Global Journal of Nanomedicine
ISSN: 2573-2374

Juniper Publishers
key to the Researchers

Mini Review
Volume 3 Issue 2 - October 2017
DOI: 10.19080/GJN.2017.03.555607

Glob J Nanomed

Silver Nanoparticles as Drug Delivery Vehicle against Infections

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Submission: September 22, 2017; **Published:** October 25, 2017

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Abstract

In spite of the advancement of medical and pharmaceutical sciences, the chemotherapy is still a major problem for delivery drugs to specific site of interest against various life-threatening infectious diseases. Most of the drugs having high toxicity, leads to several side effects, reducing the quality of life. The use of conventional microbicidal agents against the infections has associated inadequate therapeutic index, low drug bioavailability, development of multiple drug resistance and adverse systemic side effects. In this concern, antimicrobial silver nanoparticle has emerged as potent efficient agent against infection due to its ultra small controllable size as high surface area and increased reactivity with active functional structure. The surface ligand coating of silver nanoparticle incorporated drug as drug delivery vehicle enlightens its sustained release with reduced side effects when administered into the body. This review also focuses on the mechanism of action of the silver nanoparticle system as antimicrobial drug targeting.

Keywords: Silver nanoparticles; Drug delivery vehicle; Infection; Toxicity; Drug resistance; Mechanism of action

Abbreviations: AgNPs: Silver Nanoparticles; CRP: C-Reactive Protein; IFNs: Interferon's; ROS: Reactive Oxygen Species; AST: Aspartate Amino Transferase, ALT: Alanine AminoTransferase; Silver Nanoparticles against Infections

Introduction

When microorganisms such as viruses, bacteria and parasites enter into the body, innate immunity functions through phagocytes mainly macrophages as a first line of defense against these infectious agents and checks before they develop an overt infection. If these first defenses become hampered, the adaptive immune system mediated by lymphocytes becomes activated producing a specific reaction to each infectious agent for its eradication and further preventing by memorizing infectious agent to cause disease later. During infection, the serum concentration of C-reactive protein (CRP) becomes elevated.

This CRP, in turn, binds to C-protein of microorganisms' cell wall promoting binding of complement to facilitate their uptake by phagocytes such as macrophages through chemo taxis opsonisation. The destruction of microorganisms' cell wall in the phagolysosomal compartment of macrophages by proteolytic lysozyme facilitates an attack on the cell membrane by the complement system.

Interferon's (IFNs) compose a group of proteins that are significant in viral infections. When host cells become infected by viruses, they may produce IFNs. Different types of cell when become infected, produce IFN-α or IFN-β whereas T-lymphocytes produced in the thymus when become activated by antigen release IFN-γ. These IFNs, altogether, function on uninfected cells to induce a state of antiviral resistance.

In cell mediated immunity, antigen-presenting cells present processed antigen to helper T cells, which represent central to the development of immune responses. These events can help B cells, produced in bone marrow and fetal liver, to make antibodies and modulate the activities against infections of varieties of other effectors cells, including natural killer cells, granulocytes, macrophages, cytotoxic T cells and antibody-dependent cytotoxic cells. Many of these effects become mediated by lymphokines, as well as cytokines, specifically macrophages, though both T and B cells may be influenced by suppressor T cells.

In the development of the state of diseases, micro-organisms proliferate in the phagolysosomes of the host macrophages through escaping proteolytic effect of lysozyme and suppressing protective host immune responses. Therefore, infectious

diseases, caused by intra or extra cellular infection, biofilm or medical device-mediated infections, have demonstrated a global public health hazards causing millions of deaths every year.

Though applications of antibiotics in the 20th century established a sensible reduction in public illness and death caused by the infectious microorganisms, the development of antimicrobial drug resistance [1] has created an emerging problem in public health. The development of new antibiotics and chemical modifications of existing antimicrobial drugs can not only resolve the problem of microbial resistance but also requires a more long term effective metallic nanotechnology in medicine against infectious diseases [2].

Silver nanoparticles (AgNPs) in suspension release silver ions [3-5] which are highly toxic to microorganisms. This microbicidal activity depends on the structure, dimension, size, concentration, ionic strength, coating, temperature, and time on the dissolution behavior of AgNPs [5-7]. Additionally, this material with surface coating can be used as a carrier for delivering a wide range of therapeutic components such as drugs, antibodies and pharmaceuticals in several biomedical applications [8]. Controlled release of biologically active silver from nanosilver can be regulated by different ligand coatings in preventing silver ions from releasing and increasing half-life in systemic circulation for passive targeting [5,7,9]. Moreover, surface functionalizations on this AgNP can be made by decorating various ligands such as sugars, proteins, peptides and genetic materials for active targeting which require further investigations on their therapeutic efficacies. Taken together, this review focuses that ligand coated drug incorporated AgNPs may be useful as potent oral therapeutic tool in reducing toxicity, enhancing release, improving solubility and bioavailability, and providing better formulation for synergistic effect against pathogenic microbial diseases.

Preparation of Silver Nanoparticles incorporated Nanodrug Conjugate

AgNPs incorporated nanodrug conjugate is prepared chemically by reduction of metal salt precursor i.e. 0.01M AgNO3 with 0.01M NaBH4 reducer followed by the addition of 0.001mg drug and kept under stirring for 2h [10]. The homogeneous slurry is spun at 4000 rpm for 25min to get a pellet which is lyophilized and used for further investigations

Preparation of Ligand Coated Silver-Nanodrug Conjugate

Chitosan coated silver nanodrug conjugate is prepared by ionotropic gelation method. Silver nanodrug conjugate is mixed with 100mg chitosan and 1% acetic acid. Sodium triphosphate solution is then added drop wise and kept stirring for 2h. The obtained slurry is lyophilized and used for further studies. Citrate-capped AgNPs are synthesized following the method [11] while 5mM sodium citrate and 25μM tannic acid are added into the 250μM AgNO3 solution.

The mixture is stirred continuously and refluxed until the solution turns to light yellow. Citrate AgNPs are purified by ultra filtration, washed and stored at 4 °C for future use. The other types of ligands such as mercaptopropionic acid, mercaptohexanoic acid, mercaptopropionic sulfonic acid, polyvinylpyrrolidone, polyethylenimine, mono, di or poly -ethylene glycol, and sugars are also used to coat AgNPs [12,13].

Mechanism of Action of Silver Nanoparticles

Since time immemorial, silvers are familiar for their broad spectrum of antimicrobial activities. The antimicrobial potential of AgNPs has been increased by reducing their size to less than 10nm with modified surface dimension [14] which is useful to combat also multidrug resistance where multidrug resistant proteins and P-glycoprotein are responsible for effluxing drugs [15]. Various investigations have sought to establish a mechanism of action of AgNPs against pathogenic microbes. Under ambient condition, O_2 molecules may chemically adsorb on the 111 facet of AgNP surface and oxidize the surface Ag atom to form Ag+ ions while O_2 molecules are incompletely reduced to reactive oxygen species (ROS) such as 0_2.-, .OH.

The released positive silver ions can bind negatively charged cell membrane to interfere membrane integrity [16]. Furthermore, the endocytosed or pinocytosed AgNPs may exhibit a Trojan-horse-type effect to release silver ions in the cytoplasm to interact with organelles e.g. mitochondria [16]. The intracellular Ag+ ions released from AgNPs can bind with thiol groups (-SH) of proteins and enzymes located on the cellular surface, causing cellular membrane destabilization and mitochondrial ATP synthesis breakdown resulting ROS generation that induces oxidative stress leading to irreversible damage to DNA replication [17-19]. Ag+ ions may also adhere to the membrane wall, causing holes through which they also can penetrate cell-inside microbes and interact with intracellular components as well as protein containing sulphur.

Biochemical Analysis in Blood

Several investigators studied the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), the markers for hepatotoxicity, in plasma after oral exposure of AgNPs and demonstrated that AST and ALT levels do not increase despite the higher oral exposure (>500mg/kg bw) of AgNPs (~60nm) for 28-day except mild enhancements of alkaline phosphatase and cholesterol levels signifying no indication of acute hepatotoxicity [20-23].

Immunotoxicity Analysis

Several attempts were made to evaluate immunotoxic responses after oral exposure of AgNPs. Some reports demonstrate that not only serum levels of IgG and IgM but also proliferations of T-or B-cells isolated from spleen and mesenteric lymph nodes in response to lipopolysaccharides or concanavalin A were not significantly altered by the exposure of AgNPs. Furthermore, oral AgNPs exposure did not affect the levels of

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cytokines in the supernatants of the stimulated T- and B-cells as well as the activities of natural killer cells isolated from the spleen. Therefore, these results suggest that nonspecific immune responses do not occur in vivo by the oral AgNPs administration [24].

Conclusion

Conventional antimicrobial therapies using antibiotics and other agents have raised an issue on drug resistance acquired by the infectious microbes in several diseases. Though it has been emphasized on the development of new antibiotics and chemical modification of existing drugs to solve the problem, metallic nanoparticles have emerged as new potential antimicrobial agents due to their ultra-small size, high surface to volume ratio and unique physicochemical properties stemmed from interactions with microorganisms including cellular uptake and aggregation leading to toxicity and microorganism killing [25]. Ligand-dependent Ag+ release with drug may offer potent synergistic antimicrobial activities not only for drug but also for AgNPs due to their short carbon chain and weak binding atom of oxygen. Therefore, the optimization of the surface ligands such as coordination atoms, carbon chain lengths and terminal groups is very important to prepare nanoparticles for commercial applications against infectious diseases.

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