Int J Clin Exp Pathol 2024;17(4):96-107
www.ijcep.com /ISSN:1936-2625/IJCEP0154066

Review Article

Newly designed nanoparticle-drug delivery systems against *Staphylococcus aureus* infection: a systematic review

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Received October 24, 2023; Accepted January 5, 2024; Epub April 15, 2024; Published April 30, 2024

Abstract: A nanoparticle-drug delivery system against *Staphylococcus aureus,* especially *Methicillin-resistant staphylococcus aureus,* has been recently proposed as an alternative pathway therapy. *Methicillin-resistant staphylococcus aureus* is resistance to many antibiotics, making it a a threat to human life, especially for older and immunocompromised people. Treatment of *Multidrug-resistant staphylococcus aureus* is considered an urgent need. A variety of kinds of nanoparticle-drug delivery systems with different compositions, and biological properties have been extensively investigated against *Staphylococcus aureus*. This review summarizes the novel nanoparticle-drug delivery systems against *Staphylococcus aureus.* These nanoparticle-drug delivery systems could reduce antibiotic resistance and minimize side effects of the antibiotics. Also, they can deliver a high concentration of the drugs and eliminate the bacteria in a specific and targeted site of infection. Despite these benefits of nanoparticle-drug delivery systems, the cytotoxicity, stress oxidative, genotoxicity, and inflammation that may occur *in vivo* and *in vitro* should not be ignored. Therefore, we need a better knowledge of the pharmacological properties and safety concerns of nanoparticle-drug delivery systems. The limitations of each nanoparticle-drug delivery system with high therapeutic potential have to be considered for further design.

Keywords: *Staphylococcus aureus*, nano medicine, nanoparticles, nanoparticle drug delivery system

Introduction

Methicillin-resistant staphylococcus aureus, usually known as MRSA, is a strain resistant to many antibiotics. Therefore, older and immunocompromised people may be at risk. Besides, treatment based on antibiotics, because of their resistance, is difficult. Therefore, other treatment pathways, such as nanoparticle-drug delivery system (NDDS), phage therapy, and extract and herbal therapy are now being considered. Among these alternative pathway therapies, NDDS, because of its specific and targeted therapy in high concentration, have been preferred over others. Also, NDDS can release higher doses of the drug for prolonged periods. Development and diversification of NDDS with broad application in medicine has led to patents and increased uses for many diseases. Different types of NDDS based on Solid Lipid Nanoparticles (SLN), Poly Lactic-co-Glycolic Acid (PLGA), Nano emulsions, Liposomes, Chitosan, Polymeric micelles, Alginate, Magnetic and green synthesized nanoparticles (NPs) are used for treatment against infections and cancer. NDDS minimizes the rate of consumption, provides maximum pharmacological effects, and reduces side effects that may lead to better therapy and clinical outcomes. Besides, there is an interest in NDDS design against *Staphylococcus aureus (S. aureus)* infections. This study summarizes novel NDDS designed against *S. aureus* and clearly reflects a wide array of high-quality publications and issued patents. Moreover, this review highlights recent progress in NDDS developed against *S. aureus* and focuses on the safety and pharmacological properties. For example, the designed nanosome carries ampicillin, SLNs carry DNase and penicillin, chitosans carry ursolic acid, and chrysin has a strong influence on pathogenic *S. aureus*. The progress in NDDS could reduce the

https://doi.org/10.62347/BVWH1940

risks of infection caused by this bacterium. This study summarizes novel NDDS designed against *S. aureus* and clearly reflects a wide array of high-quality publications and issued patents. Moreover, this review highlights recent progress in NDDS developed against *S. aureus* and focuses on the safety and pharmacologic properties. Different novel-designed infections are explained in **Table 1**. Some of the NDDS used against *S. aureus* are based on different biochemical materials, explained as follows.

Encapsulation of cloxacillin in PLGA

Encapsulation of antimicrobial substances in drug delivery systems can reduce their side effects. Moreover, it can strengthen the effectiveness of the drugs in the infectious sites. These benefits make these systems an essential treatment in eradicating Multi-Drug Resistant (MDR) bacterial infections, including MRSA.

High intracellular antibacterial potential of NPs is confirmed by strengthening penetration of antibiotics inside alveolar macrophages infected with *S. aureus*. An *in vivo* study characterized determined cloxacillin loaded in a Polylactic-co-glycolic acid (PLGA)-NP physico-chemically. Then, the mouse alveolar macrophages were infected with free-cloxacillin or PLGA-cloxacillin-NP. Low minimal inhibitory concentrations (MIC) of PLGA-cloxacillin-NP indicated a better antimicrobial effect of the encapsulated drug. Besides, steady drug release occurred because of PLGA [1] (**Figure 1**). PLGA produces acidic oligomers (lactic and glycolic acids) that increase acidity in the environment. This acidity may lead to protein degradation. PLGA is a biodegradable delivery system and it does not cause significantly lethal toxicity up to 300 μg/mL concentration. However, TNF-α release after the stimulation of PLGA-NPs should not be ignored, particularly in clinical applications.

Elimination of intracellular *S. aureus* by LZD-WP5-G-NP

The most significant application of NPs as a target drug delivery system is eliminating intracellular bacteria and treating latent or recurrent infections. A study introduced a new therapeutic strategy against MRSA intracellular infections. In this study, linezolid (LZD) is loaded in a NP (Glutathione (GSH) + mannose-modified pillar [5] arene (WP5) + a near-infrared (NIR) fluorescence receptor (G)). It is used to infect macrophages and enhance the antibiotic effects. LZD-WP5-G-NP could improve the anti-intracellular MRSA activity of LZD with a great biocompatibility [2] (**Figure 2**). However, the side effects of taking GSH long-term, such as the link to lower zinc levels, should not be ignored. Inhaled GSH may cause asthma attacks and wheezing. The injection of GSH causes skin responses and toxic effects on the liver, kidney, and nervous system. So, the dosage of GSH should be considered for clinical applications, however, it is in nano size layer.

Application of targeted VNp against *S. aureus*

Vancomycin loaded nanoparticles (VNp) are used against *S. aureus* strains. Holo-transferrin (h-Tf) conjugated with this Np are used to improve targeted drug delivery. Human h-Tf, as a high-affinity transferrin, can be utilized in a wide range of cell types. Human h-Tf loaded in iron before use can be added directly to iron-poor or iron-free cell culture media. As a surfactant, VNp is produced with PLGA and PVA or DMAB using double emulsion solvent evaporation. Then, NPs are determined to be spherical shape with a 300 nm size distribution. However, h-Tf did not increase the antimicrobial effects of VNp. The non-conjugated NPs indicated a lower MIC than free vancomycin against MRSA strains and a little higher against VISA (vancomycin intermediate *S. aureus*) strain. Furthermore, the non-conjugated VNPs present a potential to develop novel treatments against *S. aureus* infections [3].

In an *in vivo* study, rifampicin loaded in a lipophilic Np (NanoRIF) successfully treated skin wound in an animal model better than the free antibiotic. Also, Cryogenic transmission electron microscopy (Cryo-TEM) was utilized to target the fabricated NP that enhances the attachment to the negatively charged membrane of the bacteria. This technique bombards flash-freezing solutions of proteins or other biomolecules with electrons to produce microscopic images of individual molecules. This is applied to reconstruct the 3D shape, or structure, of each molecule. Cryo-TEM is a type of TEM that the sample is tested at the cryogenic temperatures caused by liquid-nitrogen temperature. Cryo-EM technique is popular in structural biol-

Table 1. Biological properties of new nanoparticle-drug delivery systems designed against *Staphylococcus aureus* infections

NP	Supplementary materials	Synthesis Pathway	Loaded drug (Antibiotic or Antimicrobial agent)	Bacteria	Shape	Particle Size	Encapsulation Efficiency	PDI	Zeta Potential (mv)	Drug loading	Release Rate	Free drug	Ref.
Niosomes	-	Thin-film hydration	Amoxicillin	MDR *S. aureus*	Spherical	170.6 ± 6.8 nm	65.78 ± 1.45%	-	-	-	47 ± 1% within 8 hr.	97 ± 0.5%	[24]
SLN	Chitosan + Anacardiac acid	Homogenization method	DNase	*S. aureus*	Spherical	212.8 ± 4.21	73.8 ± 1.23%	0.285 ± 0.04	+13.5 ± 1.92	-	29.30 ± 1.27% within 1 hr. 74.86 ± 2.73% up to 24 hr.	86.19 ± 3.71% within 6 hr. and 89.24 ± 3.98% in 24 hr.	[35]
SLN	-	Ultrasonic dispersion	Penicillin	MRSA & MSSA	Roughly spherical and uniform in shape	112.3 ± 11.9 nm	98.31 ± 1.2%	0.212 ± 0.03	-27.6 ± 5.5	4.98 ± 0.05 (%*w*/*w*)	40% within 24 hr.	100% within 10 hr.	[34]
Chitosan	-	Simple method	Ursolic acid	*S. aureus*	Spherical	258 nm	-	0.409	+40.1 mV	-	-	-	[51]
Chitosan	Polysorbate 20 micelles	Ionic gelation varying NaCl concentration	*N'-(5-nitrofuran-2-yl)methylen)-2-benzhydrazide*	*ATCC 29213*, *hVISA* and *ORSA*	Spherical and regular shaped nanoparticles	321 nm	44%	0.18	+37 mV	-	-	-	[52]
Chitosan	Tpp as a linker	Ionotropic gelation method	*Chrysin*	*S. aureus*	Spherical	~355 nm	-	0.487	-	80.86 ± 0.30%	80.11% ± 0.84% within 6 hr. & 90.5% ± 0.50% within 10 hr.	36.33 ± 1.58% within 2 hr.	[53]

TPP: sodium tripolyphosphate. MDR: multi drug resistance.

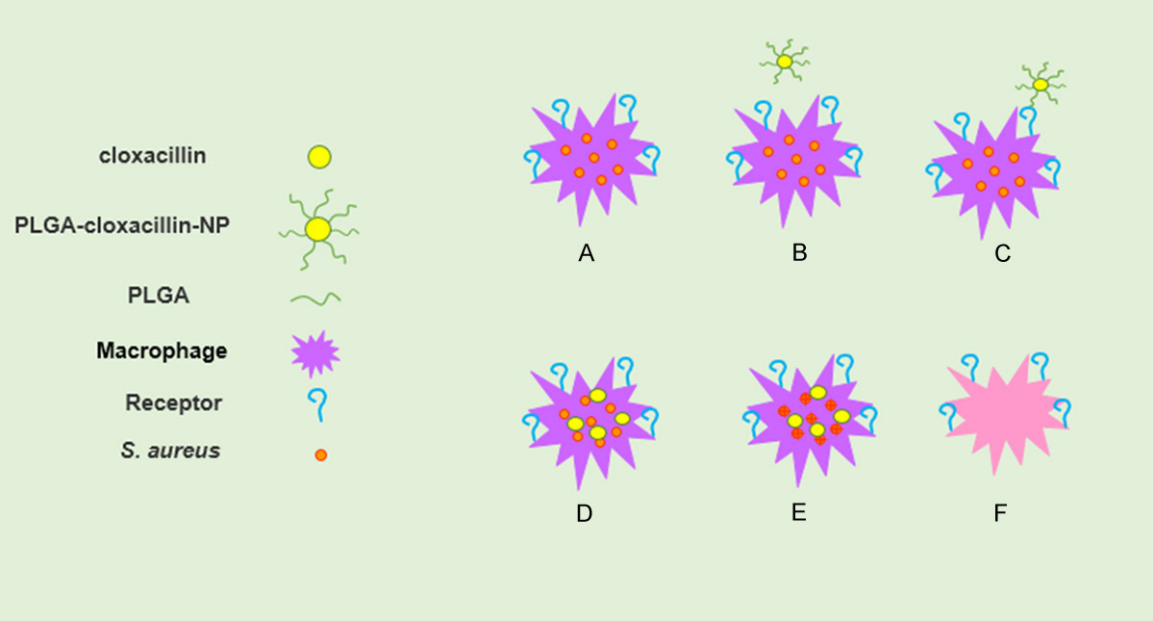

Figure 1. Schematic illustration of Cloxacillin-PLGA-NP effect on macrophages. A: Murine alveolar macrophage infected with *S. aureus*; B: Macrophage and Cloxacillin-PLGA-NP; C: Attachment of Cloxacillin-PLGA-NP to the receptor on the surface of macrophage; D: Release of cloxacillin in a macrophage; E: Removal of *S. aureus;* F: Rescued macrophage.

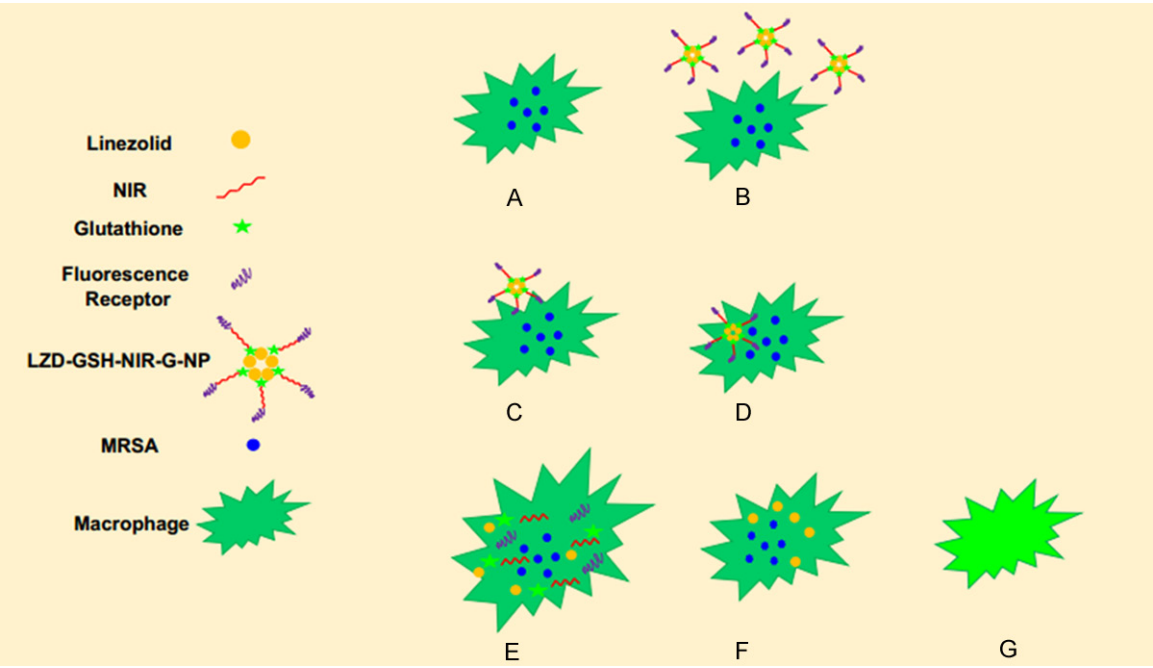

Figure 2. Schematic illustration of LZD-GSH-NIR-G-NP effect on macrophages. A: Infected Macrophage with intracellular MRSA; B: Macrophage and LZD-GSH-NIR-G-NP; C: Attachment of LZD-GSH-NIR-G-NP to the receptor on the surface of macrophage; D: Targeted cell uptake; E: Release of Linezolid in a macrophage; F: Removal of MRSA; G: Rescued macrophage.

ogy systems. A significant advantage of cryo-EM than x-ray crystallography is that the molecules do not need to be crystallized. Some proteins cannot be crystallized easily. Other

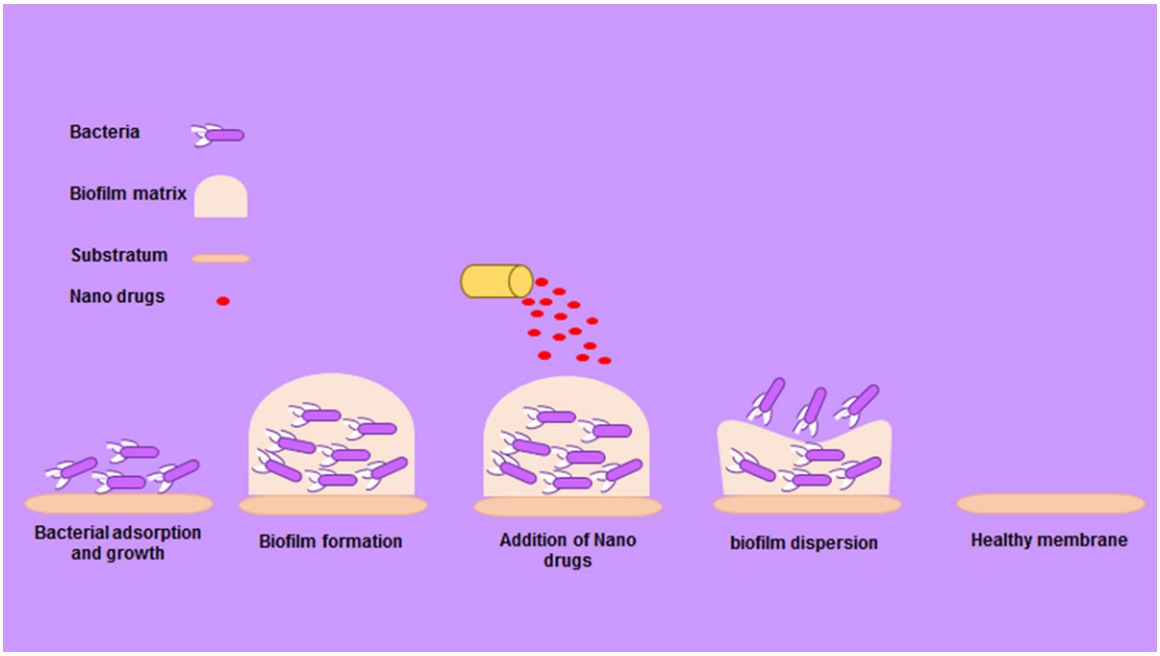

Figure 3. Schematic diagram of nano drug effects on biofilm formation.

macromolecules have irreversibly altered their structures by crystallization [4].

Drug delivery of the antibiotics embedded into NDDS against *S. aureus*

Biopolymer NPs are biocompatible and biodegradable nano-carriers in NDDS. These NPs provide optimal drug bioavailability because the entrapped drug's release rate is proportional to the degradation of the polymer matrix [5, 6]. A study found that biopolymer NPs such as polyacrylic acid (PAA), polyvinyl alcohol (PVA), and polyethyleneimine (PEI) can increase antibiotic efficiency. Curcumin-loaded PEI NP can decrease the MIC of methicillin from 0.340 to 0.200 (mg/mL). So, PEI combined with methicillin is effective against MRSA. PEI is a cationic polymer with repeating units composed of the amine groups. It is used as an intracellular gene delivery vehicle HIV-1 Tat peptide and is widely effective as a cell-permeable peptide. Also, it is an effective permeabilizer of the outer membrane of Gram-negative bacteria. Although PEI has several applications in laboratory biology, it is toxic to the cells in excess of usage in tissue culture. Toxicity happens by two different mechanisms: the disruption of the cell membrane leads to necrotic cell death and disruption of the mitochondrial membrane after internalization that leads to apoptosis. Conversely, the linear PEI is a semi-crystalline solid at room temperature, but branched PEI is a fully amorphous polymer existing as a liquid at all molecular weights [7].

Anti-biofilm activity of NDDS against *S. aureus*

S. aureus bacteria are harbored in a matrix of extracellular polymeric substance (EPS) called biofilm that is highly resistant to antimicrobial drugs. *S. aureus* biofilm matrix has a complicated paste that covers all the mature cells. It is supposed to contain host factors, carbohydrates, DNA, and secreted and lysed proteins. Thus, biofilm decomposition would decrease the bacteria and the resistance to the antimicrobial drugs. NDDS can disperse biofilms, reduce the bacterial load, and subsequently reduce antibiotic resistance. So, it has anti-biofilm activity [8] (**Figure 3**).

PLGA and poly-lactic acid (PLA) have several advantages than other nano carriers such as encapsulation of materials with various sizes and properties, the integrity of the structure, beingenvironmentally friendly, and a flexible and functional potential [9, 10]. In addition, they can maintain drug pharmacokinetics and improve bioavailability. So, these NPs are efficient in biofilm dispersion [11]. Costa et al.

observed the increased antibiotic efficacy of rifampicin-loaded PLA NP compared to free rifampicin against *S. aureus* biofilm. PLA could penetrate biofilm because of its submicron size [12]. Another study approved the anti-biofilm activity of ciprofloxacin (CIP)-loaded PLGA for improving drug release. This study indicated that free NPs with the smallest size (60 nm) are capable of eliminating bacterial culture after 24 hr. in comparison with CIP-loaded NPs, even in the presence of serum proteins. However, CIP-loaded NPs have better anti-biofilm effects than free antibiotics, because of penetration among the polymer matrix and a progressive release of the drug next to the bacterium [13].

Also, the effective roles of α-toxin-loaded PLGA-PEG NPs to eradicate *S. aureus* biofilms and treat chronic rhinosinusitis were approved in an animal model. In this study, not only did this NP not have any toxic effects, but it also decreased the inflammatory cytokines significantly [14].

Furthermore, confocal microscopy images revealed that PLG NPs accumulate antibiotics in biofilm and osteoblast cells. Therefore, it has an effective role in the treatment of MRSA-induced bone infections and osteomyelitis recurrence. For this reason, a linezolid-loaded lipid-polymer hybrid NP is designed to achieve intracellular and biofilm-embedded MRSA. Although this NP had lower activities against planktonic bacteria, it could significantly suppress the intracellular MRSA inside osteoblast cells. It could also significantly suppress the MRSA biofilm growth up to 35-60% compared to free linezolid [15, 16].

In a study, Qiu et al. reported that cationic-PLGA free drug NPs had time- and concentration-dependent effects against MRSA. These developed NPs could kill about 90% of bacterial cells in 3 hours in 400 μg/ml concentration and entirely inhibit biofilm formation in 1000 μg/ml concentration. They also could reduce MIC of vancomycin and biofilm formation to 25% and 50%, respectively [17].

Overall, biofilms represent a survival mechanism of bacteria and are ubiquitous. They are complex and bacteria communities could cause just a slime layer in water. The effects of NDDS against biofilms have to be examined *In vivo,* since they might differ from *In vitro* investigations.

Anti-biofilm activities of carbon dots

Carbon-Dots (CDs) are a type of carbon-based nanomaterial, less than 10 nanometers in size. CDs have antibacterial properties through many mechanisms including the production of reactive oxygen mediators [18], destruction of essential cell components such as cell membranes, and disruption in DNA repair systems [19]. These NPs can eradicate bacterial biofilms and destroy biofilm components of extracellular matrix and directly kill resident bacteria. The wide antibacterial and anti-biofilm activities of CDs against gram-negative and positive bacteria and also their excellent optical features make them favorable NPs. A study comparing different types of CDs (based on source materials and method of preparation) found that CDs based on quaternary ammonium salt of chitosan and ethylenediamine had an excellent ability to eliminate the most bacteria, especially *S. aureus* biofilm at 10 μg/mL MIC and MBIC (minimum inhibitory biofilm concentration). Also, these NPs have non-cytotoxicity for human hepatocytes with low hemolytic effects. However, CDs are non-toxic, facile, scalable, and low-cost NPs, but poor control over the size of obtained NPs is one of the CDs' disadvantages that influences the penetration into the biofilms [20].

Anti-biofilm activities of niosomes

Niosomes are lipid-based NPs that have higher stability than liposomes because of non-ionic surfactants in their composition. Also, suitable release patterns, being non-immunogenic, biodegradability, biocompatibility, and appropriate physicochemical properties make them one of the candidates for drug delivery systems, especially topical administration [21-23]. In a study, the antibacterial properties of amoxicillin-loaded niosomes were investigated against multi-drug-resistant (MDR) *S. aureus*. These fabricated NPs increased antibacterial activity 2 to 4 fold while optimizing the drug release pattern. Furthermore, it significantly extended anti-biofilm effects compared to free antibiotics at ½ MIC. Also, in this study, low toxicity of niosomes against the human kidney cell line and their anti-biofilm properties was shown [24]. But, Niosomes are expensive, and their ingredients, such as phospholipids, are chemically unstable because of their predisposition to oxidative degradation. They require special storage and

handling. Physical instability, aggregation, fusion, leakage of entrapped drugs, and hydrolysis of encapsulated drugs limits their shelf life. Also, the purity of natural phospholipids is variable which is another disadvantage of niosomes.

Anti-biofilm activities of magnetic NPsh

Magnetic NPs (MNPs) have an ability to carry antimicrobial agents. Thereby, content efficiency and adverse effects of medicinal agents are important [25]. The antibacterial properties of MNPs have made them successful NPs to use widely in the last decade. The most impressive property of MNPs in drug delivery is the controlled release of antimicrobial agents through magnetic fields which enhances drug accumulation at the injection site [26]. Besides, these NPs have high potency to destroy cell membranes, do damage to DNA, and kill the bacteria [27]. However, there are some disadvantages related to drug delivery. One cannot maintain efficacy in target organ when the magnetic field is removed. Another drawback is the difficulty in maintaining the therapeutic activity in three dimensions inside the body.

Gold NPs are one of the magnetic NPs which have anti-inflammatory properties, good biocompatibility, and low cytotoxicity. Also, it has been shown that gold NPs are useful for the treatment of MRSA infections by increasing the production of reactive oxygen species [28].

Anti-biofilm activities of SLNs

In 1991, SLNs were introduced as an alternative type of nano material for drug delivery rather than traditional colloidal carriers such as liposomes, emulsions, and polymeric NPs. The ability to entrap both hydrophilic and lipophilic drugs, increased stability, and controlled drug release makes them suitable nano carriers [29, 30]. The results of Zhao et al. study showed that penicillin SLN has a double inhibitory effect against MRSA. This indicated that the ability of these NPs is attributed to increased drug penetration into the bacterial cells and increased concentration of the antibiotic. In this study, penicillin SLN was developed to demonstrate the inhibitory effects of MSSA and MRSA [31]. In a study, SLN was developed by anacardic acid, chitosan for positively charged with good adherence to biofilm, and DNase. The designed NP had a remarkable influence on MBIC and minimum biofilm eradication concentration (MBEC). Also, it significantly decreased biofilm biomass and thickness approved by confocal laser scanning microscopy. Besides, it did not show any toxicity for human skin cells. So, this NP can introduce a new approach to eradicate and inhibit *S. aureus* biofilm and prevent antibiotic resistance [32]. Also, the combination therapy of SLN and other therapeutic agents including stem cells could increase the treatment effect in different diseases [33]. On the other side, SLNs have low drug loading efficiency because of their perfect crystalline structure and the possibility of drug expulsion because of the crystallization process during the storage conditions that influence the anti-bacterial activities of these NPs.

Anti-bacterial activities of mesoporous silica

In the 1990s, mesoporous silica NP (MSN) was first introduced by Japanese scientists. Their considerable advantages led to expanding the application of MSPs in nano medicine. Biological stability, high capacity, safety, porous structure, and functionalization made MSNs a suitable candidate for NDDS. There are various strategies for MSNs functionalization that could respond to stimuli such as pH, temperature, enzyme and light, and limit cytotoxicity effect and improve biodegradability [34, 35]. In a study, MSNs were functionalized with serrapeptase, lysostaphin and DNase I. Thus, the inhibitory effects of these enzymes against MRSA biofilm significantly promoted. More degradation of the extracellular matrix was seen and the cell viability remarkably was decreased [36]. It was observed that cysteine functionalized MSNs (Cys-MSNs) can penetrate into the *S. aureus* biofilm within 18 hours of incubation. Moreover, Cys-MSNs can decrease bacterial viability and also have high antibacterial effects [37]. The functionalization of MSNs protects the loaded antimicrobial agents from inactivation in the biofilm and delivers antibiotics to the bacteria embedded into the biofilm. In a study, the negatively charged bare- and carboxyl-MSNs demonstrated increased vancomycin loading than positively charged amine- and aromatic-MSNs. Decreased cell viability in the MSSA and MRSA biofilms was related to the cellular attachment by 0.25 mg/mL MSN suspensions. Therefore, the low concentration of

MSN could maintain the high antibiotic concentrations around the bacterial cells. As a result, the surface functionalization of MSN could target NPs to achieve the bacterial cells and destroy biofilms. But, the surface density of silanol groups could interact with the surface of the phospholipids of the red blood cell membranes and result in hemolysis [38].

Anti-bacterial activities of alpha-mangostin

The astounding properties of alpha-mangostin (AMG), such as antibacterial, anticancer and anti-inflammatory, increase the application potential in pharmaceutical industries [39-41]. However, the low water solubility and fast reaction kinetics of AMG limit its clinical application, but nanotechnology has a suitable solution for these disadvantages [42]. A study investigated the anti-biofilm properties of AMG-loaded NP against MRSA. It concluded that 24 μmol/L AMG-loaded NP could significantly mitigate biofilm biomass by 53-62%, in comparison with 40-44% of free AMG. These NPs had more anti-biofilm activities than free AMG and reduced the expression of biofilm genes such as clfB, icaC, and fnbA. However, alpha-mangostin has suitable anti-bacterial activities, but has some physicochemical properties are drawbacks. Minimal water solubility, resulting in poor absorption and low bioavailability on intravenous and oral administration can affect its effectiveness as an anticancer therapeutic agent [43].

Anti-bacterial activities of hydrogels

The excellent physicochemical properties of hydrogels, such as three-dimensional structure, hydrophilic, biodegradable and anti-inflammatory attracted a lot of attention to these NPs. The porous hydrogel structure allows loading higher drug dose into the gel matrix and consequently appropriate drug release rate. Also, hydrogels are suitable for wound healing because of their similarity to extracellular matrix scaffolds [44]. A study showed that polyacrylamide hydrogels with polyamidoamine and platensimycin not only were effective treatment for biofilm-induced infections but also had potent anti-MRSA and wound healing properties compared to mupirocin, without any cytotoxicity. The main problem of hydrogels is the lack of mechanical strength. So, maintaining and improving the mechanical integrity of the processed scaffolds has become a vital issue regarding three-dimensional hydrogel structures [45].

Anti-bacterial activities of chitosan

Chitosan ($C_6H_{11}NO_4$) is a polysaccharide polymer and chitin derivative. This NP is widely used because of non-toxicity, cost-effective, its high absorption properties, and biocompatibility [46, 47]. Ghasemzade et al.'s study approved that chitosan could enhance the antibacterial efficiency of ursolic acid with increasing aqueous solubility of this material. In this study, the atomic force microscopic images showed that biofilm formation between *S. aureus* isolates treated with chitosan-ursolic acid NPs and untreated isolates were very different. In this study, the MIC of ursolic acid and fabricated NP against *S. aureus* were 64 and 32 μg/mL, respectively. Also, the expression of icaA and icaD genes was decreased. This suggests that chitosan is a promising application for *S. aureus* eradication [48]. Also, in another study, N'-((5-nitrofuran-2-yl) methylen)-2-benzhydrazid (5-NFB) was loaded in Polysorbate 20 micelles and also in chitosan. Antibacterial activity, growth inhibitory effect, tissue regenerator potential, and ability to destroy biofilm were shown by this NP. It was more effective than 5-NFB in reducing MIC concentration up to 3 times [49]. Another chitosan application was its ability to increase the biosorption and bioavailability of several drugs that have been used in Siddhartha et al. study. Chrysin-loaded chitosan NP reduces the cell surface hydrophobicity and inhibits exopolysaccharide production. It could prevent *S. aureus* biofilm development in early stages [50]. Also, rifampicin and ascorbic acid co-loaded in alginate/chitosan NP could reduce the MIC level between 2- and 8-fold compared to the free drug by disrupting the *S. aureus* membrane integrity. This NP has high potential to combat pulmonary intracellular infections of *S. aureus*. Despite the many advantages, the mechanical resistance of chitosan is less, pore size control is difficult, and it may contract with other compounds; also electrospinning is difficult for pure chitosan [51].

Nano vaccines

Recently, nanotechnology has provided new approaches in vaccine design. Several nano vaccines have been introduced for human

immunization. PLGA has high potential because of low side effects, FDA approval, and biodegradability [52, 53]. In this regard, the role of NPs as a suitable candidate for vaccine and immunity against MRSA has been approved. Haghighat et al. designed a conjugated vaccine NP based on r-PBP2a and autolysin loaded in PLGA to promote a humoral immune response against MRSA in an animal model. The level of IgM in the vaccinated mice group was five fold higher than the control group after 28-day. Also, this nano vaccine could eradicate MRSA from the kidney of infected mice and decrease the mortality rate [54].

Conclusion

Different NPs were designed and evaluated against *S. aureus* in recent years based on CDs, PLGA, SLN, Chitosan, Niosome, magnetic, and hydrogel. *S. aureus* has various virulence factors at various expression rates [55-60]. Nano medicines have a strong potential in clinical applications to prevent biofilm production and treat MRSA infections. This paper explored the application of designed NPs, which could be used as a therapeutic agent to treat infections caused by *S. aureus*. Continuous release of the targeted antibiotics is essential to destroy entrapped bacteria in biofilms. Besides, extensive accumulation of antibiotics occurs in cells and biofilm, as confirmed by confocal microscope images. Recognition and encapsulation of the natural materials with antibacterial, antioxidant, and anti-inflammatory effects could be a new treatment pathway. Biopolymers improve the stability, bioavailability, solubility, and antibacterial effect of NPs against *S. aureus*. However, the volume and concentration of the solvent have a significant influence on NP size, and the size is essential for penetration into the biofilms. The inhibitory properties of NPs are significantly in favor of smaller ones because of increased penetration into the bacteria. Overall, especially with natural components loaded into the NPs, they are promising drug carriers for treating infections, cancer, and other degenerative diseases. Antimicrobials loaded into the NPs are promising because the bacteria have not yet developed resistance mechanism. Thus encapsulation of these drugs could protect them from the surrounding media. Despite these noteworthy pharmacological properties of NPs, the toxicity, oxidative stress, inflammation, and genotoxicity features of NDDS have been noted *in vitro* and *in vivo*. More knowledge of the pharmacological properties and safety of NDDS and the limitation of each delivery system is important for the further design of functionalized NDDS with high therapeutic potential. Variety kinds of nanoparticle-drug delivery systems with different compositions and biologic properties have been extensively investigated against *S. aureus*. This review summarized the novel NDDS designed against *S. aureus*. The NDDS could reduce antibiotic resistance and minimize side effects of the antibiotics. Also, it could deliver a high concentration of the drug and eliminate the bacteria in a specific and targeted site of infection. Despite the benefits of NDDS, the cytotoxicity, stress oxidative, genotoxicity, and inflammation that may occur *in vivo* and *in vitro* should not be ignored. Therefore, we need a better knowledge of the pharmacological properties and safety concerns of NDDS. The limitations of each NDDS with high therapeutic potential have to be considered for further design. Among these alternative pathway therapies, NDDS, because of specific and targeted therapy in high concentration, have been preferred over others. Also, NDDS can release higher doses of the drugs for prolonged periods. Development and diversification of NDDS with broad application in medicine has led to patents and increased relationships between many diseases. Different types of NDDS based on SLN, PLGA, Nano emulsions, Liposomes, Chitosan, Polymeric micelles, Alginate, Magnetic and green synthesized NPs may be used for treatment against infections and cancers. NDDS minimizes the rate of consumption, provides maximum pharmacologic effect, and reduces side effects that may lead to better therapeutic admission and clinical outcomes. Regarding NDDS design against *S. aureus* infections, the designed nanosome carries ampicillin, SLNs carry DNase and penicillin, and chitosans carry ursolic acid, and chrysin has more influence on pathogenic *S. aureus*. Progress on NDDS could reduce the risks of infection cause by this bacterium. Overall, biofilms represent a survival mechanism of bacteria and are ubiquitous. These complex bacterial communities can cause just a slime layer in water. The effects of NDDS against biofilms have only been examined *in vivo,* which might differ from *in vitro.* Nano materials have even

been found that penetrate both gloves and skin. They might be considered for design fabricated NPs.

Acknowledgements

The authors would like to thank the Research Council of Hamadan University of Medical Sciences, Hamadan, Iran (No. 140108247027).

Disclosure of conflict of interest

None.

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