising alternative that enhances therapeutic effectiveness

and minimizes the undesirable side effects of drugs. The major goals in designing nanoparticles as delivery systems are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action at the therapeutically optimal rate and dose regimen. This chapter focuses on nanoparticle-based drug delivery systems and clinical applications to treat a variety of bacterial infectious diseases and their potential applications in the field of medicine and biology.

2. Types of infections

Infectious disease is a clinically obvious disorder resulting from the presence of a pathogenic agent which can either be a virus, bacterium, fungus or parasite. These diseases are also called communicable diseases due to their ability to get transferred from one person to another (malaria, tuberculosis) and also sometimes from one species to another (flu, influenza). Infectious diseases can be vastly classified as: 1) known diseases which are insistently there (e.g., dengue, malaria, tuberculosis); 2) new, previously unknown diseases (e.g., severe acute respiratory syndrome); and 3) diseases which threaten to enhance in the near future (e.g., avian influenza). These diseases own a great risk as more than half of the deaths happening worldwide can be attributed to these diseases, particularly in developing countries [1]. Parasitism is based on the benefits acquired by a pathogenic bacterium invading the host and causing an infection. A bacterial infection is the process occurring when the microbe manifests its pathogenicity, and thus its capacity of inducing disease, by invading and causing a damage (locally or systemically) of the host organism. Consequently, the infectious disease could result in an acute infection, with a short and severe course, or a chronic, low-grade and long lasting infection [2].

3. Classification of bacterial pathogens

The classification of infectious agents inregards to their infective lifestyles in the host and corresponding pathogenic indications must be precisely described [3]. In the life of a microbe, the intracellularity and extracellularity are unclear designations unless obviously related to the situation where it is living. For a microbial pathogen, what matters is whether intra-or extracellularity is in the basis of the *in vivo* life and in relationship with pathogenicity. Classically, infectious agents are indicated as extracellular and intracellular pathogens [4-6].

3.1. Extracellular pathogens

Staphylococcus aureus, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* are typical examples of bacteria which have been considered extracellular pathogens, and lesion infections, osteomyelitis, scarlet fever, specified forms of pneumonia, urinary tract infections are examples of infections caused by these pathogens [7]. To produce disease, extracellular

http://dx.doi.org/10.5772/58423

pathogens utilize any portal of entry provided a satisfactory fluid medium be recognized at the site of lesion [4]. Extracellular pathogens utilize virulence mechanisms to avoid the antimicrobial capabilities of humoral immunity and phagocytosis thus advancing extracellular reproduction [8], in contrast with intracellular pathogens that promote the entry in to host cells containing macrophages and non-professional phagocytes such as epithelial cells [9].

3.2. Intracellular pathogens

Classical examples of intracellular pathogens are *Brucella abortus*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Salmonella enterica*, and typical infectious diseases caused by them include brucellosis, listeriosis, tuberculosis, and salmonellosis [10]. Intracellular pathogenic bacteria have the ability to establish a relationship in the sensitive host which includes a stage of intracellular reproduction [11]. To establish an infection, these pathogens have to make contact with the appropriated type of host cell that provides suitable intracellular conditions for growth [4]. Bacteria such as *Mycobacterium, Legionella, Brucella* or *Listeria* have extended the ability to resist and replicate inside various mammalian cells including the aggressive phagocytic cells, which establish the first-line defense against invading pathogens [12].

4. Targeted therapy of infections using nanoparticles

The hydrophilic nature of some antibiotics prevents thier capacity to penetrate the cells and, furthermore, the internalized molecules are mostly accumulated in lysosomes, where the bioactivity of the drug is low. Therefore, limited intracellular activity against sensitive bacteria is often found [13, 14]. Thus, the use of drug delivery systems (DDS) has been suggested for passive targeting of infected cells of the mononuclear phagocytic system to enhance the therapeutic index of antimicrobials in the intracellular environment, while minimizing the side effects associated with the systemic administration of the antibiotic [15]. The pathophysiological and anatomical changes of the affected tissues in a disease state offer many possibilities for the delivery of various nanotechnology-based products [16]. Bacteria gains antibiotic resistance due to three reasons namely: 1) modification of active site of the target resulting in reduction in the efficiency of binding of the drug, 2) direct destruction or modification of the antibiotic by enzymes produced by the organism or, 3) efflux of antibiotic from the cell [17]. Nanoparticles (NPs) can target antimicrobial agents to the site of infection, so that higher doses of drug can be given at the infected site, thereby overcoming existing resistance mechanisms with fewer harmful effects upon the patient [18]. As with nanoparticles targeting intracellular bacteria, nanoparticles targeting the site of infection can release high concentrations of antimicrobial drugs at the site of infection, while keeping the total dose of drug administered low. Nanoparticles can be targeted to sites of infection passively or actively. Passively targeted nanoparticles selectively undergo extravasation at sites of infection, where inflammation has led to enhanced blood vessel porousness. Actively targeted nanoparticles contain ligands (e.g. antibodies) that bind receptors (e.g. antigens) at sites of infection [19]. Passive targeting with nanoparticles, however, faces multiple barriers on the way to their target; these include

mucosal barriers, nonspecific uptake of the particle and non-specific delivery of the drug (as a result of uncontrolled release) [20]. Passive nanoparticulate targeting of chemotherapeutics to the cells and organs of the reticuloendothelial system (RES) has been a significant area of research for the treatment of chronic infectious diseases. The RES comprises monocyte-lineage immune cells such as macrophages and dendritic cells, as well as the spleen, liver, and kidneys. These components of the RES are consistently implicated as sites of nanoparticle clearance and localization [21]. The few studies that have compared targeted and nontargeted systems have demonstrated that the role of targeting ligands in localization at the target site is application dependent. Targeted delivery to atherosclerotic lesions is greatly enhanced by targeting ligands which impart an improved ability to accumulate at the target site [22]. Many active targeting strategies use the enhanced permeability and retention (EPR) effect, so that active and passive targeting mechanisms act synergistically that lead to higher concentration of nanostructures in the infected region than that in healthy tissues [23]. Targeted antimicrobial drug delivery to the site of infection, particularly intracellular infections, using NPs is a sensational prevision in treating infectious diseases [24, 25]. Intracellular microorganisms are taken up by alveolar macrophages (AMs), intracellulary survive or reproduce, and are persistent to the antimicrobial agents. Antibiotics loaded NPs can enter host cells through endocytosis, followed by releasing the payloads to delete intracellular microbes [26, 27]. The need to target drugs to specific sites is increasing day by day as a result of therapeutic and economic factors. Nanoparticulate systems have shown enormous potential in targeted drug delivery, specially to the brain [28].

5. Challenges in treating infectious diseases using nanotechnology

Use of antibiotics began with commercial production of penicillin in the late 1940s and claimed to be a great success until the 1970–1980s when newer and even stronger antibiotics were additionally improved [29]. Resistance to antimicrobial drugs becomes a threatening problem not only in hospitals but also in communities, resulting in fewer effective drugs available to control infections by "old" well-known bacteria [30]. Carrier systems allow antibiotics to be delivered selectively to phagocytic cells and to increase their cellular penetration in order to treat intracellular infections, particularly in the case of antibiotics active against microorganisms that produce this type of infection but that have a low intracellular penetration capacity [31]. Nevertheless, significant challenges remain for implementation of clinically viable therapies in this field. New challenges in the development of nanotechnology-based drug delivery systems include: the possibility of scale-up processes that bring innovative therapeutic techniques to the market rapidly, and the possibility of obtaining multifunctional systems to carry out several biological and therapeutic requirements [32]. Thus, a drug delivery system should be multifunctional and possess the ability to switch on and switch off specified functions when urgent. Another important requirement is that different properties of the multifunctional drug delivery systems are harmonized in an optimal fashion [33]. Therefore, design, discovery, and delivery of antimicrobial drugs with improved efficacy and avoidance of resistance are extremely requested [34].

5.1. Advantages of nanoantibiotics

The use of NPs as delivery vehicles for antimicrobial agents suggests a new and promising model in the design of effective therapeutics against many pathogenic bacteria [35]. Antimicrobial NPs propose several clinical advantages. First, the surface properties of nanoparticles can be changed for targeted drug delivery for *e.g.* small molecules, proteins, peptides, and nucleic acids loaded nanoparticles are not known by immune system and efficiently targeted to special tissue types [36]. Second, nanocarriers may overcome solubility or stability issues of the drug and minimize drug-induced side effects [37]. Third, using nanotechnology, it may be possible to achieve co-delivery of two or more drugs or therapeutic modality for combination therapy [33]. Fourth, NP-based antimicrobial drug delivery is promising in overcoming resistance to common antibiotics developed by many pathogenic bacteria [38]. Five, administration of antimicrobial agents using NPs can progress therapeutic index, extend drug circulation (i.e., extended half-life), and achieve controlled drug release, increasing the overall pharmacokinetics [30]. Six, the system can be used for several routes of administration including oral, nasal, parenteral, intra-ocular etc [39]. Thus, antimicrobial NPs are of great interest as they provide a number of benefits over free antimicrobial agents [35].

5.2. Disadvantages of nanoantibiotics including nanotoxicology

Although nanoantibiotics promises significant benefits and advances in addressing the key obstacles in treating infectious diseases, there are foreseeable challenges in translating this exciting technology for clinical application [40]. Profound knowledge about the potential toxicity of nanoantibiotics is also needed to guarantee successful clinical translation [41]. The toxic effects of antimicrobial NPs on central nervous system (CNS) are still unknown, and the interactions of NPs with the cells and tissues in CNS are poorly understood [42]. Furthermore, NPs represent size-specific properties that limit the use of currently available *in vitro* experiments in a general way, and there is no standardized definition for NP dose in mass, number, surface area, and biological samples (e.g., blood, urine, and inside organs) [43, 44]. This means that there is a high request to develop new characterization techniques that are not affected by NP properties as well as biological media [45]. NPs usually have short circulation half-life due to natural defense mechanism of human body for eliminating them after opsonization by the mononuclear phagocytic system. Therefore, the particles surfaces need to be changed to be hidden to opsonization [46]. A hydrophilic polymer such as polyethylene glycol is prevalently utilize for this purpose because it has worthwhile characteristics such as low degree of immunogenicity and antigenicity, chemical inertness of the polymer backbone, and availability of the terminal primary hydroxyl groups for derivatization [47].

6. Nanotechnology-based drug delivery systems

Perfectly, nanoparticulate drug delivery system should selectively accumulate in the necessary organ or tissue and at the same time, penetrate target cells to deliver the bioactive agent [48]. It has been proposed that, organ or tissue accumulation could be achieved by the passive or

antibody-mediated active targeting, while the intracellular delivery could be mediated by specified ligands or by cell-penetrating peptides [49-53]. The purpose of drug delivery is to carry out sustained (or slow) and/or controlled drug release and therefore to improve efficacy, safety, and/or patient comfort [54]. Thus, the use of drug delivery systems has been suggested for passive targeting of infected cells of the mononuclear phagocytic system to enhance the therapeutic index of antimicrobials in the intracellular environment, while minimizing the side effects related with the systemic administration of the antibiotic [55]. These systems propose many advantages in drug delivery, mainly focusing on improved safety and efficacy of the drugs, e.g. providing targeted delivery of drugs, improving bioavailability, extending drug or gene effect in target tissue, and improving the stability of therapeutic agents against chemical/enzymatic degradation [56]. The nanoscale size of these delivery systems is the basis for all these advantages [57]. It is therefore assumed that, DDS with enhanced targeting property is highly promising in increasing the efficiency and efficacy of therapy while at the same time minimizing side effects [33].

7. Types of drug carriers in medicine

7.1. Polymeric nanoparticles

Polymer-based nanoparticles are submicron-sized polymeric colloidal particles in which a therapeutic agent of interest can be embedded or encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface [59]. The drugs may also be sensitive to gastrointestinal degradation by digestive enzymes. The advantage of using polymeric nanoparticles is to permit encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation [60]. Therapeutically used polymeric nanoparticles are composed of biodegradable or biocompatible materials, such as poly (ε-caprolactone) (PCL), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), alginic acid, gelatin and chitosan [61-64]. Polymeric nanocarriers (NCs) may suggest an opportunity to target chlamydial organism within the contents, as NCs have been shown to be excellent intracellular carriers, and can be appropriate to encapsulate a variety of therapeutics containing biomacromolecules. Compared to free drugs, polymeric NCs have many other advantages including improved drug bioavailability, high carrier capacity, the ability to release the payload in a controlled behavior and to adapt to different routes of administration and to concentrate in inflammatory and infectious locations by virtue of their enhanced permeability and preservation. Conjugating NCs with specific moieties have also been shown to enhance their targeting to specific cells and tissues [65]. Polymeric nanoparticles have been extensively explored as means for drug solubilization, stabilization and targeting [66]. Polymeric nanoparticles possess several unique characteristics for antimicrobial drug delivery. Firstly, polymeric nanoparticles are structurally stable and can be synthesized with a sharper size distribution. Secondly, particle properties such as size, zeta potentials, and drug release profiles can be accurately tuned by selecting different polymer lengths, surfactants, and organic solvents during the synthesis. Thirdly, the surface of polymeric nanoparticles typically contains functional groups that can be chemically changed with either drug moieties or targeting ligands [67]. For targeted antimicrobial delivery, polymeric

nanoparticles have been repeatedly ornamented with lectin, which is a protein that binds to simple or complex carbohydrates present on most bacterial cell walls. For example, lectin-conjugated gliadin nanoparticles were studied for treating *Helicobacter pylori* related infection diseases. It has been found that lectin-conjugated nanoparticles bind specially to carbohydrate receptors on cell walls of *H. pylori* and release antimicrobial agents into the bacteria [30, 67]. Rifampicin-loaded polybutylcyanoacrylate nanoparticles have also shown enhanced antibacterial activity both *in vitro* and *in vivo* against *S. aureus* and *Mycobacterium avium* due to an effective delivery of drugs to macrophages [68].

7.2. Hydrogels

A hydrogel is a network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure [69]. Drugs can be loaded into the polymer matrix of these materials and controlled release is dependent on the diffusion coefficient of the drug across the hydrogel network [70]. Amongst the several types of drug delivery systems that have been developed in order to improve effectiveness and biocompatibility, hydrogels are extremely promising. Hydrogels are biocompatible hydrophilic networks that can be constructed from both synthetic and natural materials [71]. In an overall view, hydrogels can be classified based on a variety of characteristics, containing the nature of side groups (neutral or ionic), mechanical and structural features (affine or phantom), method of preparation (homo-or co-polymer), physical structure (amorphous, semicrystalline, hydrogen bonded, supermolecular, and hydrocollodial), and responsiveness to physiologic environment stimuli (pH, ionic strength, temperature, electromagnetic radiation, etc.) [72-75]. Classically, hydrogels have been used to deliver hydrophilic, small-molecule drugs which have high solubilities in both the hydrophilic hydrogel matrix and the aqueous solvent swelling the hydrogel [76]. Hydrogel-based hydrophobic drug delivery is in many respects a more difficult problem given the innate incongruity of the hydrophilic hydrogel network and the hydrophobic drug. A variety of strategies for introducing hydrophobic domains directly into otherwise hydrophilic hydrogel networks have permitted significant improvements in the loading of hydrophobic drugs [76]. Hydrogel/glass composite (Nitric oxide-releasing nanoparticles) NO NPs have also been shown to have a high degree of effectiveness against (Methicillin-resistant *Staphylococcus aureus*) MRSA infection in several different mouse models. In one mouse study by Martinez et al., administration of topical hydrogel/glass composite NO NPs into skin wounds infected with MRSA reduced bacterial burden significantly compared to controls [77]. Despite these many advantageous properties, hydrogels also have several limitations. The low elastic force of many hydrogels limits their use in load-bearing applications and can result in the precocious decomposition or flow away of the hydrogel from a targeted local site. This limitation may not be important in many typical drug delivery applications (e.g. subcutaneous injection) [78].

7.3. Metal nanoparticles

Metal-based nanoparticles of different shapes, sizes (between 10 to 100 nm) have also been investigated as diagnostic and drug delivery systems. Most common metallic nanoparticles contain gold, nickel, silver, iron oxide, zinc oxide, gadolinium, and titanium dioxide particles

[79]. Metal nanoparticles, which have a high specific surface area and a high fraction of surface atoms, have been studied extensively because of their unique physicochemical characteristics including catalytic activity, optical properties, electronic properties, antimicrobial activity, and magnetic properties [80-82]. Even though metallic nanoparticles are biocompatible and immobile carriers, a significant fraction of metal particles can be retained and accumulated in the body after drug administration, probably causing toxicity. Consequently, the use of metallic nanoparticles for drug delivery is a concern [83].

7.3.1. Gold nanoparticles

Gold nanoparticles (GNPs) have found many applications in many fields such as cancer diagnosis and therapy, drug and gene delivery, DNA and ptotein determination, etc. Due to their unique properties of small size, large surface area to volume ratio, high reactivity to the living cells, stability over high temperatures and translocation into the cells [84]. GNPs are suitable for the delivery of drugs to cellular destinations due to their ease of synthesis, functionalization and biocompatibility. GNPs functionalized with targeted specific biomolecules can effectively destroy cancer cells or bacteria [85]. The efficacy of GNPs conjugated to several antibiotics has also been the subject of some studies by Grace and Saha et al. They discovered that GNPs conjugates were more efficient in inhibiting the growth of Gram-positive and Gram-negative bacteria in comparison with the same dosage of antibiotics utilized alone. Their results suggest that GNPs can act as an effective drug carrier in a drug delivery system [86, 87]. Conjugates of gold nanoparticles with antibiotics and antibodies also have been used for selective photothermal killing of protozoa and bacteria [88]. Gu et al. synthesized stable gold nanoparticles covered with vancomycin and showed significant enhancement of antibacterial activity, in comparison with the activity of the free antibiotic [89]. In another report, Selvaraj et al. utilized the anticancer compound 5-fluorouracil bound to GNPs and found that the resulting conjugate was significantly more effective against a range of bacterial and fungal organisms in comparison with alone [90]. Recently, it has been reported that the gentamicin conjugated with gold nanospheres was significantly more effective against *S. aureus* in comparsion with free gentamicin [91]. Each GNP surrounded by a number of drug moieties acts as a single group against the microbial organisms [92]. The greater antibacterial effect of the GNPs conjugates has been ascribed to their ability to bind to and/or penetrate the cell wall and, in doing so they are able to deliver a large number of antibiotic molecules into a highly localized volume [93].

7.3.2. Silver nanoparticles

Silver nanoparticles of size smaller than 100 nm contain about 10000–15000 silver atoms [94, 95]. They are prepared by engineering the metallic silver into ultrafine particles by numerous physical methods, which include spark discharging, electrochemical reduction, solution irradiation and cryochemical synthesis [96]. The most widely used and known application of silver nanoparticles is in the medical sciences. These include topical ointments and creams containing silver to prevent infection of burns and open wounds [97]. Among the many different types of metallic and metal oxide NPs, silver nanoparticles have demonstrated to be

the most effective against bacteria, viruses, and other eukaryotic microorganisms [98, 99]. Antibacterial properties inhibit the reproduction of bacteria, which is a microbe. The silver nanoparticles can "inactivate proteins, blocking respiration and electron transfer, and subsequently inactivating the bacteria" [100]. The antibacterial properties of the silver nanoparticles depend on the size of the particles; the smaller the particles the better the effect. The particle size is a major factor because the smaller the particle the greater the surface area, which allows for greater interaction with the bacteria [100]. It has been reported that combined use of silver nanoparticles with antibiotics, such as penicillin G, amoxicillin, erythromycin, and vancomycin, resulted in enhanced and synergistic antimicrobial effects against Gram-positive and Gram-negative bacteria (e.g., *E. coli* and *S. aureus*) [80, 101, 102]. Although beneficial as antimicrobial agents, silver nanoparticles have adverse effects on cells such as the production of reactive oxygen species which are toxic to both bacteria and eukaryotic cells [103, 104]. In contrast, the cytotoxicity of gold nanoparticles is quite low, and they have been used for medical imaging and have served as scaffolds for drug delivery [105, 106].

7.3.3. Magnetic nanoparticles

Magnetic nanoparticles engineered as drug delivery devices retain the ability to track their movement through the body. This is significant because it allows clinicians to monitor the effectivity of injected therapeutics to reach their target sites [107]. Iron oxide nanoparticles (IONPs) are magnetic Fe_3O_4 or Fe_2O_3 nanocrystals which can interact with external magnetic fields, offering different opportunities in nanomedicine, e.g., as contrast agents in MRI, for magnetic hyperthermal therapies, or as magnetically triggerable drug delivery systems [108]. There are some studies on evaluating the toxicity of magnetite nanoparticles on eukaryote cells, which their results showed negligible toxicity in eukaryote cells of the modified magnetite nanoparticles with different surfactants such as glycine or oleic acid. But the toxicity of magnetite nanoparticles on bacteria cells has not been reported [109]. However, in most of the cases where magnetic nanocarriers have been used, difficulties in achieving these objectives appeared. In turn, magnetic force may not be strong enough to overcome the force of blood flow and to accumulate magnetic drugs only at target site [110]. Therefore, designing magnetic drug delivery systems requires taking into consideration many factors, e.g., magnetic properties and size of particles, strength of magnetic field, drug loading capacity, the place of accessibility of target tissue, or the rate of blood flow [111]. The vancomycin functionalized magnetic nanoparticles for pathogen detection have been investigated by Gu et al. [112]. Vancomycin can be attached to the magnetic nanoparticles surface by activating the–COOH group of vancomycin followed by reaction with the amine groups on the surface of the iron oxide nanoparticles. The vancomycin conjugated iron oxide nanoparticles were utilized as probes to selectively entrap *S. saprophyticus* (a pathogen that usually infects the urinary tract of young women) and *S. aureus* bacteria from urine specimen using a magnetic field [1, 112]. It has been reported that the various nanoparticles, Al_2O_3, Fe_3O_4, CeO_2, ZrO_2 and MgO were subjected to evaluate its antibacterial potential against ophthalmic pathogens such as *Pseudomonas aeruginosa, Acinetobacter* sp., *Klebsiella pneumoniae, E. coli, Streptococcus viridans* and *Streptococcus pyogenes*. Among the nanoparticles, Fe_3O_4 showed maximum activity against

Pseudomonas aeruginosa. The reactive oxygen species (ROS) generated by Fe_3O_4 nanoparticles could kill bacteria without harming nonbacterial cells [113].

7.4. Silica nanoparticles

Silica materials are suitable for several important biological applications, such as drug delivery, imaging, oxygen carrier or controlled release [114]. Silica materials have been proved to be efficient carriers for the local release of antibiotics, which could be of interest in the context of biofilm associated infections, which are a real challenge for the modern medicine [115]. Moreover, mesoporous silica has been found to be relatively "non-toxic" and biocompatible, however of course depending on dose and administration route [116]. Nanoporous silica materials possess large pore volumes and high surface areas, allowing the absorption of large amounts of drugs, thus providing sufficient concentrations for local treatment. The surface of silica materials is reactive due to the presence of silanol groups. This allows for facile modification by silanization reactions and thus opens possibilities for enhancing the drug loading and for controlling the drug release [117]. Till present there are only few reports concerning the application of silica materials, crystalline or amorphous, in the antimicrobial therapy [115]. Zhang et al. suggested a highly-sensitive fluoroimmunoassay for the determination of *staphylococcal* enterotoxin C_1 (SEC_1). This method utilizes anti-SEC_1 coated NPs for detection which is possible in food samples and enables fluorescence microscopy imaging for the determination of SEC_1 [118]. Recently, Grumezescu et al. reported that silica nanostructures have significantly improved the anti-*staphylococcal* activity of bacitracin and kanamycin sulfate, as revealed by the drastic decrease of the minimal inhibitory activity of the respective antibiotics loaded in the SiO_2 nanopowder. These results, correlated with the high biocompatibility of the porous silica structure recommend it as an efficient vehicle for the local delivery of antibiotics in lower active doses, reducing thus their cytotoxicity and side effects [119].

7.5. Micelles

Micelles are submicroscopic aggregates of surfactant molecules assembly of amphiphillic block copolymers or polymer-lipid conjugates or other surface-active molecules that self-assemble in aqueous media to form structures with a hydrophobic core [120, 121]. The ability to functionalise the micelles as well as tailor the disintegration behaviour by varying the co-polymer composition are beneficial parameters in making them drug carriers of choice. Their small size (1-50 nm) makes them ideal for intravenous delivery. In addition they are also more stable, when compared to liposomes due to be ability to design them to be chemically stable and biocompatible [122]. One specific feature of micelles is that the amount of drug released can be controlled by an external stimulus like pH, temperature, ultrasound or certain enzymes [123]. Other unique properties of polymeric micelles are that they are easily altered with small functional groups that enhance their targeting potential [124]. Generally, polymeric surfactants are known to be less toxic than low-molecular-weight surfactants, such as sodium dodecyl sulfate. Furthermore, in theory, polymeric micelles are considered very safe in relation to chronic toxicity [125]. The disadvantage for the polymeric micelle systems is the immature technology for drug incorporation in a physical manner. The another disadvantage is much

slower extravazation of polymeric carrier systems than that of low molecular weight drugs. This results from a difference in extravazation mechanisms between polymeric carrier systems and low molecular weight drugs [126].

7.6. Liposomes

Liposomes are small spherical vesicles in which one or more aqueous parts are completely surrounded by molecules that have hydrophilic and hydrophobic functionality. Liposomes change with composition, size, surface charge and method of preparation. They can be single or in multiple bilayers. Those including one bilayer membrane are called small unilamellar vesicles or large unilamellar vesicles based on their sizes [127]. Nanoparticulate DDS, such as liposomes, are mostly used to enhance the efficacy of drug and DNA delivery and targeting [128, 129]. Liposomes are also the most broadly used antimicrobial drug delivery vehicles because their lipid bilayer structure imitators the cell membrane and can readily fuse with infectious microbes [30]. One of the disadvantages of liposomal antibiotics is the short shelf-lives of lipid vesicles, which limits drug stability. Short shelflives can be conditioned by both physical and chemical processes [130]. There are many advantages of liposomes as antibiotic carriers: improved pharmacokinetics and biodistribution; decreased toxicity; enhanced activity against intracellular pathogens; target selectivity; enhanced activity against extracellular pathogens, in particular to overcome bacterial drug resistance [131]. The ability of liposomes to alter drug distribution depends mostly on their size and surface properties [132]. Thus, liposomal encapsulation of antibiotics helps to increase their therapeutic index with mode of action related to increasing the drug concentration at the site of infection and/or reducing its toxicity [133]. For instance, encapsulation of vancomycin and teicoplanin in liposomes resulted in significantly improved elimination of intracellular methicillin resistant *S. aureus* (MRSA) infection [35]. Netilmicin liposomes showed an increase in pharmacological activity in a peritonitis model of mice infected with *E. coli*, in terms of survival both prophylactically and therapeutically [134]. Recently, Deol and Khuller produced lung-specific liposomes made of phosphatidylcholine, cholesterol, dicetylphosphate, O-steroyl amylopectin and monosialogangliosides/distearylphosphatidylethanolamine-poly (ethylene glycol) 2000 for the targeted delivery of anti-Tuberculosis (TB) drugs to the lung [135].

7.7. Solid lipid nanoparticles (SLN)

Solid lipid nanoparticles (SLN) were developed at the beginning of 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery [20]. SLNs are sub-micron colloidal carriers, ranging from 50 nm to 1 μm, that are composed of physiological lipid dispersed in water or in aqueous surfactant solution [136]. In the last decade SLNs have gained considerable interest as novel particulate drug delivery systems. SLNs are suitable for the incorporation of lipophilic and hydrophilic drugs within the lipid matrix in considerable amounts [137]. SLN consist of a solid lipid matrix at room and body temperature, where the drug is normally incorporated in the submicron size range (below 1 μm) [35]. Some advantages of SLNs are

possibility of controlling drug release and drug targeting, increased drug stability, high drug payload, possibility of the incorporation of lipophilic and hydrophilic drugs, lack of biotoxicity of the carrier, no problems with respect to large-scale production, sterilization possibility, and good tolerability [138]. Common disadvantages of SLN are their particle growing, their unpredictable gelation tendency, their unexpected dynamics of polymorphic transitions and their inherent low incorporation rate due to the crystalline structure of the solid lipid [139]. SLNs are considered good drug carriers to obtain sustained release of antibiotics [140]. SLNs can act as promising carriers for sustained ciprofloxacin release in infections or to enhance the bioavailability of tobramycin from antibiotic-loaded SLN in the aqueous humor for topical ocular delivery [141, 142]. Nimje et al. (2009) reported the selective delivery of rifabutin, another antituberculosis drug, to alveolar tissues, using drug-loaded solid lipid nanoparticles, increasing the therapeutic margin of safety and reducing side effects [143]. Another prominent example of SLNs-based drug delivery is pulmonary delivery of antimicrobials to treat tuberculosis, a serious lung infection caused by *Mycobacterium tuberculosis*. In some severe cases, tuberculosis infection spreads from the lungs and affects the lymphatic systems. SLNs can facilitate the delivery of anti-tuberculosis drugs such as rifampin, isoniazidand pyrazinamide to the lungs as well as to the lymphatic systems [144]. Even though the development history of SLN-based antimicrobial drug delivery systems is relatively shorter than other nanoparticle systems such as liposomes and polymeric nanoparticles, SLNs have shown great therapeutic potentials [145].

7.8. Fullerenes

Fullerenes are a new form of carbon, other forms being diamond, graphite, and coal. They can take three forms of a hollow sphere, ellipsoid, or tube. Their small size, spherical shape, and hollow interior all provide therapeutic opportunities [146]. The most abundant form of fullerenes is buckminsterfullerene (C60) with 60 carbon atoms arranged in a spherical structure [147]. The shape of the molecule, recognized as truncated icosahedron, resembles that of a football ball, containing 12 pentagons and 20 hexagons, in which every carbon atom forms bond to three other neighbor atoms through sp^2 hybridization [148]. Friedman et al and Schinazi et al distinguished that the hydrophobic cleft of the human immunodeficiency virus (HIV)-1 protease can seamlessly host a C60 molecule [149]. This discovery was the first piece of evidence that fullerenes could have pharmaceutical significance through interactions with biological targets, highlighting the great potential of fullerenes in medicinal applications. Since fullerenes possess unique geometrical shapes, as well as novel photophysical properties, in addition to being efficient radical scavengers, a wide variety of biological applications have been considered [150-152]. Some studies asserted that C60 could be also utilized for the photodynamic inactivation of bacteria, as persuasively demonstrated in studies examining the effects of water-soluble and nanoparticulate C60 on various bacterial strains [153]. The effects were significantly more pronounced in Gram positive *(Staphylococcus* spp., *Streptococcus* spp.) than in Gram negative bacteria (*Klebsiella Pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Streptococcus pyogenes*), indicating that the bactericidal action was dependent on the fullerene insertion into the microbial cellwall, the structure of which differs between

http://dx.doi.org/10.5772/58423

Gram positive and Gram negative bacteria [154]. Additionally, the quinazolin–fullerene conjugate 18 was reported to have an inhibitory potential of 98.83% at a minimal inhibitory concentration of 1.562 μg/mL when treating *M. tuberculosis* [155].

7.9. Dendrimers

First discovered in the early 1980's by Tomalia and co-workers, such hyperbranched molecules were called dendrimers [156]. Dendrimers are globular repeatedly branched macromolecules that exhibit controlled patterns of branching with multiple arms extending from a central core [157]. The well defined structure, monodispersity of size, surface functionalization capability, and stability are properties of dendrimers that make them attractive drug carrier candidates [20]. Asymmetric dendrimers are synthesized by coupling dendrons of different generations (G1-G4) to a linear core, which yields a branched dendrimer with a nonuniform orthogonal architecture. This asymmetry allows for tunable structures and molecular weights, with precise control over the number of functional groups available on each dendron for attachment of drugs, imaging agents, and other therapeutic moieties [158]. Dendrimers also possess many unique properties that make them a good nanoparticle platform for antimicrobial drug delivery. They are highly arranged and regularly branched globular macromolecules, with a core, layers of branched repeat units emerging from the core and functional end groups on the outer layer of repeat units [159]. Dendrimer biocides may contain quaternary ammonium salts as functional end groups displaying greater antimicrobial activity against bacteria than small drug molecules, due to a high density of active antimicrobials on the dendrimer surfaces [160]. Dendrimers can be made from a wide variety of biocompatible materials, the most frequently used are polyamidoamine (PAMAM), polyethylene oxide (PEO), polypropylene imine (PPI), polyethyleneimine (PEI), polyethylene glycol (PEG) etc [161]. PAMAM dendrimers are dendritic polymers characterized by regular branching and radial symmetry. PAMAM dendrimers have illustrated useful drug delivery and antimicrobial applications with amino-terminated dendrimers showing high antibacterial efficacy [162]. It is well known that PAMAM dendrimers with primary amine surface functional groups may enter the cellular membrane. Sulfomethoxazole (a sulfonamide derivative poorly soluble and thus presenting low bioavailability) was administered with PAMAM dendrimers *in vitro* [163]. Sulfamethoxazole (SMZ)-encapsulating PAMAM dendrimers led to sustained release of the drug *in vitro* and 4–8 folds increased antibacterial activity against *E. coli,* compared to free SMZ [163].

7.10. Zeolites

Zeolites are solid hydrated crystalline materials with frame-works comprising silicon, aluminum and oxygen and featuring nano-channels and cages of regular dimensions [164]. Silica is a neutral regular tetrahedronin in which positive charge of silicon ion is balanced by oxygen [165]. The capacity of cation exchange depends on the ratio of silica/alumina in the structure. Generally, zeolits with a low silica/alumina (Si/Al) ratio have higher ion exchange capacity. According Si/Al ratio, there are several types of natural and synthetic zeolites including zeolite-β, zeolite A, zeolite X and zeolite Y, which are the most common commercial adsorbents [165]. Zeolites are minerals with selective pores that can be used to sieve molecules

having certain dimensions [166]. Several recent studies showed that the potential of zeolites in medical applications is due to their structural properties and stability in biological environments [167]. Zeolites have also been explored as suitable hosts for the encapsulation of drug molecules, in search for efficient drug delivery sysytems. Both zeolites and drugs have been administrated simultaneously to a patient without loss of the individual pharmacological effect of the drugs [164, 167]. Coating or impregnating zeolite with metallic silver nanoparticles to prepare zeolite composites can enhance the antibacterial ability of materials, and these materials can inhibit bacterial growth effectively [168]. It has been reported that silver embedded zeolite A was found to be antibactrerial against *E. coli*, *Bacillus subtilis* and *staphylococcus aureus* [165]. Moreover, polymer composites of plasticized poly (vinylchloride) pellets with silver zeolites demonstrated activity against *S. epidermidis* and *E. coli*, while polyurethane composites with silver zeolites showed antimicrobial action against *E. coli* and polylactid acidpolylactide (PLA)/silver zeolite composites also presented activity against *S. aureus* and *E. coli*, with silver being effectively released from the films [169].

7.11. Quantum dots

Quantum dots (QDs) are nanocrystals formed by semiconductor materials, showing attractive photophysical properties, containing high quantum yield, resistance to photobleaching, and harmonic photoluminescence, making them potentially powerful tools in a range of biomedical applications [170, 171]. QDs are typically in the size range between 1 nm and 10 nm, composed of groups II–VI (e.g., CdSe) or II–V (e.g., InP) elements of the periodic table. QDs are highly bright, photostable and possess high quantum yield [172]. Due to their very small size, they possess unique properties and behave in different way than crystals in macro scale [173]. Water-soluble QDs may be cross-linked to biomolecules such antibodies, oligonucleotides, or small molecule ligands to render them specific to biological targets [174]. A variety of techniques have been explored to label cells internally with QDs, using passive uptake, receptor-mediated internalization, chemical transfection, and mechanical delivery. QDs have been loaded passively into cells by exploiting the innate capacity of many cell types to uptake their extracellular space through endocytosis [175, 176]. Krauss group utilized CdSe/ZnS streptavidin-coated QDs to detect solitary pathogenic *E. coli* O157:H7 in phosphate buffer saline solution [177]. Biotinylated anti-*E. coli* O157:H7 distinguished streptavidin-coated QDs via famous avidin–biotin binding. Once treated, QD labeled antibody selectively targeted pathogenic *E. coli* O157:H7 over common lab strain *E. coli* DH5α. This assay represented 2 orders of magnitude more sensitivity than using an organic dye with minimal non-specific binding between the QDs and the bacterial cells [178]. Recently, Luo et al. reported that CDTe QDs coupled to a rocephin antibiotic complex exhibited antibacterial activity against *Escherichia coli* [179]. The mechanism for the antimicrobial activity of QDs is unclear, but it is possible that QDs can produce singlet O_2, a source of free radicals, under irradiation. Heavy metal ion oxides can also form the QDs core and result in antimicrobial activity [180]. A recent and excellent review emphasized the application of bioconjugated quantum dots for the detection of food contaminants such as pathogenic bacterial toxins like botulinum toxin, enterotoxins produced by *Staphylococcus aureus* and *Escherichia coli* [181].

http://dx.doi.org/10.5772/58423

8. Antibacterial activity of carrier systems for intracellular infection

Treatment of intracellular bacterial infection remains both a medical and economic challenge. Pathogens thriving or maintaining themselves in cells, or simply taking transient refuge therein, are indeed shielded from many of the humoral and cellular means of defense. They also seem more or less protected against many antibiotics [182]. Various infectious diseases are caused by facultative organisms that are able to survive in phagocytic cells. The intracellular location of these microorganisms protects them from the host defence systems and from some antibiotics with poor penetration into phagocytic cells. Intracellular infections are especially difficult to eradicate because bacteria fight for their survival using several ingenious mechanisms: inhibition of the phagosome–lysosome fusion, resistance to attack by lysosomal enzymes, oxygenated compounds and defensins of the host macrophages, escape from the phagosome into the cytoplasm [183]. Thus, the need for the development of improved antimicrobial chemotherapeutics and prophylaxis strategies is increasing [4]. In spite of the availability of a wide variety of *in vitro* active antibiotics, therapeutic deficiencies are reported, mainly because of the inability of the drugs to reach the bacteria harboring intracellular compartments or to perform their activity in the intracellular environments [182, 183]. However, the poor cellular penetration limits these use in the treatment of infections caused by intracellular pathogens [183]. One strategy utilized to improve the penetration of antibiotics into phagocytic cells is the use of carrier systems that deliver these drugs directly to the target cells [185]. Several *in vivo* and *in vitro* studies have reported the potential applications of various carrier systems to enhance the selectivity of antibiotics for phagocytic cells and sustain therapeutic efficiency in the treatment of intracellular infections [31].

8.1. Infections due to mycobacteria

Tuberculosis, caused by *Mycobacterium tuberculosis*, is a ordinary lung infection that is even endemic to specified regions. Its prevalence has increased recently because it is often associated with AIDS. The *Mycobacterium avium* complex (MAC) complex is the main cause of hardships in immunodepressed patients [186]. There are drugs that are efficient against tuberculosis, but these are used in extended treatment, increasing the risk of side effects [187]. Moreover, tuberculosis has emerged as an occupational disease in the health care set-up. Although an effective therapeutic regimen is available, patient non-compliance (because of the need of taking antitubercular drugs daily or several times a week) results in treatment failure as well as the emergence of drug resistance [188]. The use of delivery systems facilitates the selective shuttling of antibiotic to the site of infection and such systems provide slow and prolonged drug release, which permits administration over longer intervals of time [189]. The encapsulation of antitubercular drugs in polymeric particles is another strategy to improve the current therapeutic regimen of tuberculosis. In the last few years several antitubercular drugs-containing PLGA and PLA microparticles and mainly nanoparticles have been comprehensively studied [190]. Fawaz et al. encapsulated the synthetic drug ciprofloxacin in polyisobutylcyanoacrylate (PIBCA) nanoparticles. When testing these nanoparticles against a *M. avium* infection in a human macrophage culture, it was found that though nanoparticle associated ciprofloxacin was more effective than unbound ciprofloxacin, it was much less so

than anticipated [191]. Rifampicin-loaded polybutylcyanoacrylate nanoparticles have shown enhanced antibacterial activity both *in vitro* and *in vivo* against *S. aureus* and *M. avium* due to an effective delivery of drugs to macrophages [192]. The encapsulation of different antibiotics in liposomes has shown good antibacterial efficacy in both macrophage cell lines and in animal models of MAC-due disease [193]. Ciprofloxacin efficiently inhibits the growth of *M. avium in vitro* in a murine macrophage-like cell line using negatively charged liposomes and *in vivo* using specific stealth liposomes in a mouse model of tuberculosis infection [194]. Similar results have been obtained using stealth liposomes of isoniazid and rifampicin, which show controlled release and reduce toxicity *in vivo* in mice infected with *M. tuberculosis* [195].

8.2. Brucellosis

Brucellosis is an infectious disease caused by *Brucella* spp. Four species, *Brucella abortus*, *Brucella melitensis*, *Brucella suis* and *Brucella canis*, have been recognized as human pathogens each associated with a different natural host animal [196]. These small coccobacilli are mainly localized intracellularly within phagocytic cells making treatment difficult, since most antibiotics, although highly active *in vitro*, do not actively pass through cellular membranes [197]. However in the last two decades many experiments have provided good evidence criteria for its antibiotic treatment, the most suitable antimicrobial therapy for human brucellosis continues to be a controversial subject [198]. Because of its intracellular location, long treatments with several antibiotics are required. Relapses are frequent owing to the low efficacy of many drugs and the lack of patient agreement [199]. Thus, alternative methods such as drug delivery systems to achieve high intracellular bactericidal activity should be considered [198]. Gentamicin, encapsulated in different types of liposomes, has been evaluated against murine monocytes infected with *B. abortus*. All such liposomes reduced the number of bacteria, the most effective being SPLVs (stable plurilamellar vesicles) [200]. Rifampicin-loaded mannosylated dendrimers have indicated specific pH-dependent delivery of this antibiotic to rat alveolar macrophages [201]. Recently, gentamicin loaded poly (D, L-lactide-co-glycolide) (PLGA) have been obtained by the several emulsion solvent evaporation method for the treatment of brucellosis [202]. Thus, alternative methods such as DDS to achieve high intracellular bactericidal activity seem promising. The possible use of drug delivery systems containing aminoglycosides may be one of the most appropriate therapeutic advances in human brucellosis treatment in the recent years [203].

8.3. Salmonellosis

Salmonellosis is one of the most serious food-borne diseases affecting humans. It may be considered the most important pandemic zoonosis under natural conditions [204]. Bacteria of the genus *salmonella* are facultative intracellular parasites that cause salmonellosis and typhoid fever. Antibiotics effective against this type of bacteria have limitations owing to the problems of formulation, low penetration, or the appearance of side effects; these can be solved using carrier systems [205]. Several studies using antibiotic-loaded nanoparticles have been performed in order to recognize the suitability and efficacy of these carriers in experimental models of salmonellosis [204]. In order to recognize whether polyalkycyanoacrylate nanopar-

ticles were also effective against non-dividing bacteria, Page-Clisson *et al.* studied the effectiveness of these carriers in a model of persistent *Salmonella typhimurium* infection [206]. They found that although at early stages of the infection, when bacteria are actively dividing, there was an antibacterial effect, neither free nor nanoencapsulated ciprofloxacin or ampicillin could significantly reduce infection in the liver or the spleen at later stages [206]. Liposomal ciprofloxacin, administered intravenously and intraperitoneally to mice infected with intracellular *S. typhimurium*, has increased habitation time in plasma and the concentration of drug in the liver, spleen, lungs and kidneys is also increased, while when administered intratracheally its pulmonary retention is increased. Compared with free ciprofloxacin, it extends survival and reduces the number of bacteria in the liver and spleen [207]. Therefore, alternative methods such as DDS which achieve high protective and bactericidal activity should be taken into account in the future as suitable treatments for *Salmonella*-induced infections [203].

8.4. Lysteriosis

Lysteria monocytogenes is a facultative intracellular parasite able to cause meningitis and septicaemia. The encapsulation of ampicillin in liposomes decreases the survival of *L. monocytogenes* in mouse peritoneal macrophages to different extents, depending on the composition of the liposomes [208]. Chitosan-coated plastic films, alone or loaded with antimicrobial agents, were evaluated for their effect against *L. monocytogenes*. These chitosan-coated films inhibited this pathogen growth in a concentration-dependent manner whereas chitosancoated films impregnated with antibiotics were significantly more effective against *L. monocytogenes* [209]. Formulation of gentamicin in liposomes containing DOPE (dioleylphosphatidylethanolamine) and sensitive to pH has been reported to increase the concentration of drug in mouse macrophages infected with *L. monocytogenes*, increasing its bactericidal activity. This formulation is more effective against *L. monocytogenes* than against other bacteria owing to its location in the cytosol [210]. Furthermore, the efficacy of liposomes and free antibiotic were distinguished in *Listeria*-infected mice. Seven days after the treatment, ampicillin-loaded liposomes had reduced the infection by 3.2 logs in the liver and 2.8 logs in the spleen, while free ampicillin was ineffective [208]. In another example, ampicillin-encapsulated polyisohexylcyanoacrylate nanoparticles have been investigated against *L. monocytogenes* in mouse peritoneal macrophages [211].

9. Specific applications of biodegradable NPs

Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various routes. One major problem with the intravenous administration of colloidal particles is their interaction with the reticulo-endothelial system [212]. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery

have been discovered. However, their applications in buccal, nasal and topical delivery are still awaiting exploration [213].

9.1. Oral delivery

In recent years, significant research has been done using nanoparticles as oral drug delivery vehicles. Oral delivery of drugs using nanoparticles has been shown to be far superior to the delivery of free drugs in terms of bioavialability, residence time, and biodistribution [214]. Oral drug delivery is the choicest route for drug administration because of its non-invasive nature [215]. The drugs may also be susceptible to gastrointestinal degradation by digestive enzymes. The advantage of using polymeric nanoparticles is to permit encapsulation of bioactive molecules and maintain them against enzymatic and hydrolytic degradation [214] The use of submicron-size particular systems in oral drug delivery, especially peptide drugs, has attracted considerable pharmaceutical interest [216]. The efficacy or proficiency of the orally administered drug commonly depends on its solubility and absorption through the gastrointestinal tract. Therefore, a drug candidate that represents poor aqueous solubility and/or decomposition-rate limited absorption is believed to possess low and/or highly variable oral bioavailability [212]. Despite numerous studies providing evidence that oral delivery of encapsulated antigens can efficiently elicit immune responses, up to now, less studies report a protection induced by antigen loaded particles administrated by the oral route against a challenge with the pathogen [217]. Fattal et al. achieved the protection of mice against *S. typhimurium* following oral administration of *S. typhimurium* phosphorylcholine antigen encapsulated in PLGA particles [218]. Pinto and Muller (1999) incorporated SLN into spherical pellets and investigated SLN release for oral administration [219]. Orally administered antibiotics such as atovaquone and bupravaquone replicate this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and consequently bioavailability [212].

9.2. Pulmonary delivery

Besides its non-invasive nature, pulmonary drug delivery has many other advantages compared to alternative drug delivery strategies, containing a large surface area for solute transport, rapid drug uptake, and improved drug bioavailability [220, 221]. Delivery of antimicrobial agents to the lung via systemic NP administration is persistent and potentially harmful upon systemic exposure to the drugs. Alternatively, various NPs exhibiting preferential accumulation in the lung and other organs have been tried. It was reported that intratracheally administered antibiotics loaded NPs were able to penetrate through the alveolar-capillary barrier into the systemic circulation and accumulate in extrapulmonary organ containing liver, spleen, bone, and kidney [222]. Micronization of drugs plays an important role in improving the drug dosage form and therapeutic efficiency today. If a drug is micronized into microspheres with suitable particle size, it can be addressed directly to the lung by the mechanical prevention of capillary bed in the lungs [223]. Nanosuspensions may demonstrate to be an ideal approach for delivering drugs that display poor solubility in pulmonary secretions [212]. Furthermore, because of the nanoparticulate nature and uniform size distribution of nanosuspensions, it is very likely that in each aerosol droplet at least one

drug nanoparticle is contained, leading to even distribution of the drug in the lungs as compared to the microparticulate form of the drug. In regular suspension aerosols many droplets are drug free and others are highly filled with the drug, directing to uneven delivery and circulating of the drug in the lungs. Nanosuspensions could be utilized in all available types of nebulizer [224]. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1–2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonar delivery [212]. Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes [225].

9.3. Ocular delivery

Nanosuspensions can assay to be a advantage for drugs that show poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been proposed. Although suspensions present advantages such as extended residence time in a cul-desac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity produced by water-soluble drugs, their actual performance depends on the native solubility of the drug in lachrymal fluids. Thus, the intrinsic decomposition rate of the drug in lachrymal fluid governs its release and ocular bioavailability [226]. An approach that has recently been investigated to achieve the desired duration of action of the drug is the formulation of polymeric nanosuspensions loaded with the drug [212]. Ocular drug administration via SLN has been reported several times. Ocular drug administration via SLN has been reported several times [227]. Cavalli et al (2002) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. As a result SLN significantly enhanced the drug bioavalability in the aqueous humor within 6 hours [228]. In addition, poly-cationic polymers may be useful penetration enhancers for ocular drug delivery [229]. De Campos et al. discovered the potential of cyclosporin-A loaded nanoparticles for the management of extraocular disorders, i.e. keratoconjunctivitis sicca or dry eye disease. They reported that the advantages of these systems in ocular drug delivery contain their ability to contact intimately with the corneal and conjunctival surface, thereby increasing delivery to external ocular tissues without compromising inner ocular structures and systemic drug exposure, and to provide these target tissues with long term drug level [230]. De Salamanaca et al. have reported that chitosan nanoparticles readily penetrate conjunctival epithelial cells and are well suffered at the ocular surface of rabbits [231].

9.4. Brain delivery

There is a great interest in the development of drug delivery systems that could allow an efficient and sitespecific transport of drugs to the target tissues affected by the disease. One of the most challenging barriers in the body is the blood–brain barrier (BBB) [232]. Endothelial cells of the BBB limit the solute movement into the brain by regulating transport mechanisms at the cell surface. These transport mechanisms help to keep the harmful substances out of the brain in order to maintain homeostasis [233]. Besides the development of simple prodrugs, an

emerging approach to circumvent the BBB is the use of liposomes, polymeric nanoparticles or solid lipid nanoparticles, in which the therapeutic drugs can be adsorbed or entrapped [234]. A drug can passively spread through the BBB in a more efficient manner after it is transformed into a more lipophilic prodrug. The same principle can be applied to brain targeting by delivering drugs on nanocarriers with enhanced lipophilicity. Fenart et al demonstrated that when polysaccharide nanoparticles were coated with a lipid bilayer, a 3 to 4-fold improvement in brain uptake without disruption of the BBB integrity was observed [235]. It has been reported that poly (butylcyanoacrylate) nanoparticles were able to deliver hexapeptide dalargin, doxorubicin and other agents into the brain which is significant because of the great difficulty for drugs to cross the BBB [236]. Recently dendrimers have been evaluated for CNS delivery of antiretrovira (ARVs) too. Polyamidoamine dendrimers loaded with lamivudine, a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) commonly utilized in HIV treatment, were evaluated for their *in vitro* antiviral activity inMT2 cells infected with HIV-1. When loaded on dendrimeric nanocarriers, a 21-fold increase in cellular lamivudine uptake and 2.6-fold reduction in the viral p24 levels were observed when compared to the group treated with free drug solution [237]. In summary, nanoparticles are a very useful and universal method to deliver drugs to the brain. Industrial applications of the nanosphere technology would have several benefits: 1) Nanoparticles deliver drugs to the brain that normally do not cross the blood-brain barrier. 2) They reduce peripheral side effects of (approved) drugs that cross the BBB by increasing the relative dose of drugs reaching the brain; 3) Nanoparticles can also be used as a screening tool. Delivering drug candidates to the brain by nanosphere technology for initial screening of CNS activity obviates direct CNS injections [238].

10. Conclusion

In many healthcare facilities around the world, bacterial pathogens that express multiple resistance mechanisms are becoming the norm, complicating treatment and increasing both human morbidity and financial costs. Until now, no antibiotic therapy has been reported to eliminate most intracellular bacteria such us *Brucella* or *Mycobaterium* too. Furthermore, a prolonged exposure to combined antibiotics is required to reduce the disease relapses down to 5-15%. In this sense, drug delivery scientists are searching for the ideal nanovehicle for the ideal nanodrug delivery system; one that would dramatically reduce drug dosage, improve in the drug absorption so that the patient can take a smaller dose, and yet have the same benefit, deliver the drug to the right place in the living system, increase the local concentration of the drug at the favorite site and limit or eliminate side effects. Compared with other colloidal carriers, polymeric particles, mainly nanoparticles, have appeared more recently as attractive carriers for the delivery of drugs to infected cells. Synthetic biodegradable and biocompatible polymers have been shown to be effective for encapsulating a great variety of antibiotics. In addition, these polymeric particles powerfully enhance phagocytosis and are suitable for intracellular delivery of antibacterial agents. With the continuous attempts in this field, there is no doubt that nanoparticle-based drug delivery systems will continue to improve treatment to bacterial infections, particularly in life-threatening diseases such as tuberculosis infections.

Today the application of nanotechnology in drug delivery is widely expected to change the scenery of pharmaceutical and biotechnology industries for the foreseeable future. Target-specific drug therapy and methods for early diagnosis of pathologies are the precedency research areas where nanotechnology would play a prominent role.

Author details

Mojtaba Salouti[1*] and Azam Ahangari[2]

*Address all correspondence to: saloutim@yahoo.com

1 Biology Research Center, Zanjan Branch, Islamic Azad University, Zanjan, Iran

2 Department of Microbiology, Hidaj Branch, Islamic Azad University, Hidaj, Iran

References

[1] Tallury P, Malhotra A, Byrne L, Santra S. Nanobioimaging and sensing of infectious diseases. Advanced Drug Delivery Reviews 2010; 62: 424–437.

[2] Baldoni D. Innovative Methods for the Diagnosis and Treatment of Implant-associated Infections. PhD thesis. University of Basel; 2009.

[3] Yildiz F H. Processes control-ling the transmission of bacterial pathogens in the environment. Res. Microbiol 2007; 158:195–202.

[4] Silva M. Classical labeling of bacterial pathogens according to their lifestylein the host:inconsistencies and alternatives. Frontiers in microbiology 2012; 71(3): 1-7.

[5] Brubaker R R. Mechanisms of bacterial virulence. Annu.Rev. Microbiol 1985; 39: 21–50.

[6] Goodpasture E W. Intracellular parasitism and the cytotropism of viruses. South. Med.J. 1936; 29: 297–303.

[7] Nahm M H, Apicella M A, Briles D E. Immunity to extracellular bacteria, in Fundamental Immunology, ed.W.E. Paul (Philadelphia, PA, Lippincott-Raven) 1999;1373–1386.

[8] Weiser J N, Nahm M H. Immunity to extracellular bacteria, in Fundamental Immunology, ed. W.E. Paul(Philadelphia: Lippincot Williams & Wilkins) 2008; 1182–1203.

[9] Sansonetti P. Phagocytosis of bacterial pathogens: implications in the host response. Semin.Immunol 2001;13: 381–390.

[10] Pamer E. Immune responses to intracellular bacteria, in Fundamental Immunology, ed.W.E. Paul (Philadelphia: Lippincott Williams & Wilkins) 2008; 1165–1181.

[11] Moulder J W. Comparative biology of intracellular parasitism. Microbiol.Rev 1985; 49: 298–337.

[12] Chono S, Tanino T, Seki T, Morimoto K. Efficient drug targeting to rat alveolar macrophages by pulmonary administration of ciprofloxacin incorporated into mannosylated liposomes for treatment of respiratory intracellular parasitic infections. J. Control. Release 2008; 127:50–58.

[13] Carryn S, Van Bambeke F, Mingeot-Leclercq M P, Tulkens P M. Comparative intracellular (THP-1 macrophage) and extracellular activities of beta-lactams, azithromycin, gentamicin, and fluoroquinolones against Listeria monocytogenes at clinically relevant concentrations. Antimicrob Agents Chemother 2002;46:2095-2103.

[14] Seral C, Van Bambeke F, Tulkens P M. Quantitative analysis of gentamicin, azithromycin, telithromycin, ciprofloxacin, moxifloxacin, and oritavancin (LY333328) activities against intracellular *Staphylococcus aureus* in mouse J774 macrophages. Antimicrob Agents Chemother 2003;47:2283-2292.

[15] Gamazo C, Prior S, Lecaroz M C, Vitas A I, Campanero M A, Perez G, et al. Biodegradable gentamicin delivery systems for parenteral use for the treatment of intracellular bacterial infections. Expert Opin Drug Deliv 2007;4:677-688.

[16] Vasir J K and Labhasetwar V. Targeted drug delivery in cancer therapy. Technol Cancer Res Treat 2005; 4: 363-374.

[17] Sheldon AT. Antibiotic resistance: a survival strategy. Clin. Lab. Sci. Summer 2005; 18: 170–180.

[18] Leid J G, Ditto A J, Knapp A, Shah P N, Wright B D, Blust R et al. In vitro antimicrobial studies of silver carbene complexes: activity of free and nanoparticle carbene formulations against clinical isolates of pathogenic bacteria, J. Antimicrob. Chemother 2012; 67 (1): 138–148.

[19] Pelgrift R, Friedman A. Nanotechnology as a therapeutic tool to combat microbial resistance. Advanced Drug Delivery Reviews 2013; 1-13.

[20] Abhilash M. Potential applications of Nanoparticles. International Journal of Pharma and Bio Sciences 2010; 1:1-12.

[21] Look A, Bandyopadhyay A, Blum J, Fahmy T. Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Advanced Drug Delivery Reviews 2010; 62: 378–393.

[22] Phillips M, Gran M, Peppas N. Targeted nanodelivery of drugs and diagnostics. Nano Today 2010; 5: 143—159.

[23] Heidari Z, Sariri R, Salouti M. Gold nanorods-bombesin conjugate as a potential targeted imaging agent for detection of breast cancer. Journal of Photochemistry and Photobiology B: Biology 2014; 130: 40–46.

[24] Grossman H L, Myers W R, Vreeland V J, Bruehl R, Alper M D, Bertozzi C R, Clarke J. Detection of bacteria in suspension by using a superconducting quantum interference device. Proc. Natl. Acad. Sci 2004; 101 (1):129–134.

[25] Zhang L, Pornpattananangkul D, Hu CM, Huang CM. Development of nanoparticles for antimicrobial drug delivery. Curr. Med. Chem 2010; 17:585–594.

[26] Alphandary H P, Andremont A, Couvreur P. Targeted delivery of antibiotics using liposomes and nanoparticles: research and applications, Int. J. Antimicrob. Agents 2000; 13: 155–168.

[27] Onyeji C O, Nightingale C H, Marangos M N. Enhanced killing of methicillinresistant *Staphylococcus aureus* in human macrophages by liposome-entrapped vancomycin and teicoplanin. Infection 1994; 22 (5): 338–342.

[28] Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Del. Rev 2001; 47: 65–81.

[29] Rai M, Gade A, Gaikwad S, Marcato P, Duran N. Biomedical Applications of Nanobiosensors: the State-of-the-Art. J. Braz. Chem. Soc. 2012; 1: 14-24.

[30] Zhang L, Pornpattananangkul D, Hu M J, Huang M. Development of nanoparticles for antimicrobial drug delivery. Curr Med Chem 2010; 17:585–594.

[31] Briones E, Colino C I, Lanao J M. Delivery systems to increase the selectivity of antibiotics in phagocytic cells. Journal of Controlled Release ;2008 125: 210–227.

[32] Bonifacio B, Silva P, Aparecido dos M, Ramos S et al. Nanotechnology-based drug delivery systems and herbal medicines: a review. International Journal of Nanomedicine 2014; 9: 1-51.

[33] Emeje M O, Obidike I C, Akpabio E I, Ofoefule S I. Nanotechnology in Drug Delivery. Rijeka: InTech; 2012. p70-106.

[34] Turos E, Reddy G S, Greenhalgh K, Ramaraju P, Abeylath S C, Jang S, Dickey S, Lim D V. Penicillin-bound polyacrylate nanoparticles: restoring the activity of β-lactam antibiotics against MRSA. Bioorg. Med. Chem. Lett. 2007; 17: 3468–3472.

[35] Huh A J, Kwon Y J. "Nanoantibiotics": A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. Journal of Controlled Release 2011;156: 128–145.

[36] Rawat M, Singh D, Saraf S, Saraf S. Nanocarriers: Promising Vehicle for Bioactive Drugs. Biol. Pharm. Bull. 2006; 29(9):1790-1798.

[37] Neut D, Kluin O S, Crielaard B J, van der Mei H C, Busscher H J, Grijpma D W. A biodegradable antibiotic delivery system based on poly-(trimethylene carbonate) for the treatment of osteomyelitis. Acta Orthop 2009; 80 (5): 514–519.

[38] Taubes G. The bacteria fight back. Science 2008; 321: 356–361.

[39] Jahanshahi M and Babaei Z. Protein nanoparticle: A unique system as drug delivery vehicles. African Journal of Biotechnology 2008; 7 (25):4926-4934.

[40] Sandhiya S, Dkhar S A, Surendiran A. Emerging trends of nanomedicine-an overview. Fundam. Clin. Pharmacol 2009; 23 (3): 263–269.

[41] El-Ansary A, Al-Daihan S. On the toxicity of therapeutically used nanoparticles: an overview. J. Toxicol 2009; 754-810.

[42] Hu Y L, Gao J Q. Potential neurotoxicity of nanoparticles. Int. J. Pharm 2010; 394: 115–121.

[43] Hagens W I, Oomen A G, Jong W H, Cassee F R, A.J. Sips A J. What do we (need to) know about the kinetic properties of nanoparticles in the body? Regul. Toxicol. Pharmacol 2007; 49 (3): 217–229.

[44] Kroll A, Pillukat M H, Hahn D, Schnekenburger J. Current in vitro methods in nanoparticle risk assessment: limitations and challenges. Eur. J. Pharm. Biopharm 2009; 72: 370–377.

[45] De Jong W H, Borm P J. Drug delivery and nanoparticles: applications and hazards. Int. J. Nanomedicine 2008; 3 (2):133–149.

[46] Moghimi S M, Hunter A C and Murray J C. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev 2001; 53: 283-318.

[47] Haiss W, Thanh N, Aveyard J, Fernig D G. Dermination of Size and Concentration of Gold Nanoparticles from Uv-Vis Spectra. Analytical Chemistry 2007;79: 4215-4221.

[48] Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J. Controlled Release 2000; 65: 271-84.

[49] Jaracz S, Chen J, Kuznetsova L V, Ojima I. Recent advances in tumortargeting anticancer drug conjugates. Bioorg. Med. Chem 2005; 13: 5043-54.

[50] Torchilin V P. Targeted polymeric micelles for delivery of poorly soluble drugs. Cell Mol. Life Sci 2004; 61: 2549-59.

[51] Gabizon A, Shmeeda H, Horowitz A T, Zalipsky S. Tumor cell targeting of liposome-entrapped drugs with phospholipid-anchored folic acid-PEG conjugates. Adv. Drug Delivery Rev 2004; 56: 1177-92.

[52] Gupta B, Levchenko T S, Torchilin V P. (2005) Intracel-lular delivery of large molecules and small particles by cell-penetrating proteins and peptides. Adv. Drug Delivery Rev 2005; 57: 637-51.

[53] Lochmann D, Jauk E, Zimmer A. Drug delivery of oligonucleotides by peptides. Eur. J. Pharm. Biopharm 2004; 58: 237-51.

[54] Varshosaz J. Insulin delivery systems for controlling diabetes. Recent Pat Endocr Metab Immune Drug Discovery 2007; 1:25–40.

[55] Gamazo C, Prior S, Lecaroz MC, Vitas AI, Campanero MA, Perez G, et al. Biodegradable gentamicin delivery systems for parenteral use for the treatment of intracellular bacterial infections. Expert Opin Drug Deliv 2007;4:677-688.

[56] Moghimi S M, Hunter A C, Murray J C. Long-circulating and target specific nanoparticles: theory to practice, Pharmacol. Rev 2001; 53: 283–318.

[57] Vinagradov S V, Bronich T K, Kabanov A V. Nanosized cationic hydrogels for drug delivery: preparation, properties and interactions with cells. Adv. Drug Deliv. Rev 2002; 54 (1): 135–147.

[58] Labhasetwar V, Song C, Levy RJ: Nanoparticle drug delivery system for restenosis. Advanced Drug Delivery Reviews 1997; 24(1):63-85.

[59] Mahapatro A, Singh D. Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines. Journal of Nanobiotechnology 2011; 9-55.

[60] Kumari A, Yadav SK, Yadav SC: Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and Surfaces B: Biointerfaces 2010; 75(1):1-18.

[61] Cheng J, Teply B A, Sherifi I, Sung J, Luther G, Gu F X, Levy-Nissenbaum E, Radovic-Moreno A F, Langer R, Farokhzad O C. Formulation of functionalized PLGA-PEG nanoparticles for in vivo targeted drug delivery. Biomaterials 2007; 28: 869-76.

[62] Gu F X, Zhang L, Teply B A, Mann N, Wang A, Radovic-Moreno A F, Langer R, Farokhzad O C. Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. Proc. Natl. Acad. Sci 2008; 105:2586-91.

[63] Szlek J, Paclawski A, Lau R, Jachowicz R, Mendyk A. euristic modeling of macromolecule release from PLGA microspheres. International Journal of Nanomedicine 2013; 8: 4601–4611.

[64] Gan Q, Wang T. Chitosan nanoparticle as protein delivery carrier–Systematic examination of fabrication conditions for efficient loading and release. Colloids and Surfaces B: Biointerfaces 2007; 59(1):24-34.

[65] Bharatwaj B, Wu L, Whittum-Hudson J, Rocha S. The potential for the noninvasive delivery of polymeric nanocarriers using propellant-based inhalers in the treatment of Chlamydial respiratory infections. Biomaterials 2010; 31: 7376-7385.

[66] Sosnik A, Carcaboso A M, Glisoni R J, Moretton M A, Chiappetta D A. New old challenges in tuberculosis: Potentially effective nanotechnologies in drug delivery. Advanced Drug Delivery Reviews 2010; 62: 547–559.

[67] Umamaheshwari R B, Jain N K. Receptor mediated targeting of lectin conjugated gliadin nanoparticles in the treatment of *Helicobacter pylori*. J. Drug Target 2003; 11: 415-23.

[68] Skidan I N, Gelperina S E, Severin S E, Guliaev A E. Enhanced activity of rifampicin loaded with polybutyl cyanoacrylate nanoparticles in relation to intracellularly localized bacteria. Antibiot. Khimioter 2003; 48 (1(: 23-26.

[69] Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Advanced Drug Delivery Reviews 2001; 53: 321–339.

[70] Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. J Control Release 2008; 126(3):187-204.

[71] Schwall C T, Banerjee I A. Micro-and Nanoscale Hydrogel Systems for Drug Delivery and Tissue Engineering. Materials 2009; 2: 577-612.

[72] Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Advanced Drug Delivery Reviews 2008; 60: 1638–1649.

[73] Peppas N A, Mongia N K. Ultrapure poly(vinyl alcohol) hydro gels with mucoadhesive drug delivery characteristics. Eur. J. Pharm. Biopharm 1997; 43: 51–58.

[74] Kabanov V A, Papisov I M. Formation of complexes between complementary synthetic polymers and oligomers in dilute solution. Vysokolmol. Soedin 1979; 21: 243–281.

[75] Coviello T, Matricardi P, Marianecci C, Alhaique F. Polysaccharide hydrogels for modified release formulations. J. Control. Release 2007; 119: 5–24.

[76] Hoare T R, Kohane D S. Hydrogels in drug delivery: Progress and challenges. Polymer 49 (2008) 1993-2007.

[77] Martinez L R, Han G, Chacko M, Mihu M R, Jacobson M, Gialanella P, Friedman A J, Nosanchuk J D, Friedman J M. Antimicrobial and healing efficacy of sustained release nitric oxide nanoparticles against *Staphylococcus aureus* skin infection. J. Investig. Dermatol 2009; 10: 2463–2469.

[78] Ti Peng K, Fu Chen C, Chu I M, Li Y M, Hsiu Hsu W, Wei Hsu R W, Chang P J. Treatment of osteomyelitis with teicoplanin-encapsulated biodegradable thermosensitive hydrogel nanoparticles. Biomaterials 2010; 31: 5227-5236.

[79] Diaz M R, Vivas-Mejia P. Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing Nanoliposomes. Pharmaceuticals 2013; 6: 1361-1380.

[80] Shahverdi A R, Fakhimi A, Shahverdi H R, Minaian S. Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against *Staphylococcus aureus* and *Escherichia coli*. Nanomedicine: Nanotechnology, Biology, and Medicine 2007; 3:168– 171.

[81] Kowshik M, Ashtaputre S, Kharrazi S. Extracellular synthesis of silver nanoparticles by a silver-tolerant yeast strain MKY3. Nanotechnology 2003; 14:95-100.

[82] Duran N, Marcato P D, Alves O L, Souza G. Mechanistic aspects of biosynthesis of silver nanoparticles by several *Fusarium oxysporum* strains. J Nanotechnology 2005; 3:8.

[83] Wang A Z, Langer R, Farokhzad O C. Nanoparticle delivery of cancer drugs. Annu. Rev. Med. 2012; 63:185–198.

[84] Sheikhloo Z, Salouti M, Katiraee F. Biological synthesis of gold nanoparticles by fungus *Epicoccum nigrum*. J Clust Sci 2011; 22:661–665.

[85] Tiwari P M, Vig K, Dennis V A, Singh S R. Functionalized Gold Nanoparticles and Their Biomedical Applications. Nanomaterials 2011; 1: 31-63.

[86] Grace NA, Pandian K. Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles-A brief study. Colloids Surf A Physicochem Eng Asp 2007; 297:63–70.

[87] Saha B, Bhattacharya J, Mukherjee A, et al. In vitro structural and functional evaluation of gold nanoparticles conjugated antibiotics. Nanoscale Res Lett 2007; 2:614–22.

[88] Burygin GL, Khlebtsov BN, Shantrokha AN, et al. On the enhanced antibacterial activity of antibiotics mixed with gold nanoparticles. Nanoscale Res Lett 2009; 4:794–801.

[89] Gu, H. et al. Presenting vancomycin on nanoparticles to enhance antimicrobial activities. Nano Lett 2003; 3, 1261–1263.

[90] Selvaraj V, Alagar M. Analytical detection and biological assay of antileukemic drug 5-fluorouracil using gold nanoparticles as probe. Int J Pharm 2007; 337:275–81.

[91] Ahangari A, Salouti M, Heidari Z, Kazemizadeh A, Safari A. Development of Gentamicin-Gold Nanospheres for Antimicrobial Drug Delivery to *Staphylococcal* Infected Foci. Drug Deliv 2013; 20 (1): 34–39.

[92] Gargani G, Pacetti AM. Sensitivity of 115 strains of the genus *Brucella* to some antibiotics (cephalosporins, ureidopenicillins and aminoglycosides). Chemioterapia 1998; 5:7–13.

[93] Duncan B, Kim C, Rotello V M. Gold nanoparticle platforms as drug and biomacromolecule delivery systems. J. Contr. Release 2010; 148: 122–127.

[94] Oberdorster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Part Fibre Toxicol 2005; 2: 38–43.

[95] Warheit D B, Borm P J, Hennes C, Lademann J. Testing strategies to establish the safety of nanomaterials: conclusions of an ECETOC workshop. Inhal Toxicol 2007; 19: 631–643.

[96] Chen X, Schluesener H J. Nano-silver: a nanoproduct in medical application. Toxicol Lett 2008; 176: 1–12.

[97] Shivai Karkaj O, Salouti M, Sorouri Zanjani R. Extracellular Deposition of Silver Nanoparticles by *Bacillus Megaterium*. Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 2013; 43:903–906.

[98] Liu Y, He L, Mustapha A, Li H, Hu Z Q, Lin M. Antibacterial activities of zinc oxide nanoparticles against *Escherichia coli* O157:H7. J. Appl. Microbiol 2009; 107: 1193–1201.

[99] Sharma V K, Yngard R A, Liu Y. Silver nanoparticles: green synthesis and their antimicrobial activities, Adv. Colloid Interface Sci 2008; 145: 83–96.

[100] Araujo E, Andrade N J, Da Silva L H, Bernardes P C, Teixeira AV, et al. Antimicrobial effects of silver nanoparticles against bacterial cells adhered to stainless steel surfaces. Journal of Food Production 2011; 74(4): 701-705.

[101] Fayaz A M, Balaji K, Girilal M, Yadav R, Tech M, Kalaichelvan P T, Venketesan R. Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria, Nanomedicine 2010; 6:103–109.

[102] Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials, Biotechnol. Adv 2009; 27: 76–83.

[103] Carlson C, et al. Unique cellular interaction of silver nanoparticles: size-dependent generation of reactive oxygen species. J. Phys. Chem 2008; 112:13608-13619.

[104] Park H J, Kim et al. Silver-ion-mediated reactive oxygen species generation affecting bactericidal activity. Water Res 2009; 43:1027–1032.

[105] Bar-Ilan O, Albrecht R M, Fako V E, Furgeson D Y. Toxicity assessments of multisized gold and silver nanoparticles in zebrafish embryos. Small 2009; 5:1897–1910.

[106] Bechet D, et al. Nanoparticles as vehicles for delivery of photodynamic therapy agents. Trends Biotechnol 2008; 26:612– 621.

[107] Veiseh O, Gunn J W, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. Advanced Drug Delivery Reviews 2010; 62: 284–304.

[108] Mok H, Zhang M. Superparamagnetic iron oxide nanoparticle-based delivery systems for biotherapeutics. Exp Opin Drug Deliv 2013;10:73–87.

[109] Kafayati M E, Raheb J, Torabi Angazi M, Alizadeh S, Bardania H. The Effect of Magnetic Fe3O4 Nanoparticles on the Growth of Genetically Manipulated Bacterium, *Pseudomonas aeruginosa* (PTSOX4). Iran J Biotech 2013;11(1): 41-6.

[110] Neuberger T, Schopf B, Hofmann H, Hofmann M, von Rechenberg B. Superparamagnetic nanoparticles for biomedical applications: possibilities and limitations of a new drug delivery system. J Magn Magn Mater 2005; 293: 483–496.

[111] Cao Q, Han X, Li L. Enhancement of the efficiency of magnetic targeting for drug delivery: Development and evaluation of magnet system. J Magn Magn Mater 2011; 323: 1919–1924.

[112] Gu H W, Xu K M, Xu C J, Xu B. Biofunctional magnetic nanoparticles for protein separation and pathogen detection, Chem. Commun 2006; 941–949.

[113] Senthil M, Ramesh C. Biogenic synthesis of Fe_3O_4 nanopraticles using tridax procumbens leaf extract and its antibacterial activity on Pseudomonas aeruginosa. Digest Journal of Nanomaterials and Biostructures 2012; 7: 1655-1660.

[114] Liu M, Gan L, Chen L, Zhu D, Xu Z, Hao Z, Chen L. A novel liposome-encapsulated hemoglobin/silica nanoparticle as an oxygen carrier. Int. J. Pharm 2012; 427: 354–357.

[115] Yokoyama R, Suzuki S, Shirai K, Yamauchi T, Tsubokawa N, Tsuchimochi M. Preparation and properties of biocompatible polymer-grafted silicananoparticle. Eur. Pol. J 2006; 42: 3221–3229.

[116] Vivero-Escoto J L, Slowing I I, Trewyn B G, Lin VS-Y. Mesoporous silica nanoparticles for intracellular controlled drug delivery. Small 2010; 6:1952–67.

[117] He Q, Shi J. Mesoporous silica nanoparticle based nano drug delivery systems: synthesis, controlled drug release and delivery, pharmacokinetics and biocompatibility. J Mater Chem 2011;21(16):5845–55.

[118] Hun X, Zhang Z J. A novel sensitive staphylococcal enterotoxin C, fluoroimmunoassay based on functionalized fluorescent core–shell nanoparticle labels, Food Chem 2007; 105: 1623–1629.

[119] Grumezescu A M, Ghitulica C D, Voicu G, et al. New silica nanostructure for the improved delivery of topicalantibiotics used in the treatment of *staphylococcal* cutaneous infections. International Journal of Pharmaceutics 2013; 1-7.

[120] Bae Y, Kataoka K. Intelligent polymeric micelles from functional poly(ethylene glycol)-poly(amino acid) block copolymers. Advanced Drug Delivery Reviews 2009; 61: 768-784.

[121] Gaucher G, Dufresne M H, Sant V P, Kang N, Maysinger D, Leroux J C. Block copolymer micelles: preparation, characterization and application in drug delivery. Journal of Controlled Release 2005; 109: 169-188.

[122] Nishiyama, N., Bae, Y., Miyata, K., Fukushima, S., and Kataoka, K. Smart polymeric micelles for gene and drug delivery Drug Discovery Today. Technologies 2005; 2: 21-26.

[123] Rapoport N. Physical stimuli-responsive polymeric micelles for anti-cancer drug delivery. Prog. Polym. Sci 2007; 32: 962–90.

[124] Kagaya H, Oba M, Miura Y, Koyama H, Ishii T, Shimada T, Takato T, Kataoka K, Miyata T. Impact of polyplex micelles installed with cyclic RGD peptide as ligand on gene delivery to vascular lesions. Gene Ther 2012; 19: 61–69.

[125] Harada A, Kataoka K. Novel polyion complex micelles entrapping enzyme molecules in the core: Preparation of narrowly-distributed micelles from lysozyme and poly (ethylene glycol)-poly (aspartic acid) block copolymer in aqueous medium. Macromolecules 1998; 31:288-94.

[126] Yokoyama M. Clinical Applications of Polymeric Micelle Carrier Systems in Chemotherapy and Image Diagnosis of Solid Tumors. J Exp Clin Med 2011; 1-8.

[127] Mozafari M R, Sahin N O. Manufacturing methods and mechanism of formation of lipid vesicles. In: Nanoliposomes: From Fundamentals to Recent Developments.Trafford Publishing Ltd, Oxford, UK. p 39–48; 2005.

[128] Torchilin V P. Lipid-core micelles for targeted drug delivery. Curr. Drug Delivery 2005; 2: 319-27.

[129] Torchilin V P. Recent advances with liposomes as pharmaceutical carriers. Nat. ReV. Drug Discovery 2005; 4: 145-60.

[130] Drulis-Kawa Z, Dorotkiewicz-Jach A. Liposomes as delivery systems for antibiotics. International Journal of Pharmaceutics 2010; 387: 187–198.

[131] Abeylath S C, Turos E. Drug delivery approaches to overcome bacterial resistance to beta-lactam antibiotics. Expert Opin. Drug Deliv 2008; 5931–5949.

[132] Fielding, R.M. Liposomal drug delivery: advantages and limitations from a clinical pharmacokinetics and therapeutic perspective. Clin. Pharmacol 1991; 21(3): 155-164.

[133] Schiffelers R M, Storm G, Bakker-Woudenberg I. (2001). Host factors influencing the preferential localization of sterically stabilized liposomes in *Klebsiella pneumoniae*-infected rat lung tissue. Pharm. Res 2001; 18 (6): 780–787.

[134] Mimoso I M, Francisco APG, Cruz MEM. Liposomal formulation of netilmicin. Int J Pharm 1997;147:109–17.

[135] Deol P, Khuller G K. Lung specific liposomes: stability, biodistribution and toxicity of liposomal antitubercular drugs in mice. Biochem. Biophys. Acta 1997; 1334: 161–172.

[136] Mukherjee S, Ray S, Thakur R S. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci 2009; 71(4): 349-58.

[137] Gupta U, Jain N K. Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. Advanced Drug Delivery Reviews 2010; 62: 478–490.

[138] Varshosaz J, Ghaffari S, Khoshayand M R, Atyabi F, Azarmi S, Kobarfard F. Development and optimization of solid lipid nanoparticles of amikacin by central composite design. Journal of Liposome Research 2010; 20(2): 97–104.

[139] Muller R H, Radtke M, Wissing S A. Nanostructured lipid matrices for improved microencapsulation of drugs. Int. J. Pharm 2002; 242: 121-128.

[140] Han C, Qi C M, Zhao B K, Cao J, Xie S Y, Wang S L, Zhou W Z. (2009). Hydrogenated castor oil nanoparticles as carriers for the subcutaneous administration of tilmicosin: in vitro and in vivo studies. J. Vet. Pharmacol. Therap 2009; 32 (2): 116-123.

[141] Ribeiro A, Barbassa L, Melo L. Antimicrobial Biomimetics, Biomimetic Based Applications: InTech; 2011:1-59.

[142] Cavalli R, Gasco M R, Chetoni P, Burgalassi S, Saettone M F. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int. J. Pharm 2002; 238: 241-245.

[143] Nimje N, Agarwal A, Saraogi G K, Lariya N, Rai G, Agrawal H, Agrawal G P. (2009). Mannosylated nanoparticulate carriers of rifabutin for alveolar targeting. J. Drug Targeting 2009; 17(10): 777-787.

[144] Pandey R, Khuller G K. Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. Tuberculosis (Edinb) 2005; 85: 227-34.

[145] NairR, Arun Kumar K, Vishnu Priya K, Sevukarajan M. Recent advances in solid lipid nanoparticle based drug delivery systems. J Biomed Sci and Res 2011; 2: 368-384.

[146] Nasir A. Nanotechnology and dermatology: Part I-potential of nanotechnology. Clinics in Dermatology 2010; 28: 458–466.

[147] Markovic Z, Trajkovic V. Biomedical potential of the reactive oxygen species generation and quenching by fullerenes (C60). Biomaterials 2008; 29: 3561–3573.

[148] Kratschmer W, Lamb L D, Fostiropoulos K, Huffman D R. Solid C60: a new form of carbon. Nature 1990; 347: 354–8.

[149] Friedman S H, DeCamp D L, Sijbesma R P, Srdanov G, Wudl F, Kenyon G L. Inhibition of the HIV-1 protease by fullerene derivatives: model building studies and experimental verification. J Am Chem Soc 1993;115(15):6506–6509.

[150] Pantarotto D, Tagmatarchis N, Bianco A, Prato M. Synthesis and biological properties of fullerene-containing amino acids and peptides. Mini Rev Med Chem 2004;4(7): 805–814.

[151] Yang X, Ebrahimi A, and Li J, Cui Q. Fullerene–biomolecule conjugates and their biomedicinal applications, International Journal of Nanomedicine 2014; 9:77-92.

[152] Bosi S, Da Ros T, Spalluto G, Prato M. Fullerene derivatives: an attractive tool for biological applications. Eur J Med Chem 2003;38(11–12): 913–923.

[153] Mroz P, Tegos G P, Gali H, Wharton T, Sarna T, Hamblin M R. Photodynamic therapy with fullerenes. Photochem Photobiol Sci 2007; 6:1139–49.

[154] Tsao N, Luh T Y, Chou C K, Chang T Y, Wu J J, Liu C C, et al. In vitro action of carboxyfullerene. J Antimicrob Chemother 2002; 49:641–9.

[155] Patel M B, Harikrishnan U, Valand N N, Modi N R, Menon S K. Novel cationic quinazolin-4(3H)-one conjugated fullerene nanoparticles as antimycobacterial and antimicrobial agents. Arch Pharm (Weinheim) 2013; 346(3):210–220.

[156] Tomalia D A, Baker H, Dewald J R, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: starbust-dendritic macromolecules. Polym. J 1985; 17: 117-132.

[157] Svenson S N, Tomalia D A. 2005, Dendrimers in biomedical applications-reflections on the field Advanced Drug Delivery Reviews 2005; 57: 2106-2129.

[158] Medina S H, El-Sayed M E. Dendrimers as carriers for delivery of chemotherapeutic agents. Chem. Rev 2009; 109: 3141–3157.

[159] Grayson S M, Frechet J M. Convergent dendrons and dendrimers: from synthesis to applications. Chem. Rev 2001; 101: 3819-3868.

[160] Chen C Z, Cooper S L. Interactions between dendrimer biocides and bacterial membranes. Biomaterials 2002; 23: 3359-3368.

[161] Dokos Ch, Mironidou-Tzouveleki M. New trends and prospects of nanotechnology application in drug delivery. Epitheorese Klinikes Farmakologias kai Farmakokinetikes 2006; 24(3):165-172.

[162] Bielinska A, Kukowska-Latallo J F, Johnson J, Tomalia D A, Baker J R. Regulation of in vitro gene expression using antisense oligonucleotides or antisense expression plasmids transfected using starburst PAMAM dendrimers. Nucleic Acids Res 1996; 24:2176-82.

[163] Ma M, Cheng Y, Xu Z, Xu P, Qu H, Fang Y, Xu T, Wen L. Evaluation of polyamidoamine (PAMAM) dendrimers as drug carriers of anti-bacterial drugs using sulfamethoxazole (SMZ) as a model drug. Eur J Med Chem 2007; 42-1:93-8.

[164] Vilaca N, Amorim R, Machado A, et al. Potentiation of 5-fluorouracil encapsulated in zeolites as drugdelivery systems for in vitro models of colorectal carcinoma. Colloids and Surfaces B: Biointerfaces 2013; 112: 237–244.

[165] Demirci S, Ustaoglu Z, Yilmazer G A, Sahin F, Bac N. Antimicrobial properties of zeolite-X and zeolite-A ion-exchanged with silver, copper, and zinc against a broad range of microorganism. Appl biochem biotechnol 2013; 647-7.

[166] Ma YM, Tong W, Zhou H, Suib S. A review of zeolite-like porous materials. Microporous Mesoporous Materials 2000; 37:243-52.

[167] Amorim R, Vilaca N, Martinho O, et al. Zeolite structures loading with an anticancer compound as drug delivery systems. J. Phys. Chem 2012; 116: 25642−25650.

[168] Cheng H, Hsieh C, Tsai C. Antibacterial and regenerated characteristics of Ag-zeolite for removing bioaerosols in indoor environment. Aerosol and Air Quality Research 2012; 12: 409–419.

[169] Fernandez A, Soriano E, Hernandez-Munoz P, Gavara R. Migration of antimicrobial silver from composites of polylactide with silver zeolites. J. Food Sci 2010; 75 (3): 186-193.

[170] Obonyo O, Fisher E, Edwards M, Douroumis D. Quantum dots synthesis and biological applications as imaging and drug delivery systems. Crit Rev Biotechnol 2010;30:283–301.

[171] Luo G, Long J, Zhang B, Liu C, Ji S, Xu J, et al. Quantum dots in cancer therapy. Exp Opin Drug Deliv Rev 2012; 9:47–58.

[172] Agrawal A, Tripp R A, Anderson L J, Nie S. Real-time detection of virus particles and viral protein expression with two-color nanoparticle probes. J. Virol 2005 79: 8625–8628.

[173] Geszke-Moritz M, Moritz M. Quantum dots as versatile probes in medical sciences: Synthesis, modification and properties. Materials Science and Engineering 2013; 33: 1008–1021.

[174] Xing Y, Chaudry Q, Shen C, Kong K Y, Zhau H E, Chung L W, Petros J A, O'Regan R M, Yezhelyev M V, Simons J W, Wang M D, Nie S M. Bioconjugated quantum dots for multiplexed and quantitative immunohistochemistry, Nat. Protoc 2007; 2: 1152–1165.

[175] Hanaki K, Momo A, Oku T, Komoto A, Maenosono S, Yamaguchi Y, Yamamoto K, Semiconductor quantum dot/albumin complex is a long-life and highly photostable endosome marker. Biochem. Biophys. Res. Commun 2003; 302: 496–501.

[176] Jaiswal J K, Mattoussi H, Mauro J M, Simon S M. Long-term multiple color imaging of live cells using quantum dot bioconjugates. Nat. Biotechnol 2003; 21: 47–51.

[177] Hahn M A, Tabb J S, Krauss T D. Detection of single bacterial pathogens with semiconductor quantum dots, Anal. Chem 2005; 77: 4861–4869.

[178] Goldman E R, Clapp A R, Anderson G P, Uyeda H T, Mauro J M, Medintz I L, Mattoussi H. Multiplexed toxin analysis using four colors of quantum dot fluororeagents, Anal. Chem 2004; 76: 684–688.

[179] Li X, Lu Z, Li Q. Multilayered films incorporating CdTe quantum dots with tunable optical properties for antibacterial application. Thin Solid Films 2013; 548: 336-342.

[180] Rameshkumar A, Sivasudha T, Jeyadevi R, et al. In vitro antioxidant and antimicrobial activities of Merremia emarginata using thio glycolic acid-capped cadmium telluride quantum dots. Colloids and Surfaces B: Biointerfaces 2013; 101: 74– 82.

[181] Rai M, Gade A, Gaikwad S, Marcato P, Duran N. Biomedical Applications of Nanobiosensors: the State-of-the-Art. J. Braz. Chem. Soc 2012; 23: 14-24.

[182] Carryn S, Chanteux H, Seral C, et al. Intracellular pharmacodynamics of antibiotics. Infect Dis Clin N Am 2003; 17: 615–634.

[183] Heym B, Cole ST. Multidrug resistance in *Mycobacterium tuberculosis*. Int J Antimicrob Agents 1997;8:61–70.

[184] Imbuluzqueta E, Elizondo E, Gamazo C, et al. Novel bioactive hydrophobic gentamicin carriers for the treatment of intracellular bacterial infections. Acta Biomaterialia 2011; 7: 1599–1608.

[185] Prior S, Gander B, Blarer N, Merkle H P, Subira M L, Irache J M, Gamazo C. In vitro phagocytosis and monocyte–macrophage activation with poly(lactide) and poly(lactide-co-glycolide) microspheres. Eur. J. Pharm. Sci 2002; 15 (2): 197–207.

[186] Mehta R T, Keyhani A, McQueen T J, Rosenbaum B, Rolston K V, Tarrand J J. In vitro activities of free and liposomal drugs against *Mycobacterium avium*–M. intracellulare complex and *M. tuberculosis*, Antimicrob. Agents Chemother 1993; 37 (12): 2584–2587.

[187] Vyas S P, Kannan M E, Jain S, Mishra V, Singh P. Design of liposomal aerosols for improved delivery of rifampicin to alveolar macrophages. Int. J. Pharm 2004; 269 (1): 37–49.

[188] Kilinc O, Ucan E S, Cakan MDA, et al. Risk of tuberculosis among healthcare workers: can tuberculosis be considered as an occupational disease? Respir Med 2002;96: 506–10.

[189] Agrawal A k, Gupta C M. Tuftsin-bearing liposomes in treatment of macrophage-based infections. Adv. Drug Deliv. Rev 2000; 41 (2): 135–146.

[190] Pandey R, Sharma A, Zahoor A, Sharma S, Khuller G K, Prasad B: Poly (DL-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. J Antimicrob Chemother 2003; 52 (6): 981-986.

[191] Fawaz F, Bonini F, Maugein J, Lagueny A M. Ciprofloxacin-loaded polyiosbutylcyanoacrylate nanoparticles: pharmokinetics and in vitro antimicrobial activity. International Journal of Pharmaceutics. 1998; 168: 255-259.

[192] Skidan I N, Gelperina S E, Severin S E, Guliaev A E. Enhanced activity of rifampicin loaded with polybutyl cyanoacrylate nanoparticles in relation to intracellularly localized bacteria. Antibiot Khimioter 2003; 48: 23-6.

[193] Khuller G K, Kapur M, Sharma S. Liposome technology for drug delivery against mycobacterial infections. Curr. Pharm. Des 2004; 10 (26): 3263–3274.

[194] Yanagihara K. Design of anti-bacterial drug and anti-mycobacterial drug for drug delivery system. Curr. Pharm. Des 2002; 8 (6): 475–482.

[195] Deol P, Khuller G K, Joshi K. Therapeutic efficacies of isoniazid and rifampin encapsulated in lung-specific stealth liposomes against *Mycobacterium tuberculosis* infection induced in mice, Antimicrob. Agents Chemother 1997; 41 (6): 1211–1214.

[196] Hall W H. Modern chemotherapy for brucellosis in humans. Review of Infectious Diseases 1990; 12: 1060–99.

[197] Prior S, Gander B, Lecaroz C, Irache J, Gamazo C. Gentamicin-loaded microspheres for reducing the intracellular *Brucella abortus* load in infected monocytes. Journal of Antimicrobial Chemotherapy 2004; 53, 981–988.

[198] Ariza J, Gudiol F, Pallares R, Viladrich P F, Rufi G, Corredoira J, Miravitlles M R. Treatment of human brucellosis with doxycycline plus rifampin or doxycycline plus streptomycin. A randomized, double-blind study. Ann Intern Med 1992; 117(1): 25-30.

[199] Prior S, Gamazo C, Irache J M, Merkle H P, Gander B. Gentamicin encapsulation in PLA/PLGA microspheres in view of treating Brucella infections. Int. J. Pharm 2000; 196 (1): 115–125.

[200] Vitas A I, Diaz R, Gamazo C. Effect of composition and method of preparation of liposomes on their stability and interaction with murine monocytes infected with *Brucella abortus*. Antimicrob. Agents Chemother 1996; 40 (1): 146–151.

[201] Kumar P V, Asthana A, Dutta T, Jain N K. Intracellular macrophage uptake of rifampicin loadedmannosylated dendrimers, J. DrugTarget 2006; 14 (8): 546–556.

[202] Lecaroz C, Gamazo C, Renedo M J, Blanco-Prieto M J. Biodegradable micro-and nanoparticles as long-term delivery vehicles for gentamicin. J Microencapsul 2006; 23:782-792.

[203] Van Bambeke F, Michot J M, Tulkens P M. Antibiotic efflux pumps in eukaryotic cells: occurrence and impact on antibiotic cellular pharmacokinetics, pharmacodynamics and toxicodynamics. J Antimicrob Chemother 2003; 51(5): 1067-1077.

[204] Fattal E, Youssef M, Couvreur P and Andremont A. Treatment of experimental salmonellosis in mice with ampicillin-bound nanoparticles. Antimicrob Agents Chemother 1989; 33(9): 1540-1543.

[205] Fierer J, Hatlen L, Lin J P, Estrella D, Mihalko P, Yau-Young A. Successful treatment using gentamicin liposomes of Salmonella Dublin infections in mice. Antimicrob. Agents Chemother 1990; 34 (2): 343–348.

[206] Page-Clisson M E, Pinto-Alphandary H, Chachaty E, Couvreur P, Andremont A. Drug targeting by polyalkylcyanoacrylate nanoparticles is not efficient against persistent Salmonella 1998; Pharm Res 15(4): 544-549.

[207] Webb M S, Boman N L, Wiseman D J, Saxon D, Sutton K, Wong K F, Logan P, Hope M J. Antibacterial efficacy against an in vivo *Salmonella typhimurium* infection model and pharmacokinetics of a liposomal ciprofloxacin formulation. Antimicrob. Agents Chemother 1998; 42 (1): 45–52.

[208] Bakker-Woudenberg I A, Lokerse A F, Roerdink F H. Effect of lipid composition on activity of liposome-entrapped ampicillin against intracellular *Listeria monocytogenes*, Antimicrob. Agents Chemother 1998; 32 (10): 1560–1564.

[209] Pranoto Y, Rakshit S K, Salokhe V M. Enhancing antimicrobial activity of chitosan films by incorporating garlic oil, potassium sorbate and nisin. LWT Food Sci. Technol 2005; 38(8): 859–865.

[210] Lutwyche P, Cordeiro C, Wiseman D J, et al. Finlay, Intracellular delivery and antibacterial activity of gentamicin encapsulated in pH-sensitive liposomes, Antimicrob. Agents Chemother 1998; 42 (10): 2511–2520.

[211] Forestier F, Gerrier P, Chaumard C, Quero A M, Couvreurr P, Labarre C. Effect of nanoparticle-bound ampicillin on the survival of *Listeria monocytogenes* in mouse peritoneal macrophages. J. Antimicrob. Chemother 1992; 30: 173–179.

[212] Aggarwal P, Hall J B, McLeland C B, Dobrovolskaia M A, McNeil S E. Nanoparticle Interaction with plasma proteins as it relates to particle biodistribution, biocompatibility and therapeutic efficacy. Adv. Drug Deliv. Rev 2009;61: 428–437.

[213] Patravale V B, Date A, Kulkarni R M. Nanosuspensions: a promising drug delivery strategy. Journal of Phatmacy and Pharmacology 2003; 56: 827-840.

[214] Damge C, Michel C, Aprahamian M, Couvreur P, Devissaguet J P. Nanocapsules as carriers for oral peptide delivery. Journal of Controlled Release 1990; 13(2-3):233-239.

[215] Rieux A, Fievez V, Garinot M, Schneider Y, Preat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. Journal of Controlled Release 2006; 116:1–27.

[216] Olbrich C, Kayser O, Muller R H. Lipase degradation of Dynasan 114 and 116 solid lipid nanoparticles (SLN)–effect of surfactants, storage time and crystallinity. Int J Pharm 2002; 237:119–28.

[217] Foster N, Hirst B H. Exploiting receptor biology for oral vaccination with biodegradable particulates. Adv. Drug Deliv. Rev 2005; 57:431–450.

[218] Fattal E, Pecquet S, Couvreur P, Andremont A. Biodegradable microparticles for the mucosal delivery of antibacterial and dietary antigens. Int. J. Pharm 2002; 242: 15–24.

[219] Pinto J F, Muller R H. Pellets as carriers of solid lipid nanoparticles (SLN) for oral administration of drugs. Pharmazie 1999; 54:506–9.

[220] Patton J S, Byron P R. Inhaling medicines: delivering drugs to the body through lungs. Nat Rev Drug Discov 2007; 6:67-74.

[221] Laube B L. The expanding role of aerosols in systemic drug delivery, gene delivery and vaccination. Respir Care 2005; 50:1161-76.

[222] Patton J S, Fishburn C S, Weers J G. The lungs as a portal of entry for systemic drug delivery. Proc. Am. Thorac. Soc 2004;1 (4): 338–344.

[223] Lu B, Zhang J Q, Yang H. Lung-targeting microspheres of carboplatin. Int J Pharm 2003; 265:1–11.

[224] Muller R H, Jacobs C. Buparvaquone mucoadhesive nanosuspension: preparation, optimisation and long-term stability. Int. J. Pharm 2002; 237: 151–161.

[225] Kohno S, Otsubo T, Tanaka E, Maruyama K, Hara K. Amphotericin B encapsulated in polyethylene glycolimmunoliposomes for infectious diseases. Adv. Drug Del. Rev 1997; 24: 325–329.

[226] Pignatello R, Bucolo C, Spedalieri G, Maltese A, Puglisi G. Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application. Biomaterials 2002; 23: 3247–3255.

[227] Friedrich I, Reichl S, Muller-Goymann C C. Drug release and permeation studies of nanosuspensions based on solidifi ed reverse micellar solutions (SRMS). Int J Pharm 2005; 305:167–75.

[228] Cavalli R, Gasco M R, Chetoni P, et al. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm 2002; 238:241–5.

[229] Nagarwal R C, Kant S, Singh, et al. Polymeric nanoparticulate system: A potential approach for ocular drug delivery. Journal of Controlled Release 2009; 136: 2–13.

[230] De Campos A M, Diebold Y, Carvalho E L S, Sanchez A, Alonso M J. Chitosan nanoparticles as new ocular drug delivery systems: in vitro stability, in vivo fate, and cellular toxicity. Pharm. Res 2004; 21 (5): 803–810.

[231] De Salamanca A E, Diebold Y, Calonge M, Garcia-Vazquez G, Callejo S, Alonso M J. Chitosan nanoparticles as a potential drug delivery system for the ocular surface:

toxicity, uptake mechanism and in vivo tolerance. Invest. Ophtlamol. Vis. Sci 2006; 47: 1416–1425.

[232] Lockman P R, Mumper R J, Khan M A, Allen D D. Nanoparticle technology for drug delivery across the blood–brain barrier. Drug Dev. Ind. Pharm 2002; 28 (1): 1-13.

[233] Roney C, Kulkarni P, Arora V, et al. Targeted nanoparticles for drug delivery through the blood–brain barrier for Alzheimer's disease. Journal of Controlled Release 2005; 108: 193–214.

[234] Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv. Drug Deliv. Rev 2001; 47 (1): 65–81.

[235] Wong H, Chattopadhyay N, Wu X, Bendayan R. Nanotechnology applications for improved delivery of antiretroviral drugs to the brain. Advanced Drug Delivery Reviews 2010; 62: 503–517.

[236] Pardridge W M. Drug and gene targeting to the brain with molecular trojan horses. Nat Rev Drug Discov 2002; 1(2):131-139.

[237] Dutta T, Jain N K. Targeting potential and anti-HIV activity of lamivudine loaded mannosylated poly(propyleneimine) dendrimer, Biochim. Biophys. Acta 2007; 1770:681–686.

[238] Ring K, Walz C M, Sabel B A. Nanoparticle drug delivery to the brain. Eocyclopedia of Nanoscience and Nanotechnology. 2004; 7: 91-104.