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REVIEW ARTICLE

Silver Nanoparticles and its Antibacterial Activity

M.Dhanalakshmi*, S.Thenmozhi, K.Manjula Devi, S.Kameshwaran

Swamy Vivekanandha College of Pharmacy, Thiruchengode, Namakkal (Dist), Tamil Nadu, India

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ABSTRACT

Nanotechnology is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer-length scale (a nanometer is one billionth of a meter). The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both *in vivo* and *in vitro* biomedical research and applications. The nanoparticles of silver showed high antimicrobial and bactericidal activity. All major pharmaceutical companies are currently investing significantly in the development of medicines with a nanotechnology component. Such research promises therapeutic drugs with greater efficacy and a wider range of clinical indications. In the current global financial crisis such systems are likely to become increasingly attractive. The importance of bactericidal nanomaterials study is because of the increase in new resistant strains of bacteria against most potent antibiotics. This has promoted research in the well known activity of silver nanoparticles. Silver nanoparticles exhibiting bactericidal properties are reviewed and discussed.

Key words: Nanoparticles ; Silver nanoparticles; antibacterial effect; Application of silver nanoparticles

1. INTRODUCTION

Nanotechnology is the science of the small with big potential it will revolutionize our world. Nanotechnology involves the production, manipulation and use of materials ranging in size from less than a micron to that of individual atoms [1]. Nanotechnology often referred as the manipulation of matter at the atomic molecular level. The word ‘nano’ derives from the greek nanos, which means dwarf. A nanometer is the one billionth of a meter, or roughly 75,000 times smaller than the width of a human hair. Approximately 3 to 6 atoms can fit inside a nanometer (nm), depending upon the atom. Nanotechnology involves the study, manipulation, creation and use of materials, devices and systems typically with dimensions smaller than 100 nm [2].

The term "nanotechnology" was first defined by Tokyo Science University, Norio Taniguchi in a 1974 paper as follows: "'Nano-technology' mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or one molecule [4]. Nanotechnology and nanoscience got a boost in the early 1980s with two major developments: the birth of cluster science and the invention of the scanning tunneling microscope (STM).

Nanotechnology is expected to open some new aspects to fight and prevent diseases using atomic scale tailoring of materials. The ability to uncover the structure and function of biosystems at the nanoscale, stimulates research leading to improvement in biology, biotechnology, medicine and healthcare.

This development led to the discovery of fullerenes in 1985. There are three distinct nanotechnologies:

1. **"Wet" nanotechnology** is the study of biological systems that exist primarily in a water environment. The functional nanometer-scale structures of interest here are genetic material, membranes, enzymes and other cellular components. The success of this nanotechnology is amply demonstrated by the existence of living organisms whose form, function, and evolution are governed by the interactions of nanometer-scale structures.
2. **"Dry" nanotechnology** derived from surface science and physical chemistry focuses on fabrication of structures in

***Corresponding Author:** M.Dhanalakshmi**, Email:** dhana_booma@yahoo.co.in, **Phone No:** +91-9443873051

carbon (for example, fullerenes and nanotubes), silicon, and other inorganic materials. Unlike the "wet" technology, "dry" techniques admit use of metals and semiconductors. The active conduction electrons of these materials make them too reactive to operate in a "wet" environment, but these same electrons provide the physical properties that make "dry" nanostructures promising as electronic, magnetic, and optical devices. Another objective is to develop "dry" structures that possess some of the same attributes of the self-assembly that the wet ones exhibit.

3. **Computational nanotechnology** permits the modeling and simulation of complex nanometer-scale structures. The predictive and analytical power of computation is critical to success in nanotechnology: nature required several hundred million years to evolve a functional "wet" nanotechnology; the insight provided by computation should allow us to reduce the development time of a working "dry" nanotechnology to a few decades, and it will have a major impact on the "wet" side as well.

These three nanotechnologies are highly interdependent. The major advances in each have often come from application of techniques or adaptation of information from one or both of the others [4].

2. NANOPARTICLES

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes [5-8]. The use of nanoparticles in biological applications is being widely explored eg: polymeric nanoparticles, metallic nanoparticles and quantum dots have been found applicable in drug delivery, bioimaging and biosensing [9-11].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties. The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc [12,13].

2.1 Preparation of Nanoparticles

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix

materials is dependent on many factors including: (a) size of nanoparticles required; (b) inherent properties of the drug, e.g., aqueous solubility and stability; (c) surface characteristics such as charge and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e) Drug release profile desired; and (f) Antigenicity of the final product [14].

3. Silver as antimicrobial agent

For centuries silver has been in use for the treatment of burns and chronic wounds. As early as 1000 B.C. silver was used to make water potable [15,16]. Silver nitrate was used in its solid form and was known by different terms like, "Lunar caustic" in English, "Lapis infernale" in Latin and "Pierre infernale" in French [17]. In 1700, silver nitrate was used for the treatment of venereal diseases, fistulae from salivary glands, and bone and perianal abscesses [17,18]. In the 19th century granulation tissues were removed using silver nitrate to allow epithelization and promote crust formation on the surface of wounds. Varying concentrations of silver nitrate was used to treat fresh burns [16,17]**.** In 1881, Carl S.F. Crede cured opthalmia neonatorum using silver nitrate eye drops. Crede's son, B. Crede designed silver impregnated dressings for skin grafting [17,18]**.** In the 1940s, after penicillin was introduced the use of silver for the treatment of bacterial infections minimized [19-21]. Silver again came in picture in the 1960s when Moyer introduced the use of 0.5% silver nitrate for the treatment of burns. He proposed that this solution does not interfere with epidermal proliferation and possess antibacterial property against *Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli* [22,23]. In 1968, silver nitrate was combined with sulfonamide to form silver sulfadazine cream, which served as a broad-spectrum antibacterial agent and was used for the treatment of burns. Silver sulfadazine is effective against bacteria like *E. coli, S. aureus, Klebsiella sp., Pseudomonas sp.*It also possesses some antifungal and antiviral activities [24]**.**Recently, due to the emergence of antibiotic-resistant bacteria and limitations of the use of antibiotics the clinicians have returned to silver wound dressings containing varying level of silver [25,21]**.**

3.1 Mechanism of action

The exact mechanism of action of silver on the microbes is still not known but the possible mechanism of action of metallic silver, silver ions and silver nanoparticles have been suggested according to the morphological and structural changes found in the bacterial cells.

3.1.1 Mechanism of action of silver

The mechanism of action of silver is linked with its interaction with thiol group compounds found in the respiratory enzymes of bacterial cells. Silver binds to the bacterial cell wall and cell membrane and inhibits the respiration process [17]. In case of *E. coli*, silver acts by inhibiting the uptake of phosphate and releasing phosphate, mannitol, succinate, proline and glutamine from *E. coli* cells [26-30]**.**

3.1.2. Mechanism of action of silver ions/AgNO3

The mechanism for the antimicrobial action of silver ions is not properly understood however, the effect of silver ions on bacteria can be observed by the structural and morphological changes. It is suggested that when DNA molecules are in relaxed state the replication of DNA can be effectively conducted. But when he DNA is in condensed form it loses its replication ability hence, when the silver ions penetrate inside the bacterial cell the DNA molecule turns into condensed form and loses its replication ability leading to cell death. Also, it has been reported that heavy metals react with proteins by getting attached with the thiol group and the proteins get inactivated [31,32].

3.1.3 Mechanism of action of silver nanoparticles

The silver nanoparticles show efficient antimicrobial property compared to other salts due to their extremely large surface area, which provides better contact with microorganisms. The nanoparticles get attached to the cell membrane and also penetrate inside the bacteria. The bacterial membrane contains sulfur-containing proteins and the silver nanoparticles interact with these proteins in the cell as well as with the phosphorus containing compounds like DNA. When silver nanoparticles enter the bacterial cell it forms a low molecular weight region in the center of the bacteria to which the bacteria conglomerates thus, protecting the DNA from the silver ions. The nanoparticles preferably attack the respiratory chain, cell division finally leading to cell death. The nanoparticles release silver ions in the bacterial cells, which enhance their bactericidal activity [32-35].

4.SYNTHESIS OF SILVER NANOPARTICLES

The apparatus used in the experiment is shown in (**Fig 1**). Added 50 ml silver nitrate solution (1.0 ×

10-3 mol L-1) into a 500 ml flask (A), which was placed into a constant temperature water bath on a magnetic stirrer. Then 50 mL ammonia solution (1.0 mol L-1) was added into another 500 ml flask (D). Flasks A and D were connected with glass tubes and short pieces of rubber tubes, through which the ammonia gas in flask D volatilized and diffused slowly into the flask A and reacted with the silver nitrate solution. In all stirring procedures of preparing silver nanoparticles, the vessel was exposed to the light of a daylight lamp (40 W) at a distance of 100 cm. The whole experiment lasted 54 hours. The detailed procedure of preparing silver nanoparticles contained five steps: (1) keep the reaction 11 hours under stirring (~39 ºC water bath); (2) keep the reaction for 13 hours without stirring and heating; (3) keep the reaction for 10 hours (conditions are same as step 1); (4) repeat the step 2; (5) keep the reaction for 7 hours [36].

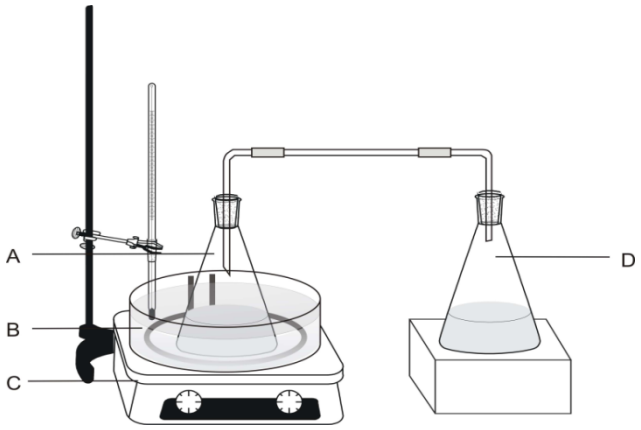

Figure 1: Apparatus for silver nanoparticles synthesis (A. conical flask with AgNO3 solution; B. constant temperature water bath; C. magnetic stirrer; D. conical flask with NH3.H2O).

5.SILVER NANOPARTICLES AS ANTIBACTERIAL AGENT

Over the past few decades, inorganic nanoparticles, whose structures exhibit significantly novel and improved physical, chemical, and biological properties, phenomena, and functionality due to their nanoscale size, have elicited much interest. Nanophasic and nanostructured materials are attracting a great deal of attention because of their potential for achieving specific processes and selectivity, especially in biological and pharmaceutical applications [37,38]**.** Discoveries in the past decade have demonstrated that the electromagnetic, optical, and catalytic properties of noble-metal nanocrystals are strongly influenced by shape and size [39,40]. This has motivated an upsurge in research on the synthesis routes that allow better control of shape and size [41-43], with projected applications in nanoelectronics and spectroscopy [44-46]. Recent studies have demonstrated that specially formulated metal oxide nanoparticles have good antibacterial activity [47], and antimicrobial formulations comprising nanoparticles could be effective bactericidal materials [48,49]. Among inorganic antibacterial agents, silver has been employed most extensively since ancient times to fight infections and control spoilage. The antibacterial and antiviral actions of silver, silver ion, and silver compounds have been thoroughly investigated [50-52]. However, in minute concentrations, silver is nontoxic to human cells. The epidemiological history of silver has established its nontoxicity in normal use. Catalytic oxidation by metallic silver and reaction with dissolved monovalent silver ion probably contribute to its bactericidal effect [53]. Microbes are unlikely to develop resistance against silver, as they do against conventional and narrow-target antibiotics, because the metal attacks a broad range of targets in the organisms, which means that they would have to develop a host of mutations simultaneously to protect themselves. Thus, silver ions have been used as an antibacterial component in dental resin composites [54], in synthetic zeolites [55], and in coatings of medical devices [56]. Recent literature reports encouraging results about the bactericidal activity of silver nanoparticles of either a simple or composite nature [57,33].It is found that silver nanoparticles undergo a size-dependent interaction with human immunodeficiency virus type 1, preferably via binding to gp120 glycoprotein knobs [58]**.** The size-dependent interaction of silver nanoparticles with gram-negative bacteria has also been reported by the same group [34].

The silver nanoparticle showed high antimicrobial and bactericidal activity against gram positive bacteria such as *Escherichia Coli*, *Pseudomonas aureginosa* and *Staphylococcus aureus.* Colloidal silver nanoparticles inhibited the growth and multiplication of the tested bacteria, including highly multiresistant bacteria such as methicillin-resistant *Staphylococcus aureus,*. *Escherichia coli* and *Pseudomonas aeruginosa*. Such high antibacterial activity was observed at very low total concentrations of silver below 6.74 µg/ml [4]. The microorganisms such as bacteria, yeast and now fungi play an important role in remediation of toxic metals through reduction of the metal ions, this was considered interesting as nanofactories very recently. A new generation of

dressing incorporating antimicrobial agents like silver was development to reduce or prevent infections. Extracellular production of silver nanoparticles by *F. oxysporum* strain and its effect bactericide in cotton and silk cloth against *S. aureus*. Antibacterial activity was observed when silver nanoparticles were incorporated in cotton cloth. It is reported successfully that biological synthesized silver nanoparticles incorporated in materials with the objective to make them sterile [59].

Silver nanoparticles dispersed in chitosan solution can be directly applied in antimicrobial fields, including antimicrobial food packaging and biomedical applications. The silver nanoparticles exhibited antimicrobial activities against *Escherichia coli* and *Staphylococcus aureus* Silver nanoparticles were prepared by γ ray irradiation–reduction under simple conditions, i.e., air atmosphere, using chitosan as a stabilizer. The obtained silver nanoparticles dispersed in a 0.5% (w/v) γ ray irradiated chitosan–aqueous acetic acid solution were stable for more than 3 months without tendency to precipitate [60]. Antibacterial properties of differently shaped silver nanoparticles against the gram-negative bacterium *Escherichia coli*, both in liquid systems and on agar plates and successfully reported that silver nanoparticles undergo a shape-dependent interaction with the gram-negative organism *E. coli.* Silver nanoparticles undergo shape-dependent interaction with the gram-negative bacterium *E. coli*. The interactions of silver nanoparticles with biosystems are just beginning to be understood, and these particles are increasingly being used as microbicidal agents. It may be speculated that silver nanoparticles with the same surface areas but with different shapes may also have different effective surface areas in terms of active facets [61].

The preparation of silver nanoparticles in the range of 10–15 nm with increased stability and enhanced anti-bacterial potency. The antibacterial effect was dose dependent and was more pronounced against gram-negative bacteria than gram-positive organisms. The antibacterial effect of nanoparticles was independent of acquisition of resistance by the bacteria against antibiotics. The major mechanism through which silver nanoparticles manifested antibacterial properties was by anchoring to and penetrating the bacterial cell wall, and modulating cellular signaling by dephosphorylating putative key peptide substrates on tyrosine residues [62]. Wound healing is accelerated by silver nanoparticles. Furthermore, through quantitative PCR, immunohistochemistry, and proteomic studies, showed that silver nanoparticles exert positive effects through their antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenic cytokines. The actions of silver nanoparticles and have provided a novel therapeutic direction for wound treatment in clinical practice **(63).**Silver nanoparticles (Ag-NPs) have been known to have inhibitory and bactericidal effects. The antibacterial activities of penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin were increased in the presence of silver nanoparticles against both test strains. The highest enhancing effects were observed for vancomycin, amoxicillin, and penicillin G against *S. aureus* [64].

6. CONCLUSION

In Summary, it can be concluded that among different types of antibacterial agents, silver found to be effective. Silver nanoparticles have been extensively reviewed and it is seen that silver nanoparticles are non-toxic to human in minute concentrations. Silver nanoparticles have also found its application in wound dressings, medical devices etc.Silver nanoparticles found to be effective against various bacteria.

Thus, it can be concluded from the review that, silver nanoparticles can be extensively used as an antibacterial agents. The following questions has to be yet addressed.1.The exact mechanism of interaction of nanoparticles with the bacterial cells.2.Toxicity if any of silver dressings.

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