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Toxicity Assessment of Silver Nanoparticles in Drug Delivery System

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Abstract:
Nanoparticles can help solve important issues related to traditional small molecules or bio macromolecules like DNA, RNA, and proteins used for diseases. They enable targeted delivery and can get past biological barriers. Recently silver nanoparticles have been used as delivery vehicles for therapeutic agents, such as anti-sense oligonucleotides and other small molecules. The toxicological evaluation of three common types of nanoparticles used in drug delivery. Metal, lipid and protein nanoparticles. It highlights the toxic effects associated with these nanoparticles. Metal based nanoparticles can increase oxidative stress and may enter the cell nucleus. Protein-based nanoparticles have been noted to cause liver and kidney toxicity. Nanoparticles are being used more in drug delivery, but there are rising concerns from regulatory authorities about their toxicity in living organisms.

Introduction
Silver Nanoparticles are tiny particles made of silver, containing between 20 and 15,000 silver atoms and are usually small then 100 nanometres. They have unique properties that make them different from larger silver materials, including biological, electronic, anti-bacterial, magnetic, chemical, and physical characteristics. Ag NP's are increasingly used in biomedicine attracting a lot of research interest. Their performance in various applications, such as catalysis, thermal management and optics[1]. Silver nanoparticles are becoming important for their ability to fight germs that cause infections. They are found in many products, including healthcare items, fitness tools, cleaning supplies, food packaging, household goods, electronic gadgets and toys. Because these products are so common, there is higher chance that these nanoparticles could accidently spill into the environment, leading to more exposure to humans and other living things[2].

Many everyday products, like fabric, laundry food and medicine have been researched for their use of silver particles[3]. Various methods have been used to create silver nanoparticles (Ag NP's) because of the different forms of silver and it's compounds. There are natural methods to produce Ag NP's. These processes are simple, safe, cost-effective, and produce consistent results, making them suitable for use with sodium citrate or sodium borohydride in Ag NP production[4].

Many medications affect how platelets and blood clotting work. They often enhance the natural blockage of blood clotting, especially involving thrombin and factor Xa. Most oral anticoagulants stop vitamin K, which is needed for creating important factors for clotting common oral anticoagulants include warfarin, dicoumarides, and phenindione (PID). Warfarin helps lower the risk of blood clots in people and atrial fibrillation. Although PID works similarly to warfarin, it is less used because it can cause serious side effects[5]. New silver nanoparticles were created as drug-delivery systems for treating thrombosis and for use in coating medical devices. **[6,7-10]**

Why silver nanoparticles?
Silver nanoparticles have garnered significant interest within the scientific community[11,12,13]. Silver has historically been used as an antiseptic and antimicrobial agent to combat diseases caused by both gram-positive and gram-negative bacteria[14,15,16]. Silver nanoparticles, have become popular in recent years as potential new antimicrobials. They are being explored due to their promising properties in fighting bacteria and other microbes. Researchers are interested in using them to create a new class of antimicrobial agents[17].

Copper-based nanoparticles were found to have even higher antibacterial properties than silver nanoparticles[18].

Nanoparticles are classified into three categories:-

Inorganic Nanoparticles :-

Inorganic Nanoparticles do not contain carbon atoms and include matal oxide and metal-based nano-sized particles.

Metal Nanoparticles:-

Metals like cadmium,[20] aluminium,[19] copper,[21] and others are common in this category. These Nanoparticles have unique properties due to their size and characteristics such as expanded surface area and shape environmental factors like air and sunlight can affect these properties.[22]

Metal oxide Nanoparticles:-

Metal oxides offer enhanced characteristics, such as iron oxide formed from iron and oxygen, making them more reactive.[23]

E.g. includes titanic oxide, silicon oxide, zinc oxide, showing superior properties compared to metal nanoparticles. [24,25,26,27,28]

Organic based Nanoparticles:-

It is known as Nano capsules include ferritin, liposomes, micelles and dendrimers. These eco-friendly particles are sensitive to light and heat, making them ideal for drug delivery. [29]Their stability and ability to carry and release drugs effectively enhance targeted delivery.[30]

Carbon-based Nanoparticles:-

It is made entirely from carbon and include types like graphene, fullerenes, carbon nanofibers, carbon nanotubes, black carbon and activated carbon.[31]

Synthesis Of Silver Nanoparticles

Nanoparticles can be made using two main methods:

Top-down

The top-down method creates nanoparticles from larger materials using physical forces such as mechanical, electrical or thermal energy. Techniques like ball milling and laser ablation are used, producing nanoparticles that are usually between 10 & 100nm in size. This method typically results in pure nanomaterials because it doesn't use chemical additives. The nanoparticles made this way often have a uniform size and high purity, but preventing them form clumping together poses a challenge as no stabilizing agents are used in this process.

Bottom-up

The bottom-up approach is used to create complex clusters and obtain nanoparticles from molecular components though nucleation and growth processes. It includes two main methods achieve Nanoparticles by reducing precursor salts. Chemical synthesis can be enhanced using alternatives energies like photochemical, electrochemical, microwave-assisted and sono chemical methods. This method can produce various nanoparticles shapes quickly but may use harmful chemicals that limit medical applications. To address this issue, the biological method is considered an alternative option. The text discusses different methods for creating silver nanoparticles [32,33,34]These method fall into three main categories:

Physical Method:

The synthesis of silver nanoparticles (AgNP's) involves mechanical and vapor-based processes to reduce particle size. Mechanical energy, like ball milling, uses high-speed collisions for grinding metal into fine powders. Electrical energy in the arc-discharge method uses an arc-discharge device under direct current power with electrodes in dielectric liquids. Other methods include using light energy for laser ablation and thermal energy for physical vapor deposition.[35,36,37,38,39,40]

Chemical Method:

Chemical synthesis is the most common way to create silver nanoparticles involving the reduction of silver ions via electron transfer. [41]This process typically uses reducing agents like sodium borohydride or sodium citrate and can be combined with energy sources such as photochemical, electrochemical, microwave-assisted and sonochemical methods. This synthesis process includes two main stages: nucleation & growth.[42,43]

Characterization of Silver Nanoparticles

The solution changing from yellow to brown is the first sign of successful Silver Nanoparticles synthesis. Various techniques are used for characterization nanoparticles focusing on aspects

like size & shape. These methods include UV-Visible Spectrophotometry, FT-IR, SEM, TEM, AFM, XRD, DLS and Zeta-Potential measurements.

- *UV-Visible Spectrophotometry*

It is simple and reliable technique for analyzing nanoparticles. It measures how metal nanoparticles absorb or scatter UV and visible light, resulting in a strong absorption band called surface plasmon resonance (SPR) in the 400-500nm range, caused by light interacting with the mobile surface electrons of AgNP's .[44,45,46]

- *Scanning Electron Microscopy Analysis*

Scanning Electron Microscopy is a common method to study nanoparticle shapes and surface structures. It works by directing an electron beam at a sample, causing interaction that emit secondary electrons influenced by the sample's surface and makeup.[47,48,49]

- *Transmission Electron Microscopy Analysis*

Transmission Electron Microscopy is a high-resolution method to analyse the shape, size, and distribution of nanoparticles. It works by transmitting an electron beam through metal nanoparticles to produce an image. Both scanning electron microscopy and TEM study nanoparticle topography and surface morphology. [50]

Important applications of silver nanoparticles

Chemical reduction with different organic and inorganic reducing agents is a popular way to produce silver are still being improved, facing challenges like the stability and clumping of particles. It remains hard to extract and purify the particles for future use. [51]The availability of silver nanoparticles has ensured a rapid adoption in medical practice. Their application can small proportion of burn patients who received ionic silver treatment. Some in-vitro studies suggest that nanoparticles may harm certain cell lines, with smaller particles showing more toxicity. However, other studies indicate that silver nanoparticles are relatively non-toxic. Silver nanoparticles are the most promising nanomaterials for current commercial uses. They are used as coatings for cardiovascular implants and in central venous and neuro-signal catheters. Silver nanoparticles are also applied in latex membrane as a biomaterial for skin regeneration treatment and to monitor the delivery rate of nanoparticles in these membranes. Silver nanoparticles, are used in biosensors for detecting biological tags. They can also be found in various products such as clothing, shoes, paints, wound dressings, appliances, cosmetics and plastics, silver nanoparticles enhance conductivity in timing and are part of composite materials.[52] In optical applications, they help with better collection and improved spectroscopy techniques, including metal fluorescence and surface-enhanced Raman scattering. There figures showing the different applications of silver nanoparticles and their advantages & disadvantages.

Antimicrobial activity of silver nanoparticles

Silver nanoparticles, are known for their strong ability to kill microbes like staphylococcus aureus[53]and important uses in medicine for treating bacterial and viral infections, including those caused by hard-to-treat germs. Silver nanoparticles are more effective than regular silver because their larger surface area allows them to better enter bacterial cells and cause harm. Once inside, they can damage DNA and disrupt cell functions. Silver nanoparticles also interact with proteins, damaging bacterial cell walls and interfering with protein production. Silver has a long history as an antimicrobial agent, and its nanoparticle forms are more effective and compatible with living organisms. Extensive research has been conducted to understand the antimicrobial potential of nano silver and its compounds. This research highlights the possible future use of silver nanoparticles in addressing microbial diseases, overcoming the limitations of traditional antimicrobial treatments, fighting drug-resistant pathogens, and establishing a combined approach in drug development.

Silver nanoparticles can be made using plant extracts, resulting in stable, eco-friendly particles. These particles have strong combined effects of the Nano silver and natural compounds in the plants that also fight microbes.

A study by Loo et al. [54]found that silver nanoparticles synthesized from pu-erh tea leaves exhibited strong antimicrobial activity against gram-negative food-borne pathogens such as salmonella enteritidis, Klebsiella pneumonia, Escherichia coli, and Salmonella typhimurium, with MIC values of 3.9, 3.9, 7.8, 3.9 ml,

respectively. Garibo et al. also synthesized silver nanoparticles using lysiloma acapulcensis extract and found them to be effective antimicrobials. Selim et al. reported that chemically synthesized silver nanoparticles of approximately 50nm inhibited Mycobacterium tuberculosis and Mycobacterium bovis, with MIC values ranging from 1 to 32 ml for various strains. [54]

Toxicity mechanisms of Ag NPs

The toxicity of silver nanoparticles (Ag NPs) is primarily due to their release of a large amount of reactive oxygen species (ROS), which can damage cell membranes and cause cell death.[55] Ag NPs easily oxidize, producing more ROS, leading to oxidative stress.[56] They disrupt endoplasmic reticulum (ER) homeostasis, affecting protein folding and causing excessive ER stress. This stress is a protective mechanism to prevent protein clumping. Ag NPs can also damage mitochondrial functions through non-ROS pathways.[57] These findings highlight three main toxicity mechanisms of Ag NPs: oxidative stress, ER stress, and mitochondrial damage through non-ROS pathways.

Oxidative stress

Oxidative stress occurs when there's an imbalance between creating and removing oxygen free radicals in cells, causing ROS and RONS accumulation and damage.[58]

Studies have shown that the toxicity of silver nanoparticles is connected to the silver ions they produce. Ag NPs are oxidized by oxygen and other molecules in organisms, resulting in Ag+ ions.[59] These ions form stable bonds with sulphur and nitrogen, interacting with sulphur-containing proteins and peptides like glutathione, thioredoxin, and superoxide dismutase.[60] The interaction changes functional proteins, affecting their ability to resist damage from reactive oxygen species (ROS), and leads to iron release and alteration of sulphur-hydrogen residues in proteins.[61] Additionally, antioxidant levels decrease significantly. Toxic reactive oxygen and nitrogen species (RONS) like peroxy nitrite and hydroxyl may contribute significantly to toxicity.[62]Ag NPs can also penetrate liver cell membranes, triggering the production of ROS, leading to lipid and protein oxidation and DNA damage, which harms cellular components and function.[63]

Endoplasmic Reticulum stress

The endoplasmic reticulum is a biosynthesis site for lipids, membrane proteins, and secreted proteins. Disruptions in its homeostasis can lead to accumulation of unfolded and misfolded proteins, which cause ER stress.[64] This stress response aims to reduce unfolded protein concentrations and prevent aggregation. However, excessive stress damages cells and organs. Three stress-sensing proteins- IRE1, PERK, and ATF-6 are regulated by GRP78/BIP during ER stress, activating genes to manage stress. Silver nanoparticles can effect these proteins and endoplasmic reticulum, leading to increased stress markers like CHOP, associated with apoptosis. This process also involves changes in stress-related proteins like PERK, eIF-2, and others, further disrupting ER homeostasis and increasing damage.[65]

Mitochondrial Damage

Mitochondria are crucial for aerobic respiration, oxidative phosphorylation, and producing ATP, which provides energy for cells, thus earning the nickname "cell power factories".[66] Studies show mitochondria are sensitive to silver nanoparticles toxicity.[67] Ag NPs can interfere with mitochondrial functions, penetrate membranes, cause swelling, and damage structures. This affects mitochondrial fusion and fission by influencing proteins like Drp1, Mito fusin 1, and OPA1, and inhibiting PGC-1. Drp1 dephosphorylation induced by Ag NPs triggers mitochondrial fission.[68]

Toxicity assessments techniques

Transmission electron microscopy

Transmission electron microscopy (TEM) is widely used to characterize nanoparticle (NP) size and shape. TEM images are taken in brightfield mode and analysed with software to determine particle size and shape uniformity. However, the analysis is limited by small sample sizes and variability in sample preparation, which involves casting and drying NP solutions onto polymer-coated grids.

Dynamic light scattering

Dynamic light scattering (DLS) measures particle size in solution analysing light scattering and Brownian motion. It calculates the hydrodynamic radius, often yielding larger values than transmission electron microscopy (TEM) due to organic surface coating and aggregations.

Atomic force microscopy

Scanning probe microscopies, like atomic force microscopy, are used to analyse the size and surface of nanoparticles on substrates in liquids and air. Nano meter-sized probes on cantilevers move across samples to record force changes. Although the lateral resolution is lower than TEM, the technique is highly sensitive in the z-direction, making it excellent for depth profiling at Nano meter resolution.[69]

Anticoagulant activity

Venous thromboembolism is a leading cause of death due to cardiovascular issues worldwide, following closely behind heart attacks and strokes. () This condition affects patients of all ages, including children, in different settings. The most common type of venous thromboembolism is deep vein thrombosis, which can progress to a severe form called acute pulmonary thromboembolism.

The main treatment for both situations is fully anticoagulant therapy to reduce the risk of venous thromboembolism happening again. The body's way of stopping ongoing bleeding after injury is called coagulation. This involves the interaction of platelets, plasma clotting factors, and damaged tissue. The fibrinolytic cascade helps break down fibrin and fibrinogen, preventing too much thrombus formation, balancing the coagulation process. Coagulation, fibrinolysis, and platelet function work together to achieve normal clotting and hemostasis.[70] Anticoagulant prevent blood clotting by blocking vitamin K-dependent clotting factors II, VII, IX and X. Warfarin acts 8-12 hours after being taken. Their main use is to stop blood clots, which cause thromboembolic disorders. Experiments used platelet-poor plasma; PID showed no coagulation. PID was tested for its coagulant ability and showed no coagulation, indicating it can cause prolonged bleeding, a serious risk. The intrinsic biological activity of substance is studied in vivo and ex vivo using functionality active isolated tissues. The ex vivo method assesses new compounds and drugs on tissues responsive to stimuli. [1,11-14]

SM cells, known for maintaining active tension outside the body, were chosen for studying contractility.[71,72] Many internal organs mainly contain SM tissues, which shows bioelectrical and contractile activities, measurable isometrically, and related to stomach motor function. Smooth muscle mainly contracts and can keep its elasticity for up to 10hours outside the body, showing changes in tone and contractions when exposed to certain drugs. The isolated tissue bath experiment is a traditional method used by pharmacologists and physiologists to study concentration response relationships in various tissues because its versatile and reliable. Maximum tonic relation occurs around 10.47 minutes and lasts for 6hours. The Ach response stays the same after PID administration, showing the neurotransmitter pathway is unaffected, unlike with Ag NP's. Indane and its analogous have anticoagulant activity and impact smooth muscles.[73]

Conclusion

The number of applications for Ag NPs is expected to grow, but understanding their environmental fate, accumulation, and long-term effects on humans and organisms is still lacking. Studies show their release is increasing, with unclear transport, migration into food chains, and health impacts.

At the cellular level, Ag NP toxicity includes ROS generation, DNA damage, and cytokine induction, as shown in vitro studies. Few in vivo studies suggest potential adverse effects on circulatory, respiratory, nervous, hepatic, and dermal systems. More research is needed to understand bio distribution and toxicity using in vivo system, including assessing Ag NPs from textiles. Monitoring physicochemical properties during studies is essential to evaluate changes affecting NP uptake and bioavailability.

This text discusses the self-referencing micro sensors for real-time physiological sensing and new imaging techniques using Ag NPs strong Plasmon resonances for label-free tracking. These tools can be added to experiments to improve risk assessment quality for Ag NPs.

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