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 REVIEW

Silver and Gold Nanoparticles: Challenges and Perspectives

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Abstract
Syntheses of gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) were evaluated with an emphasis on controlling the size, shape and stability of nanoparticles (NPs). Various reducing and capping agents of NPs from the sphere of chemistry and biology were identified together with their role in synthesis and controlled NPs properties. Those NPs were characterized with a variety of methods in order to determine the activities of nanoparticles and their applications in real life. In addition, carriers of these NPs in-vitro and in-vivo investigations and models of nanoscale interactions are presented. This review also addresses systematically the biomedical applications of AuNPs and AgNPs taking into account the actual challenges and perspectives in this research field.

Key words*:* silver nanoparticles; gold nanoparticles; syntheses, properties, nanoscale interaction models, biomedical applications.

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Introduction

The term of "nano" comes from Latin, which means "dwarf" and from the Greek term “nanos”, which means “little”. It is used as a prefix for size orders of 10^{-9} m ranging from 1 to 100 nm; particles of this size are called “nanoparticles”. The most popular and studied metal nanoparticles are gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) [1-8]. The most important uses of these nanoparticles are biomedical applications [1, 5-7], such as the treatment of cancer and infections occurring in dentistry and orthopedic surgery.

An example is the replacement of defect bones with hydroxyapatite, HAP, which is the main component of enamel and bone. Due to the high risk of infection, hydroxyapatite functionalization with silver nanoparticles is required [9, 10]. It should be mentioned that both silver nanoparticles and gold nanoparticles are of particular interest for science, nanotechnology and medical applications [11-20]. For example, the importance of AuNPs in nanotechnology and nanoscience is due to their ability to bind to amino acids, such as glycine, isoleucine, asparagine [14] cysteine [4, 15], lysine [17], arginine [19] and other biomolecules, as proteins [12, 16, 18, 20].

Generally, from the clinical and commercial point of view, the use of nanoparticles is due to their large contact surface and physico-chemical properties [21-27]. The relationships between the physico-chemical properties [28] and the toxic potential of nanoparticles are established by nano-toxicology [29].

The importance of nanoparticles in various applications is due to their optical, catalytic, magnetic and electronic properties [30-47]. The advantages of using nanoparticles are also related to, increased bioavailability, increased dissolution rate, increased surface area, low dosage and rapid therapeutic action [3].

Further, a characteristic of NPs is their shapes. A variety of shapes of gold nanoparticles are shown in **Table 1**. It starts from spheres, hexagons, triangles and continues to octahedron or clusters. All these forms appear colored red-wine, for the smallest in the case of AuNPs and light yellow in the case of AgNPs.

The AuNPs have been synthesized in a multitude of forms (Table 1), while in the case of AgNPs, they are usually found in spherical form [1, 3, 9, 10].

Preparation methods start usually from silver nitrate and chloroauric acid with polysaccharides, synthetic proteins and polymers as reducing or capping agents. In this context, it is very important to study the crystalline structure, shape and aspect ratio, size and surface area, aggregation, solubility and surface properties of the nanoparticles [29].

The impact of cytotoxicity of metallic nanoparticles is tested both in-vitro and in-vivo. One of the model membranes used basically to simulate interactions of nanoparticles with cell membranes is Langmuir monolayer. This is a single layer of molecules, oriented at the air/water interfaces, being insoluble in water and it involves an organic material spread over an aqueous surface in a Langmuir-Blodgett trough. They are made of amphiphilic molecules having a hydrophilic headgroup and a hydrophobic tail. Langmuir monolayers are formed at the air/water interface and can be made of L-α–dipalmitoyl phosphatidylcholine, DPPC, with or without procaine [48-50]. These ideal membranes are a simplified model of biological membranes, and can be transferred on solid supports as mono- or multi-layers. The advantage is that they provide quantitative information on the physico-chemical properties of lipid membranes [51-54]. They are usually flat bilayers [50, 51]. Other types are represented by polymer-cushioned lipid bilayers and hybrid bilayers [55-63].

Table 1. Shapes of AuNPs

Shape	*Reference*
Nano-sphere 	[4], [7], [9], [13], [15], [16], [18], [19], [39-42], [46]
Hexagonal 	[12], [18], [40], [44]
Triangular 	[18], [40], [43], [46]
Pentagonal 	[12], [18], [40], [44]
Star shape 	[45]
Nano-rod 	[39]
Nano-cube 	[40], [42]
Ellipsoidal 	[4], [13], [18], [40] [47]

Lipid membranes are a barrier in cellular processes and are present in living cells. They play a role in cell communication by exchanging ions and molecules and can be used in biotechnology. Generally, biological membranes as monolayers or multi-layers of various biomolecules oriented at the fluid interfaces, like fatty acids, phodpholipids and proteins are considered the models of nanoscale interactions [64-81]. Examples of interfacial models to unveil the nanoscale interactions are also given in various publications [82-150].

Considering this aspect, it is of major importance to conduct studies regarding the effect of AgNPs and AuNPs on Langmuir and Lamgmuir-Blodgett layers, named also artificial membranes. Because in-vivo studies are almost impossible to be directly performed, the model membranes, such as Langmuir-Blodgett layers, that mimic the behavior of natural membranes are very useful. Of great interest are the interfacial membranes to simulate the pulmonary alveoli major component, e.g., DPPC, which are spread at the water-air interface, as the Langmuir monolayers or as tranfered Langmuir-Blodgett films [50, 52, 54]. Thus, studies on these model membranes may show, for example, the effects of inhaled AgNPs and AuNPs, which are very important in toxicology [151, 152] and for public health.

Synthesis

Gold nanoparticles and silver nanoparticles can be synthetized by different methods, the most known being reduction of chloroauric acid ($HAuCl_4$) and silver nitrate ($AgNO_3$), respectively, with a large variety of reducing agents, from chemical or biological sources.

Two major methods for the preparation of AgNPs and AuNPs are shown in **Figure 1**, namely chemical and biological methods.

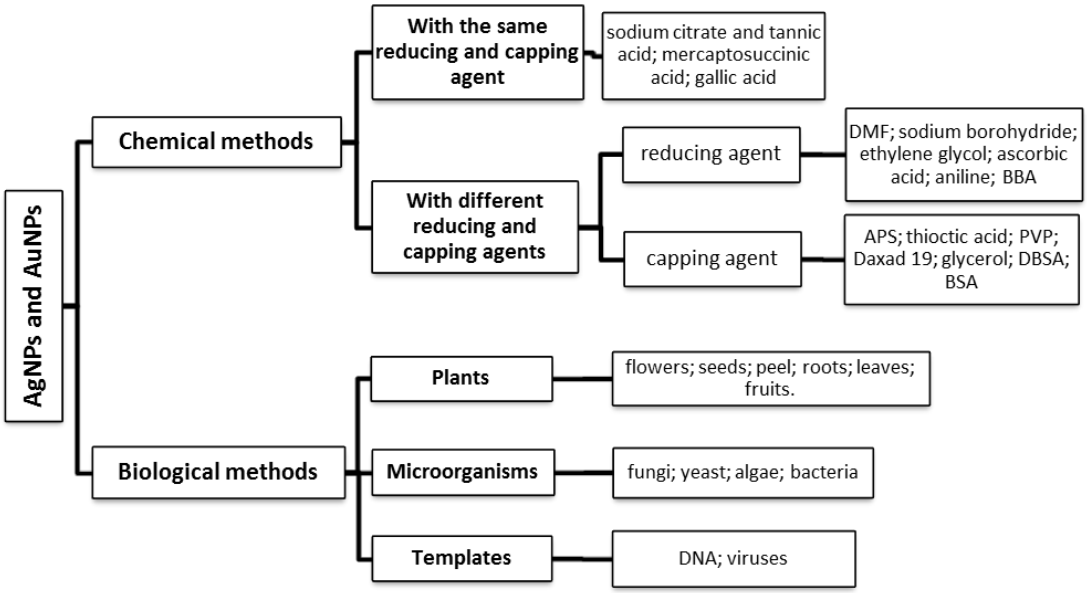

Figure 1. Methods of AgNPs and AuNPs synthesis

Chemical methods use either the same reducing and capping agent, such as trisodium citrate and tannic acid, or different reducing agent such as sodium borohydride and capping agents, such as thioctic acid (lipoic acid). The biological methods use plants and microorganisms.

- **Chemical synthesis of silver nanoparticles**

The literature study of the agents involved in the preparation of AgNPs as well the temperature conditions are highlighted in **Table 2** [153-167]. Depending on these factors, the shape and size characteristics of the nanoparticles are determined.

Recently, at 100^{o}C, by changing the reaction parameters (volume and concentration) AgNPs were obtained only with trisodium citrate as reducing and capping agent. The obtained AgNPs have an average diameter of around 23 nm, and 29 nm [153, 154] and about 6 nm [155].

Table 2. The preparation conditions and characteristics of chemical synthesis of AgNPs

Reducing agent	*Capping agent*	*Temperature/ Time of reaction*	*Particle characteristics*		*Ref.*
			Shape	*Size (nm)*	
Trisodium citrate	Trisodium citrate	70-100ºC	Spherical	29 (DLS) 23 (AFM)	[153], [154]
Trisodium citrate	Trisodium citrate	100ºC	Spherical	6	[155]
Trisodium citrate and tannic acid	Trisodium citrate and tannic acid	Room temperature	Spherical homogenous	11 ± 1; 68 ± 15 (DLS) 46 ± 19 (STEM)	[156]
		100ºC		40 ± 12 (DLS) 32 ± 6 (STEM)	
Trisodium citrate and iron (II) sulfate	Trisodium citrate and iron sulfate $FeSO_4 \cdot 7H_2O$	Room temperature	Spheroids	10-12 ± 5	[157]
			nanoplates	20-50 in the lateral dimension	
Ascorbic acid	Daxad 19	-	Spheroids	15	[158]
		-	spheroids, triangles	26	
Trisodium citrate and ascorbic acid	Glycerol	95ºC	quasi-spherical	30.0 ±5.2	[159]
Sodium borohydride	Sodium borohydride	Room temperature	roughly spherical	36 (DLS)	[160]
Sodium borohydride	Thioctic acid	Room temperature	Spherical	51(DLS) 44 (AFM)	[153]
Gallic acid	Gallic acid	Room temperature	Spherical	33.7	[161]
Mercaptosuccinic acid	Mercaptosuccinic acid	100ºC	Spherical	69 (DLS) 65 (AFM)	[153]
Ethylene glycol	PVP	120ºC	Spherical	18 ± 4	[162]
		100ºC		17 ± 2	
DMF	APS	60ºC	Spherical (few)	17.4 ± 3	[163]
		156ºC	Spherical (more)	19.7 ± 2	
		100ºC	Spherical	13 ± 1	[164]
Aniline	DBSA	90ºC	Spherical	8.9±1.1	[165]
Glucose	TEOS	50ºC	Spherical	12±5	[10]
Glucose	TEOS + L-asparagine	50ºC	Spherical	24.5±5.3	[166]

Trisodium citrate	tannic acid	100 °C	Spherical	AFM at different mole ratio 30±5 (1:7:2) 22±4 (1:3:0.2) 16±4 (1:7:0.2) 10±3 (1:20:0.1) STEM at mole ratio 31±7 (1:7:2) 10±5 (1:20:0.1)	[167]

Co-reducing agents, consisting of trisodium citrate and tannic acid, are used to obtain AgNPs with controlled size better than when using only trisodium citrate or only tannic acid [156, 167]. Temperature is a parameter that can influence the size of nanoparticles. For example, at 100˚C it turned out that the size of the nanoparticles is smaller than those obtained at room temperature. Also, at room temperature, small NPs were obtained by co-reduction with iron (II) sulfate and trisodium citrate [157].

Another example of co-reducing agents used to obtain AgNPs are trisodium citrate and ascorbic acid. The resulting nanoparticles have quasi-spherical shapes and the average diameter is around 30 nm [159].

Ascorbic acid alone has reducing properties on $AgNO_3$. The spherical and triangular shapes of NPs are stabilized with sodium salt of a heavy-weight formaldehyde sulfonate naphthalene condensate. The reaction time 1 or 7 minute results in different shapes and sizes of AgNPs [158].

By using N,N-dimethylformamide (DMF) as a reducing agent and 3-amino propyl trimethoxysilane (APS) as capping agent, spherical AgNPs with average diameter around 19 nm at 156^{o}C or 17 nm at 60^{o}C are formed. Glucose and TEOS is another example for obtaining spherical nanoparticles and further stabilizing their growth to 50^{o}C [166]. It should be mentioned that at low temperature the density of NPs is lower than at higher ones [163, 164].

Sodium borohydride and gallic acid is another example of a reducing and capping agents which results in approximately spherical forms of AgNPs obtained at room temperature [160, 161]. By adding thioctic acid as capping agent, AgNPs with an average diameter around 45-50 nm are obtained [153].

Most of the reaction parameters lead to the formation of spherical nanoparticles, the difference being given by the reactants used. At boiling temperature, $AgNO_3$ mixed with mercaptosuccinic acid as a reducing and

stabilizer agent produces diameters around 65 nm [153]. Ethylene glycol with polyvinylpyrolidone (PVP) formed AgNPs ranging in size from 15 to 19 nm [162] and aniline with dodecylbenzensulfonic acid (DBSA) formed AgNPs with diameters (around 9 nm) [165].

- **Biological synthesis of silver nanoparticles**

Biological synthesis of AgNPs uses also as a precursor agent $AgNO_3$ and the Ag^+ is reduced at Ag^0 with different extracts. The most widely used biological sources of reducing and capping agents are fungi and plants (Figure 1). A few examples of reducing and capping agents together with the specific conditions of reaction and resulted characteristics of AgNPs are highlighted in **Table 3** [168-175].

Table 3. The preparation conditions and characteristics of biological synthesis of AgNPs

Reducing and capping agent	*Plant/ microorganism*	*Conditions*	*Size (nm)*	*Ref.*
Culture extract	Fungi *Penicillium italicum*	pH 6 and pH 7 were found to be best condition for synthesis of fungal mediated silver nanoparticles	~33	[168]
Cell free-filtrate (CFF)	Fungi *Fusarium chlamydosporum* NG30 and *Penicillium chrysogenum* NG85 utilized as cell factories for the AgNPs production	pH 6.8 The CFF color of F. chlamydosporum NG30 and P. Chrysogenum NG85 changed to brown after mixing with AgNO3. This brown color indicates the AgNPs formation.	DLS 11.1 (PAgNPs) 16.1 (FAgNPs) TEM 6 to 26 (FAgNPs) 9 to 17.5 (PAgNPs) Spherical particles	[169]
Extracts of the phylloplane fungus	Fungi *Aspergillus tamari*	Visual observation of colour change from pale white to yellowish brown in the dark and light conditions.	40 (AFM)	[170]

Filtrate of filamentous fungus	Fungi *Fusarium oxysporum*	72h 28°C	57.6 ± 1.7 Spherical shape	[171]
Tea Polyphenols obtained from extract powder	*Camellia sinensis* (plant)	60ºC pH=10,5 stirred 15 min centrifuged 10 min	3.9 ± 1.6 (AFM) Spherical shape with little agglomeration (TEM)	[172]
Aqueous **leaf** extract	*Getonia floribunda* (plant)	Visual observation of colour change from yellow to dark brown 15–20 min pH 8	Spherical shape with ranges between 10 - 25 (AFM, TEM)	[173]
Phytochemicals from **seeds** extract	*Cuminum cyminum* (herbaceous flowering plant)	pH 10 25ºC Dark conditions and monitored visually for variation in color from pale yellow to reddish brown	16 ± 2 (TEM) with spherical shape	[174]
Polysaccharide isolated from the **fruit** rind which is a galactomannan	Pomegranate *of Punica granatum* (plant)	Stirred at 460 rpm for 24h and kept at 60ºC	~30 nm (TEM) with spherical morphology	[175]

The pH is of particular importance for both plant extracts and mushroom crops. Thus, in the case of fungi [168, 169], the optimal pH value is ~7, while for plants the optimal range is about 10 [172, 174].

The reaction can be carried out both at room temperature and at 60°C [175]. Furthemore, the presence or absence of light plays an important role for mushrooms extracts [170]. In addition to their NPs characteristics, they influence the reaction time required for silver to be reduced to its metallic form.

It is worth noting that, in the case of biological synthesis, the reaction time is several hours (between 24h and 72h) as compared to the chemical synthesis which are more rapid. The stable spherical shapes [169, 171-175], obtained from AgNPs have a controllable size and the main advantage is that they are small (~4 nm) [172].

- **Chemical synthesis of gold nanoparticles**

Table 4 briefly shows the literature study on the chemical method of synthesis of AuNPs, working conditions and the resulting characteristics [176-179].

Table 4. The preparation conditions and characteristics of chemical synthesis of AuNPs

Precursor agent	*Reducing agent*	*Capping agent*	*Conditions*	*Shape and size*	*Ref.*
$HAuCl_4$	Trisodium citrate	Trisodium citrate	pH 7.4 Anti EGFR antibody conjugated gold nanopartitcles	Nanospheres ~40 nm (TEM)	[176]
$HAuCl_4$	Trisodium citrate	Trisodium citrate	Boiling temperature	14.2 ± 2.6 nm (TEM) spherical or elliptical shape	[4], [14], [18], [19], [41]
$HAuCl_4$	Trisodium citrate	Trisodium citrate	100°C 20 min	Spherical	[177]
$HAuCl_4$	Trisodium citrate	Trisodium citrate	Turkevich method	Spherical 14±2 nm	[178]
$HAuCl_4$	Sodium borohydride	Cysteamine	(Room temperature)	Spherical 9±3 nm	
diazonium gold(III) salt	9-BBN	BSA	Overnight stirring at room temperature	Spherical ~7 nm	[179]
$AuCl_3$	Trisodium citrate + tannic acid	Trisodium citrate + tannic acid + potassium carbonate	Boiling temperature	Spherical or ellipsoidal shape 6.9 ± 1.3 nm (TEM) 5.0 ± 1.3 nm (TEM)	[4], [13]
$Na_3Au(SO_3)_2$ (sodium disulfitoaurate(I))	Trisodium citrate	Trisodium citrate	Boiling temperature	Spherical or elliptical, triangles, pentagons or hexagons shape ~ 48 nm 47.8 ± 5.2 (TEM)	[16] [18]

Usually the precursor in the synthesis of AuNPs is gold (III) chloride or chloroauric acid, but diazonium gold (III) salt can also be used. The latter can be reduced with 9-BBN (9-borabicyclo [3.3.1] nonane) overnight at room temperature and coated with bovine serum albumin (BSA) to obtain stable spherical shapes of AuNPs with a mean diameter around 7 nm [179].

Au^{3+} of chloroauric acid can be reduced to Au^0 with sodium borohydride and coated with cystamine to obtain spherical shapes of NPs with a mean diameter around 9 nm [178].

The most widely used reducing and capping agent is trisodium citrate with the best potential at elevated temperatures (around 100^{o}C), neutral pH and average reaction time (~20 minutes). Modifying the reaction parameters results spherical AuNPs shapes, having controllable dimensions of about ~9 nm, ~14 nm or ~40 nm [176-179].

- **Biological synthesis of gold nanoparticles**

The sources of $HAuCl_4$ reducing and stabilizing agents are composed of plant and bacterial extracts. Because the use of extracts from bacterial cultures is quite dangerous, we chose just to mention them, the emphasis being placed on extracts from different parts of plants. Thus, in **Table 5**, the literature study on the biological method of obtaining AuNPs, the working conditions and the shape and size is presented [180-186].

Table 5. The preparation conditions and characteristics of biological synthesis of AuNPs

Reducing and capping agent	*Plant/ microorganism*	*Conditions*	*Shape and size (nm)*	*Ref.*
Polyphenols from **flower** extract (Hypericum tincture)	*Hypericum perforatum* (plant) St. John's wort herba	pH 10 room temperature	4 to 6 At lower concentration of Hypericum the tendency is to form larger aggregates	[40]
Leaf extract	*Anacardium occidentale* (plant)	incubated overnight and visual observation of colour change from yellow to ruby red	Spherical ~40	[180]
Leaf extract	*Ficus retusa* (plant)	room temperature kept in dark place	Spherical 10-25 nm	[181]
Phytochemicals from **fruit** extract	*Tribulus terrestris* (plant)	Ambient conditions and visual observation of colour change from yellow to ruby red in time (6h, 8h, 10h and 12h)	spherical particles 7 (1mM $HAuCl_4$) and few triangular 55 (2 mM $HAuCl_4$)	[182]

Polyphenols from **roots** extract	*Angelica archangelica* garden angelica roots (plant)	room temperature 12h 2M $HAuCl_4$	spherical and few triangular 55 nm	[40]
		pH 8 room temperature	spherical or ellipsoidal shape 3 to 4 nm	
Phytochemicals from **bark** extract	*Salacia Chinensis* (plant)	visual method had a colour change from colorless to red wine colour (≤1 min).	distorted spherical shape 71.5 ± 0.8 nm (AFM) 80.33 ± 7.63 nm (zeta potential) spherical morphology with few triangular, hexagonal and rod-shaped particles 30-50 nm (TEM-SAED)	[183]
Polyphenols from **bark** extract	*Hamamelis virginiana* witch-hazel bark (plant)	pH 10 room temperature	triangular, cubic, pentagonal, hexagonal, heart shaped along with nearly spherical ones 4 to 6 nm	[40]
Pulp extract	Dragon fruit	room temperature and visual observation of colour change	Spherical, oval and triangular 10-20 nm	[184]
Whole plant extract aqueous extract of Rhazya stricta decne	*Rhazya stricta decne* (plant) (medicinal herb)	24ºC 1h visual observation of the color change from light yellow to deep pink after 1 h of incubation	highly dispersed particles 40 nm (TEM) 40-45 nm (DLS)	[185]
Dried, powdered **leaves**	*Cistus incanus* (plant)	24h in the dark, at room temperature 500 μL of the cistus extract per 2 mL of 1 mM $HAuCl_4$ (chosen for the further analysis)	popcorn – shaped 45 nm to 85 nm	[186]
Fresh Vegetable waste extract	mixed vegetable waste	incubated in an orbital shaker for 12-24 h	spherical and triangle shapes 10-70 nm	[46]

Similarly to the biological synthesis of AgNPs, the parameters used in the preparation of AuNPs such as pH, temperature, presence/absence of light and reaction time are varied. The novelty is that choosing certain plants and reaction conditions can produce spherical nanoparticles and various shapes such as triangles, stars, cubes, hexagons or even heart-like [180-186]. In addition to plant parts, reducing and capping agents can be taken from the bacterial extract, such as *Rhodobacter Sphaeroides.* In this case, the obtained AuNPs are spherical with the average diameter around 10 ± 3 nm [187].

- **The role of solvents in AgNPs and AuNPs synthesis**

Syntheses of silver and gold nanoparticles and their desired stability create challenges and perspectives for the new "nano" products [188]. In addition to the beneficial characteristics, there is also a less known aspect of the nanoparticles, namely the negative effects of long-term exposure, on living organisms and the environment. The synthesis methods are chosen depending on the reactants. It should be mentioned that although biological syntheses are increasingly used, the obtained nanoparticles are not indicated to be incorporated for medical use because there is a risk of contamination. Of course, there are other synthetic pathways that integrate toxic solvents. So, we can state that some ways of synthesizing of AgNPs and AuNPs, although they have promising results in terms of size and stability of nanoparticles, remain only at the stage of study without being applicable in practice.

- **Functionalization of AgNPs and AuNPs**

In order to improve the remarkable properties of AgNPs and AuNPs, the researchers perform functionalizations with different biomolecules (**Figure 2**). These include the essential amino acid, L-cysteine to stabilize the structure and improve biocompatibility in medical applications [189], organic compounds such as catechol to enhance antibacterial activity against both Gram-negative and Gram-positive bacteria [190] and porphyrin to increase the ability of AgNPs to be used as photodynamic therapy agents [191]. Functionalization is subject to new innovations such as the idea of a group of researchers in India who combined the fiber properties of silkworm cocoons with AgNPs for use in the treatment of wounds or skin regeneration [192].

In **Figure 2** are shown some examples of biomolecules that can functionalize AgNPs and AuNPs to improve biological and practical activity.

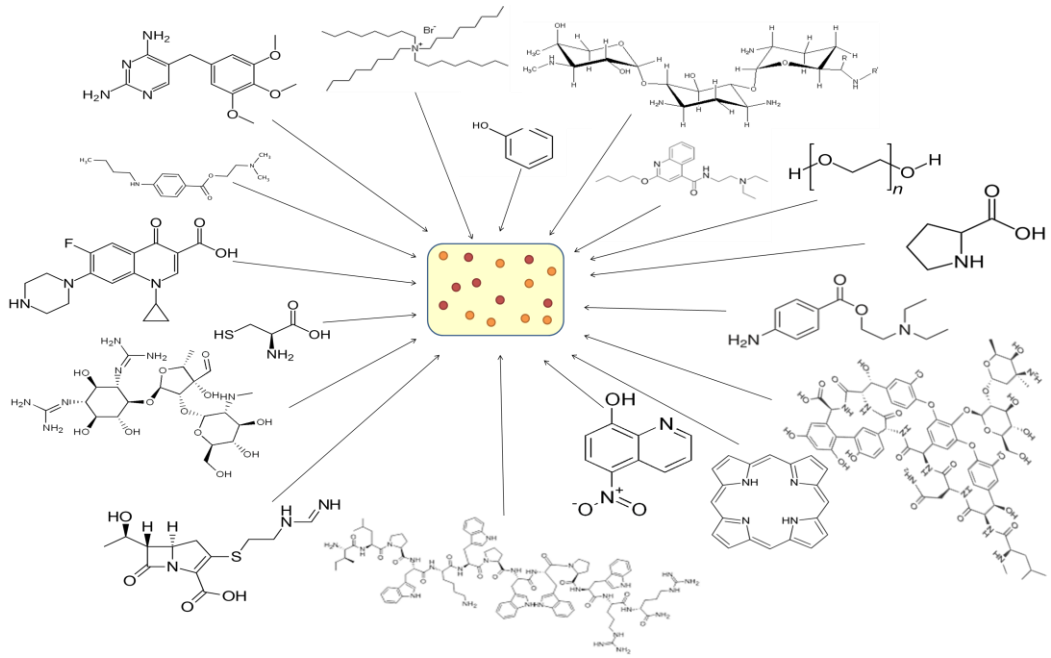

Figure 2. Functionalization of AgNPs and AuNPs

As we can see in the practical application of AgNPs, their antibacterial activity dictates the most uses, so it is normal that the enhancement of these characteristic is desirable. The most convenient biomolecules for the functionalized of nanoparticles are antibiotics, such as streptomycin, known to be effective in fighting bacteria. As a result of this conjugation, both Gram-positive and Gram-negative bacteria are more sensitive to the action of such conjugated systems than to the individual action of antibiotics [193]. An advantage of the functionalization of nanoparticles is the synergy effect. This has been demonstrated by researchers worldwide [194] who compared the antibacterial action of antibiotics (imipenem, ciprofloxacin, gentamycin, vancomycin, trimethoprim) or other compounds, such as procaine, dibucaine, tetracaine to that AgNPs and then to that of AgNPs functionalized with each of the antibiotics. Their results show that all antibiotics have increased their activity with the help of nanoparticles, which offers a chance to solve the problems of the acquired resistance. Another antibiotic is tetracycline and the functionalization of NPs with it proved to be beneficial. There was synergy effect, antimicrobial efficacy increased compared to AgNPs alone [195, 196]. The functionalization purpose of AgNPs is to fight against microorganisms that acquired antibiotic resistance. Compared to antibiotics AgNPs can also mix with HAP and nitroxoline being used against *Staphylococcus aureus* [197]. In the medical field, hydroxyapatite is

used for different bone implants, and by combining it with silver nanoparticles, an antimicrobial effect is obtained [198].

Although so far the functionalization of AgNPs has been studied and practiced, the researchers also turned their attention to the AuNPs, functionalizing them with various biomolecules in order to improve the qualities and to open new opportunities for use. The researchers wanted to increase the solubility of the complex of AuNPs with unloaded PEG in aqueous and non-aqueous solutions. They functionalized AuNPs with unloaded porphyrins derived from polyethylene glycol chains [199]. The fight against microorganisms and yeasts has recently been established in Italy as a topical issue. For this purpose, AuNPs was conjugated with indolicidin, their combined action being tested on a specific type of yeast. Knowing the effects of the two components of the pathogens, it is expected that together they will produce a synergy effect. It was found after 72 hours that the yeast was able to develop a defense mechanism against the system, which dramatically decreases the degree of apoptosis [200]. Research has shown that proline gives AuNPs extraordinary characteristics to fight against the aggregation of Hen Egg White Lysozyme [201]. In the clinical field, different types of bacteria are identified. In this context, the conjugation of AuNPs with vancomycin against Gram positive bacteria, such as *S. aureus*, is exploited. This is due to the ability of the system formed to differentiate between Gram positive and Gram negative bacteria [202]. In addition, the ideas of functional groups that can be added to AuNPs are vast, including the thiol (tetraoctylammonium bromide) group [203]. Paclitaxel can be used to functionalize nanoparticles in order to start the fight against cervical cancer cells [204], so functionalized NPs cover a larger area of uses.

The knowledge on the characteristic behavior of AgNPs and AuNPs functionalized with various biomolecules can help to maximize the biological activities in biomedical applications.

Characterization of AgNPs and AuNPs

After the synthesis of silver and gold nanoparticles, their characterization is needed in order to determine their morphology, size, shape, distribution, functional groups and other useful information for their subsequent use [205-208].

In order to provide these determinations, the researchers use modern characterization techniques that are presented in **Table 6** together with the characteristics offered by each method.

Table 6. Characterization methods of AgNPs and AuNPs

Abbre-viation	*Method name*	*Characteristics*	*Reference*
UV-VIS	Ultraviolet–visible spectroscopy	Indicates the presence of nanoparticles	[4], [19], [153], [156], [158], [160-165], [168-170], [172-175], [179-186], [205-208]
LSPR	Localized surface plasmon resonance spectroscopy	shape	[159]
TEM	Transmission electron microscopy	morphology and size distribution	[4], [10], [19], [40], [157-159], [163-165], [169], [171], [175-180], [183-187], [208]
HR-TEM	High resolution transmission electron microscopy	morphology, structure of NPs, shape	[173], [174], [182], [185], [205], [206]
SEM	Scanning electron microscopy	morphology of surfaces	[10], [157], [162], [164], [168], [171], [177], [187], [207]
SAED	Selected-area electron diffraction	pattern of the dispersed phases	[165]
STEM	Scanning transmission electron microscopy	size, size distribution and shape	[156]
AFM	Atomic force microscopy	Size, shape and agglomeration	[4], [10], [19], [40], [153], [161], [170], [172], [173], [181], [183]
FT-IR	Fourier-transform infrared spectroscopy	spectra/ compounds present on the surface	[40], [153], [160], [161], [169], [172-175], [180-182], [184], [185], [205-207]
ATR-FT-IR	Attenuated total reflection used in conjunction with infrared	spectra/ compounds present on the surface	[153], [158], [187]
DLS	Dynamic light scattering	size, size distribution and zeta potential studies	[4], [153], [156-157], [161], [169], [172], [175], [179], [183], [185]
CV	Cyclic voltammetry	electrochemical characteristics	[156]
EDX	X-ray energy dispersion	elemental composition and surface adhered biomolecules	[163], [171], [187], [205], [207]
XRD	X-ray diffraction	crystal structure	[162], [165], [171-174], [177], [180], [182-185], [206-208]

XPS	X-ray photoelectron Spectroscopy	the elemental composition, empirical formula, chemical state and electronic state of the elements, but also what other elements they are bonded to	[157], [172], [179]
XRF	X-ray Fluorescence Spectrometry	functional groups of capping molecules	[187]
XAS	X-ray Absorption Spectroscopy	functional groups of capping molecules	[187]
XANES	X-ray absorption near-edge structure spectroscopy	functional groups of capping molecules	[157]
SAXS	Small-angle X-ray scattering	Crystal structure	[157]
ICP-AES	Inductively coupled plasma atomic emission spectroscopy	detection and determination of chemical elements	[183]
ICP-MS	Inductively coupled plasma mass spectrometry	detection and determination of chemical elements	[164], [172]
GC-MS	Gas chromatography coupled with mass spectrometry	constituents present in the extract	[206]
NTA	Nanoparticle tracking analysis	particle size distribution	[171]
TGA	Thermogravimetric analysis	amount of residue on metallic surface	[172]

It is observed that some of these characterization methods are used more frequently due to accuracy, economic factor and complexity. In the diagram from **Figure 3** there are highlighted six of the most common characterization methods such as ultraviolet-visible spectroscopy, Fourier-transform infrared spectroscopy, and transmission electron microscopy, scanning electron microscopy, X-ray diffraction and atomic force microscopy being revealed by the specialized literature to be prefered in this field [209-241].

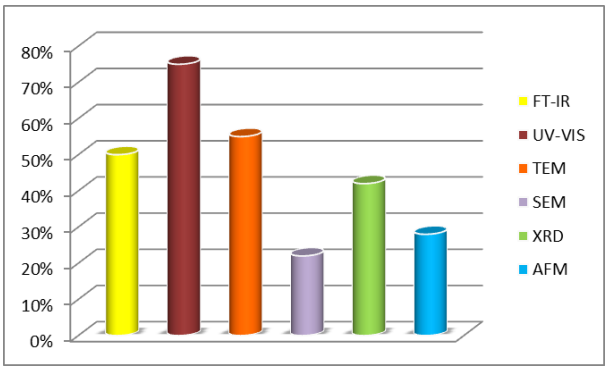

Figure 3. The most used characterization methods from the last 8 years (2012-2019)

Using these methods, researchers was able to determine the diameter of nanoparticles, the functional groups which are responsible of their formation, the absorbance, the crystalline structure, the morphology, the elemental composition and distribution of the nanoparticles [220, 222, 226-230].

Although dynamic light scattering is not one of the most commonly used methods, it is of great importance as it allows the zeta potential to be correlated with the electrophoretic mobilities of the nanoparticles. If the zeta potential is higher than 30 mV, the stability of the nanoparticles is certain [16, 231-235].

In vitro permeability studies using membranes [218, 219] where also performed. Because the results obtained vary with the time from the preparation, the researchers chose to keep them for few months to test their stability and properties [205, 236].

Biological activities of AgNPs and AuNPs

Both, AgNPs and AuNPs exhibit biological activities such as: antimicrobial, anticancer, antifungal, antiviral and anti-inflammatory, seen in **Figure 4**.

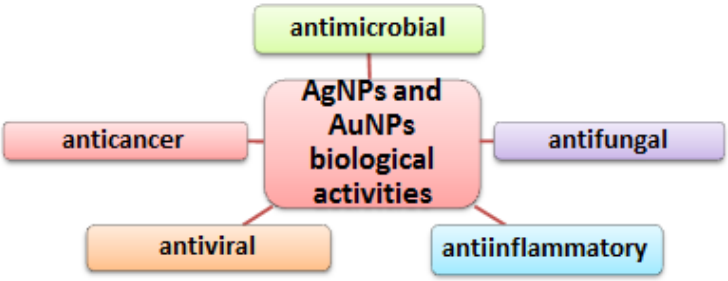

Figure 4. Properties of AgNPs and AuNPs

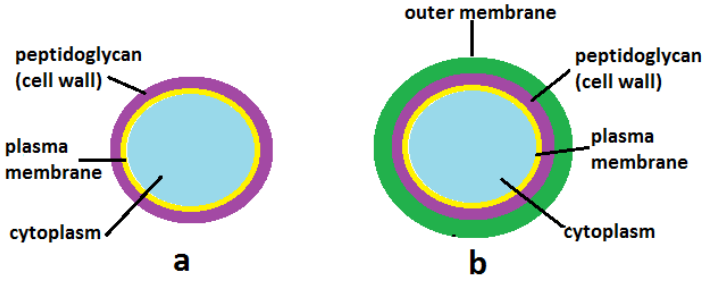

Figure 5. Membrane structure of bacteria a) Gram-positive and b) Gram-negative

The best known of these is antimicrobial activity, but their action depends on the types of bacterial: Gram positive or Gram negative [172]. In the **Figure 5** the difference between the two types of bacteria is shown. The presence of outer membrane at Gram negative bacterial made them not to become stained in the Gram test. This membrane acts as a barrier against nanoparticles. AgNPs stop the growth of the bacterial population by their predominantly bactericidal action, due to their ability to interfere with the defense mechanism of resistant bacteria making them susceptible [237].

Another biological activity of AgNPs is antifungal effect. In this way, the spore germination inhibitory effect was tested against mycotoxigenic fungi and different types of *Candida* [205].

The results from the test show that the antifungal activity of AgNPs is higher in the case of their conjugation with organic active molecules [205].

An antioxidant effect of AgNPs prepared with root extract of *Coleus forskohlii* is observed: the reducing of the oxidation state of molybdenum from Mo (VI) to Mo (V) [206].

The fight against cancerous tissues is one of the most important applications of AuNPs. This effect is based on the photothermal destruction of these cells due to the thermal energy generated by the light absorbing [238] and their bioconjugation [176]. It was observed that AuNPs with doxorubicin and resveratrol can be used against cervical tumor cell lines [7].

AgNPs exhibit anticancer activity against HEPG2 cells (liver cancer) [207], PC3 cells [239] (prostate cancer), and glioblastoma U251 cells [240]. Both AgNPs and AuNPs have potential against Caco-2 and HT-29 [241] (colon cancer) cells. In addition, AgNPs also play a role in tumor diagnosis, beside tumor targeted and controlled systems or tumor external activated treatment [242, 243].

A group of Chinese researchers accidentally discovered in 2009 that AgNPs possess anti-inflammatory activity in the treatment of post-operative incisions [244]. The anti-inflammatory properties can be tested *in vivo* using rats or human skin cells [245-247]. The NPs also exhibits an antiviral activity against viruses by improving the implementation of established drugs by inhibiting their development [248-251].

Recent studies have shown that not only the small size of nanoparticles is of particular importance in practice, but also their shape. Thus, spherical shaped nanoparticles up to 20 nm are desired, with higher activity than disc or triangular ones [252, 253].

Applications of AgNPs and AuNPs

AgNPs and AuNPs have a wide range of applications resulting from variety of practical branches. In the following, **Figures 6** and **Figure 7** show these aspects.

An example observed in **Figure 6** is that AgNPs can be applied as antifungal agent against *Candida* and *Xanthomonas* strains [254-256], and also in the combination with antifungal agents, like amphotericin B [205].

A group of researchers from Brazil created biogenic silver nanoparticles impregnated on cotton fibers with the aim to use it in medical environment and agriculture clothing [256] as a avoidance method of microbial spreading [256]. The textiles are a propitious medium for the fungi, bacteria and microbial development and transportation [257]. Having a particular importance in biomedical applications, the antibacterial properties of these nanoparticles make them optimal for use in the composition of suture wires and other textiles that can help the fight against multidrug resistant bacteria [255, 258, and 259]. Silver nanoparticles can be used as antitumor agents capable of decreasing progressive tumor cells [206]. Another domain of applicable silver nanoparticles is chemotherapy, in the treatment of American Cutaneous Leishmaniasis [171].

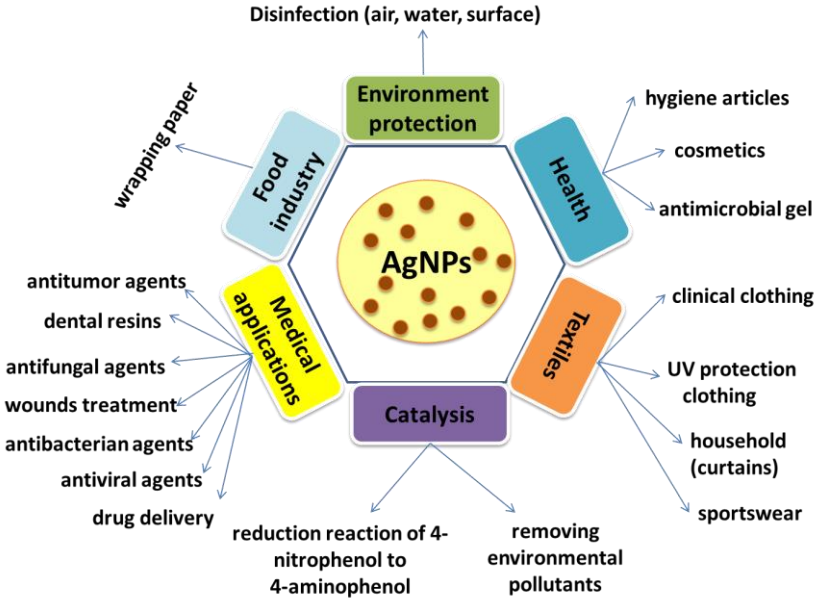

Figure 6. Applications of AgNPs

In case of immobilization on silica spheres, chemical manufactured silver nanoparticles get the ability to catalyze the reduction of organic dyes by sodium borohydride and enhance the cleaning of environmental pollutants [160].

Due to antimicrobial properties, silver nanoparticles can be incorporated into dental resin in order to prevent oral pathogens [164]. The AgNPs can be used at water filtration or purification, a very important application because there are a lot of microorganisms which have to be eliminated [260]. They can be used as such, or deposited on TiO_2 films. Antibacterial properties are not only used in the medical industry, but also in the food industry in the treatment of wrapping paper. The wrapping paper is designed in such a way as to keep the food fresh for an extended period of without the need for preservatives [261]. Based on the antibacterial properties of AgNPs, it has been successfully tested and found that these nanoparticles functionalized with polyethylene glycol, lipoic acid or reduced glutathione do not adversely affect blood platelets. This is encouraging because it shows the possibility of using AgNPs as drug carriers [262].

A revolutionary idea is the use of AgNPs and AuNPs in the treatment of wounds and infections [263], cancer [264], diabetic wounds, diabetes being one of the most widespread diseases in today's society [265-269]. In addition to incorporating nanoparticles into various creams for local applications, a study in India shows the possibility of using AgNPs in diabetic patients by reducing body weight, blood sugar level, total cholesterol, and triglyceride. A new approach to the extraordinary properties in the medical sphere has leads the researchers to use AgNPs to protect the liver from the harmful action of carbon tetrachloride. The substance is considered homologous to xenobiotics, which greatly damage the hepatocytes. Although, the study was only realized on mice, the results are promising [270]. In the **Figure 7** there are shown the AuNPs applications.

Due to their biocompatibility, they are used as carriers of drugs and in different diseases, increasing cell viability. Furthermore, their osteo-inductive potential recomand them for use in dental implants [183]. A way to fight cancer is to use angiogenesis inhibitors [271], and AuNPs have demonstrated to have this capacity, especially on the colorectal carcinoma [272-276]. Another type of cancer cells that AuNPs are able to lead to death are HepG2 cells and L02 cells [276]. Their anti-cancer potential was applied about breast cancer cells (MCF-7 and MDA-MB 231) and it was effective to inhibate cell proliferation and produce apoptosis [264]. Moreover, this special feature leads to another biomedical use, namely the fight against blindness by blocking angiogenesis in the retina [277, 278]. AuNPs also find their use in antidiabetic nanomaterials [269], in ecology as catalysts for the reaction of degradation of nitroaromatic compounds. It has been shown that gold has the effect of increasing the duration of the delay phase in multiplying the bacterium *Rhodobacter sphaeroides*. The same bacterium was used to synthesize AuNPs by reducing Au (III) to Au (0) [187] because this

method presents low cost and it is easy to obtain controlled growth environment in this way. *Rhodobacter sphaeroides* is a gram negative bacterium, purple and resistant to environmental conditions, having a known reducing character [187, 278-285].

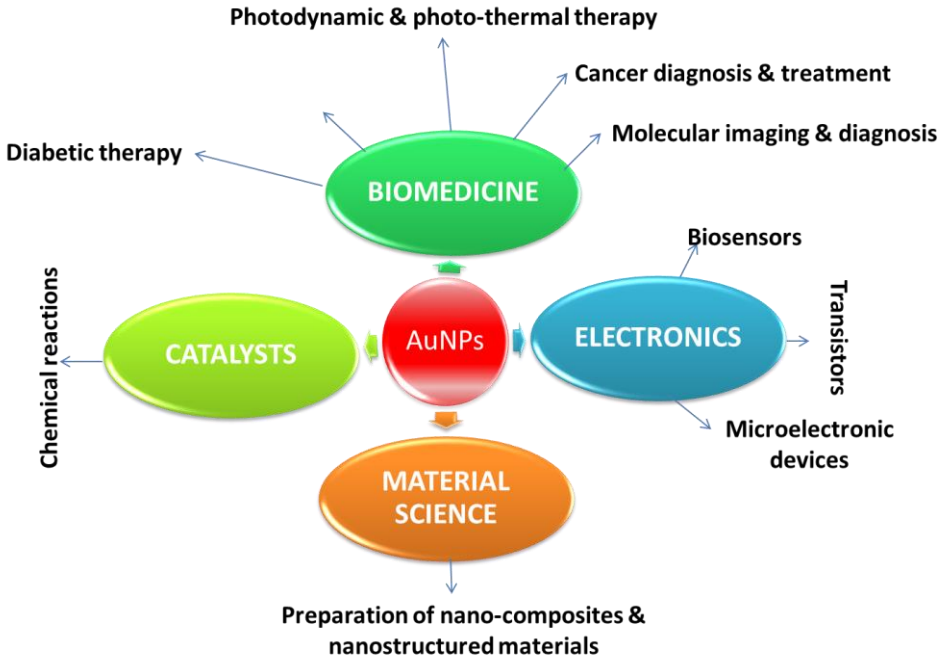

Figure 7. Applications of AuNPs

Another important use of AuNPs is the understanding of the mechanism of interaction of nanoparticles with lung surfactants. More specifically, how the monolayer of epithelial cells in the first layer of the pulmonary alveoli reacts to the integration of AuNPs. This is of particular importance in toxicology, as there are two variants: gold nanoparticles integrate into the monolayer without causing discomfort to the epithelial cells, which means that they are not harmful to the lungs, or conversely, to destroy this monolayer [151, 152].

The use of NPs single or in different complexes such as with antibodies and aptamers may include the fight against cancer cells. Aptamers are peptides/ oligonucleotides that specifically bind to a particular molecule, but must be specified as being able to attack the cancer cell thus protecting the rest of the body from side effects [176, 286, 287]. The alteration of malignant cells is, in fact, due to the energy produced by the absorption of light by the gold nanoparticles [286].

The AuNPs used in the electronics field have successfully demonstrated their role in flexible conductors, compatible with plastics [288] and for printing on

organic thin-film transistors [289]. At the beginning of ’90, two groups of researchers from California and China have embedded AuNPs in a digital memory. The results were promising with recording capacity of the device for a few days [290, 291]. Due to the ability to retain the biological activity of biomolecules immobilizing them, AuNPs are increasingly used as biosensors [292].

Both AgNPs and AuNPs can be used in the fight with various pathogens also in the case of orthopedics and dentistry. More specifically, hydroxyapatite or forsterite with adsorbed metallic nanoparticles of this kind can be applied. These two nanomaterials are used as carriers and the resulting composites are very important and usefull as coatings on metallic implants due to the well-known antimicrobial effect of these metallic nanoparticles [1, 7, 10, 12, 210, 215, 293-297].

We can also say that AuNPs have great versatility when it comes to the uses that people have discovered over time, which makes them more valuable than metallic gold. Gold nanoparticles have also emerged as attractive nanomaterials for biological and biomedical applications because of their physical and chemical properties.

Conclusions

This review is focused on metallic nanoparticles, AuNPs and AgNPs, and on various nanomaterials used for their delivery. The challenges and perspectives of gold and silver nanoparticles are also reviewed for their biological and biomedical aplications.

The syntheses of these nanoparticles are various. A thourough characterization of the NPs is needed to found the morphology, size, shape, distribution and functional groups because these factors determine their activities and applications.

In spite of numerous published papers which are controlling their synthesis and physicochemical properties, the intracellular delivery of nanoparticles remains a major challenge, and even the effect of size and chemical functionalization are still controversial. However, there is hope that this challenge can be overcome using designed nanomaterials and the interactions at nanoscale in self-assembled systems at fluid interfaces.

Functionalization of AuNPs and AgNPs with different biomolecules such as antibiotics, anesthetics, anti-cancer compounds, fatty acids, amino-acids and proteins provides their biological activities against pathogens and cancer, and the synergic effects can be revealed in different systems. Certainly, more biological experiments on animal models and cell lines are required to clarify the observed differences.

In a foreseen future, combining current methods of investigations from chemistry, biology and biophysics might better explain the present perspectives of metallic nanoparticles in medical and dental nanobiomaterials.

Abbreviations:

NPs: nanoparticles;
AuNPs: gold nanoparticles;
AgNPs: silver nanoparticles;
DMF: dimethylformamide;
BBA: bis-boric acid (Tetrahydroxydiborane);
APS: 3-aminopropyl-trimethoxy-silane;
PVP: Polyvinyl pyrrolidone;
Daxad 19: sodium salt of a high-molecular-weight naphthalene sulfonate formaldehyde condensate;
DBSA: dodecylbenzensulfonic acid;
BSA: bovine serum albumin;
9-BBN: 9-borabicyclo(3.3.1)nonane;
PEG: polyethylene glycol
TEOS: tetraethyl orthosilicate

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