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Original Article

Application of nano-antibiotics in the diagnosis and treatment of infectious diseases

Aplicação de nanoantibióticos no diagnóstico e tratamento de doenças infecciosas

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Abstract

Infectious diseases are the leading cause of death worldwide. Thus, nanotechnology provides an excellent opportunity to treat drug-resistant microbial infections. Numerous antibiotics have been used to inhibit the growth and kill of microbes, but the development of resistance and the emergence of side effects have severely limited the use of these agents. Due to the development of the nanotechnology, nanoparticles are widely used as antimicrobials. Silver and chitosan nanoparticles have antifungal, antiviral and antibacterial properties, and many studies confirm the antifungal properties of silver nanoparticles. Nowadays, the use of nanoparticles in the diagnosis and treatment of infectious diseases has developed due to less side effects and also the help of these particles in effective drug delivery to the target tissue. Liposomes are also used as carriers of drug delivery, genes, and modeling of cell membranes in both animals and humans. The ability of these liposomes to encapsulate large amounts of drugs, minimize unwanted side effects, high effectiveness and low toxicity has attracted the interest of researchers. This review article examines recent efforts by researchers to identify and treat infectious diseases using antimicrobial nanoparticles and drug nano-carriers.

Keywords: infectious diseases, antimicrobial, nanoparticles, nano-carriers, antibiotic.

Resumo

As doenças infecciosas são a principal causa de morte no mundo. Assim, a nanotecnologia oferece uma excelente oportunidade para tratar infecções microbianas resistentes a medicamentos. Numerosos antibióticos têm sido usados para inibir o crescimento e a morte de micróbios, mas o desenvolvimento de resistência e o surgimento de efeitos colaterais limitaram severamente o uso desses agentes. Devido ao desenvolvimento da nanotecnologia, as nanopartículas são amplamente utilizadas como antimicrobianos. As nanopartículas de prata e quitosana têm propriedades antifúngicas, antivirais e antibacterianas, e muitos estudos confirmam as propriedades antifúngicas das nanopartículas de prata. Atualmente, o uso de nanopartículas no diagnóstico e tratamento de doenças infecciosas tem se desenvolvido em razão do menor número de efeitos colaterais e também à ajuda dessas partículas na efetiva entrega de fármacos ao tecido-alvo. Os lipossomas também são usados como transportadores de entrega de drogas, genes e modelagem de membranas celulares em animais e humanos. Os lipossomas também são usados como transportadores de entrega de drogas, genes e modelagem de membranas celulares em animais e humanos. A capacidade desses lipossomas de encapsular grandes quantidades de fármacos, minimizar efeitos colaterais indesejados, alta eficácia e baixa toxicidade tem despertado o interesse de pesquisadores. Este artigo de revisão examina esforços recentes de pesquisadores para identificar e tratar doenças infecciosas usando nanopartículas antimicrobianas e nanotransportadores de drogas.

Palavras-chave: doenças infecciosas, antimicrobiano, nanopartículas, nanoportadores, antibiótico.

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1. Introduction

Nanotechnology is a new fashionable field as well as a new field of technological innovations. Among the applications of nanotechnology are human biology and medicine. Nanotechnology also plays a vital role in treatment, cost-effective prevention, and the realization of diagnostic tools (Tallury et al., 2010; Hauck et al., 2010; Kaittanis et al., 2010). Also, nanotechnology can be used for various medical purposes such as clinical diagnosis, pharmaceutical research, and activation of the immune system and extraction of biological materials. In COVID-19 failure, gaining a better understanding of the virus is the diagnosis, treatment, and prevention of steps in which nanotechnology can help scientists (Zhang et al., 2010; Hogberg et al., 2010). A subset of nanotechnology is called bio nanotechnology. Nano-biotechnology is a unique combination of biotechnology and nanotechnology that can be used to truly integrate classical microtechnology into a molecular biological approach . Nanomaterials have unique properties and the inherent antimicrobial activity of some of them has been proven (Rai et al., 2009). In addition, the use of new nanostructured systems for the delivery of antibiotics has received much attention in improving the pharmacokinetics of the drug and reducing its side effects. These Nano systems can increase the duration of their presence in the bloodstream by enclosing antibiotics in a polymer matrix, thereby significantly reducing the effective dose of the drug and the frequency of administration (Brunet et al., 2009; Wu et al., 2020). Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites and fungi. These diseases since the dawn of civilization, is the second leading cause of death worldwide and the leading cause of reduced disability related to quality of life and has also remained stable as a source of human morbidity and mortality.

Infectious diseases are caused by pathogens like viruses (HIV, viral hepatitis and dengue fever), parasites (malaria, trypanosomes and leishmaniosis), bacteria (tuberculosis and cholera) and fungi (Tallury et al., 2010; Hauck et al., 2010; Kaittanis et al., 2010). Infectious microorganisms are spread throughout the body by the cardiovascular system after invading the epithelial surface, then are eliminated by macrophages present within the body's major organisms like the liver, spleen and bone marrow (Zhang et al., 2010; Hogberg et al., 2010). However, most microorganisms, through one among the mechanisms of phagosome escape, inhibition of lysozyme-phagosome fusion and resistance to oxidative and non-oxidative deletion, resist macrophages and result in infectious diseases. These diseases also are called infectious diseases because of their ability to be transmitted from one person to a different (malaria and tuberculosis) and sometimes from one species to a different (influenza) (Brunet et al., 2009; Kong et al., 2017; Wu et al., 2020; Chao et al., 2020; Lei et al., 2020). As infectious diseases cause the death of numerous people within the world, especially in developing countries, they pose a heavy threat to human health (Singh et al., 2019; Song et al., 2019a; Zeng et al., 2019). within the early twentieth century, infectious diseases were the leading reason behind death worldwide. The decline within the incidence of infectious diseases and mortality from these diseases within the last century is thanks to the popularity of antimicrobial agents (Xu et al., 2019; Feng et al., 2018; Wang et al., 2021). the employment of antibiotics began with the commercial production of penicillin within the late 1990s and was claimed to be a good success until the 1990s, when newer and stiffer antibiotics were introduced. Despite extensive research and investment, with the event of antimicrobial drugs, resistance to those agents has expanded. Increasing the speed of bacterial resistance has made the employment of the foremost potent antibiotics ineffective (Figure 1). Antibiotic-resistant bacteria were studied to beat drug resistance by discovering newer antibiotics and chemically modifying existing drugs (Seki et al., 2021; Zeng et al., 2018; Kong et al., 2017). However, today resistance to antibiotics

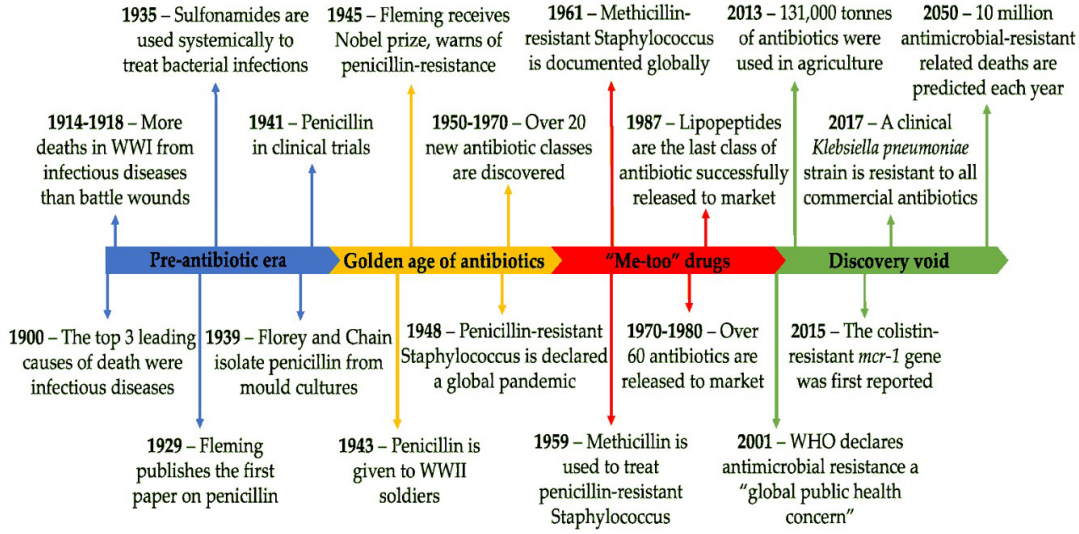

Figure 1. Introduction of antibiotics and development of resistance to these agents (Hogberg et al., 2010).

has reached a critical level, and unfortunately there's no guarantee that with the event of latest antimicrobial drugs, the continual and rapid spread of resistance may be overcome in a very timely manner. as an example, drug-resistant infections are growing in hospitals and therefore the community, posing a heavy threat to human health. So challenging treatment of infectious diseases requires long-term solutions (Pissuwan et al., 2020; Szczęch and Szczepanowicz, 2020; Ferrari et al., 2012; Kumari et al., 2010). one among the recent efforts of researchers to beat these challenges is that the use of nanotechnology strategy. Materials at the nanoscale (1-100 nm) show unique physicochemical properties, including higher surface-to-volume ratio, electrical, magnetic, and optical properties, and better reactivity (Athanasiou et al., 1996; Danhier et al., 2012; Suh et al., 2009). as an example, recent studies have shown that some metal nanoparticles have intrinsic antimicrobial activity. These particles are accustomed control infectious diseases and microbial pathogens aren't ready to develop resistance to those particles (Kumari et al., 2010; Kianfar, 2021a; Cai et al., 2021). Antimicrobial nanoparticles (NPs) offer many advantages over conventional antibiotics in reducing drug side effects, resistance, and treatment costs (Conceicao et al., 2020; Ageitos et al., 2017; Reddy et al., 2004). Drug Nano carriers even have a major effect on improving the pharmacokinetics of medication and reducing side effects. Theoretically, Nano carriers are kept longer within the body than antibiotic molecules, which is helpful for long-term therapeutic effects. Nanotechnology promises promising advances altogether areas of immunization, drug design, drug delivery, diagnosis and control of infectious diseases (Mohammed et al., 2017; Ninan et al., 2020; Ernst et al., 2021; Dong et al., 2011). Because the results of studies show that nanotechnology can overcome a number of the challenges related to a way to diagnose and treat infectious diseases (Kharwade et al., 2020; Hutapea et al., 2021; Al-Shawi et al., 2017, 2021). Therefore, during this article, a quick study of molecular diagnosis and control of infectious diseases using nanotechnology is presented.

Since the first reports of a novel severe acute respiratory syndrome (SARS)-like COVID-19 in December 2019 in Wuhan, China, there has been intense interest in understanding how severe acute respiratory syndrome COVID-19 emerged in the human population. Recent debate has coalesced around two competing ideas: a "laboratory escape" scenario and zoonotic emergence. Here, we critically review the current scientific evidence that may help clarify the origin of COVID-19. COVID-19 have long been known to present a high pandemic risk. Severe acute respiratory syndrome COVID-19 is the ninth documented coronavirus that infects humans and the seventh identified in the last 20 years. All previous human coronaviruses have zoonotic origins, as have the vast majority of human viruses. The emergence of COVID-19 bears several signatures of these prior zoonotic events. It displays clear similarities to SARS-CoV that spilled over into humans in Foshan, Guangdong province, China in November 2002, and again in Guangzhou, Guangdong province in 2003. Both these SARS-CoV emergence events were associated with markets selling live animals and involved species, particularly civets and raccoon dogs, that were also sold live in Wuhan markets in 2019 and are known to be susceptible to SARS-CoV-2 infection. Animal traders working in 2003, without a SARS diagnosis, were documented to have high levels of immunoglobulin G (IgG) to SARS-CoV (13% overall and >50% for traders specializing in civets) (Centers for Disease Control). Subsequent serological surveys found ~3% positivity rates to SARS-related coronaviruses (SARSr-CoV) in residents of Yunnan province living close to bat caves, demonstrating regular exposure in rural locations. The closest known relatives to both SARS-CoV and SARS-CoV-2 are viruses from bats in Yunnan, although animals from this province have been preferentially sampled. For both SARS-CoV and SARS-CoV-2, there is a considerable geographic gap between Yunnan and the location of the first human cases, highlighting the difficulty in identifying the exact pathway of virus emergence and the importance of sampling beyond Yunnan. COVID-19 also shows similarities to the four endemic human coronaviruses: human coronavirus-OC43 (HCoV-OC43), human coronavirus-HKU1 (HCoV-HKU1), human coronavirus-229E (HCoV-229E), and human coronavirus NL63 (HCoV-NL63). These viruses have zoonotic origins, and the circumstances of their emergence are unclear. In direct parallel to SARS-CoV-2, HCoV-HKU1, which was first described in a large Chinese city (Shenzhen, Guangdong) in the winter of 2004, has an unknown animal origin, contains a furin cleavage site in its spike protein and was originally identified in a case of human pneumonia. Based on epidemiological data, the Huanan market in Wuhan was an early and major epicenter of SARS-CoV-2 infection. Two of the three earliest documented coronavirus disease 2019 (COVID-19) cases were directly linked to this market selling wild animals, as were 28% of all cases reported in December 2019. Overall, 55% of cases during December 2019 had an exposure to either the Huanan or other markets in Wuhan, with these cases more prevalent in the first half of that month (Cai et al., 2021; Conceicao et al., 2020).

2. Application of Nano-technology in Diagnosis of Infectious Diseases

Researchers and clinicians need accurate tools to spot pathogens to combat the spread of infectious diseases (Abed et al., 2023; Abderrahmane et al., 2023; Younis et al., 2022; Smaisim et al., 2022a; Wang et al., 2022). Despite the importance of correctly diagnosing pathogens, methods of diagnosing infectious diseases have changed little over the last 50 years. Standard techniques for diagnosing infectious diseases include microscopy, tissue culture, ELISA, and PCR. These techniques have high cost, limited ability to differentiate pathogens, low speed, and poor detection threshold (Xiao and Smaisim, 2022; Mourad et al., 2022; Cheng et al., 2022; Smaisim et al., 2022b; Abderrahmane et al., 2022; Tan et al., 2022; Mir et al., 2022; Ruhani et al., 2022). At present, the molecular diagnosis of diseases is concentrated on recent advances in nanotechnology. Because the unique electrical, magnetic, luminescent and catalytic properties

of nanoparticles are very useful for rapid, sensitive and effective detection of microbial agents and overcoming drug resistance (Bhale et al., 2020; Muluk et al., 2020; Giorgadze et al., 2020).

Nanoparticles are accustomed diagnose infectious diseases in three alternative ways to form biosensors:

- Lateral flow immunochromatographic tests (Hauck et al., 2010).
- Nanoparticle aggregation assays (Hauck et al., 2010).
- Nanoparticle labels of whole pathogens (Hauck et al., 2010).

2.1. Lateral flow immunochromatographic tests

In this method, antibody-conjugated nanoparticles generate signals for biological analysis and counting of pathogenic bacteria, which leads to fast, convenient and selective detection of bacteria within 20 min. This method is based on detection and colorimetry that pathogens with the naked eye are identified using latex particles or gold nanoparticles as contrast agents. The detection also depends on the pathogenic species (Li et al., 2022; Cai et al., 2022; Moarrefzadeh et al., 2022; Liu et al., 2022; Hai et al., 2022; Smaisim et al., 2022a). This method is predicated on detection and calorimetry within which pathogens are identified with the optic using latex particles or gold nanoparticles as contrast agents. Detection also depends on pathogenic species (Figure 2) (Hauck et al., 2010).

2.2. Nanoparticle aggregation assays

This assay is predicated on the interaction of antibodies attached to the nanoparticle and also the target molecule. The target molecule acts as a bridge between several nanoparticles and these aggregations result in a change within the optical signal of the nanoparticle (Pathare et al., 2020; Arliny et al., 2021; Burhan et al., 2019). Changes in light coefficient is assessed using visible-ultraviolet spectroscopy. This assay is additionally cherishing the ELISA method but requires minimal sample preparation and purification (Jiang et al., 2022; Tian et al., 2022; Alharbi et al., 2022; Wu et al., 2022; Tian et al., 2022). for instance, silver and gold nanoparticles have strong light absorption and, following aggregation, produce an appropriate optical signal for evaluation (Alshetaili et al., 2018; Alwan et al., 2021; Zharif et al., 2018; Salimi et al., 2017a). Also using this assay, magnetic nanoparticles create a rapid and sensitive strategy to show microbial infections. as an example, dextran-coated super magnetic iron oxide nanoparticles are wont to detect the metabolic activity of microbes and to work out the quantity of polysaccharides (to assess susceptibility to microbes) within the blood (Figure 3) (Tallury et al., 2010).

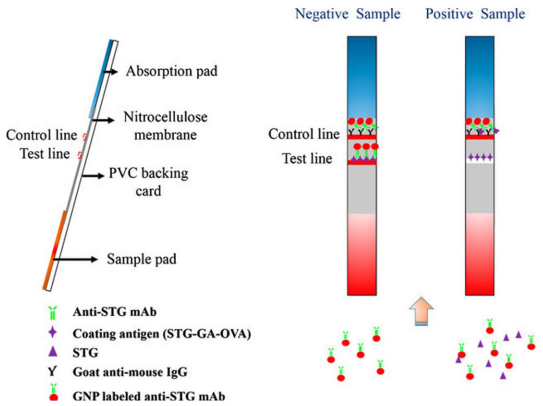

Figure 2. imaging Lateral flow immunochromatographic tests (Kong et al., 2017).

2.3. Nanoparticle labels of whole pathogens

In this method, metal nanoparticles are coated with a selected nucleotide sequence that enhances the target genome. within the presence of the target genome, complementary sequences are paired, and these interactions result in a change within the color of the answer or a change within the spectrum (Brontowiyono et al., 2022; Tian et al., 2022; Smaisim et al., 2022a). This particular method also has applications in identifying single-nucleotide polymorphisms and viral detection systems supported supramolecular liposomes (Kianfar, 2018, 2019a, b; Kianfar et al., 2018). because the interaction of designed liposomes and viral particles ends up in changes in absorption spectra to be identified. A team of researchers also used silica nanowires to detect influenza an endemic. during this evaluation, the researchers attached virus-specific antibodies to the nanowires and analyzed the change in nanowire conductivity after antigen-antibody interaction. Quantum nanoparticles are good candidates for molecular detection in vivo because their high molar absorb, remarkable stability against light and wide spectrum and narrow emission. These particles even have regenerative properties, so quantum particles with different oxidation potentials are accustomed identify several target molecules simultaneously. These nanoparticles have a large range of applications in histology, pathology and cytology analyzes of complex specimens (Salimi et al., 2017a; Kianfar and Kianfar, 2019; Kianfar et al., 2020a, b). Therefore, nanotechnology provides the proper conditions for valid clinical trials and identification of pathogens, which are performed in an exceedingly non-transparent environment like blood or milk and don't require any sample preparation (Figure 4).

3. Nano Antibiotics: The Role of Nanotechnology in the Control and Treatment of Infectious Diseases

Nanomaterials that inherently have antimicrobial activity or increase the effectiveness and safety of antibiotics are called Nano antibiotics. Nano antibiotics don't have severe and direct side effects compared to other antimicrobial agents employed in clinical settings. However, extensive studies on the toxicity of Nano antibiotics have to be performed (Liu and Kianfar, 2020; Kianfar et al., 2018). The nanoparticles can be made by a variety of materials to serve different purposes. There are different types of Nano formulations employed for antibacterial application. For drug delivery, the Nano particulate core or shell can load several payload drugs (Mozafarifard et al., 2022; Sharba et al., 2022; Smaisim et al., 2022a; Abdul

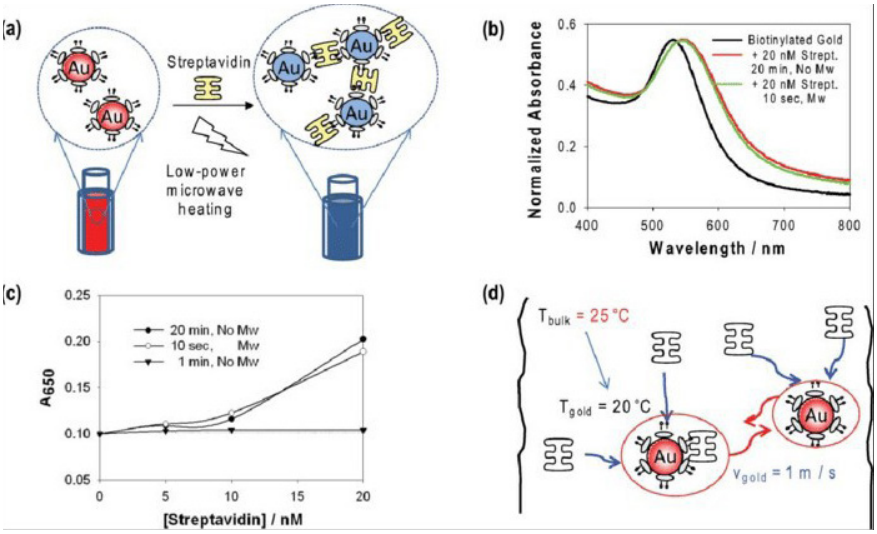

Figure 3. Microwave-accelerated nanoparticle aggregation assays (MA-AAs) in solution. (a) Model protein-nanoparticle system used to demonstrate MA-AA in solution; biotinylated-BSA-coated 20 nm gold nanoparticles cross-linked by streptavidin; (b) Change in absorbance of biotinylated-BSA 20 nm gold nanoparticles cross-linked by 20 nM addition of streptavidin, both without (room temperature) and after low-power microwave heating; (c) Change in absorbance at 650 nm for both the room-temperature-incubated and microwave-heated samples; (d) Schematic representation of the aggregation process driven by a temperature gradient and kinetic energy of the nanoparticles (Aslan and Geddes, 2008).

Hussein et al., 2022). The shape, size, and surface charge of the nanoparticles can be finely tuned by modulation of material types, contents and preparation processes for optimizing drug release and organ/cell targeting. Inorganic met al., polymeric, lipid-based, micellar, silica, and cell membrane-coated nanoparticles are the commonly studied Nano systems for antibiotic drugs (Ahamad et al., 2022; Doss et al., 2022; Lefteh et al., 2022; Sallal et al., 2021). Figure 5 summarizes the nanoparticle classes applied to antimicrobial chemotherapy.

Metallic nanoparticles mainly made by Au, Ag, or Cu are found to present strong antimicrobial activity. However, the application may be hindered because of their potential toxicity to mammalian cells. Reforming of the metallic nanoparticles is needed to improve the biocompatibility. Compared to the other inorganic metal nanoparticles, Au nanoparticles are attracting great attention due to their acceptable biocompatibility, stable storage, and easy surface functionalization (Kianfar et al., 2018, 2019). Due to the unique physical and chemical characteristics, Au nanoparticles have been extensively applied in drug delivery carrier, bio imaging, and anti-carcinogenic therapy (Smaisim et al., 2016a, b; Smaisim, 2017, 2018; Kianfar, 2022a). The adsorption of drug molecules on the Au particle surface allows the delivery of active ingredients to target sites. Some antimicrobial agents such as antibiotics, antibacterial peptides, and surfactants can be conjugated onto the Nano particulate shell to initiate potential bactericidal activity (Kianfar, 2020a; Kianfar et al., 2015a, 2020b). Ag nanoparticles themselves reveal a broad spectrum to eradicate bacteria, including some drug-resistant strains. Nano-sized Ag shows greater biocidal effect than the bulk material. The mechanisms of killing

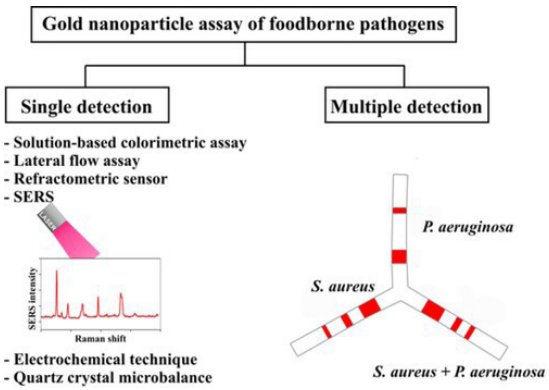

Figure 4. Nanoparticle labels of whole pathogens (Pissuwan et al., 2020).

bacteria by Ag nanoparticles are the disintegration of bacterial wall and the subsequent leakage of cytoplasmic contents and inactivation of proteins responsible for DNA and RNA replication. The superparamagnetic iron oxide nanoparticles (SPIONs) are widely investigated as powerful bactericidal agents due to their magnetic hyperthermia property. Moreover, SPIONs are applicable as bacteria separation agents and bio imaging contrast agents for bacteria diagnosis. SPIONs adsorb electromagnetic radiation and then convert the magnetic energy into heat under a magnetic field with high frequency and amplitude. The hyperthermia causes the increased bacterial membrane permeability to kill the targeted bacteria since most bacteria become vulnerable at the temperature of >45°C. In order to potentiate the antibacterial activity, SPIONs

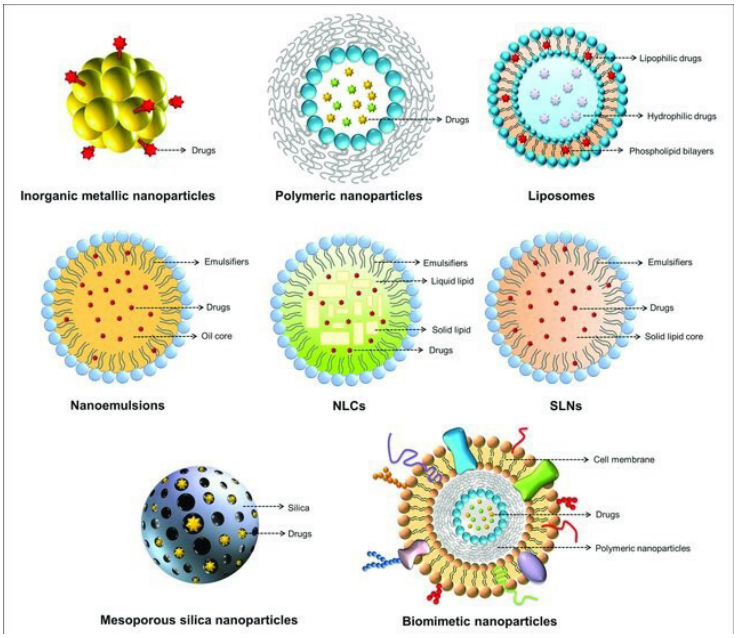

Figure 5. The nanoparticle classes applied for antimicrobial chemotherapy (Szczęch and Szczepanowicz, 2020).

can be functionalized with antibodies, antimicrobial peptides, and aptamers for targeting specific bacteria. The magnetic nanoparticles made with iron oxide are also effective in deep penetration into biofilm by the triggering of a magnetic field. Natural or synthetic polymers can be utilized to fabricate nanoparticles for biomedical use. The antibiotics can either be covalently bound to a polymer backbone or physically incorporated into a polymer matrix. The biopolymers can form nanoparticles with high biocompatibility and biodegradability. They are classified into polysaccharides, nucleic acids, and peptides/proteins. Chitosan is one of the biopolymers with linear polysaccharide composed of randomly distributed β-(1→4)-linked D-glucosamine and N-Acetyl-D-glucosamine. Chitosan itself can act as antibacterial and ant biofilm agents due to its polyatomic nature's ability to disrupt bacterial membrane (Kianfar, 2020a; Kianfar et al., 2017; Kianfar and Cao, 2021). Chitosan-based nanoparticles have been broadly used as drug delivery systems. The mucoadhesive character of chitosan nanoparticles contributes to the prolonged residence time in bio membranes, such as cornea, gastrointestinal epithelium, and buccal mucosa for sustained drug release. Alginate is another biopolymer commonly used to fabricate drug delivery Nano carriers. Contrary to chitosan, alginate is the anionic polysaccharide derived from the cell wall of algae. Alginate-based nanoparticles are reported to load antimicrobial agents for treating tuberculosis and fungal infection. Proteins are interesting ingredients for the preparation of nanoparticles because of the variety of molecular weights and easy chemical modification. Several proteins have been employed to develop Nano delivery systems, such as heat shock albumin, proteins, and ferritin. Although the synthetic polymers meet the challenges in regard to their biocompatibility and biodegradability, recent studies prove that some synthetic polymers can be generally regarded as safe (GRAS) as recognized by the USFDA. An example is poly(lactide-co-glycolide) (PLGA); Yang et al., 2020). This polymer can be hydrolyzed to non-toxic oligomers or monomers of lactic acid and glycolic acid. PLGA nanoparticles are designed for drug delivery to aid therapeutic efficacy by drug protection, prolonged residence time, and nidus-targeting ability. According to the industrial consideration, there are many procedures for fabricating PLGA nanoparticles. Most of these techniques are easy to scale-up. The drug release and degradation rate can be tuned and controlled by changing the ratio of lactic acid and glycolic acid. Another case of synthetic polymers with acceptable biocompatibility is poly (malic acid) (PMLA), a biocompatible amphiphilic polymer based on polyesters. The features of PLMA are water soluble, biodegradable, and less toxic. The pendent carboxyl moieties in PLMA enable the introduction of various chemical modifications for nanoparticle development; these include antibodies, proteins, and specific drugs, including antibiotics. Lipid-based nanoformulations, such as liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs), are frequently applied for transporting antibacterial drugs (Kianfar et al., 2020a; Kianfar, 2020a, b). Lipid nanoparticles can facilely fuse with bacterial membrane, delivering antibiotics directly to bacteria. Liposomes, as the carriers for drug delivery, can prolong circulation time and accelerate cellular uptake, thus countering therapeutic resistance; these Nano-sized vesicles consist of membrane-like phospholipid bilayers in an aqueous solution. Liposomes have gained much attention because of their non-toxicity and structural similarity to cells. Liposomes can fuse with mammalian cells, tumor cells, and microbes,

facilitating the transport of drugs across bio membranes. Lipid Nano carriers, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) and Nano emulsions, appear suitable as drug-carrier systems due to their very low cytotoxicity relative to polymeric nanoparticles. The predominant difference among SLNs, NLCs and Nano emulsions is the composition of the inner core. SLNs are particles made from crystalline solid lipids, whereas NLCs are composed of a solid lipid matrix with a certain content of a liquid lipid; they are a more advanced generation of SLNs. Nano emulsions are Nano carriers with neat liquid oil in the inner phase (Kianfar, 2020a, 2020b; Kianfar and Mazaheri, 2020). These lipid Nano carriers were introduced as antibacterial drug carriers for targeting bacteria and diminishing biofilm. Because of their physicochemical stability, uniform porosity, great surface area, and biocompatibility, mesoporous silica nanoparticles (MSNs) are widely employed as drug delivery carriers, biosensors, catalysts, and adsorbents. MSNs with tunable particle size, pore volume, and morphology are promising carriers for drug delivery. The antibacterial agents inside the porous matrix are effectively shielded against enzymatic degradation. The surface chemistry of MSNs can be modified to facilitate the passage through bio membranes. The coating of natural cell membrane on nanoparticles has gained much attention recently. This strategy leverages native cell function for improving therapeutic effect. The biomimetic nanoparticles show therapeutic benefits, including prolonged nanoparticle circulation, cell-specific targeting, and immune system targeting. The nanoparticles can be coated with the membranes of cancer cells, erythrocytes, neutrophils, macrophages, or platelets to show their capability to bind with the source cells. The platelet membrane-coated nanoparticles are able to mimic the platelet binding with bacteria for targeted antibiotic therapy (Kianfar et al., 2020a; Kianfar, 2020b). The characterizations of chemically or biologically synthesized nanoparticles can be conducted by several techniques, such as FTIR, SEM, TEM, XRD, etc. (Figure 6).

3.1. Nanoparticles with inherent antimicrobial activity

Nanoparticles with antimicrobial properties include a large range of particles, including metals, metal oxides, natural antimicrobial substrates, carbon-based nanomaterials, and surfactant-based Nano emulsions. The antimicrobial activity of nanoparticles is especially their high surface-to-volume ratio and their unique physicochemical properties. Preparation of antimicrobial nanoparticles is low compared to the synthesis of antibiotics, and these compounds remain completely stable for a protracted time. additionally, some nanoparticles can withstand harsh conditions like high-temperature sterilization, under which conventional antibiotics are inactivated (Faghih and Kianfar, 2018; Kianfar and Mazaheri, 2020; Kianfar, 2020b). Nanoparticles result in the destruction of microbial species from several biological pathways, and so as to develop resistance to those particles, simultaneous and multiple mutations must occur, which is one among the foremost important advantages of antimicrobial nanoparticles. the foremost important antimicrobial mechanisms of nanoparticles are through photocatalytic production of reactive oxygen species (ROS), destruction of bacterial membrane and cell membrane, interruption of energy transfer, inhibition of enzymatic activity and inhibition of DNA synthesis (Figure 7) (Kianfar et al., 2019; Kianfar, 2020a, b). during this section, the antimicrobial properties of some nanoparticles are mentioned.

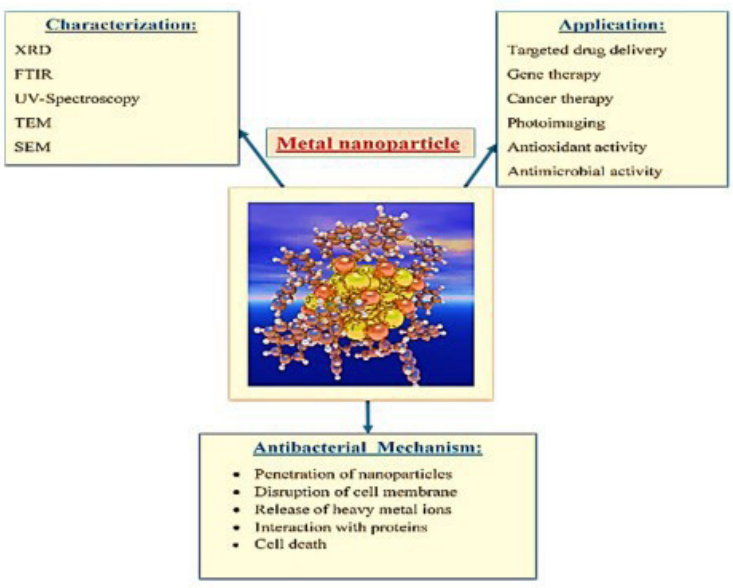

Figure 6. Characterization of metal nanoparticles using different instrumental-based techniques (Zhu et al., 2018).

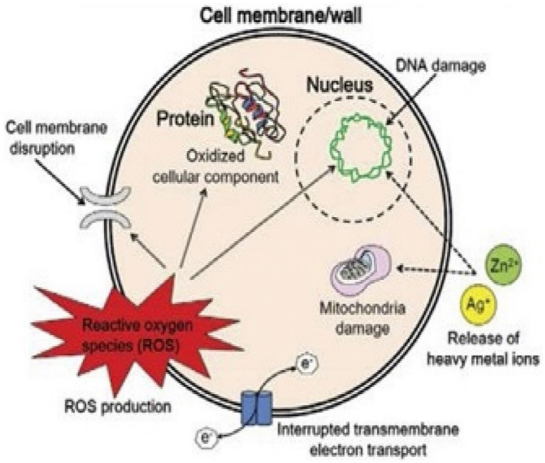

Figure 7. Types of antimicrobial mechanisms of nanoparticles (Huh and Kwon, 2011).

3.1.1. Silver nanoparticles

Silver atoms, usually ranging in size from 1 nm to 100 nm, make up silver nanoparticles (Kianfar, 2019a, b). To produce AgNP, many artificial methods have been created ("Kianfar and Salimi,2020"). The antibacterial properties of silver have been around since ancient times. Various studies have shown that silver nanoparticles have the highest antimicrobial activity compared to other metal nanoparticles (Kianfar, 2020a; Kianfar et al., 2015a, 2020b). Silver nanoparticles are known to act against HIV and hepatitis viruses due to their antibacterial and antiviral properties (Kianfar, 2020a). In general, using the production methods of spherical, elongated (bar) or short (triangular) Ag NPs Ag these nanoparticles can be synthesized (Kianfar et al., 2017). The mechanism of silver germination is through attack on the respiratory chain and cell division and the release of silver ions, which eventually lead to microbial cell death. The use of silver nanoparticles in combination with antibiotics such as penicillin G, amoxicillin, erythromycin, and vancomycin leads to synergistic and antimicrobial effects against gram-negative and gram-positive bacteria (Yang et al., 2020). These nanoparticles are used in the preparation of burn healing ointments, medical instrument coatings and surgical masks, in the production of deodorant and antibacterial fabrics, nanogels, and nanolotions (Kianfar et al., 2020a; Kianfar, 2020b). The antibacterial effect of silver and ampicillin nanoparticles on E. coli and P. aeruginosa increased 8.1 and 4.2 times, respectively; While this effect on S. aureus has increased only 2.0 times (Kianfar, 2020a). Silver particles and antimicrobial peptides such as polymyxin-B and gramicidin-A against 9 bacterial strains consisting of: E. coli, Acinetobacter calcoaceticus, Enterobacter helveticus, Aeromonas bestiarum, Proteus myxofaciens, Pseudomonas fluorescens, Bacillus subtilis, Kocuria rhizophila and Micrococcus luteus have antimicrobial synergistic effects (Kianfar, 2020b).

The antibacterial properties of silver are around for an extended time. Various studies have shown that silver nanoparticles have the very best antimicrobial activity compared to nanoparticles of other metals. The antimicrobial properties of those particles rely on the scale and shape of the particles. The mechanism of silver germination is by attacking the respiratory chain and organic process and also the release of silver ions, which eventually cause microbial death. the employment of silver nanoparticles together with antibiotics like penicillin G, amoxicillin, erythromycin, and vancomycin ends up in synergistic and antimicrobial effects against gram-negative and gram-positive bacteria (Kianfar, 2020a, b). These nanoparticles are employed in the preparation of burn healing ointments, instrument coatings and surgical masks, within the production of odorless and antibacterial fabrics, Nano gels and annulations.

Silver nanomaterials can enter the human body via many pathways, including the respiratory tract, digestive tract, skin, or even through the placenta. Once the NPs overcome the classical barriers of the human body, they reach the bloodstream where they encounter the 'guard cells' of the immune system. Immune cells include lymphocytes (B cells, T cells, Natural K cells) and granulocytes (basophils, eosinophils, neutrophils, mast cells, dendritic cells, and macrophages) (Figure 8). Silver can react with these immune cells and incite stimulation or suppression, resulting in various pathological conditions. Mammalian immune cells use five ways to internalize particles: phagocytosis, pinocytosis, clathrin-mediated, caveolin-mediated, and caveolin/clathrin-mediated endocytosis (Figure 9). In phagocytosis, immune cells engulf silver particle to form an internal compartment called phagosome, which then fuses with a lysosome to form a phagolysosome. The enzymes present in phagolysosome will then digest the particles. In pinocytosis, silver is brought out to the mitochondria and then expelled from the cell forming an invagination which is then suspended within a vesicle. Clathrin-mediated endocytosis is a receptor-mediated endocytosis in which cells absorb silver by the inward budding of the plasma membrane containing receptors that specifically bind to silver. Caveolin-mediated endocytosis is a receptor-mediated process in which cells absorb silver by bulb-shaped plasma membrane invaginations driven by integral membrane proteins called caveolin as well as peripheral membrane cavin proteins.

The immune system of higher vertebrates encompasses a collection of different specialized cells and specialized soluble molecules distributed throughout the body, being present in all organs and tissues, circulating in blood and lymph (to reach every corner of the body in case of need), and concentrated in some lymphoid organs (lymph nodes, spleen, bone marrow, where hematopoiesis takes place in adult life). These cells have been classified into two functional branches, namely innate and the adaptive immunity, which have different roles, complementing each other very efficiently in complex organisms such as mammals (simpler organisms such as invertebrates only display a perfectly efficient innate immunity) (Kianfar et al., 2015a, b, c; Kianfar, 2019a). The innate immune system's role is to scan the body to remove apoptotic bodies, cell debris, and protein aggregates; recognize and eliminate pathogens or abnormal cells; and keep commensals outside tissues. Additionally, it promotes the repair of damaged

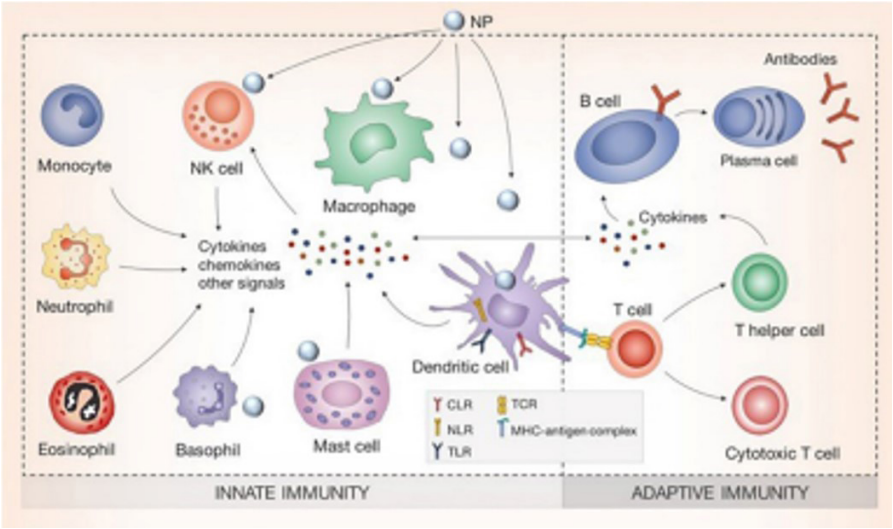

Figure 8. Schematic diagram showing different types of immune cells of the innate and adaptive immunity that may interact with silver nanomaterials (Ninan et al., 2020).

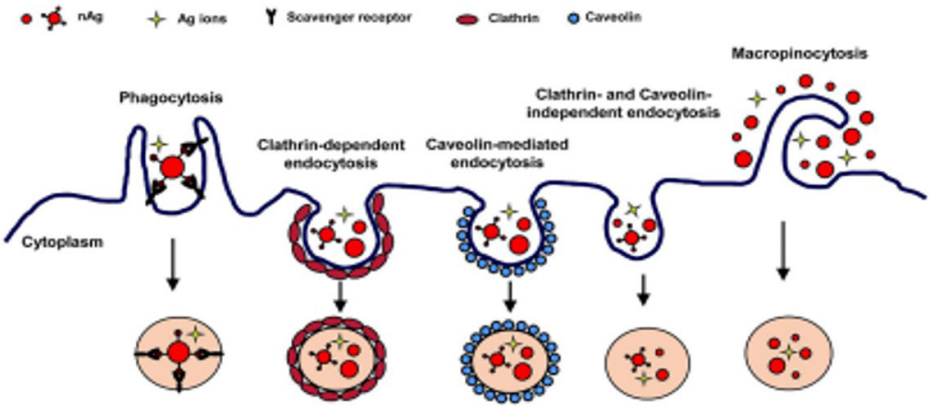

Figure 9. Schematic diagram showing the uptake mechanisms of silver nanomaterials by immune cells (Ernst et al., 2021).

tissue and is involved in the control of embryogenesis and delivery. We can say that the innate immune system is the actual immune system, active throughout evolution with conserved and very efficient defensive mechanisms. The other system, adaptive immunity, developed much later as a complement of innate immunity, providing slower but more specific protective responses, good for long-living and mobile organisms that do not stably reside in the same environment. The adaptive immune responses are tools for the innate immune system with subordinated or programmed functions—tools because they develop without making any decision. It is the innate immune system that detects, categorizes, and triggers the immune response and, in the case of additional needs, calls for adaptive immunity to come in when the innate activation has reached a certain threshold level indicative of excessive danger and the need for more specific defensive tools. These complex defensive actions that body tissues perform in response to harmful stimuli, such as pathogens or damaged cells, are described as inflammation. Inflammation requires an excess biological workout and therefore it is closely related to metabolism. Immunometabolism has become increasingly popular since the publication of Mathis and Shoelson's perspective in 2011. This is crucial in the context of interactions with nanoparticles (NPs), since they have been observed to have the capacity to increase or decrease reactive oxygen species (ROS), which directly correlates with the onset or remission of inflammation. ROS are free radical molecules resulting from natural metabolism, which, when excessive and unregulated, may contribute to cell damage and aggravate human pathologies such as cancer, neurodegeneration, and stroke, among others. Following the great oxidation event some 2.3 billion years ago, oxidation has been the leading force of metabolism. A delicate equilibrium between heat generation (enthalpy) and biological organization (entropy) was established, which allowed natural systems to decrease their free energy in a particular controlled fashion. Deregulation of a living

system, for instance, in the case of a disease, increases enthalpy generation at the expense of entropy (Kianfar, 2021b). The system over-burns, which in biological terms is described as inflammation (literally setting in flames). Inflammation is correlated with a particular metabolic pathway, anaerobic glycolysis, providing higher energy power output, in which cells defend themselves from aggression. Furthermore, aerobic glycolysis, with a broken Krebs cycle, provides important metabolic intermediates and ROS. Inflammation provokes the unbalance between endogenous production of free radicals and antioxidant defenses, resulting in oxidative stress. While this metabolic defense mechanism is an ability of all eukaryotic cells, it is reasonable to imagine that, through evolution, some cells adapted the unbalanced energy equation to becoming professional defensive cells forming a whole discontinued system distributed across the body and responsible for the maintenance, defense, and repair of our biological tissues. In normal conditions, these cells have a patrolling role based on scanning and surveying tissues to eliminate senescent or damaged cells and become aggressive when encountering some possible dangers, capable of initiating, developing, and controlling inflammation. The innate cell response is different, depending on the type of stimulus or combination of stimuli, the stimulus intensity (quantitative and temporal), the location of the innate cells (the tissue and its specialization), and the microenvironmental conditions (Raya1 et al., 2021; Majdi et al., 2021; Meade et al., 2020). All these cues trigger a defined activation profile in innate cells, which is different based on the combination of micro environmental conditions that have triggered it. Engineered NPs may share several characteristics of microbial agents, such as size and ordered molecular surface patterns, presenting "eat-me" or "eat-me-not" surface signals that favor or prevent macrophages from engulfing them. Thus, they are expected to develop complex and intense interactions with immunity. Bachmann et al. showed that the immune system readily recognized antigen repetitive organization on the surface of viral particles. In contrast, poor antigen organization does not induce an immune response. The same holds for complement (in particular C1q, an ancient version of immunoglobulins), which recognizes ordered antigenic structures as those present on microorganisms but do not react to disordered patterns as those present in mammalian cell surfaces. The same has been observed with NP coatings. These interactions mainly concern innate immunity, as responsible for detecting and categorizing foreign matter inside the body (Biswaro et al., 2018; Kumar et al., 2018; Martin-Serrano et al., 2019).

3.1.2. Zinc oxide nanoparticles

Zinc oxide nanoparticles are non-toxic, biocompatible and stable compounds to processing conditions. These particles are reported to possess selective toxicity to bacteria but have shown minimal side effects on human and animal cells. The antibacterial mechanism of flowers of zinc nanoparticles is thru photocatalytic production of peroxide, release of Zn^2 + ions, degradation of proteins and lipids in bacterial cell membranes, and at last leakage of contents inside the cell and death of the bacterial cell (Huang et al., 2021a). These particles are utilized in the pharmaceutical industry as pharmaceutical carriers, within the restoration of teeth to provide high-gloss filling compounds, and in cosmetics. Studies also show the antimicrobial activity of those particles against food-borne pathogens. In some studies, polyvinyl alcohol polymer is employed as a coating for silver and oxide nanoparticles, which contains a stabilizing property and results in a rise within the membrane permeability of those nanoparticles (Wang et al., 2021).

3.1.3. Titanium dioxide nanoparticles

Titanium dioxide (TiO_2) nanoparticles are employed in a good range of industries because of their excellent photocatalytic properties. TiO_2 nanoparticles are widely used as photo catalysts to get rid of microbes. The results of studies show that the antimicrobial properties of those nanoparticles rely on the dimensions, intensity and wavelength of the sunshine source. In studies, TiO_2 nanoparticles have shown the best effect on the virus, followed by the bacterial wall and spores. The antimicrobial mechanism of those compounds is thru the photocatalytic formation of hydroxyl and peroxide radicals (Figure 10). The hydroxyl radicals produced are very strong, highly reactive oxidants that concentrate on the surface of microbes. Radiation-independent bacterial death has also been reported using these particles. Studies also show the activation of those particles in actinic ray conditions. so, the addition of other metals like silver results in changes in photocatalytic properties and thus the absorption wavelength of ultraviolet is closer to visible. This method also improves light absorption and increases the photocatalytic removal of bacteria and viruses. oxide nanoparticles are most typically employed in water treatment because they're stable and non-toxic in water and inactivate chemical compounds and microbes more effectively. These particles are utilized in the food, cosmetics and orthodontics industries to provide fillers, toothbrushes and dental implants (Seki et al., 2021; Zeng et al., 2018).

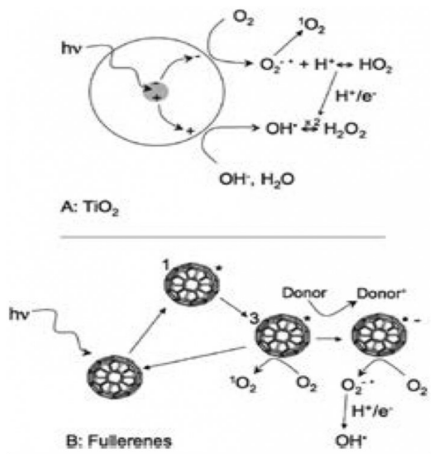

Figure 10. Mechanisms of production of reactive oxygen species by titanium nanoparticles (A) and fullerenes (B) (Brunet et al., 2009).

3.1.4. Gold nanoparticles

Gold nanoparticles, Nano rods and nanoparticles kill bacterial infections by irradiating concentrated laser pulses at the correct wavelength. The antimicrobial activity of gold nanoparticles is mediated by strong electrostatic interactions with the bacterial plasma membrane bilayer. In studies, conjugated gold nanoparticles with antimicrobial agents and antibodies have shown more selective and stronger antimicrobial effects. as an example, the effect of gold nanoparticles conjugated with anti-protein A antibody on the surface of aureus has been proven (Brunet et al., 2009).

3.1.5. Copper and aluminum nanoparticles

Aluminum oxide nanoparticles have antimicrobial effects only at very high concentrations, the mechanism of action of which is thru the creation of cracks within the plasma membrane. Although the antibacterial activity of silver nanoparticles is on top of that of other nanoparticles, it also depends on the microbial species. for instance, the results of studies indicate that copper nanoparticles at high concentrations compared to silver nanoparticles have a high tendency to amine and carboxyl groups on the surface of B, in order that they have shown more antibacterial activity against this species. Other advantages of oxide nanoparticles include low cost compared to silver nanoparticles, easy mixing with polymers and stability of those compounds (; Pissuwan et al., 2020).

3.1.6. Chitosan and antimicrobial peptides

The focus of this review is to provide an overview of the chitosan-based nanoparticles for various non-parenteral applications and also to put a spotlight on current research including sustained release and mucoadhesive chitosan dosage forms. Chitosan is a biodegradable, biocompatible polymer regarded as safe for human dietary use and approved for wound dressing applications. Chitosan has been used as a carrier in polymeric nanoparticles for drug delivery through various routes of administration. Chitosan has chemical functional groups that can be modified to achieve specific goals, making it a polymer with a tremendous range of potential applications. Nanoparticles (NP) prepared with chitosan and chitosan derivatives typically possess a positive surface charge and mucoadhesive properties such that can adhere to mucus membranes and release the drug payload in a sustained release manner (Diniz et al., 2020; Souto et al., 2020b; Carbone et al., 2016). Chitosan-based NP have various applications in non-parenteral drug delivery for the treatment of cancer, gastrointestinal diseases, pulmonary diseases, drug delivery to the brain and ocular infections which will be exemplified in this review. Chitosan shows low toxicity both in vitro and some in vivo models. This review explores recent research on chitosan-based NP for non-parenteral drug delivery, chitosan properties, modification, toxicity, pharmacokinetics and preclinical studies. The mucosal route is gaining attention for noninvasive drug delivery via the oral, nasal, pulmonary or vaginal routes (Carbone et al., 2016; Dong et al., 2020; Pramanik et al., 2017). At the same time, nanoparticle technology has also come to the forefront as a viable drug delivery strategy, presenting opportunities for controlled release, protection of active components from enzymatic or environmental degradation and localized retention. Nanoparticle fabrication methods are readily scalable and applicable to a broad range of drugs. Of all the nanoparticle drug delivery approaches, polymeric nanoparticles have gained significant importance as they are biodegradable, biocompatible and because formulation methods are more widely available; the range of applications has been expanding to include a variety of chemical drug classes and dosage forms (Geetha Bai et al., 2018; Zhang et al., 2018; Zhu et al., 2018). Chitosan-based NP are particularly appropriate for the mucosal route, with their low toxicity, mucoadhesion and tunable physical properties. Examples will be given of chitosan-based nanoparticles used for the treatment of cancer, gastrointestinal diseases, pulmonary diseases, drug delivery to the brain and ocular infections. Recent research on chitosan-based NP for nonparenteral drug delivery is based on the field's expanding understanding of chitosan properties and methods of chemical or physical modification, which are applied to the optimization of nanoparticle drug loading and release features. We will also discuss the current understanding of in vitro and in vivo toxicity and the effect of chitosan nanoparticle formulation on drug pharmacokinetics in preclinical studies. The chitosan backbone can be modified to alter properties such as solubility, mucoadhesion and stability as discussed throughout this paper for specific applications. Both the -NH_2 and -OH groups of chitosan are the active sites for modification. Some of the commonly used techniques described below for preparing chitosan polymers are: blending, graft co-polymerization and curing. Blending involves the simple mixing of two or more polymers. Graft co-polymerization involves the covalent bonding of polymers, while curing converts the polymers into a solidified mass by formation of three-dimensional bonds within the polymer mass by means of thermal, electrochemical or ultraviolet radiation processing methods (Loh et al., 2018; Yeh et al., 2020). There are several mechanisms which govern drug release from chitosan nanoparticles such as: swelling of the polymer, diffusion of the adsorbed drug, drug diffusion through the polymeric matrix, polymer erosion or degradation and a combination of both erosion and degradation as represented in Figure 3. The initial burst release from the chitosan nanoparticles is either because of swelling of the polymer, creating pores, or diffusion of the drug from the surface of the polymer. Chitosan nanoparticles also exhibit a pH-dependent drug release because of the solubility of chitosan (Khurana et al., 2016). Chitosan derivatives alter the release of drug from the NP, affording tunable drug release and impacting the pharmacokinetic profile of the loaded drug (Figure 11) (Mohammed et al., 2017).

Chitosan (-N-acetylglucosamine) and its nanoscale derivatives have shown significant antimicrobial effects. Chitosan is more practical in controlling viral and fungal infections than bacterial infections. it's also been shown that the antimicrobial activity of those particles against gram-positive bacteria is more than that of gram-negative bacteria. The antimicrobial effect of chitosan strongly

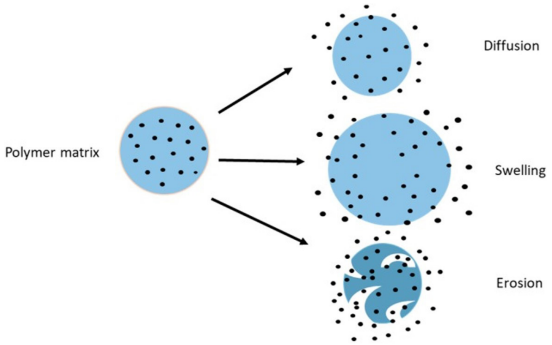

Figure 11. Diagram representing the possible mechanisms of drug release by diffusion, swelling and erosion of polymer (chitosan) matrix (Mohammed et al., 2017).

depends on the relative molecular mass, variety of organism, pH, degree of polymerization of the polymer and also the presence of lipids and proteins on the microbial surface. one in all the antimicrobial mechanisms of chitosan is binding to the bacterial surface, which results in agglutination, increased permeability of the microbial wall, and at last leakage of intracellular compounds. Chitosan also results in the chelating of metals in small amounts and thus inhibits the activity of enzymes and also the growth of microbes. Chitosan in fungi also inhibits protein and RNA synthesis. But one amongst the foremost important limitations for using chitosan is that the low solubility of this nanoparticle. The soluble derivatives of chitosan have a stronger antimicrobial activity than natural chitosan. Nanoscale chitosan is employed for water treatment which has advantages like low cost, high antibacterial activity, unparalleled microbicide efficiency and low cell toxicity.

Antimicrobial peptides (AMPs), also called host defence peptides (HDPs) are part of the innate immune response found among all classes of life. Fundamental differences exist between prokaryotic and eukaryotic cells that may represent targets for antimicrobial peptides. These peptides are potent, broad-spectrum antibiotics which demonstrate potential as novel therapeutic agents. Antimicrobial peptides have been demonstrated to kill Gram negative and Gram-positive bacteria (Ageitos et al., 2017). enveloped viruses, fungi and even transformed or cancerous cells (Reddy et al., 2004). Unlike the majority of conventional antibiotics, it appears that antimicrobial peptides frequently destabilize biological membranes, can form transmembrane channels, and may also have the ability to enhance immunity by functioning as immunomodulators (Mohammed et al., 2017).

3.1.7. Fullerenes (C60) and fullerene derivatives

A fullerene is an allotrope of carbon whose molecule consists of carbon atoms connected by single and double bonds so as to form a closed or partially closed mesh, with fused rings of five to seven atoms. The molecule may be a hollow sphere, ellipsoid, tube, or many other shapes and sizes. Graphene (isolated atomic layers of graphite), which is a flat mesh of regular hexagonal rings, can be seen as an extreme member of the family. Fullerenes with a closed mesh topology are informally denoted by their empirical formula Cn, often written Cn, where n is the number of carbon atoms. However, for some values of n there may be more than one isomer. The family is named after buckminsterfullerene (C60), the most famous member, which in turn is named after Buckminster Fuller. The closed fullerenes, especially C60, are also informally called buckyballs for their resemblance to the standard ball of association football ("soccer"). Nested closed fullerenes have been named bucky onions. Cylindrical fullerenes are also called carbon nanotubes or buckytubes. The bulk solid form of pure or mixed fullerenes is called fullerite. Fullerenes had been predicted for some time, but only after their accidental synthesis in 1985 were they detected in nature and outer space. The discovery of fullerenes greatly expanded the number of known allotropes of carbon, which had previously been limited to graphite, diamond, and amorphous carbon such as soot and charcoal. They have been the subject of intense research, both for their chemistry and for their technological applications, especially in materials science, electronics, and nanotechnology. Fullerenes have been extensively used for several biomedical applications including the design of high-performance MRI contrast agents, X-ray imaging contrast agents, photodynamic therapy and drug and gene delivery, summarized in several comprehensive reviews.

Fullerenes are compounds with unparalleled electrical conductivity, optical and thermal properties. The antimicrobial properties of fullerenes are among the recent findings of researchers. Fullerenes are almost insoluble in water. However, some soluble derivatives of fullerenes have significant antimicrobial effects. Fullerenes can form stable nanoparticle suspensions called nc60, which have stronger antimicrobial effects. Polyhydroxylated fullerenes [C60 (OH) n], called fullerenes, have stronger antimicrobial activity and fewer toxicity than nC60. The antibacterial mechanism of fullerenes is thru the photocatalytic production of reactive oxygen species (ROS) in eukaryotes (Figure 8) and lipid peroxidation within the plasma membrane of prokaryotes. Also, the antimicrobial effect of carboxyfullenes is mediated by attachment to the cell membrane (Ninan et al., 2020).

3.1.8. Carbon Nanotubes (CNT)

Carbon nanotubes are cylindrical structures made from pure carbon atoms and have unique thermal, mechanical, electrical and optical properties. Despite the antimicrobial effects of carbon nanotubes, insolubility in aqueous solutions has weakened the employment of those particles as antimicrobial agents. Recent studies have shown an improvement within the diffusion of nanotubes using surfactants or polymers as stabilizing agents (such as sodium dodecyl benzene sulfate and Triton-X). Among the assorted carbon-based compounds, monolayer carbon nanotubes (SWCNTs) have the best antimicrobial effect through oxidative stress mechanisms and membrane oxidation. the power to extend stability and simple functionalization have made nanotubes useful as antimicrobial compounds. Carbon nanotubes are accustomed purify water and supply filters. Unlike

conventional filters, nanotube filters are repeatedly cleaned and regained filter capability (Ninan et al., 2020).

3.1.9. Nanoparticles capable of releasing nitric oxide

Nitric oxide (NO) free radicals are molecular regulators of the immune reaction to infection. Some studies also show the antibacterial effects of NO and its derivatives. NO, together with other antimicrobial agents, has significant antimicrobial activity while the antimicrobial properties of NO donors haven't been independently proven. Recent studies suggest that bacteria are sensitive to gaseous NO and tiny molecular NO donors. However, one in all the foremost important limitations for the employment of NO as an antimicrobial agent is that the lack of an acceptable carrier for storage and delivery of NO. Recently, NO release under conditions of physiological temperature and pH has been investigated using various Nano carriers. The results of those studies indicate that NO nanoparticles with the power to release NO have higher antimicrobial effects and it's also been shown that these nanoparticles don't cause toxicity to mammalian cells. The physicochemical properties of those nanoparticles like hydrophilicity / hydrophobicity, surface charge and particle size are easily adjustable. These nanoparticles may be wont to treat infected wounds (Ninan et al., 2020).

Nitric oxide (NO) is a free-radical gas and one of the smallest endogenous molecules with the ability to function as a chemical messenger, particularly in cells of the vascular endothelium and immune and neural systems. NO plays a critical role in regulating a diverse range of physiological processes, including cellular differentiation and apoptosis. Medical and scientific interest in NO has grown exponentially since 1992, when it was nominated "Molecule of the Year." Its documented physiological impacts are ever-expanding. Until 1987, NO was known solely as a dangerous atmospheric pollutant generated by industrial processes and automotive engines and as a potential carcinogen. However, by the end of 1987, the discovery of NO synthesis in mammalian cells revealed that this molecule exerts physiological effects, many of which still have not been completely characterized. This discovery led to a rapid increase in research focused on NO. NO is now known as one of the most important mediators of intra- and extracellular processes and is a major target of the pharmaceutical industry. Endogenous NO is produced enzymatically by three distinct nitric oxide synthases via L-arginine conversion. The NO generated by each enzyme differs considerably in its pattern of expression and regulation, likely reflecting site-specific functions. These functions result in both beneficial and detrimental outcomes. Regarding the former, NO may help to improve the prognosis of different human pathologies, including cardiovascular, hematological, metabolic, gastrointestinal, respiratory, neurological, renal, genitourinary, musculoskeletal/connective tissue, and obstetric/gynecological diseases as well as cancer. Some of the specific functions of NO are as follows (Ninan et al., 2020).

Maintenance of Vascular Tone and Blood Pressure: Vascular tone is usually maintained by a steady release of tiny amounts of NO from the vascular endothelium. This NO release is triggered by friction exerted by circulating cells (shear stress) and results in slight vasodilatation. Blood pressure and pulsate flow also regulate the release of NO under physiological conditions, with NO inhibition leading to a drastic increase in blood pressure (Ninan et al., 2020);

Regulation of Immunity and Inflammation: NO is an important cytotoxic mediator of activated immune cells capable of killing pathogenic agents, such as bacteria, parasites, and viruses, as well as tumor cells. NO can also inhibit the inflammation of blood vessels by blocking exocytosis of various mediators from endothelial cells, macrophages, and cytotoxic T lymphocytes (Ninan et al., 2020);

Inhibition of Monocyte and Neutrophil Adhesion to the Vascular Endothelium: NO donors have shown to be potent inhibitors of neutrophil and monocyte adhesion to the vascular endothelium, a complicating factor in the pathogenesis of atherosclerosis (Ninan et al., 2020);

Anti-proliferative Effects: Cellular proliferation in the muscular layer of the blood vessel has a key role in narrowing the vascular lumen. NO produced by the vascular endothelium or arising from exogenous donors can inhibit this proliferation although the mechanism underlying its Anti-proliferative activity is not well understood (Ninan et al., 2020);

Antioxidative Effects: Oxidative stress contributes to thromboembolic disease. NO induces the production of the enzyme superoxide dismutase in the muscular layer of the blood vessels and in the extracellular space, decreasing the O_2^- available and the production of ONOO– (Ninan et al., 2020);

Regulation of Neurotransmission: NO regulates the activity of certain motor neurons in the parasympathetic branch of the autonomic nervous system (Ninan et al., 2020);

Regulation of Platelet Function: NO mediates the adhesion and aggregation of platelets;

Direct and Indirect Stimulation of Endocrine and Exocrine Secretion: NO regulates the release of gonadotropin-releasing hormone (GSH) from the hypothalamus and adrenaline from the adrenal medulla as well as exocrine secretions (e.g., amylase from the pancreas);

Regulation of Kidney Function: Release of NO at the level of the glomerulus increases blood flow and the rate of filtration, and urine formation (Ninan et al., 2020);

Regulation of Reproductive Function: NO can improve penile erection, fertilization and uterine relaxation during pregnancy;

Role as a Messenger/Modulator: NO functions in a variety of essential biological processes.

Meanwhile, in addition to its beneficial effects, NO is a potentially toxic agent. This toxicity is particularly apparent during oxidative stress; when NO generates, O_2 intermediates and leads to antioxidant deficiency (Huang et al., 2021a).

3.1.10. Surfactants based on Nano emulsions

Nano emulsions are a combination of two immiscible and suspended phases at the nanoscale. Emulsions are divided into two categories, oil in water [W / O] and water in oil [W / O], looking on the form, which are determined by the water-to-oil ratios. In recent years, some Nano- and micro-emulsions of oil in water, which are thermodynamically stable and transparent, are shown to own antimicrobial properties. The antibacterial properties of Nano emulsions supported vegetable oil and stable micro emulsions with compounds of Tuvin 80, pentanol, and ethyl oleate are proven. The mechanism of action of emulsions is by disrupting the membranes of viruses and bacteria and breaking the spore-covering of bacilli (Huang et al., 2021b).

4. Nano carriers for effective delivery of antimicrobial drugs

Despite extensive advances within the development of antimicrobial drugs and also the undoubted effectiveness of those drugs, the treatment of most infectious diseases is difficult and requires targeted and controlled delivery so as to attain maximum and effective therapeutic effects. Among the issues of using antimicrobial drugs within the traditional way are the utilization of enormous amounts of the drug, improper interactions of those agents during transmission, very low transfer of antimicrobial agents from the semipermeable membrane and therefore the emergence of resistance to those drugs. Over the past few decades, the appliance of nanotechnology has been studied in many clinical fields, especially drug delivery. Nano carriers with their unique physicochemical properties are a promising tool to beat these limitations. Advantages of delivery of antimicrobial agents using Nano carriers include improving the solubility of hydrophobic drugs, increasing the half-life of the drug, long circulation time, slow release and control of the drug, reducing the dose of medicine and targeted delivery of drug compounds to focus on tissues and cells. additionally, with the employment of Nano carriers, drug side effects are minimized and resistance is overcome by delivering a range of medication during a combined Nano carrier. As a result, various kinds of Nano communication systems for the treatment of infectious diseases are evaluated (Huang et al., 2021a).

4.1. Liposomes

Alec D Bangham while was testing the new electron microscope by adding a negative stain to the dry phospholipids. For the first time in in 1961 (published 1964), he was able to describe liposomes (Huang et al., 2021a). Liposomes are micro- and nanoscale vesicles that range in size from 20 to 30 nanometers and are composed of two phospholipid layers with hydrophilic nuclei (Huang et al., 2021b). Because the lipid bilayer structure of liposomes is similar to that of cell membranes and they are easily attached to infectious microbes (fuses) (Huang et al., 2021b), liposomes are the most widely used carriers of antimicrobial drugs. Placing hydrophobic compounds within the bilayer as well as hydrophilic compounds in the nucleus is one of the capabilities of liposomes (Zhang et al., 2021). In addition, both hydrophilic and hydrophobic drugs can be encapsulated and stored in the aqueous core and phospholipid bilayers of liposomes, respectively, without chemical changes (Li and Wang, 2021; Abbas, 2020). Purification of the obtained liposomes, lipid dispersion in aqueous media, a lipid film of organic solvents, and resizing of the liposomes are the four main steps in liposome preparation (Jasim et al., 2022a; Abed Hussein et al., 2022). Important parameters for the use of liposomes as carriers of antimicrobial drugs include physical-chemical properties of lipids and drugs, particle size and polydispersity, surface charge (zeta potential), stability during storage, and the possibility of production in greater quantities. However, one of the most important limitations for the use of these nanoparticles in vivo is their rapid clearance by the mononuclear phagocytic system (MPS). According to studies by Sullivan et al., The use of antigen-containing liposomes can help treat infectious diseases such as HIV or herpes simplex virus. In 1994, the hepatitis A vaccine was successfully tested by the Swiss Serum Institute. The same company also developed vaccines against influenza, hepatitis B, diphtheria and tetanus with the help of liposomal nanoparticles (Ansari et al., 2022). Liposomes can act as carriers to deliver the drug to the target site (Hachem et al., 2022). Also, the presence of the drug in liposomes and other lipid complexes significantly reduces the toxicity of the free drug (Smaisim et al., 2022a; Kianfar, 2022b). In this way, the dose of the drug can even be increased up to 5 times (Salahdin et al., 2022). Amphotericin B is a drug that is involved in the treatment of fungal infections. When this drug is encapsulated in liposomes, its delivery efficiency to target cells is increased and its toxicity is greatly reduced. Liposomes cause increase the immune response to various pathogens such as viruses, bacteria or microbes (Isola et al., 2022).

Lysosomes are micro- and nanoscale vesicles composed of two phospholipid layers with a hydrophilic nucleus. Because the lipid bilayer structure of liposomes is analogous to it of a cell wall and simply attaches to infectious microbes (fuses), liposomes are the foremost widely used carriers of antimicrobial drugs. additionally, both hydrophilic and hydrophobic drugs is encapsulated and stored within the fluid nucleus and phospholipid bilayers of liposomes, respectively, without chemical changes. Important parameters for the employment of liposomes as carriers of antimicrobial drugs include the physicochemical properties of lipids and medicines, particle size and polydispersity, surface charge (zeta potential), stability during storage, and also the possibility of production in greater quantities. However, one amongst the foremost important limitations for the utilization of those nanoparticles in vivo is their rapid clearance by the mononuclear phagocytic system (MPS). to beat this limitation, various strategies are evaluated. as an example, binding of specific glycolipids (such as monocialoganglioside and phosphatidic inositol) and polyethylene glycol (PEG) to the surface of liposomes reduces MPS uptake into the liver and spleen. Imaging of inflammatory and infectious centers has also been reported using polyethylene glycol-labeled liposomes

(Isola et al., 2022). Antibiotics encapsulated in liposomal carriers include polymyxin B, Laurie acid (acne treatment), ampicillin, streptomycin, gentamicin, vancomycin, and benzyl penicillin. the same old use of those antibiotics is restricted severe side effects, while liposomes cause a major reduction in side effects and improve the antimicrobial effects of those drugs.

4.2. Solid lipid nanoparticles (SLNP)

Solid lipid nanoparticles have the benefits of older solid lipid nanoparticles and liposomes and don't have a number of the disadvantages of those nanoparticles. The biological availability and targeted delivery of encapsulated antimicrobial drugs in solid lipid nanoparticles from different drug delivery routes like injection, topical, oral, ocular, and pulmonary routes are investigated. When these nanoparticles are applied through the skin, they attach to the surface of the skin and form a dense, obstructive hydrophilic film that ends up in a protracted period of the drug on the stratum carenum. additionally, the results of studies indicate that the dermal application of antifungal drugs within the type of capsules in these nanoparticles, results in increased transdermal release of medication. These nanoparticles are utilized in various formulations orally and by injection. Intestinal absorption of the antibiotic tobramycin, for instance, the presence of P-glycoproteins (P-glycoproteins: ATP-dependent diffusion pumps on the margin of the tiny intestine, resulting in the active transfer of tobramycin out of the cell and reduced intestinal absorption of the drug). it's low if, in line with a report, by injecting this drug within the variety of capsules in solid lipid nanoparticles, the intestinal absorption of the drug increases, high concentrations of the drug accumulate within the lungs, and also the ability to cross the barrier is significantly improved. Another study reported that in ocular fluid, the biological availability of tobramycin in capsule form in SLNP was significantly on top of in standard ocular eye drops. Solid lipid nanoparticles also are suitable carriers for the controlled release of ciprofloxacin in ocular and ocular lens infections through topical delivery. But one among the issues with injecting colloidal drug carriers is that they're absorbed by the MPS system. Therefore, so as to focus on drug delivery and better drug accumulation, the inhaled (pulmonary) route has been studied. Unlike liposomes and polymer nanoparticles, solid lipid nanoparticles are stable, breathable, have a high drug loading capacity and fewer side effects. as an example, isoniazid, rifampicin, and pyrazinamide were administered as capsules in SLNP and inhaled in pigs, and no tuberculous bacilli were observed within the lungs and spleen after 7 days. These valuable results are suggested for the treatment of tuberculosis using inhalable lipid nanoparticles (Isola et al., 2022).

4.3. Polymer nanoparticles

The surface of polymer nanoparticles contains functional groups that are chemically modified with targeted ligands. as an example, lectin-conjugated starch nanoparticles selectively bind to microbial surface carbohydrate receptors (such as Helicobacter pylori) and deliberately release antimicrobial agents in these bacteria. Linear polymers (such as polyalkyl acrylate and polymethyl methacrylate) and dual-block copolymers are the most polymers for the delivery of antimicrobial drugs. Linear polymers are accustomed synthesize nanoparticles. Drug-carrying polymer nanoparticles are available two forms, Nano capsules and Nano spheres. Nano capsules are vesicular systems within which the drug is enclosed in cavities and surrounded by a polymer membrane. Whereas in Nano spheres, drugs are evenly distributed in polymer matrices. Duplicate block copolymers spontaneously form micelle nanoparticles that contain a hydrophobic interior (to encapsulate the drug) and a hydrophilic coating (to protect the inside from ossification and degradation). a group of biodegradable polymers like polylactic acid (PLA), polyglycolic acid (PGA), polylactide glycolide (PLGA), polycaprolactone (PCL) and polycyanoacrylate (PCA) are used as hydrophobic moieties. While polyethylene glycol (PEG) is commonly used because the hydrophilic fraction of micelles. For targeted delivery, targeted ligands are conjugated to the top portion of the PEG. Polymer nanoparticles are studied for the delivery of assorted antimicrobial agents and reports indicate that these particles have an awfully high ability to treat infectious diseases. as an example, ampicillin in capsule form in polyisoyxyl cyanoacrylate (PIHCA) nanoparticles is incredibly effective in treating Salmonella typhimurium and monocytogenes (L. monocytogenes) infections in mice. The results of ultrasonography studies confirm the passage of nanoparticles through the human cytomembrane and therefore the effect on the cell membrane of intracellular bacterial parasites. Also, beta-lactam N-tubule antibiotics covalently conjugated to the polymer network of polyacrylic nanoparticles showed much stronger antibacterial properties than the free drug. Another study showed very strong antimicrobial activity of gentamicin antibiotic in capsule form in PLA / PLGA nanoparticles against intracellular Brucella infection (Isola et al., 2022). Figure 12 shows Transmission electron microscopy (TEM) (left) and scanning electron microscope (SEM) (right) images of the silica–polymer core–shell nanoparticles.

4.3.1. Biodegradable Nano polymers PLA drug delivery system

Biodegradable nanoparticles are accustomed improve the therapeutic quality of assorted medical drugs (soluble or insoluble in water) and bioactive molecules, which is related to improved bioavailability, solubility and storage time. Nanoparticle-drug formulations reduce patient costs and also the risk of drug poisoning. Nano capsulation of medicine (Nano drugs) increases drug efficiency, drug properties, tolerability and therapeutic indices and has many benefits in protection against premature degradation, interaction with the biological environment, increased uptake into selected tissues, increased bioavailability, Improves storage time and intracellular penetration. Several drug molecules or bioactive molecules associated with some diseases are successfully encapsulated to enhance bioavailability, bioactivity, and controlled delivery (Dong et al., 2011). Narcotic drugs like cancer, AIDS,

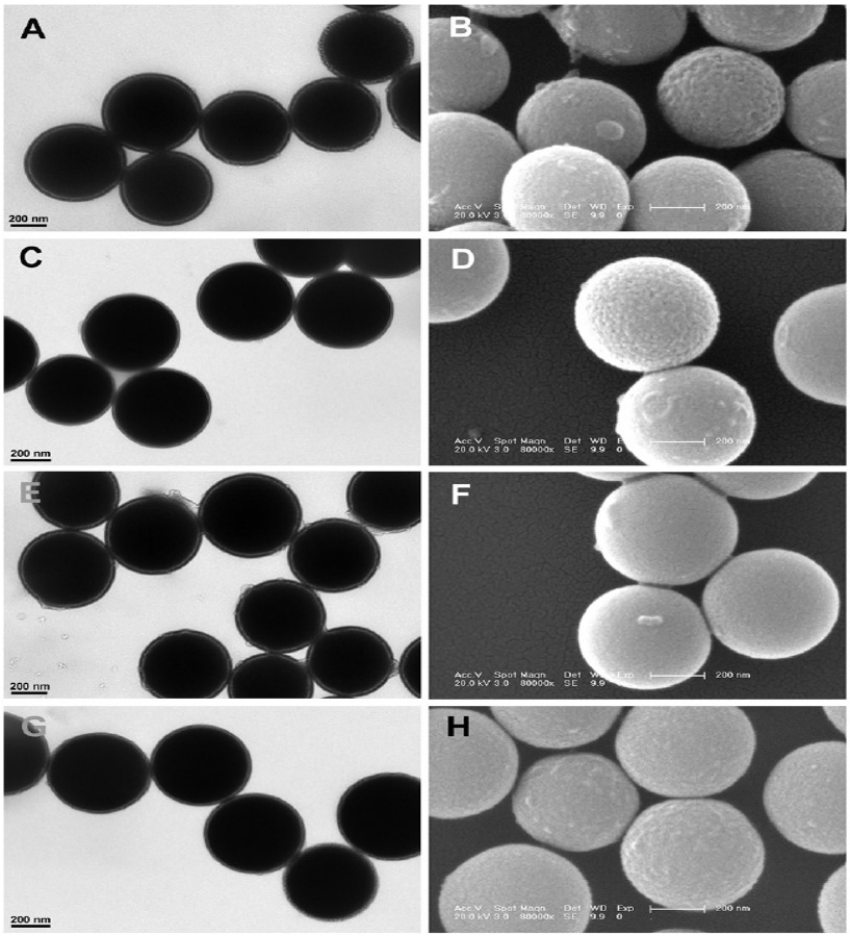

Figure 12. TEM (left) and SEM (right) images of the silica–polymer core–shell nanoparticles: SiO_2 @PAS ((A) and (B)), SiO_2 @PAA ((C) and (D)), SiO_2 @PAM ((E) and (F)), and SiO_2 @PAV ((G) and (H)) (Dong et al., 2011).

diabetes, malaria and tuberculosis are available for testing in various phases, a number of which are commercialized. However, the emergence of drug-carrying Nano carriers raises new hopes for improving therapeutic indicators and drug delivery quality. An example of such a drug system is polylactic acid (Figure 13), which is able to be considered during this article.

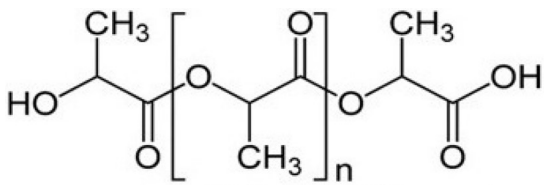

Figure 13. Polylactic acid polymer (PLA) (Danhier et al., 2012).

4.3.2. Polylactic acid (PLA)

PLA (polylactic acid) polymers are biocompatible and biodegradable materials that are converted into carboxylic acid monomeric units within the body following neutral carbohydrate metabolism, which are neutral mediators. PLA is widely employed in medicine its biocompatibility and biodegradability. thanks to its simple hydrophobicity change, it's mostly utilized in PLGA (copolymer of PLA and poly (glycolide) (PGA)) forms. PLA nanoparticles are one among the foremost promising systems for drug delivery and targeted drug delivery. so as for PLA nanoparticles to be effective, special requirements like size, surface charge, encapsulation efficiency, and drug release behaviors must be observed. for instance, nanoparticles smaller than 100 nanometers and narrow in size are required for target tumor tissue through passive targeting or for penetration into biological barriers (such because the blood-brain barrier). But traditional methods result in PLA nanoparticles with dimensions larger than 100 nm. Figure 14 shows an outline of the way to prepare PLA nanoparticles with biodegradability and biocompatibility (Danhier et al., 2012).

4.3.3. PLA manufacturing methods

PLA nanoparticles are mostly prepared by methods like solvent evaporation, solvent displacement, solvent diffusion, emulsion polymerization, salting, Nano sorption and precipitation. The salting method relies on the separation of a water-miscible solvent from a solution with

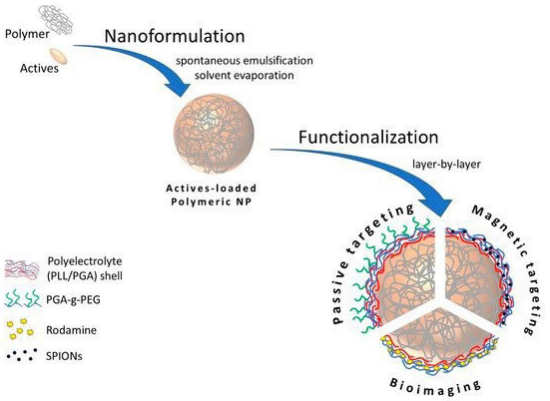

Figure 14. Scheme of how to prepare PLA nanoparticles with biodegradability and biocompatibility (Szczęch and Szczepanowicz, 2020).

salt agents like magnesium chloride or salt, and also the emulsion polymerization method is incredibly suitable for providing nanoparticles with dimensions but 20 nm. during this method, PLA is modified with the assistance of catalyst, with acrylate end groups. The resulting macro monomers are polymerized by emulsion polymerization to provide thin dispersed nanoparticles (Figure 8). The degradability and hydrophobicity of those nanoparticles are controlled by PLA side chains of various lengths. during this way, PLA nanoparticles with PE degradability and hydrophobicity in an exceedingly reaction medium and within the absence of surfactant, are easily PEG. PLA may also be functionalized with acrylics and other groups (Kumari et al., 2010).

4.3.3.1. Surface modification

As mentioned, PLA nanoparticles don't seem to be only widely utilized in medicine but also as surgical sutures and body implants. However, because of the stimulation of the system as a distant body, their use is restricted. this is often because of the rapid absorption of protein from biological fluid at the PLA level, which usually triggers a response or curdling. To eliminate or reduce the adsorption of protein on the surface of biomaterials and nanoparticles, the surface properties of delivery tools must be modified. Surfaces should be hydrophilic and natural acceptor layers should be more accepting of hydrogen bonds than donors. For this purpose, gelatin or dextran has been accustomed cover PLA. But this surface modification failed because the nanoparticles were removed by the system. Polyethylene glycol (PEG), or (poly (ethylene oxide) = PEO) is one in every of the foremost effective polymers that stops the absorption of protein from the biological fluid. In targeted drug delivery, PEG-laden nanoparticles are preferred thanks to the long circulating time within the body. Tocopherol polyethylene glycol succinate (TPGS) is additionally accustomed modify the surface of nanoparticles (Ferrari et al., 2012). This coating also removes plasma proteins by creating hydrophilic barriers. Surface modification with TPGS increases the adhesion of nanoparticles to the surface of tumor cells. PLA-TPGS nanoparticles create a softer environment than PLA alone. Figure 15 shows the preparation of degradable PLA nanoparticles PEG-coated by emulsion polymerization.

4.4. Transfer of drug to the body with PLA carriers

PLA Nano carriers have been used to deliver various drugs (Table 1) (Ferrari et al., 2012).

4.4.1. Capsulation of hormones (progesterone) in PLA nanoparticles

Progesterone may be a steroid. Progesterone loaded with PLA-PEG-PLA nanoparticles is obtained by solvent evaporation. Drug uptake efficiencies are reported to be about 0.7% with dimensions of 261-260 nm. This difference is said to the scale of PLA nanoparticles thanks to surface modification with PEG with variable relative molecular mass (60-120 KDa). Larger nanoparticles prepared with PEGs of various molecular weights have higher release than unmodified PLA nanoparticles. the number of drug release increases with increasing PEG content and also the relative molecular mass of PLA-PEG-PLA copolymers and also the total relative molecular mass of the nanoparticle copolymer decreases. The initial explosive release of the drug was reduced by removing the low mass portions of the polymer. the discharge of PLA-PEG-PLA nanoparticles seems to be controlled by hydrophilic parts located on the hydrophobic parent polymer (PLA) (Ferrari et al., 2012).

4.4.2. Encapsulation of Oridonin in PLA nanoparticles

Oridonine could be a natural diterpenoid (terpenoid: $C_{10}H_{16}$ unsaturated hydrocarbon found in essential oils). It stops growth and breaks down cells from malignant lymphoid. The success of its clinical application is extremely limited thanks to its low solubility in aqueous medium and low therapeutic index. Oridonin loaded with poly (lactide acid) nanoparticles was prepared by simultaneous emulsion-solvent diffusion method. The loading efficiency is 83.1% and also the actual drug loading rate in nanoparticles is 32.2%. Pharmacosynthetic results show that oridonine encapsulated in PLA nanoparticles is significantly effective within the long-term circulation of oridonine within the blood. After injection of Oridonin-PLA nanoparticles, stable and high concentrations of Oridonin were reported in liver, lung and spleen. While the distribution of this drug within the heart and kidneys was significantly reduced (Ferrari et al., 2012).

4.4.3. Protein encapsulation (BSA) in PLA nanoparticles

The frog-shaped polymer mono (6- (2-aminoethyl) amino-6-doxy) 1- cyclodextrin-PLA was prepared for successful encapsulation of bovine serum albumin (BSA) by dual emulsion and Nano-precipitation. The encapsulation efficiency was more than 6.70%. The results showed that the new copolymer could effectively load the BSA and that the BSA would remain stable after release from the nanoparticles. Successful encapsulation and delivery of proteins related to various diseases with this method raises new hopes for protein therapy (Ferrari et al., 2012).

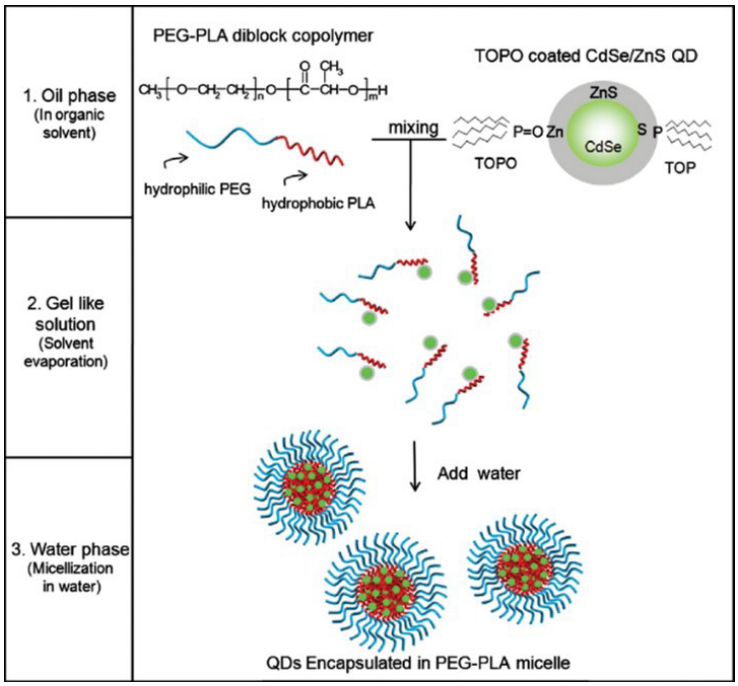

Figure 15. of emulsion polymerization for the preparation of degradable PLA-coated PEG nanoparticles (SDS surfactant) (Ferrari et al., 2012).

Table 1. Drugs transported with PLA nanoparticles.

Capsule material	Capsulation efficiency (%)	Progressive Therapy	Capsule material	Capsulation efficiency (%)	Progressive Therapy
Haloperidol	30	Drug release over 4 days	Zidovudine	55	Less phagocytosis
Hemoglobin	9.87	Less macrophage absorption	BSA	75.6	Longer blood circulation than free drug
Dexamethasone	6	Slow release of the drug in over From 50 hours	Oridonin	88.91	Drug release in over 72 hours
Lactic acid	50	Improves oral absorption	Neurotoxin-1	5.35	Increased drug delivery to the brain
Protein c	3.86	Release of c-protein with Hydro PLA, increases.	Savoxpin	95	Controlled drug release In more than a week
Progesterone	70	-			

4.4.4. Release specifications

Drug release from polymer nanoparticles is one of the most important features of drug / polymer formulation due to its intended applications in continuous drug delivery. Various factors affect the speed of release of trapped drugs. Larger particles have less explosive initial release and longer continuous release than smaller particles. In addition, more drug loading causes a larger explosion and faster release. For example, PLA nanoparticles containing sax pine 16.7%, compared with nanoparticles containing sax pine 1.7% that release their contents within three weeks, release 90% of the drug within 24 hours. The initial explosive release appears to be due to poor drug entrapment or drug uptake outside the particles. When drug-binding polymers are used, such as PLGA, which contains free COOH groups, or proteins, explosive release is reduced and, in some cases, even eliminated, and drug release is prolonged. The addition of other polymers to PLA-based

polymers can also be used for controlled drug release. The amount of drug (progesterone) released from the PEG-PLA copolymer increases with the molecular weight of the copolymer. The presence of PEG in the copolymer affects the particle size and degradation of the polymers. Similar effects were observed with cisplatin-loaded PLGA-mPEG nanoparticles. It is possible to change the rate of drug release by changing the amount of PEG in the copolymer and the molecular weight of the polymers (Figure 16) (Ferrari et al., 2012).

5. Biodegradable Nano Polymers - Chitosan Drug Delivery System

Discovering and developing a replacement drug involves steps with enormous, laborious and expensive challenges. the event phase of every new drug is, on average, 15 years, with an estimated price of roughly 802 million $, and this price increases at an annual rate of 4.7% above the worth of general inflation. Most drugs are rejected within the clinical phase their inability to achieve the target. Most of the drugs utilized in normal tissues and organs are destroyed, often resulting in severe side effects. an efficient achievement to beat these problems is that the development of targeted drug delivery systems that release drugs or bioactive agents into the intended area of action. this will increase patient confidence and therapeutic efficacy of therapeutic agents through improved pharmacosynthesis and bioavailability. the thought of developing a drug that selectively damaged diseased cells without harming healthy cells was proposed by Paul Ehrlich almost a century ago (Ferrari et al., 2012). He called his hypothetical drug a "magic bullet." Thus, over the past several decades, many researchers have focused on developing ideal drugs that specifically target the world of action. The targeted drug delivery system consists of three components: the therapeutic agent, the targeted component, and also the carrier system. a good range of materials like natural or synthetic polymers, lipids, surfactants and dendrimers are used as carriers. Among them, polysaccharides have received widespread attention because of their outstanding physical and biological properties. Chitosan could be a linear amino polysaccharide that mixes randomly dispersed (1-4) bonds of D-glucosamine and N-Acetyl-D-glucosamine units. Chitosan is produced by the distillation of chitin (a natural and abundant polysaccharide found within the exoskeletons of crustaceans like crabs and shrimp). This cationic polysaccharide has received widespread attention in biomedical and pharmaceutical applications because of its high availability, unparalleled adhesion, suitable medicinal properties and other biologically beneficial properties like biocompatibility, biodegradability, non-toxicity and low system stimulation. The physicochemical and biological properties of chitosan are strongly influenced by mass and degree of distillation. The presence of reactive functional groups in chitosan creates enormous opportunities for chemical modification that produces a good range of derivatives like N, N, N-trimethyl chitosan, carboxyalkyl chitosan, sulfur chitosan, steroid regulating chitosans and related chitosans. Contains cyclodextrin. These chitosan derivatives are designed to boost the precise properties of natural chitosan. for instance, desulfurization of chitosan significantly improves its mucosal adhesion properties the formation of disulfide bonds with cysteine-rich mucosal glycoproteins (Jasim et al., 2022a). The chemical modification of chitosan reveals their hydrophilicity, which is a vital property for the formation of self-aggregating nanoparticles and is inherently suitable for drug delivery applications. Hydrophobic cavities can act as storage or micro-containers for various bioactive materials. because of their small size, nanoparticles may be used for targeted drug delivery by shot. Binding of target components to the surface of drug-loaded nanoparticles can improve drug therapeutic efficacy. Chitosan has been widely used as a drug delivery system for low mass drugs, peptides or genes (Jasim et al., 2022b).

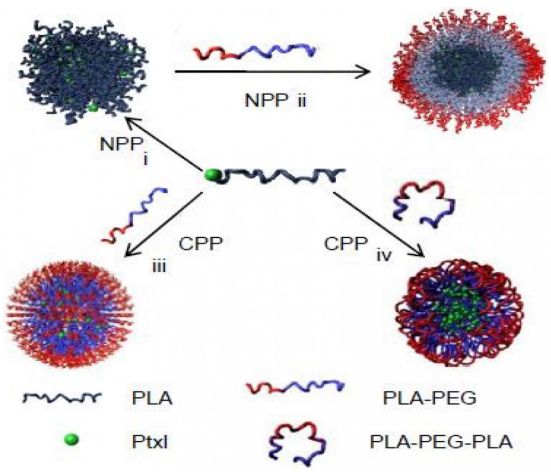

Figure 16. Anti-cancer drug formulation of Paxi-Ptxl-PLA nanoparticles, i: Ptxl-PLA nanosorbent, ii: Ptxl-PLA nanosorbent after PLA-PEG coating, iii: Ptxl-PLA and PLA-PEG co-sequestration, NPPat = nanoprrecip co- precipitation (Ferrari et al., 2012).

6. Drug Delivery Based on PLGA Base Polymer Nanoparticles

Polylactic-co-glycolic acid (PLGA) is one in all the foremost successful polymers utilized in drug delivery because its hydrolysis results in the assembly of metabolic monomers of carboxylic acid and Glycollic acid (Figure 17). Because these two monomers are endogenous and are easily metabolized by the body through the biological process, PLGA produces the smallest amount systematic toxicity in drug or biomedical applications. PLGA is approved by the FDA (Food and Drug Administration) and also the European Medical Agency (EMA) to be used in various human drug delivery systems. These polymers are commercially available in several molecular masses and copolymer compositions, and their degradation time, reckoning on molecular mass and copolymerization, can take several months to many years. The Nano drug formulation depends on the choice of the suitable polymer system with the best possible encapsulation (high encapsulation efficiency), improved bioavailability and storage time. The targeting

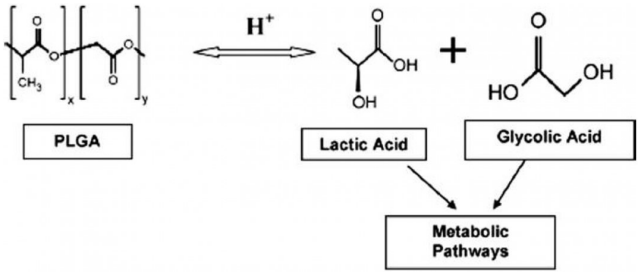

Figure 17. PLGA hydrolysis (Danhier et al., 2012).

ability of Nano drugs is littered with particle size, surface load, surface modification and water repellency. Among these, the dimensions of nanoparticles and their distribution are important to see their interaction with cell membranes and their penetration through physiological barriers (Jasim et al., 2022a). For cellular internalization of nanoparticles, it's important to understand the kind of surface charge to estimate whether the nanoparticles cluster within the bloodstream or attach to cells with opposite charges. Cationic surface charge is more desirable because it improves the interaction of nanoparticles with cells and increases the speed and extent of internalization. For targeted delivery, stable nanoparticles in systematic circulation within the body are required. But common nanoparticles with hydrophobic surfaces are quickly phagocytosed and purified. to extend circulation time and stability within the blood, the surfaces of nanoparticles are modified with various molecules (Jasim et al., 2022b). A coating of hydrophilic polymers forms a cloud of chains on the surface of the particle that repel plasma proteins. the discharge mechanism varies with the mass of the polymers used .

7. Dendrimer

Dendrimers are branched polymers with precise nanostructures within which the branches are synthesized in layers round the central core (Hachem et al., 2022). The existence of such a structure result in precise size control, the chance of drug conjugation and therefore the ability to change the particle surface. The branching nature of dendrimers provides a big surface ratio for interaction with microorganisms. Also, the presence of functional groups on the surface of dendrimers results in the precise binding of those Nano carriers to a good style of bacterial and viral receptors. Hydrophobic and hydrophilic drugs is loaded, conjugated, or adsorbed within the central nucleus and therefore the polyvalent surface of the dendrimers, respectively. additionally, functional ammonium dendrimers, referred to as antimicrobial compounds, have greater antimicrobial activity than free antibiotics (Wani et al., 2020). The antimicrobial mechanisms of dendrimers are the direct destruction of the semipermeable membrane of microorganisms and therefore the disruption of the interactions of microorganisms with the host cell. Extensive studies have examined polyamidoamines (PAMAMs) as carriers. But the limiting factor is that the amine nature of those carriers, which ends up in severe toxicity. to beat this limitation, PAMAM is modified with hydroxyl or carboxyl groups, which are more biocompatible with modified carriers and are easily conjugated to antimicrobial agents. consistent with a report, the antimicrobial activity of sulfamethoxazole in capsule form in PAMAM dendrimers was significantly increased compared to the free drug. In another study, the dissolution of capsular antimalarial in lysine and PEG-based dendrimers showed a big increase (Neerati and Palle, 2019). Therefore, many antimicrobial drugs are loaded in dendrimer nanoparticles for better solubility and greater therapeutic effect (Neerati and Palle, 2019).

Dendrimers are having novel three dimensional, synthetic hyperbranched, nano-polymeric structure. Among all of the dendrimers, Poly-amidoamine (PAMAM) dendrimer are used enormously applying materials in supramolecular chemistry. This review described the structure, characteristic, synthesis, toxicity, and surface modification of PAMAM dendrimer. Various strategies in supramolecular chemistry of PAMAM for synthesizing it at commercial and laboratory scales along with their limitations and applications has also discussed. When compared to other nano polymers, the characteristics of supramolecular PAMAM dendrimers in nanopolymer science has shown significant achievement in transporting drugs for molecular targeted therapy, particularly in host–guest reaction. It also finds its applications in gene transfer devices and imaging of biological systems with minimum cytotoxicity. From that viewpoint, this review has elaborated the structural and safety aspect of PAMAM for targeted drug delivery with pharmaceuticals in addition to the biomedical application. Monodispersity means a well distinct molecular arrangement without variations, which shows a significant role in predicting the pharmacokinetic behaviour of the molecule (Neerati and Palle, 2019). PAMAM is the class of dendritic polymers having a well distinct molecular arrangement, and reproducible nanoscale size through their controlled synthesis and purification process. The Monodispersity of PAMAM confirmed by various analytical techniques includes mass spectroscopy, size exclusion chromatography, gel electrophoresis, Mass spectroscopic data explicitly defined monodispersity of lower generation PAMAM (G1 - G5) synthesized by the divergent method. Subsequent generation leads to polydispersity because of the partial elimination of ethylenediamine in every forwarded generation. The polydispersity index is less than 1.08 for

Table 2. Advantages and disadvantages of nanotechnology-based delivery systems (Abed et al., 2023).

Advantages	disadvantages
Stable release in a controlled manner	Different toxicity characteristics when using different additives and polymers
Infiltration of lipophilic molecules into different layers and improvement of bioavailability, solubility	Nanoparticles can be antigens that due to their properties (such as size, surface properties, charge and hydrophobicity) may lead to toxicity and side effects.
Drug encapsulation using options for low cost biocompatible and biodegradable polymers	Lack of standardized protocol for in vivo tolerance testing
The effectiveness of the drug in improving various treatments	Lack of standard in regulatory approval tests due to unique nano- formulations

G5–G10 PAMAM dendrimer, which shows that even particle size distribution in every step of generation. The size of PAMAM dendrimers for G0 to G10 ranges from 10 Å to 130 Å. Lower generations possess open, highly planar, elliptical, asymmetric shapes as compared to a higher generation. The spheroidal structure of PAMAM dendrimers contains the ability to incorporate drug molecules, due to the presence of peripheral protonated primary amino groups at a physiological pH . G3, G4, and G5 PAMAM dendrimers with ammonia core have structural similarity with insulin (30 Å), cytochrome C (40 Å), and hemoglobin (55 Å), respectively. Because of its biostructural similarity, PAMAM efficiently travels throughout the body and called 'artificial protein'. Earlier researchers reviewed various scattering techniques together with small-angle X-ray diffraction, small-angle neutron scattering, and laser light scattering for characterization of PAMAM dendrimers, suggesting two types of microscopy, including transmission electrons microscopy (TEM) and atomic force microscopy (AFM) for imaging hydrodynamic radius, the structure of complete dendrimer, and radius of gyration in solution. Monodispersity and size concern its pharmacokinetic behaviour in a biological system for pharmaceutical application (Neerati and Palle, 2019).

8. Advantages and Disadvantages of Nanotechnology-based Drug Delivery Systems

Nanotechnology is also important in drug delivery, With the aim of being able to design smart drugs and purposefully send them to the desired location, so that they can identify the position and after diagnosing the conditions activate their necessary and transfer to the place of injury. The introduction of liposomes as carriers in nanotechnology has had a positive impact on this technology. Of course, other materials have been introduced for this purpose, mainly their release system is targeted and are known as the first generation of nanotechnology therapy. This generation of drug delivery system has advantages and disadvantages. Among its benefits is that they have the ability to heal due to the increased half-life of the drug and the controlled release of the drug and reduce its toxic effects (Neerati and Palle, 2019). Table 2 shows the advantages and disadvantages of nanotechnology-based drug delivery systems.

9. Conclusion

The development of bacterial resistance to antibiotics in the near future will make infectious diseases one of the greatest health challenges worldwide. Also, the use of most antimicrobial drugs due to low solubility, causing toxicity to healthy tissues, their rapid degradation and clearance in the bloodstream is severely limited. But nanoantibiotics are promising antimicrobial agents to overcome these limitations due to their higher surface-to-volume ratio and unique physicochemical properties. Some nanoparticles have inherent antimicrobial properties. The present study showed the antibacterial properties of different sizes of silver nanoparticles. The application of silver nanoparticles significantly reduced pathogenic bacteria, so that by reducing the size of nanoparticles, their bactericidal properties increased. There is also a significant relationship between antibiotic resistance and chitosan nanoparticle that were combined against bacteria. Therefore, it can be concluded that chitosan nanoparticles can be used to fight infectious diseases and kill a resistant bacterial species. The results of studies also show that nano-carriers have the greatest effect in reducing resistance. Nano-carriers, facilitate the delivery of antimicrobial agents to infected sites, also protect antimicrobials from destruction in the target microbe (destruction by beta-lactamases) and, most importantly, it is possible to use several antibiotics in combination in nano-carriers. Liposomes are one of the best forms of nano-drug delivery for a variety of reasons, including their applicability to both hydrophilic and hydrophobic and biocompatibility drugs. The use of liposomes to formulate very low-soluble drugs improves the solubility and stability of drug forms. As a result, the breadth of the horizon in pharmaceutical nanotechnology is as wide as in all areas of medicine, and in the future we will certainly see more drugs under the heading of "nanodrugs".

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