Nanogold as NEMS platform: past, present and future

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ABSTRACT

Gold has been a biomedical material since ancient times. We shall review the historical uses of gold, in different forms as well as the properties of this metal, which make it very attractive for MEMS and NEMS applications. In particular, we will discuss the synthesis and physic-chemical characteristics of nano particles of gold, emphasizing the role of surface modification, which enables the nano gold to act as a true nano reactor or a nano platform to develop various functions at the nanoscale. Finally, we will describe the use of nano gold for drug targeting and disease detection.

Keywords: gold nanoparticles, nanorods, nanoshells, nanocages, nanomedicine, NEMS.

1. INTRODUCTION

Gold has been known since ancient times, its first uses date back to 4000 B.C, as fashion decorative objects.[1] This precious metal, its brilliance, natural beauty and luster, has been associated with the power, health, and also to have spiritual connections.[2, 3] The immense gold-bearing regions of Nubia in 1500 B.C. make Egypt a wealthy nation, and the gold was recognized as standard medium of exchange for international trade. The Egyptians were pioneers in the art of beating gold into leaf to extent its use, as well as alloying it with other metals for hardness and color variations.[1] In medicine, gold was considered to have immense medicinal value, since the metal that does not corrode, symbolizes immortality, hence early alchemist set out to produce potable gold, “the elixir of life”, the idea of the potable gold is found in China by the end of the third century B.C.; it was believed to produce longevity or immortality.[4]

Gold nanoparticles have been produced since ancient times by Egyptians and the Romans, although they probably did not know it. Documentation of uses of gold nanoparticles in ancient medicine date back 2000 years ago in India. Gold in traditional Indian Ayurvedic medicine as Swarna bhasmas (gold ash) has been characterized as globular particles of gold with average size between 56 to 57 nm. Swarna bhasmas was used to treat a wide range of diseases including rheumatoid arthritis, bronchial asthma, diabetes mellitus and other diseases of the nervous system.[2, 5] Another important application of gold nanoparticles was in the art of staining glasses. The British Museum holds one of the finest Roman pieces, the Lycurgus Cup, which shows different color, depending on whether or not light is passing through it; in the reflected light it is green, and in the transmitted light it is red. The Lycurgus cup is made of ruby glass containing one crucial ingredient, gold nanoparticles, typically 5-60 nm in size, which are responsible of the extraordinary color of the cup.[2, 6]

The first scientific study about the optical properties of gold nanoparticles smaller than the wavelength of the light was by Michael Faraday in 1857. He analyzed the variety of the resultant colors of gold, as the particle size change.[7] About fifty years later, Gustav Mie study the mathematical relationship of the nanoparticles size and its optical manifestations based on the solution of the Maxwell equations. The paper published by Gustav Mie is one of the most cited physical papers.[8] At the present time, Mie theory is cited in many papers related to nanotechnology and nanoscience.

In 1959, at the annual meeting of the American Physical Society Richard, Feynman give a lecture entitled “There´s plenty of room at the bottom”. He considered the possibility of direct manipulation of individual atoms as a more powerful tool to make the things, and the biology as an example to follow. Faraday also talked about the necessity to have new theories and new tools to study very small things. He visualized the necessity of make better electron

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microscopes, equipment with the capacity of see individual atoms distinctly.[9] Faraday hit at the potential for nanoscale design to influence a wide range of fields such as optics and electronics.

Gold nanoparticles have been proposed for use in practically all the fields of the science, especially in medicine, for diagnostics, imaging, chemical detection, therapy, prophylaxis, and hygiene.[10-12] Their unique physical and chemical properties; their size and shape dependent optical and electronic features, their plasmon resonance localized from the visible to infrared as well as its chemical stability, facile synthesis, and surfaces that can be readily modified with ligands containing functional groups such as thiols, phosphines, and amines have made the gold nanoparticles an important material for nanotechnology up to day.[13-15]

In this paper, we call review the past, present, and future synthesis and uses of gold main forms as nanospheres, nanoshells, nanorods and nanocages. An emphasis on the optical, physical and chemical properties of gold based nanostructures is made along with its potential applications on the development of novel nanoelectromechanical systems (NEMS).

2. FABRICATION OF GOLD NANOMATERIAS

The fabrication of nanomaterials generally can be done by two well defined approaches: top-down and bottom-up. The top-down approach starts with a bulk piece of material, which is then gradually or step-by-step removed to form objects in the nanometers-size regime. In the bottom-up approach all begins from atoms and molecules that get rearranged and assembled to obtain nanostructures.[16] The advantages and disadvantages of any approach depend basically on the technique used, the desired properties of the product, the quantity of the product to be required, and also the facilities of the manufacturer. The top-down approach for nanofabrication is the one first suggested by Feynman, while Eric Drexler, a pioneer in nanotechnology made emphasis in the molecular assembly (bottom-up approach) as a method to fabricate nanosystems.[17]

In this article, we will focus on the bottom-up approach, particularly in the chemical synthesis for the fabrication of gold nanomaterials. Chemical synthesis permits the manipulation of matter at the molecular level. Because of mixings at the molecular level, good chemical homogeneity can be achieved. Also, by understanding the relationship between how matter is assembled on an atomic and molecular level along with the material macroscopic properties; molecular synthetic chemistry can be tailor designed to prepare novel starting components.[18]

2.1 Gold nanospheres

Gold nanoparticles with spherical form (or almost spherical form) have been produced since ancient times in China, Egypt and Roma, where colloidal gold was first used for therapeutic and decorative purposes.[13, 19] Ancient colloidal gold it is supposed to be prepared using gold salts and all kinds of organic substances including urine as reducing agent.[20] Despite the long time that gold nanoparticles (AuNPs) have been used, the modern era of AuNPs synthesis began with M. Faraday in 1850s.[7] Faraday showed that gold chloride can be reduced by heat alone or by reaction with many different reagents including organic matter, phosphorus, tartaric acid, and others. For approximately fifty years the scientific community working with colloidal solutions was unconscious of Faraday´s work. It was not until Zsigmondy´s studies which take care on Faraday´s procedures for colloidal solutions.[21, 22] Zsigmondy formulated a method for preparing colloidal gold by using formaldehyde as reducer and combining his method with phosphorous reduction of Faraday he developed the "nuclear method" or seed-mediated synthesis, and invented the ultramicroscope which allowed to visualize the colloidal gold nanoparticles.[23]

Svedberg a pioneer in the research of electrochemical methods for the synthesis of gold nanoparticles use every conceivable reducing agent available in his time, like hydrogen, hydrogen peroxide, hydrogen sulphide, carbon monoxide, carbon disulphide, nitric oxide, phosphorus, phosphorus tertoxide, hypophosphoric acid, sulphur disoxide, sodium thiosulphate, sodium bisulphate, ferrous sulphate, tin, stannous chloride, acetylene, terpenes, alcohols, glycerine, aldehydes, acrolein, oxalic acid and oxalates, tartaric acid, sugar, starches, phenols, hydroxide acids, hydrochinones, hydrazines, hydroxylamines, protalbic acid, electric sparks, alpha, beta, gamma-rays, etc.[24, 25] Svedberg constructed his ultracentrifuge and was pioneered in ultramicroscopic research to study mainly particles size, particle size distribution and sedimentation.[26] W. Ostwald in his book published in 1917, showed several useful principles for the theoretical and synthesis of gold colloids.[20] Ostwald´s observations showed the importance of particle size in keeping particles dispersed, the acidity of the solutions, the spontaneous productions nuclei and the velocity of the growth of particles. Turkevich and co-workers in 1951 introduced the citrate reduction of gold ions (Au^{III}) to metallic gold (Au^0) in water to produce gold nanoparticles.[27] Turkevich and his group investigated the process of nucleation and growth in gold colloids and making use of the electron microscope were able to make an extensive study of the shape, mean size and size distribution including the factors than govern these properties. Frens in 1973 studied the effects of the concentrations of sodium citrate during the nucleation of the particles obtaining gold particles ranging from 12 to 160 nm.[28] He demonstrated that only changing the concentration of the citrate concentration different diameters of monodispersed gold nanoparticles can be obtained and come to the conclusion that the final particle size in the suspension is governed by the number of nuclei which form and growth into particles. In 1990´s Brust reported one step method for the synthesis of hydrophobic small gold nanoparticles bearing a surface coating of thiol, using two-phase (water-toluene) reduction of $AuCl_4$- by sodium borohydride in the presence of an alkanethiol.[29] The great advance with the Brust method is the possibility to obtain gold nanoparticles ranging from 1-3 nm and behaving like simple chemical compounds. The nanoparticles can be precipitated, redissolved and chromatographed without any apparent change in their properties.

Up to the present time, several modifications of the methods mentioned above have been published, the main objective of the techniques is achieve improvements in the monodispersity, fine control of the size, green synthesis, and obtain stable gold nanoparticles with surfaces ready to be conjugated with seemingly limitless chemical functional groups o ligands[2, 13, 30, 31] which made the nanoparticles a potential tool for a variety of applications, and also a promising nanomaterials for NEMS.

2.2 Gold nanorods

Nanorods are one dimensional nanoparticles. Unlike nanospheres, the optical properties, hydrodynamic behavior as well as phase behavior of gold nanorods are influenced by their shape anisotropy.[32] The absorption profile of gold nanorods includes two absorption bands: one due to light absorbed along the short axis and the other due to absorption along the long axis. As a result, they have plasmon-resonant absorption and scattering ranging from the visible to the near-infrared region, making them useful materials for sensing, photothermal therapy, and imaging.[33]

Predominantly, there are three methods for the synthesis of gold nanorods through wet chemistry, a) template method, b) electrochemical methods, and c) seeded growth method. Wet chemical methods are characterized for reduction of an aqueous solution of chloroauric acid where reduced gold atoms initially can form a sub-nanometer cluster particle in the first nucleation stage, leading to growth. Particle aggregation is prevented through vigorous stirring and by adding appropriate stabilizing agents.[32] Recent improvements in the synthesis of gold nanorods have allowed better uniformity, higher production, and simple production processes.[34, 35] Template method is considered the initial method for the synthesis of gold nanorods,[36] it was introduced by Martin and co-workers in 1994.[37-39] The method is based on the electrochemical deposition of gold within the pores of nanoporous polycarbonate or alumina template membranes. The diameter of the nanorod is determined by the pore diameter of the membrane, while the length can be controlled through the amount of gold deposited within the pores of the membrane. The electrochemical method for gold nanorods production was introduced by Wang´s group;[36, 40] this method provides a synthetic route for preparing high yields of Au nanorods. The synthesis is conducted within a simple two-electrodetype electrochemical cell. A gold metal plate is used as a sacrificial anode while the cathode is platinum plate. Both electrodes are immersed in an electrolytic solution containing a cationic surfactant such as, hexadecyltrimethylammonium bromide (CTAB). The anode is initially consumed forming $AuBr_4$-. These anions are complexed to cationic surfactants and migrate to the cathode where reduction occurs. An important factor for controlling the dimensions of gold nanorods according to Wang´s group is the presence of a silver plate inside the electrolytic solution. The redox reaction between gold ions generated from the anode and the silver metal leads to the formation of silver ions. The concentration of silver ions and their release rate determined the length of the nanorods. Seeded growth method was initially used to synthesize small seed gold nanoparticles to growth performed, mainly to make more monodisperse colloids.[41, 42] Brown´s group produce gold nanoparticles with diameters between 20 to 100 nm with improved monodispersity using hydroxylamine as surface catalyzer and sodium citrate as a reductant.[43-45] Brown´s group underlined that iterative hydroxylamine seeding leads to the formation of gold nanorods along with a small population of other gold nanostructures (5-10%).

The recent advances of gold nanorods up-to-date are based in the described methods.[34, 46, 47] CTAB alone or accompanied with an others surfactants is widely used as a morphological enlargement and as stabilizer of the gold nanorods. Free CTAB and CTAB-stabilized gold nanorods have been found to be cytotoxic. The main present efforts are focused on reaching non-cytotoxic gold nanorods, reproducible synthesis and novel surface modification.

2.3 Gold nanoshells

Gold nanoshells are spherical gold nanostructures, they are composed of a dielectric core covered by a thin gold shell, they possess large optical absorption and scattering cross-sections along with novel chemical and physical properties, which make them faultless candidates for the fabrication of novel nanodevices.[48]

Halas along with her group developed a general approach for making metal nanoshells based on molecular self-assembly and colloid reduction chemistry.[49] They used silica nanoparticles synthesized by Söber method[50] as dielectric cores and then organosilane molecules were absorbed onto these particles. The organosilane molecules bonded to the silica extent their amine groups outward as a new termination surface. Subsequently small gold nanoparticles (1-3 nm) are covalently bonded to the organosilane linkage molecules via the amine group. The gold decorated silica nanoparticles are used as nucleation sites for the reduction of an aged mixture of chloroauric acid with potassium carbonate in the presence of a reductant, obtaining silica particles covered by a thin gold shell. Several proposed improvements in the synthesis of gold nanoshells were proposed since then. Nowadays the synthesis of gold is accompanied by conjugates which make them biocompatible along with additional characteristics required for their effective application.[51, 52]

2.4 Gold nanocages

Noble-metal nanocages comprise a novel class of nanostructures possessing hollow interiors and porous walls.[53] Gold nanocages with controllable pores on the surface have been synthesized via galvanic replacement reaction between Ag nanocubes and $HAuCl_4$ in water.[54, 55] Ag nanocubes bearing truncated corners react with $HAuCl_4$ in water. The pore size is mainly determined by the molar ratio of chloroauric acid to silver. Silver nanostructures with controlled morphologies can be produced through polyol reduction, where $AgNO_3$ is reduced by ethylene glycol to generate silver atoms and then nanocrystals or seeds. Subsequent addition of silver atoms to the seeds produces the desired nanostructures through controlling the silver seed crystalline structures in the presence of the protection of poly(vinylpyrrolidone), a polymer that is capable of selectively binding to the (100) surface . The silver nanostructures, used as a sacrificial template, can then be transformed into gold nanostructures with hollow interiors via the galvanic replacement.[55, 56] The hollow interiors and wall thickness of the resultant gold nanocages could be readily controlled, to very high precision, by adjusting the molar ratio of silver to $HAuCl_4$.

Gold nanocages to be useful in biomedical applications such as cancer diagnosis and treatment must have long body circulation times and accumulate at sites of interest. Their convenient compact size, relative bioinertness and appropriate bioconjugation makes them ideal for nanomedicine applications.[53, 57]

3. OPTICAL AND CHEMICAL PROPERTIES OF GOLD BASED NANOSTRUCTURES

Properties of the nanomaterials basically depend on their size, shape, composition, inter-particle interactions, and the properties of the surrounding medium. Gold based nanostructures are probably the most studied material. Their facile synthesis, stability, controllable size, narrow size distribution, excellent biocompatibility, optical properties in the visible and the near infrared region, and their controllable surface chemical properties make them as one of the most valuable material for nanotechnological applications.[58]

The most habitual form of the nanostructures is the spherical or nearly spherical form since this shape has the smallest surface area relative to objects.[11] Spherical gold nanoparticles present their absorption and scattering properties at the visible light region, making them easily observable by the naked eye or detectable by inexpensive instruments such as UV-Vis spectrophotometers. Small gold nanoparticles (<5nm) have mostly optical absorption characteristics, and as the particle size is increased the scattering properties become the most significant while their optical absorption become irrelevant. Almost for any applications of gold nanoparticles is required their conjugation with ligands or functional groups. The conjugation protects against the agglomeration, and also provides new novel properties. In general, the conjugation of small gold nanoparticles is easier and more stable than the conjugates using bigger gold nanoparticles.

Gold nanorods, nanoshells and nanocages have attracted the attention of the scientific community owing to their fascinating chemical and optical properties; their absorption and scattering properties can be tuned from the visible to the near infrared light region. Gold nanorods are of particular interest because of their anisotropic shape; they possess two distinct plasmon bands: one owing to its transversal mode and the other owing to its longitudinal mode. As the rod length increases, its longitudinal band is red shifted, meaning that optical properties of gold nanorods controlled simply by changing rod length. The chemical properties of gold nanorods are mainly governed by their high surface area to volume ratio as well as its gold atom packing differences between the end faces and the side-faces.[33] Gold nanoshells possess a remarkable set of optical, chemical and physical properties, which make them ideal candidates for applications in nanomedicine. Gold nanoshells have larger optical absorption and scattering cross-section[59] than gold nanorods, which make them ideal for therapeutic and imaging applications. For smaller nanoshells, absorption dominates scattering, whereas for larger nanoshells scattering dominates absorption.[48] It is therefore possible to design nanoshells for dual absorption and scattering properties by appropriately choosing the relations between the diameter core and the thin gold shell. Gold nanocages comprise a novel class of novel nanostructures, having a hollow interior and a thin, porous but robust wall. Their localize surface plasmon resonance can be tuned by varying their size; small gold nanocages (edge length < 45 nm), light absorption predominates; however, light scattering prevails with larger gold nanocages.[60] In contrast to gold nanorods and gold nanoshells; gold nanocages can be fabricated in a smaller size together with a strong absorption and scattering properties. Au nanocages have been synthesized with dimensions smaller than 50 nm to potentially facilitate targeted delivery.[61] Gold nanostructures are very important for medicine owing to their optical and chemical properties. Gold nanostructures with optical resonances in the near infrared region, particularly in the “water region” are important for a wide variety of medical applications owing to the fact that in this region the highest physiological transmissivity is presented.[62]

Almost for any application, the gold-based nanostructures should be conjugated with ligands containing functional groups such as thiols, phospines, and amines which exhibit strong affinity for gold nanostructures. These functional groups can be used to bond proteins, oligonucleotides, aptamers, antibodies and other entities. Preparing stable gold conjugates basically depend on three interactions: a) the electronic attraction between the negatively charged gold nanoparticles and the abundant positively charged sites on the protein molecule, b) an adsorption phenomena involving hydrophobic pockets on the protein binding to the metal surface, and c) the potential for covalent binding of gold to free sulfhydryl groups forming covalent bonds.[63] Covalent dative bond between Au-S is the most preferable since is the most stable.

4. NANOGOLD AS NEMS PLATFORM

Highly sensitive, selective and theranostic devices working at the molecular level are some of the challenges for the future medicine. Gold based nanostructures could play an important role to overcome these goals.

Nanoelectromechanical systems (NEMS) can be operated as ultrasensitive mass sensors, ultra-high-frequency resonator, and can also be used to explore fundamental physics phenomena such as nonlinear damping and quantum effects in macroscopic objects.[64] Scientifics have described several opportunities in research about NEMS, and also challenges. NEMS offer response with extremely high fundamental resonance frequencies (greater than 1 GHz),[65] active masses in the femtograms, mechanical quality factor (Q) in the tens of thousands,[66] characteristic minimum power level in the order of 10^{-7} W, heat capacities far below a yocto calorie, and the superior characteristics tend to increase. Talking about the challenges, the ultimate limits of NEMS performance is the pursuit of ultrahigh Q, high Q directly translates into low insertion loss. Experimental evidence shows that Q seems to scale downward with linear dimension, like volume-to-surface ratio, it seems clear that the mechanical properties of the smallest NEMS devices will deviate greatly from those in bulk. It may prove quite difficult to achieve ultrahigh Q with such extreme surface-to-volume ratios, if only conventional patterning approaches are utilized. Thus surface passivation will undoubtedly become imperative for nanometer scale devices.

Among NEMS devices, nanomechanical resonator have been recently highlighted for their unprecedented dynamic characteristics, they can easily reach high and ultrahigh frequencies, these frequencies can be achieved by scaling down the size of the resonator since the resonant frequency is proportional to its length (L^{-2}), besides the high frequencies capabilities, the ability of the resonator to sense or detect physical quantities is closely related to its resonant frequency.[67] In recent years, nanomechanical resonators have attracted the scientific attention owing to their capability of label-free detection of selective biological and molecules at low concentrations. Cancer has been one of the most studied diseases using nanodevices. Nanomechanical devices are ideal candidates to be used as ultra high early detection sensors or even able to detect a single molecule. NEMS can easily overcome the present diagnostic assays limitations, serve as lab-on-in-chip biosensors, and also provide detailed mechanisms of biochemical reactions and cell functions.[67, 68] The general working principle of the nanomechanical resonator is based on the molecular adsorption onto a resonator surface which increases the effective mass, and consequently decreases the resonant frequencies of the resonators. However, this principle is insufficient to provide fundamental insights into resonator-based molecular detection at the nanoscale; this is due to recently proposed novel nanoscale detection principles including various effects such as surface effects, nonlinear oscillations, coupled resonance, and stiffness.[67]

Nanoelectromechanical systems are generally fabricated using carbon nanotubes, graphenes, and semiconductors. Nanomechanical resonators made entirely from metals are rarely reported. Metal nanomechanical resonators, particularly using gold based nanostructures could extend NEMS applications because their excellent optical and chemical properties. In addition, their excellent biocompatibility, unchallenging fabrication as well as their well established surface functionalization or conjugation. Localized surface plasmon resonances of gold based nanostructures are very sensitive to surface modifications, refractive index of the medium and interparticle interactions. Up-to-date, several techniques have been developed for biological and chemical detection using gold based nanostructures. Gold nanostructures alone or in conjunction with other materials could overcome the unwanted chemical and physical properties, like instability, reactivity, and durability of the present nanoelectromechanical resonators. These undesired properties become more significant under real environmental conditions.

Gold based nanostructures have been successfully conjugated with aptamers, oligonucleotides, antibodies, DNA, drugs and many order kind of molecules[2] which passivate the high surface area to volume ratio, which is important to obtain high Q factors[67] or small rates at which the NEMS loses energy per vibrational period due to interactions with its environment. Q factors are critical to the sensing performance of NEMS and conjugated gold based nanostructures could enhance Q factor even at room temperature. Furthermore, the ligands or functional groups attached to the surface of gold nanostructures could increase the sensitive and selective of the NEMS. Moreover, the resistance to oxidation, the absence or poor morphological defects, and the well studied physical properties of the nanogold serve as additional arguments to make gold a promising candidate to nanoelectromechanical systems.

The present and upcoming applications of gold nanostructures and NEMS in medicine are extremely broad. Gold nanostructures have been proposed for use in diagnostics, prevention, and treatment of diseases. One of the most exciting areas of nanomedicine is the development of nanodevices for theranostics, which refers to a combination of diagnostics and therapeutics in single nanoparticles. Theranostics nanodevices have been described as the next generation nanomedicines and have the potential to dramatically improve the therapeutic outcome of drug therapy and lead to the development of personalized medicine, where the device may be tailored for treatment of individual patients on the basis of their genetic profiles.

5. CONCLUSIONS

Nanoelectromechanical systems have proved to be successful in identifying chemical and biological entities at very low concentrations or even have molecular resolution. Gold based nanostructures have a vast of promising applications in sensing, detection, therapeutic and theranostic applications owning to their manipulable optical, chemical and morphological properties. The use of nanogold based nanostructures in NEMS could improve the benefits of nanoelectromechanical devices. Making use of gold based nanostructures to fabricate nanomechanical resonators significant enhancements in the sensibility, selectivity, label-free applications, real-time and fast studies could be reached. Furthermore, taking advantage of traditional spectroscopies together with the novel properties of nanogold structures and gold nanoarrays novel NEMS devices can be fabricated. Finally, gold based nanostructures alone or together with other materials can improve the working characteristics of NEMS under environmental or real conditions.

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