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Silver nanoparticles: synthesis through chemical methods in solution and biomedical applications

Review Article

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Abstract: Chemical methods provide an easy way to synthesize silver nanoparticles (Ag NPs) in solution. These metal nanoparticles have a great potential for biomedical applications as an antibacterial, antifungal, and antiviral agent or in wound healing. The adjustment of the parameters involved in these reactions permits a precise control over the size, shape, monodispersity, and the surfaces of the nanoparticles. These nanoparticles are being used in the design of new hybrid organic-inorganic or inorganic nanomaterials for biomedical applications.

Keywords: *Silver, nanoparticles • Chemical synthesis • Antimicrobial properties • Biomedical applications*

1. Introduction

The research on chemical entities of nanometer size is one of the primary research areas in chemistry due to the wide variety of new properties and potential applications that can be exploited in different fields [1,2]. This size scale corresponds, for example, to organic macromolecules such as polymers or dendrimers; proteins; micelles or vesicles formed by small molecules that self-assemble; inorganic nanoparticles, *etc*. In the latter case, metal or metal oxide based nanoparticles display interesting biological, optical, magnetic and catalytic properties that, in general, are related to the size and the shape of the new materials and can be interesting due to their potential applications. The unique properties displayed by the metal nanoparticles arise from their high surface/volume ratio, the quantum confinement of the electronic movement in semiconductor nanoparticles, the surface plasmon resonance of some types of metal particles, and/or the superparamagnetism of magnetic nanomaterials [3,4].

Silver has been used for thousands of years as a precious metal by humans in different applications as jewellery, tools, coins, photographic material or explosives. One of the most significant use of silver is as a disinfectant with hygienic for medical purposes. Since the ancient times, silver vessels were used for the storage of water or wine because it was believed that this metal preserved their conditions. Also Hippocrates described the use of silver powder for its application in wound healing and in the treatment of ulcers. In the 17th and 18th centuries, silver nitrate was used for ulcer treatment and its antimicrobial activity was established in the 19th century. Nevertheless, after the introduction of the antibiotics in 1940 the use of silver salts decreased. Subsequently silver salts and silver compounds have been used in different biomedical fields, especially in burn treatment [5,6].

The chemical synthesis of silver nanoparticles is a well established research field, although not deliberated, from centuries ago. The first recognized example is the bronze Lycurgus cup from the IVth century AD that possesses colored glass that disperses green light and transmits red light due to its content on an alloy of silver (70%) and gold (30%) nanoparticles [7]. Another curious example is the metallic luster which is a kind of ceramic decoration that consists of the use of silver nanoparticles, among other metals, for producing a beautiful metallic shine and colored iridescence on the surface of the ceramic object. After the ninth century this technology was spread from Iraq to Persia, Egypt, Spain and Italy [8,9] (Fig. 1).

The previously described historical examples are the starting point for the development of the silver-based

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nanomaterials. Nowadays, the most active working fields related to silver nanoparticles are the study and application of their optical and biomedical properties.

The optical properties of metal nanoparticles of group 11 are based on the collective oscillation of free conduction electrons resulting from the interaction with the electromagnetic radiation. The electric field of the incoming radiation induces the formation of a dipole in the nanoparticle. A restoring force in the nanoparticle tries to compensate for this effect, resulting in a unique resonance wavelength that confers the characteristic color of colloidal solutions of noble metal nanoparticles. Several interesting applications related to this property have been developed, mainly focused on the detection of chemical species of organic, inorganic or biological origin. Other properties such as SERS (Surface Enhanced Raman Scattering) or MEF (Metal Enhanced Fluorescence) are being intensively studied [10,11].

As it has been mentioned before, the biomedical properties of silver nanoparticles also represent a relevant field of research. Most of the reports on this topic are based on the antimicrobial properties of silver nanoparticles, although several studies on the antiviral, antifungal and wound healing potential properties have also been reported. Obviously, a large number of practical applications are being developed in parallel with the study of these properties [11].

Figure 1. Luster ceramic pottery from Manises (Spain), XVth century (courtesy from the Museo de Cerámica de Barcelona).

Thus, in the context of this huge development that nanoscience and nanotechnology have experienced in the last years, several physical and chemical methods for synthesis of Ag nanoparticles have been described. In this review we will highlight some of the most important chemical methods. In this sense most of the chemical methods for the synthesis of Ag nanoparticles are based on reduction reactions of silver(I) metal salts. Together with the description of some of the above mentioned chemical methods, we will also account for some of the most interesting properties of Ag NPs, paying a special attention to their great ability as antibacterial agent.

2. Synthesis of Silver Nanoparticles

From a chemical viewpoint, the synthesis of nanoparticles in solution (colloidal solution) requires the use of methods allowing a precise control over the size and the shape of the nanoparticles to yield a set of monodisperse nanoparticles displaying a specific property. In general, the synthesis of metal nanoparticles in solution is carried out by the use of the following components: i) metal precursor; ii) reducing agent and iii) stabilizing agent. The mechanism of formation of colloidal solutions from the reduction of silver(I) ions consists of two stages: nucleation and growth. The nucleation step requires high activation energy while the growing step requires low activation energy. The size and the shape of the nanoparticles will depend on the relative rates of these processes that can be controlled through the adjustment of the reaction parameters (concentration, temperature, pH, reducing ability, *etc.*) (see Fig. 2) [3,4,12].

In the case of silver nanoparticles, the first described methods are the Lee-Meisel [13] and the Creighton method [14]. The former consists of a modification of the Turkevich method for the synthesis of gold nanoparticles,

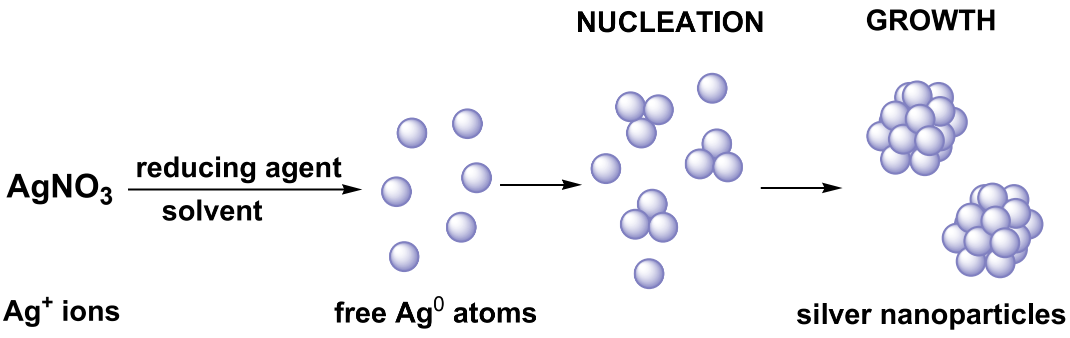

Figure 2. Mechanism of formation of silver nanoparticles from the chemical reduction in solution of the AgNO$_3$ salt.

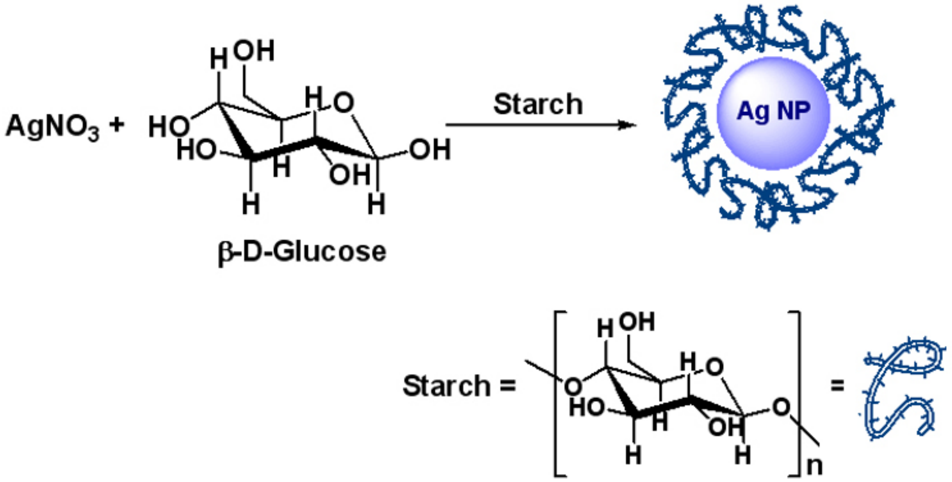

Figure 3. Green method for the synthesis of Ag NPs.

using $AgNO_3$ instead of $HAuCl_4$ as metallic precursor and sodium citrate as the reducing agent. In this method the obtained nanoparticles display a broad size distribution. The Creighton method consists of the reduction of $AgNO_3$ with $NaBH_4$ as the reducing agent. This is the most popular method and can generate Ag NPs of ca. 10 nm and showing a narrow size distribution.

Based on the above mentioned methods, a variety of chemical reactions that allow the synthesis of Ag NPs by chemical reduction of a silver salt have been described [15-24]. In this type of reactions the oxidation of the formed nanoparticles is not thermodynamically favored due to the high reduction potential of silver, which permits the aqueous or alcoholic suspensions without the presence of stabilizing agents. In addition, the double electric layers formed around the nanoparticles in colloidal solutions of low ionic strength inhibit the aggregation of the nanoparticles. In the case of colloidal solutions of high ionic strength or in organic phase, the use of stabilizing agents acting as self-assembled monolayers [25-33], surfactants [34-40], polymers [41-51] or dendrimers [52-54] is needed. These agents not only protect the nanoparticles from the environment and prevent their agglomeration, but also play an important role in the size and shape control.

The methods by which nanoparticles are synthesized by the reaction between a metallic salt and chemical reducing agents are the most versatile ones. Among them, it is worth mentioning the formation of Ag NPs from $AgNO_3$ and using soft reducing agents as ascorbic acid [15], polyols [16,17] or monosaccharides [18]. In the case of ascorbic acid acting as reducing agent, the change in the reaction conditions allows the synthesis of silver nanoparticles of large size (up to 1200 nm). The use of weak reducing agents as polyols at high refluxing temperatures gives rise to 40 nm size Ag NPs. In the case of monosaccharides, a green method for the synthesis of nanoparticles has been developed. In this case the reduction of $AgNO_3$ is provoked by the addition of β-D-glucose as reducing agent in the presence of starch as the stabilizing agent, leading to Ag NPs of small size (ca 5 nm) (see Fig. 3). Also a polysaccharide such as heparin can be used as a reducing/capping agent for the production of silver nanoparticles. The abundance of sulfonate groups in heparin facilitates the stabilization of silver nanoparticles of ca. 20 nm [55]. In addition to the synthetic methods using bioorganic molecules, it is also worth mentioning the use of glutathione [56] or L-Valine-based oligopeptides [57] as capping/reducing agents for the preparation of Ag NPs (see Table 1).

It is also possible to synthesize silver nanoparticles through the Tollens method [19]. This method has been used for decades for the electrolytic deposition of silver thin films (silver mirror). It is a reduction process of complex $[Ag(NH_3)_2]^+$ in solution by organic reducing agents such as aldehydes or sugars. In the case of silver nanoparticles lower concentrations and ultrasounds are needed for the preparation of colloidal solutions. A modification of the Tollens method has permitted the controlled synthesis of monodispersed silver nanocubes in water. Thus, the reduction of $[Ag(NH_3)_2]^+$ with glucose, in the presence of *n*-hexadecyltrimethylammonium bromide (HTAB) leads to monodisperse silver nanocubes with a mean edge length of 55±5 nm [58,59].

A very interesting method for the synthesis of silver nanoparticles is the one developed by Liz-Marzán *et al.* [20-24]. In this case dimethylformamide (DMF) has been used as solvent and reducing agent at the same time with silver salts in different reaction conditions. Nanoparticles of different sizes and shapes can be obtained by using different stabilizing agents such as aminopropyltriethoxysilane (APS) or polyvinylpyrrolidone (PVP) (Fig. 4).

Special attention has been recently paid to the synthesis and optical properties of silver nanoprisms (or nanoplates).

Some important methods described for the synthesis of these special type of nanoparticles are, for example, the above mentioned methods: (i) reduction of silver nitrate with DMF in the presence of PVP [24]; (ii) reduction of silver nitrate in the presence of ascorbic acid as reducing agent and CTAB micelles [36], or (iii) reduction of silver nitrate with hydrazine in AOT/isooctane/water reverse microemulsions [38-40]. In all cases, careful control of the reaction parameters permits a control over the shape of the particles. Also, although not strictly chemical, irradiation methods are also able to produce silver nanoprisms in a conversion reaction from a large quantity of spherical silver nanoparticles [60,61] (Fig. 5).

As it has been mentioned before, the aggregation of the nanoparticles in solution can be prevented by the use of stabilizing agents. One of the most widely used methods consists of adding to the solutions with long alkyl-chain organic ligands bearing functional groups such as thiols [25-27], carboxilates [28,29], phosphine oxides [30] or amines [31,32]. The mechanism of formation of the nanoparticles is similar to the previously mentioned one, namely, reduction of a silver salt in the presence of a reducing agent. The use of these ligands prevents the aggregation of the nanoparticles in organic solvents and, at the same time, achieves a precise control over the size, shape and the monodispersity of the nanoparticles by exploring different reaction conditions.

A curious example is the synthesis of small and highly monodispersed Ag NPs (2.8–15.4 nm) from silver(I) alkylcarboxylates through a thermolytic method [28,29]. In this process there is no need of reducing agents and the carboxylate groups acts, both as the ligand in the silver(I) compound and as the stabilizing agent of the Ag NPs (Fig. 6). Another interesting example is the synthesis of silver nanoparticles from the silver acetate salt and hexadecylamine acting as the solvent and the stabilizing agent in the presence of acetaldehyde as reducing agent [30].

At high temperatures the long alkyl-chain ligands can be used as solvent and stabilizer at the same time. Using a fast injection method for an organometallic compound such as [Ag(Mes)]$_4$ (Mes =mesityl or 2,4,6-trimethylphenyl) in a hexadecylamine solution at 300ºC, Ag NPs (ca. 8.5 nm) can be obtained in a thermolytic process [33].

Micelles or inverse micelles have also been used for the development of new methods for Ag NPs synthesis. These supramolecular entities formed by surfactants can be considered as nanoreactors, in which the chemical reduction of a silver salt can take place in the presence of a chemical reducing agent such as ascorbic acid [34-36], NaBH$_4$ [37] or N_2H_4•H_2O [38-40]. Some of the most commonly used surfactants are CTAB (cetyltrimethylammonium bromide) and AOT (sodium bis(2-ethylhexyl)sulfosuccinate). When AOT is used as surfactant in a dodecane/water mixture, it is possible to synthesize silver nanoparticles of different shapes by reduction of silver nitrate with hydrazine inside

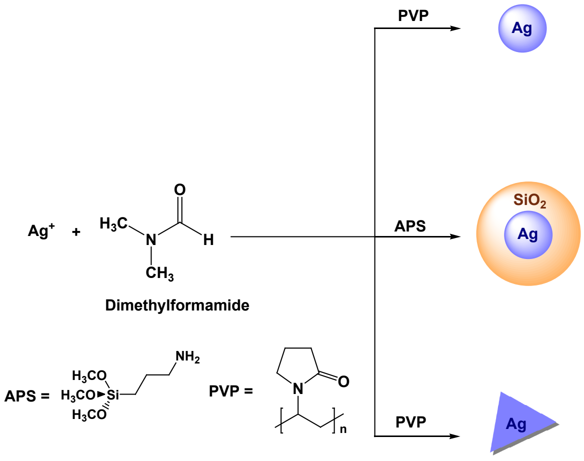

Figure 4. Synthesis of Ag NPs using DMF as reducing agent. When PVP is used as nanospheres (up) or nanoprisms (bottom) can be obtained. When APS is used silver nanoparticles with a SiO$_2$ shell are obtained.

Table 1. Summary of some synthetic chemical methods for Ag NPs synthesis

Precursor	Reducing agent	Stabilizer	Reference
AgNO$_3$	Citrate		13
AgNO$_3$	NaBH$_4$		14
AgNO$_3$	Ascorbic acid		15
AgNO$_3$	Polyol	PVP	16,17,47
AgNO$_3$	β-D-glucose	Starch	18
[Ag(NH$_3$)$_2$]$^+$	Saccharides		19
AgNO$_3$	DMF	APS	20
AgNO$_3$	DMF	PVP	21
Ag(COOR)	Thermolysis		28,29
Ag(COOCH$_3$)	Acetaldehide	HDA	30
Ag(COOCH$_3$)	Oleilamine	OLA	30
[Ag(Mes)]$_4$	Thermolysis	HDA	33
AgNO$_3$	Ascorbic acid	CTAB	34-36
AgNO$_3$	$N_2H_4 \cdot H_2O$	AOT	38-40
AgNO$_3$	UV radiation	PVP	41-46
AgNO$_3$	UV radiation	PEG	51
[Ag(C$_6$F$_5$)]		HDA	63

R = C_7H_{15}, $C_{13}H_{27}$ and $C_{17}H_{35}$, Mes = 2,4,6-trimethylphenyl ring, C_6F_5 = pentafluorophenyl ring, APS = aminopropyltriethoxysilane, PVP = polyvinylpyrrolidone, HDA = hexadecylamine, OLA = oleilamine, CTAB= cetyltriethylammonium bromide, AOT = sodium bis(2-ethylhexyl) sulfosuccinate, PEG = polyethyleneglycol.

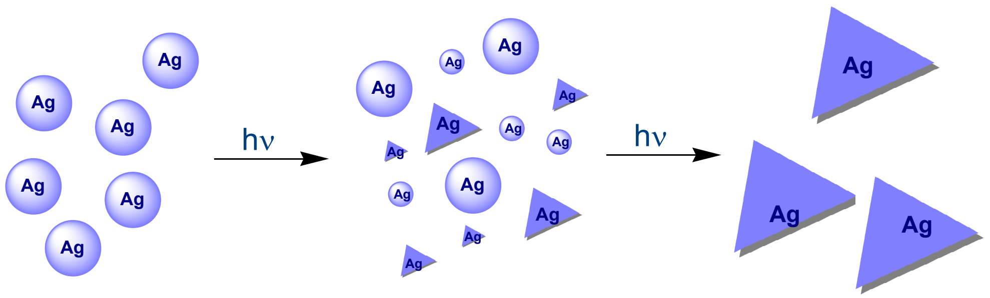

Figure 5. Ag nanoprism formation: irradiation of spherical silver nanoparticles gives rise to small silver nanoclusters and nanoprisms. The small silver nanoprisms then act as seeds and grow as the small spherical crystals are digested.

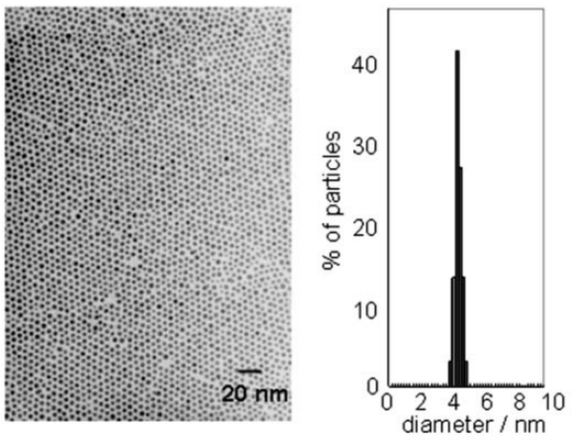

Figure 6. TEM picture of very small and monodisperse Ag NPs synthesized through the thermolysis of [$Ag(C_{13}H_{27}CO_2)$] (left) and size histogram (right) (adapted from [28] with permission of the The Royal Society of Chemistry).

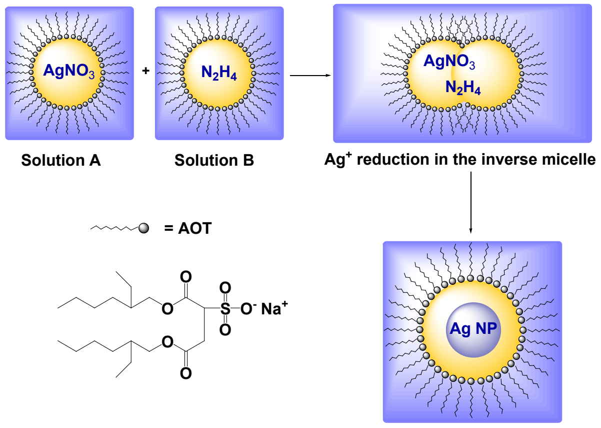

Figure 7. Synthesis of silver nanoparticles using AOT inverse micelles formed in a dodecane/water mixture.

the inverse micelles formed [40] (Fig. 7).

Murphy and coworkers developed a synthetic method of unidimensional silver nanostructures (nanorods and nanowires) using micelles formed from CTAB surfactant in a two-step process called "seed-mediated growth". This method starts from the initial synthesis of 4 nm size silver nanoparticles (seeds) by reduction of $AgNO_3$ with $NaBH_4$ in the presence of sodium citrate. From these silver nanoparticles, by adding $AgNO_3$, ascorbic acid as mild reducing agent, NaOH and CTAB as micellar template, silver nanorods and nanowires can be obtained as a function of the experimental conditions [34,35] (Fig. 8)

Although the synthesis and study of silver nanoparticles is of great interest, one of the most active research areas in this field is the preparation of new silver-based nanomaterials. For this, several templates of keeping or changing the nanoparticle properties have been developed, for example, organic polymers or silica coatings.

The polymer poly(vinylpirrolidone) (PVP) is one of the most widely used polymers for the stabilization of nanoparticles, including silver [41-46]. Thus, one of the first synthetic approaches consisted of the photoreduction of $AgNO_3$ in the presence of PVP as stabilizing agent by using UV radiation of 243 nm. Using this method, Ag NPs between 15-22 nm can be obtained by changing the Ag^+:PVP ratio [42]. Later, several methods in which PVP acts as stabilizing agent have been developed which use different chemical reducing agents such as potassium bitartrate [43] or DMF [21], and even using microwave or PVP itself as reducing agents [44]. PVP has also been used as stabilizer in reducing reactions of silver nitrate with polyols (Polyol method), which leads to the synthesis of different types of nanostructured silver shapes such as nanospheres, nanocubes, nanorods or nanowires. In general, varying the parameters affecting to the reactions and, specially, the concentration of the stabilizing polymer PVP, permits a great control over the size and the shape of the nanostructures [45,46] (Fig. 9).

Other polymers used in the synthesis of silver nanoparticles as stabilizing agents are polyacrylates [47], poly(vinylalcohol) [48], polyacrylonitrile [49], polyacrylamide [50] or poly(ethyleneglycol) [51]. Another type of polymers of interest in the stabilization of Ag NPs are dendrimers [52-54]. These are three dimensional macromolecules displaying an arborescent structure. This type of molecules are able to stabilize silver nanoparticles in two different ways: the first one is based on the steric stabilization through the

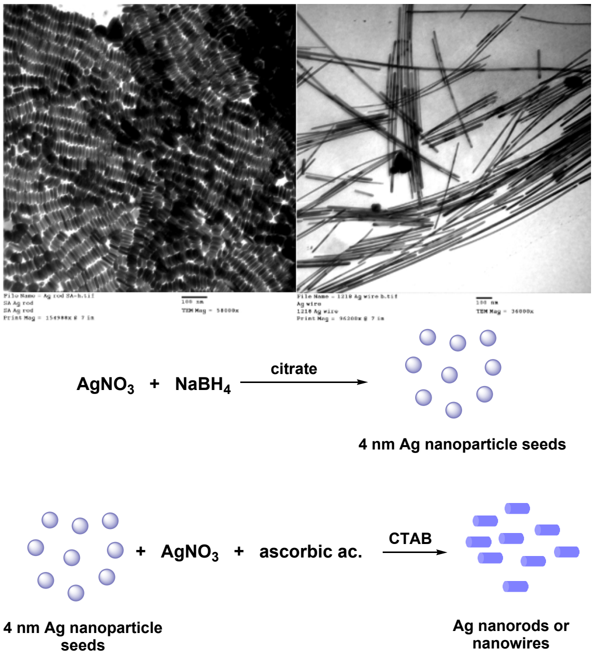

Figure 8. TEM micrographs of silver nanorods and nanowires (up). Synthesis of unidimensional silver nanostructures using CTAB micelles (TEM micrographs adapted from [34] with permission of the The Royal Society of Chemistry).

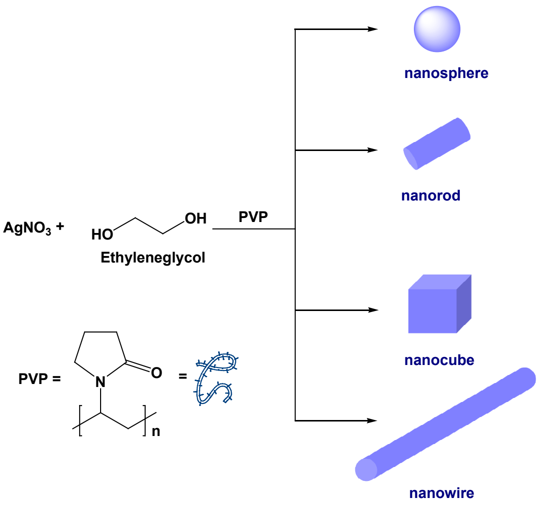

Figure 9. Different silver nanostructures synthesized through the reduction of silver nitrate in ethyleneglycol in the presence of PVP.

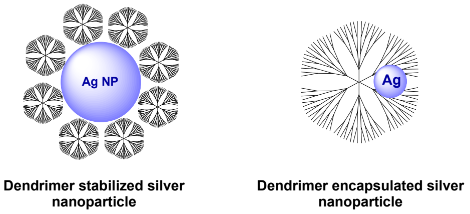

Figure 10. Dendrimer stabilized Ag NPs (left) and dendrimer encapsulated silver nanoparticles (right).

interaction of the functional groups at the periphery of the dendrimers, leading to a stabilization mechanism similar to the one observed for the above mentioned polymers; the second method is based on the stabilization of very small silver nanoparticles inside the dendrimers giving rise to encapsulation (Fig. 10).

In addition to purely inorganic stabilizers, polyoxometallate anions such as $[PW_{12}O_{40}]^{3-}$, $[SiW_{12}O_{40}]^{4-}$ can be used as reducing agents, photocatalysts and stabilizers for the synthesis of 15.3±3.4 nm size silver nanoparticles [62].

Finally, silica-coated and titanium dioxide-coated silver nanoparticles have also been prepared by using DMF as reducing agent. This type of inorganic coatings exhibit a high stability of the nanoparticles, making them stable for months [20-24].

An organometallic method has also been developed for the synthesis of silver nanoparticles [63]. This method has been largely studied by Chaudret and coworkers for the synthesis of a large number of metal and metal oxide nanoparticles [64,65]. As it has been mentioned before, the synthesis of nanoparticles requires methods allowing a control over the size and the shape of the particles. Moreover, a large portion of atoms in the nanoparticles are on the surface and, therefore, the nature of the nanoparticle surface will greatly influence its properties. Thus, a control of the nanoparticle surface is also needed. In this sense, the chemical reduction methods of metal salts with strong chemical reducing agents such as $NaBH_4$, present very little variability regarding shape control. The methods using inverse micelles do allow a good control over the size and the shape (spheres, wires, rods, cubes, *etc.*), but the presence of water and salt can modify the nanoparticle surface by mediating a passivation process, which may change the surface properties and reactivity. Organometallic compounds are susceptible of decomposition by the use of very mild reaction conditions, which give rise to the formation of metal nanoparticles in the presence of stabilizing agents. Moreover, the displacement of organic ligands from the coordination sphere of the metals opens the possibility of building up nano-objects with almost uncontaminated surfaces.

Silver nanoparticles of ca. 9.8 nm can be synthesized by the decomposition of the organometallic precursor $[Ag(C_6F_5)]$ in the presence of hexadecylamine [63]. The synthesis and characterization of organometallic gold and silver compounds with perhalophenyl ligands have been widely studied [68]. These ligands confer enough stability to the complexes for being handled easily, but the long-term exposure to air and moisture leads to decomposition (Fig. 11).

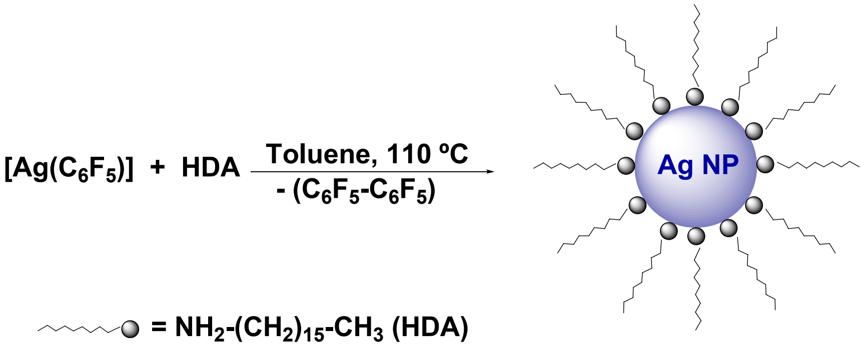

Figure 11. Organometallic method for the synthesis of silver nanoparticles.

3. Bactericidal Properties of Silver Nanoparticles

3.1. Antibacterial action mechanism of silver nanoparticles

As it has been mentioned in the Introduction section the antimicrobial effect of silver salts is well known since the 19th century. In the studies carried out in the last years, silver was defined as "oligodynamic" due to its ability to produce a bactericidal effect at very low concentrations. This feature of Ag^+ ions arises from its high affinity towards proteins, enzymes, DNA, RNA, *etc*. due to the interactions with functional groups such as thiol, carboxylate, phosphate, hydroxyl, imidazole, indole or amines what can interfere in microbial processes [11].

On the other hand, the bactericidal effect of silver nanoparticles is also known for a long time, but the mechanism of action has been studied only recently. Several questions are still not answered. For example, the possible interaction mode between silver nanoparticles and different gram-negative bacteria was thoroughly studied by using the High Angle Annular Dark Field (HAADF) Scanning Electron Transmission Microscopy (STEM) technique that permits the observation of nanoscale objects with a high contrast [67]. In this study a very strong bactericidal effect of nanoparticles in the 1-10 nm size range was observed. The nanoparticles appeared attached to the cell membrane which provoked changes in the permeability and affecting the functions of membrane-bound enzymes in the respiratory chain. The authors also proposed that, small size silver nanoparticles found inside the bacteria at the same time caused the damage of chemical structures containing sulfur or phosphorus-based functional groups such as DNA chains. Finally, as a complementary effect of the bactericidal effect, the silver nanoparticles release silver ions from the nanoparticle surface that contribute to the bactericidal effect in the same way as Ag^+ ions from silver salts proceed.

The same authors studied the interactions between silver nanoparticles of different sizes with HIV-1 virus [68]. In the same way as in the previous study, only Ag NPs with sizes in the 1-10 nm range appeared attached to the virus. The interaction produced between the nanoparticle and glycoprotein gp120 blocked the ability of the virus to bind receptor cells.

Lok *et al.* have recently carried out a study based on the proteomic analysis of the mode of action of silver nanoparticles of 9.3 nm in size [69]. This study concluded that the nanoparticles destabilize the outer bacterial membrane of *E. coli*, as they collapsed the plasma membrane potential and depleted the level of intracellular ATP in a similar way as Ag^+ ions. However, while the bactericidal effect of Ag^+ ions arising from $AgNO_3$ salts is effective when micromolar concentrations are used, silver nanoparticles show a bactericidal effect already at nanomolar level. In a further study, these authors showed that silver nanoparticles bearing a partially oxidized surface could act as nanocarriers of chemisorbed Ag^+ in amounts enough for producing a bactericidal effect, while silver nanoparticles synthesized under a nitrogen atmosphere did not present bactericidal activity [70].

The antimicrobial activity of the silver nanoparticles produced through an organometallic method has also been tested against the microorganisms *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Listeria monocytogenes* (CECT 4032). These nanoparticles were studied since their size of less than 10 nm is in the range of highest bactericidal activity and because the organometallic method leads to nanoparticles with almost uncontaminated surfaces [63]. The obtained Minimal Inhibitory Concentration (MIC) and the Minimal Bactericidal Concentration (MBC) values for the activity of the nanoparticles against the three microorganisms were very low (12.5 - 25 $\mu g\ mL^{-1}$), which shows a very good bacteriostatic and bactericidal activity of the nanoparticles, especially against *E. coli*.

As we have commented above, the High Angle Annular Dark Field (HAADF) Scanning Electron Transmission Microscopy (STEM) studies carried out by Morones *et al.* showed that a very strong bactericidal effect of nanoparticles in the 1-10 nm size range. In this sense, the influence of size and shape in the antibacterial properties of silver nanoparticles has been described in different reports. For example, the antibacterial application of silver nanoparticles of different sizes (10, 30-40 and 100 nm) has been tested against methicillin-resistant S. aureus (MRSA) microorganism. The authors concluded that silver nanoparticles are good antibacterial agents that are not affected by the drug resistant mechanism of MRSA and that Ag NPs size mediates MRSA inhibition and cytotoxicity to human cells. The smaller the nanoparticle size, the better antibacterial activity and nontoxic effect [71].

A recent study analyzed the antibacterial activity of silver nanoparticles against *E. coli* as a function of the particle size and shape. The authors proposed that truncated triangular silver nanoplates display stronger biocidal effect when compared with spherical and rod-like silver nanoparticles. This trend would be explained by taking into account the existence of different effective surface areas in the nanoparticles in terms of active facets [72].

3.2. Recent developments in hybrid inorganic antibacterial silver-based nanomaterials.

Although we have reviewed in section 2 the most significant chemical methods for synthesis of Ag NPs in solution, the preparation of new antibacterial silver-based nanomaterials is also an important class that deserves particular attention. During the last years a tremendous effort has been carried out on the synthesis of these new silver-based nanomaterials, especially focused on the development of new or enhanced antibacterial properties. In most cases the chemical synthesis of the silver nanoparticles is carried out through some of the above mentioned methods (section 2), but with slight modifications in order to introduce a new capping agent or chemical support for the nanoparticles. In this context, one of the main categories of silver-based nanomaterials that can be considered is silver nanomaterials on inorganic supports. In the next paragraphs some recent examples of new antibacterial silver nanomaterials are reviewed.

Bactericidal coatings based on Ag nanoparticles deposited on TiO_2 films are an important class of biomaterials due to their application in surgical implant procedures. These multifunctional materials display interesting properties such as antimicrobial activity and biological compatibility. The synthetic approaches for the synthesis of Ag-TiO_2 composites are varied, for example, from simple reduction of Ag^+ ions by $NaBH_4$ in the presence of a suspension of TiO_2 [73] to more complex ones such us the photoreduction of $AgNO_3$ in the presence of PVA-capped TiO_2 nanoparticles/nanotubes [74], the plasma electrolytic oxidation of a titanium medical alloy (Ti-6Al-7Nb) in the presence of silver nanoparticles [75] or the direct liquid injection metal-organic chemical vapor deposition of silver(I) pivalate and titanium(IV) tetra-iso-propoxide [76]. The antibacterial activity of these nanocomposites has been examined in all these cases. It is worth mentioning that the in the case of Ag-TiO_2 nanomaterial synthesized through plasma electrolytic oxidation [75] the antibacterial ability of composite layers of this material has been tested against multiple antibiotic-resistant pathogen methicillin-resistant *Staphylococcus aureus*, one of the most commonly encountered bacteria in the peri-implant area of orthopaedic devices. The studies showed complete bacteria killing in all tested culture conditions after 24 h.

Another emerging class of antibacterial hybrid inorganic nanocomposites is Ag-hydroxyapatite nanomaterials because of their use in industrial and medical applications. Recent results include the preparation of antibacterial silver-hydroxyapatite by the reduction of silver ions by hydroxyl groups at the surface of hydroxyapatite leading to needle-like silver nanoparticles [77]. Also, in a recent study the combination of electrospun titanium dioxide, hydroxyapatite and silver nanoparticles was tested against *E. coli* and *S. aureus* leading to a nanofiber showing promising potential for implant materials [78]. A third example showed recently that silver-hydroxyapatite nanomaterials obtained through a colloidal chemical route display interesting antibacterial and antifungal properties which make this material interesting for implant and reconstructive surgery [79].

Carbon-based nanomaterials such as carbon nanotubes or graphene display unique physical and chemical properties. The combination of these carbon-based nanomaterials with silver nanoparticles constitutes an interesting class of antibacterial materials. Ag-chemically converted graphene nanocomposite was prepared through a chemical reduction of graphene oxide [80]. This nanocomposite display antibacterial properties against several microorganisms. Also, the synthesis and study of antibacterial properties of silver coated carbon nanotubes were carried out. This nanocomposite was prepared through the chemical reduction of silver(I) acetate with dimethylformamide, in the presence of carbon nanotubes and displayed good antibacterial activity against different microorganisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli* and *Salmonella enteric* [81].

Silver-supported silica (Ag-SiO_2) nanomaterials are also suitable candidates for antibacterial materials due to their high chemical stability and antibacterial property [82]. For example, silver nanoparticles inmobilized on the surface of an aqueous sol-gel silica film display strong antibacterial activity against *E. Coli* and *S. aureus*. In a different report, silver quantum dots embedded silica/polyacrylic acid hybrid nanoparticles were prepared by reduction of silver ions in the presence of the hybrid silica/polyacrylic acid nanoparticles. This nanocomposite showed a high antibacterial efficiency [83].

A synergistic antibacterial effect was found when silver-zinc oxide nanocomposites were tested against different microorganisms. For example, Ag-ZnO nanocomposites prepared through a hydrothermal route assisted by tyrosine displayed potential applications in photodegradation of pollutants and destruction of bacteria [84]. In another report, silver nanoparticles synthesized in situ on a paper matrix composed of ceramic fibers and ZnO whiskers exhibited excellent antibacterial activity against *E. coli* and durability for repeated use [85].

Silver-magnetite (Ag-Fe_3O_4) nanoparticles have been prepared by the reduction of silver nitrate in the presence of Fe_3O_4 nanoparticles using a water-in-oil microemulsion method. These nanoparticles present a good antibacterial performance against different microorganisms such as *E. coli*, *S. aureus* and *B. subtilis*. The main advantage of these nanoparticles is that they can be easily removed from water by the use of a magnetic field in order to avoid water pollution [86]. Recently, core-shell Fe_3O_4-Ag nanostructures have been formed by the reduction of silver nitrate with oleylamine in the presence of magnetite nanoparticles. This nanocomposite is highly toxic to several microorganisms due to its high stability as a colloid in the medium [87].

A new method based on the chemical reduction of silver nitrate in the interlayers of montmorillonite clay has given rise to a new hybrid nanocomposite that displays antibacterial properties against *E. coli* even after 12 years, showing a great stability of the nanoparticles in the clay structure [88].

3.3. Recent developments in hybrid organic-inorganic antibacterial silver-based nanomaterials.

Another important class of antibacterial silver-based nanomaterials is composed by hybrid organic-inorganic nanocomposites. In this context a large number of studies have been reported from the synthetic point of view, especially by the use of organic polymers as stabilizing agents for Ag NPs. In this subsection we show some recent examples of antibacterial hybrid organic-inorganic silver nanomaterials containing mainly polymers although discrete organic molecules such us cyclodextrin or glucosamine are also included.

Antibacterial hydrogel-silver nanocomposites are suitable for many applications in the medical field. Several examples have been recently reported on this field including different types of organic polyelectrolites, polymers or copolymers. Thus, for example, charged poly-4-vinylpyridine particles were used as substrate for the synthesis of silver nanoparticles from the reduction of silver(I) nitrate with sodium borohydride inside the hydrogel nanonetwork formed within the polyelectrolyte. This nanomaterial showed antibacterial activities against *S. aureus*, *P. aeruginosa*, *B. subtilis*, and *E. coli*. The antibacterial ability of the nanocomposite is dual since both the charged poly-4-vinylpyridine and the silver nanoparticle display this property [89]. In another example, 2-3 nm size silver nanoparticles were synthesized within a hydrogel network based on poly(acrylamide)/poly(vinylalcohol) for antibacterial and wound dressing applications. Also, in a report by Mohan *et al*. the authors described the controlled synthesis and antibacterial activity of hydrogel-silver nanocomposites including silver nanoparticles of different sizes and shapes [90].

Another polymer used for the preparation of antibacterial silver nanomaterials is polyurethane. Ag nanoparticles coated with polyurethane foam was recently used as antibacterial water filters. The preparation of this nanocomposite consisted of the overnight exposure of the foams to citrate stabilized silver nanoparticles. The antibacterial activity of the silver-polyurethane nanocomposite was checked against *E. coli* through growth inhibition tests [91].

Poly(vinyl alcohol)-b-poly(acrylonitrile) (PVOH-b-PAN) copolymer based micelles with embedded silver nanoparticles showed strong antibacterial activity against *E. coli*, *S. aureus* and *P. aeruginosa* as observed in the minimum bactericidal concentration for each system (MBC). The silver concentrations used for the bactericidal effect was very low, ranging from 0.36 to 2.88 μg mL^{-1} of silver [92].

A three-step process including silver ion-poly(ethylene glycol) matrix preparation, addition of chitosan matrix, and removal of poly(ethylene glycol) from the film matrix permitted the synthesis of porous chitosan films impregnated with silver nanoparticles. This nanocomposite displayed superior bacterial growth inhibition using the disk diffusion method [93].

Apart from the polymeric substrates used in the synthetic design of antibacterial organic-inorganic hybrid nanocomposites, the use of large organic molecules displaying specific features such as PAMAM dendrimers, β-cyclodextrins or glucosamine have also been used for the preparation of this type of nanocomposites. For example, poly(amidoamine) dendrimer-silver nanocomposites were used as antibacterial agents against *S. aureus*, *P. aureaginosa*, *E. coli*, *B. subtilis* and *K. mobilis*. These dendrimer-silver nanocomposites can be synthesized by a two-step process including silver ion (Ag^{+}) trapping in the dendrimer structure and chemical reduction with sodium borohydride. In this process the dendrimer acts as a nanoreactor, in the first step, and as a chemical stabilizer for the nanoparticles after the chemical reduction [94,95].

The capping of silver nanoparticles with varying concentrations of β-cyclodextrin leads to spherical nanoparticles of 4-7 nm size. This nanomaterial displays antibacterial activity against *S. aureus*, *P. aureaginosa* and *E. coli*. The authors proposed a Trojan horse antibacterial mechanism in which the bacterial-carbohydrate affinity leads to the enhancement of silver ion absorption [96].

Glucosamine-functionalized silver glyconanoparticles were synthesized in a two-step procedure and examined as antibacterial agent against 16 types of microorganisms showing an enhanced Minimal Inhibitory Concentration (MIC) compared to classical silver nanoparticles prepared from silver nitrate and sodium borohydride [97].

4. Other Biomedical Applications of Silver Nanoparticles

In addition to widely studied bactericidal properties of silver nanoparticles, there are several interesting biomedical properties associated to these nanoparticles. Some reports were focused on the antiviral or antifungal ability of Ag NPs. For example, the inhibition of the replication of HIV-1 virus [98] or the inhibition of the growing of some types of yeast [99] in the presence of Ag NPs was studied. In the case of the activity of the nanoparticles against HIV-1 virus the authors described that the use of nanoparticle concentrations between 0.5 and 50 μM giving rise to an antiretroviral acitivty and, in addition, they observed a strong effect on the inhibition of the virus replication using a concentration of 50 μM of silver nanoparticles. On the other hand, the antifungal activity of silver nanoparticles of ca 13.4 nm using concentrations between 6.6 and 33 nM against yeast has been also studied, showing a better inhibition ability compare to that of a itraconazole control sample.

One of the most interesting properties from the point of view of potential applications of silver nanoparticles is their use on wound healing [100]. A recent study has shown that the activity of silver nanoparticles grafted dressing were more effective than the widely used silver sulfadiazine salt. The study showed that, apart from their antimicrobial characteristics, Ag NPs were able to control inflammatory response following burn injury. Taking into account the above mentioned properties a wide variety of applications using silver nanoparticles is being developed such as silver coated dressings, catheters, implants, *etc.* [101-106]. As an example, titanium implants coated with silver nanoparticles and hydroxyapatite by co-sputtering techniques has been developed in order to improve their bactericidal properties. The results showed a significant reduction in bacterial adhesion (*S. aureus* and *S. epidermidis*) on these implants. Moreover, this coating is biocompatible and non-toxic towards osteoblast-precursor cell [107].

Several recent reports reviewed the biomedical properties and applications of silver nanoparticles [108-110].

5. Conclusions

Ag NPs can be currently synthesized through different types of chemical methods in solution, allowing the design of silver-based nanomaterials of different size and shape or with specific coatings. This synthetic versatility makes these nanoparticles very attractive for potential practical applications. Thus, the bactericidal properties displayed by silver nanoparticles are a very active research field, not only because of the applications that can be derived, but also because the mechanism of action is still a matter of intense research. The latest reports suggest that this mechanism of action of Ag NPs is similar to the one displayed by silver salts, but using much lower concentration than the formers. It has also been shown that the antibacterial activity is closely related to the presence of Ag^{+} chemisorbed ions at the surface of the nanoparticles, probably due to a partial oxidation of the nanoparticle surface. Thus, one of the main advantages of silver nanoparticles is that they behave as Ag^{+} nanocarriers leading to a stable and slow ion release for long times.

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