The application of gold nanoparticles in biomedicine

Anqi Hua*
Beijing Luehe International Academy, Beijing, China
*Corresponding author:luheinternational@luheintl.com

Abstract. In the past few years, nano particles are one of the most popular scientific research fields. It has been widely used in biomedical, optics, electronics and other areas. Gold nanoparticles are quite different from other nanoparticles. Their practical application has a very long history, which has been recorded in ancient Rome. By using their scattering property, gold nanoparticles are added to glass products to make them not only have various colors, but also have photochromic effect. With the development of related fields such as new organic metal chemistry, nanotechnology, and complex research, gold nanoparticles are listed as an important research object in biomedical applications. The shape and size of gold nanoparticles have a direct impact on their optical properties and applications. Therefore, exploring the preparation method to achieve controllable preparation is of great significance for the research of gold nanoparticles. Moreover, the application research of nano gold in biomedicine filed has developed rapidly, especially in recent years. Gold nanoparticles play an increasingly important role in disease detection, targeted therapy, drug detection, enhanced device performance, and imaging. This work mainly discusses the preparation method of gold nanoparticles and its applications in biomedicine field.

Keywords: Gold Nanoparticles, Sensors, SERS, Detection.

1. Introduction

With the development of science and technology, nanomaterials have been widely used in high-resolution imaging (NMR, fluorescence) of semiconductor, metals, polymers and carbon-based nanoparticles. Nano-technology is increasingly important in disease diagnosis, drug delivery, pathogenic testing and targeting of cancer, and food safety, environmental monitoring and other fields. The surface plasmon resonance effect, size effect, surface effect and dielectric confinement effect of noble metal nanoparticles make them have unique optical, electrical and catalytic properties, which make them suitable for biomedical detection, environmental energy, biosensing, optical communication. And surface-enhanced Raman and other fields have been widely used. Gold nanoparticles are one of the noble metal nanoparticles. Their diameters range from 1 to 100 nanometers, and they have high electron density, dielectric properties and catalytic properties. Therefore, gold nanoparticles have excellent prospects in biomedicine. At present, the treatment of some diseases in the middle or late stage is particularly difficult. Therefore, the early detection of diseases is particularly important. The introduction of gold nanoparticles in some detection processes can not only enable the prime minister to be observed with the naked eye, but also more quickly. Furthermore, gold nanoparticles not only make great contributions to disease diagnosis, but also play a great role in drug detection. Nowadays, the drug problem has become a serious problem faced by the whole world. The proliferation of drugs not only affects abusers. The mental and physical health of individuals has caused great harm to national stability, social economy and public health. The strong dependence and death risk of drugs have attracted great attention from countries all over the world, but with the emergence of new drugs, it is difficult to apply existing detection technology to on-site detection. The SERS of AuNPs has great application prospects in the field of drug detection due to its many advantages such as non-damage, high sensitivity, and fingerprint recognition. In this paper, the preparation methods of gold nanoparticles and their applications in the field of disease detection and drug detection are reviewed based on relevant research data.

However, gold nanoparticles with different morphologies will have different effects, so it is extremely important to prepare gold nanoparticles with controllable morphology and excellent performance. The study found that different preparation methods yielded gold nanoparticles with different morphologies, ranging in color from yellow to black depending on the diameter. The particle size of 2-5nm is yellow, the particle size of 10-20nm is wine red, the particle size of 30-80nm is purple-red, and the particle size of 520-530nm is black. There are two methods for preparing gold nanoparticles: physical method and chemical method. Physical methods are divided into ultrasound-assisted methods and laser ablation methods. Currently, chemical methods are widely used. The chemical methods mainly include redox method and electrochemical method, seed growth method and phase transfer method. In view of this, the preparation method of gold nanoparticles and its progress in disease detection and drug detection will be introduced below.

2. Preparation of AuNPs

2.1. Redox method:

Nanoparticles are generated by reducing auric chloride ($HAuCl_4$) using stabilizers (reducing agents like sodium borohydride, sodium citrate, white phosphorus, ethanol, hydrogen peroxide, etc.), first dissolve gold chlorate, then rapidly stir the solution to dissolve and add Reducing agent, reducing Au^{3+} ions to neutral gold ions.

The method developed by Frens et al.[1] is used to control the size of gold nanoparticles, which is based on the reduction of sodium citrate, changing the ratio of the initial concentration of sodium citrate and changing the dosage to obtain 16-18 nm gold nanoparticles with good monodispersity. This method is currently very popular, and the method for preparing gold nanoparticles by reducing chloroauric acid with sodium citrate has the characteristics of simple operation, green development, easy synthesis and high stability.

2.2. Electrochemical method:

In the electrochemical preparation of gold nanoparticles, the reduction process is guaranteed by the free electrons generated by the solution. Liu et al.[2] Because PVP can be electrolyzed to form degradation products with different reducibility in a local acidic environment (anode) by an acid-catalyzed mechanism or in an alkaline environment (cathode) by a base-catalyzed mechanism, the poly(N-vinylpyrrolidone) (PVP) Gold precursor ($HAuCl_4$) was added to the electrolytic aqueous solution of) and KNO_3 to prepare gold nanoparticles (30-50 nm) with different features, and the pH changed greatly near the cathode and anode. Therefore, this method is not only beneficial to control the shape and size of AuNPs, but also friendly to environmentally, simple and pollution-free. However it requires high equipment and is not easy to control due to environmental influences.

2.3. Phase transfer method:

There are two main methods for the preparation of AuNPs by the phase transfer method. One is the metal ion phase transfer method, which transfers the chloroaurate ions in the aqueous solution to toluene containing alkyl mercaptan under the coating of tetraoctyl ammonium bromide. In the system, the reducing agent is then added to the organic solvent. Brust et al.[3] used this method to obtain AuNPs of 5-30 nm with very good monodispersity. The other is the AuNPs phase transfer method, in which Sarathy et al.[4] is catalyzed by an acid in a gold salt solution to obtain a superstructure of 1-10 nm gold particles, which is then transferred to thiol-containing toluene for stable existence. The gold nanostructures prepared by this method are ordered, monodisperse and stable. But it is more complicated and the consumption of organic solution is large.

2.4. Seeding method：

The seeding method adopts a green, efficient and controllable synthesis method to obtain gold nanoparticles of different sizes with good dispersion, uniform size and stable properties. In the first step, a strong reducing agent is used to reduce Au^{3+} to small gold particles as seeds. ; In the second step, in another solution containing Au^{3+}, Au^{3+} is reduced to Au^{+} with a weaker reducing agent, and then mixed with the seed crystal solution. Au^+ is further reduced to gold particles on the already formed seed crystal. Hu Qing et al.[5] synthesized small gold nanorods by seed growth method, and their morphology and properties could be regulated by changing the synthesis parameters. Small gold nanorods with an aspect ratio of 3.8 were prepared. The analytical balance weighed 0.328 g (0.1 mol/dm^3) of CTAB and dissolved it in 9 cm^3 of pure water, and then added 0.01 mol/dm^3 $HAuCl_4$ solution 0.5 cm^3 and 0.01 mol/dm^3 silver nitrate ($AgNO_3$, 0.1 cm^3 of analytically pure) solution and 0.2 cm^3 of 1 mol/dm^3 HCl solution, mix them evenly, and then add 0.08 cm^3 of 0.1 mol/dm^3 ascorbic acid (analytically pure) solution, then, the color changes of the solution from deep yellow to colorless. After stirring with a magnetic heating stirrer for 2 min, 1 cm^3 of the seed solution was added quickly. The resulting solution was allowed to stand overnight at room temperature, and the preparation process was shown in the (Figure.1), The final solution was centrifuged at 12000 for 30 min with a centrifuge (model HC-2518), the supernatant was discarded, a certain amount of pure water was added for redispersion, and gold nanorods were obtained after centrifugation twice. Min Zou et al. [6] used cationic pyrrolidine amphiphile (CmCsCmPB) as a stabilizer to study the effect of surfactant hydrophobic tail chain and spacer length on the morphology of gold nanoparticles by seed method, and successfully prepared gold nanoparticles. Gold nanorods with good monodispersity.

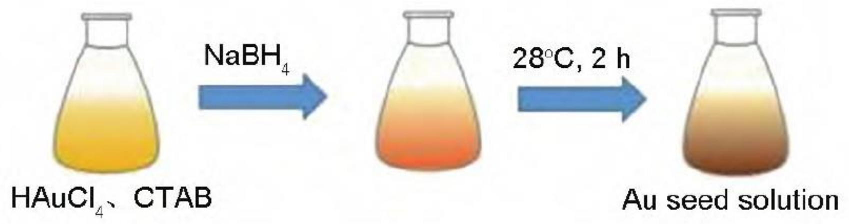

Figure.1 A diagram for the preparation of gold seed solution.[5]

3. Application of gold nanoparticles in disease diagnosis

The early diagnosis of disease is particularly important in the process of treatment. The high molar absorption coefficient and good biocompatibility of gold nanometers make it attract much attention in the fields of biology and chemistry.

3.1. HIV detection

Labeling [7] and surface functionalization of gold nanoparticles based on copper oxide, the nanoparticle "click" reaction is a new immunoassay method that sends a signal that can be observed directly without the aid of tools. The method uses Cu(I) as a catalyst to make the alkynyl and azide groups on the surface of AuNPs undergo Click reaction, and the color change of solution from red to purple through the aggregation of AuNPs in solution. In this research work, copper oxide nanoparticles are labeled on the secondary antibody for antigen-antibody reaction, and then copper ions are released through dilute acid to catalyze the Click reaction, It leads to the aggregation of AuNPs, so the detection of target protein (Figure 2) can be done by observing the color change of the solution after the aggregation of gold nanoparticles. The way can analyze HIV-positive serum samples, and the effective analysis of negative and positive samples was successfully achieved.

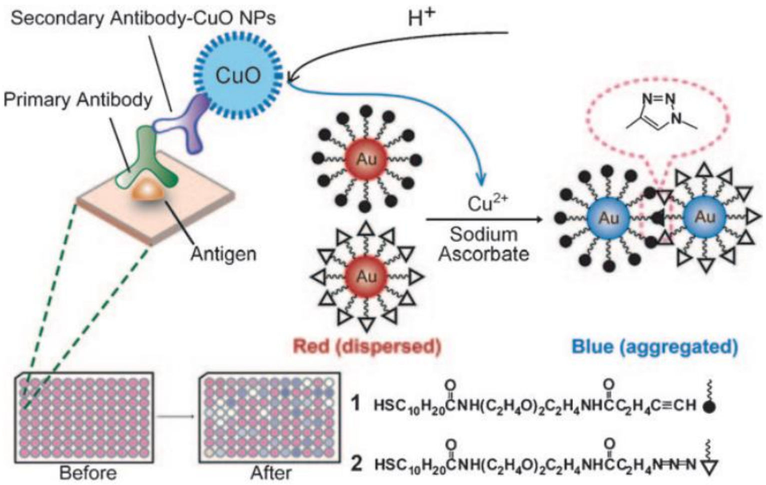

Figure 2. Methods for CuO-labeled antibodies and click chemistry immunoassays.[7]

3.2. Detection and treatment of liver cancer

The most common disease of the liver is liver cancer, and the subsequent treatment is greatly hindered due to insufficient early diagnosis. Due to the strong optical scattering and absorption properties of gold nanoparticles, they can be used as optical probes for the study of biological cell imaging. Due to the changes in DNA, respiratory pathways and cell surface receptor distribution, diseased cells can be distinguished from normal cells. But currently,Ultrasound, CT and MRI scans do not detect tumors until they grow to about 5 centimeters in diameter, when the cancer cells are resistant to chemotherapy and difficult to remove. Christoph's et al.[8] has used the biocompatibility, non-toxicity, and ability to amplify the Raman spectral signal of gold nanoparticles by combining charged polymer coating of gold nanoparticles with X-ray scattering imaging technology, through X-ray diffraction. The ray-scattering signal distinguishes the tissue cells labeled with gold nanoparticles from normal tissue cells, and tumor-like masses as small as 5 mm are found. This method provides an efficient method for the detection of early-stage liver cancer and marks the first time that AuNPs have been used as an X-ray scattering signal-enhancing factor to image tumor-like substances. Tan Manman et al.[9] designed a novel multifunctional gold nanocomposite GAL-GNR-siGPC-3, the nanocarrier contains D-galactose (GAL) and siGPC-3, which can induce the targeted silencing of GPC-3 gene in liver cancer tumors; At the same time, the GNR nano-skeleton structure can generate thermal energy and kill tumor cells under the irradiation of near-infrared laser. More importantly, GAL-GNR-siGPC-3 can induce GPC-3 gene photothermal effect at the same time, and the synergistic effect of the two increases the targeted killing ability of nanocarriers on tumor cells.

3.3. Diabetes detection

Glucose content is an important marker of diabetes, so in order to accurately measure the glucose content, Jiang Xingyu's et al.[10] research group developed a gold nanoparticle-assisted silver mirror reaction method for high-sensitivity detection of glucose. In this method（Scheme.2）, gold nanoparticles were combined with silver mirror reaction, and Ag^+ was adsorbed on the surface of AuNPs when AuNPs were added to silver ammonia solution. In the presence of glucose, Ag^+ was reduced to silver and wrapped on the surface of AuNPs, resulting in the color of the solution changing from the red of AuNPs to the yellow of Ag-shell nanoparticles. At this time, Can be observed without tools.

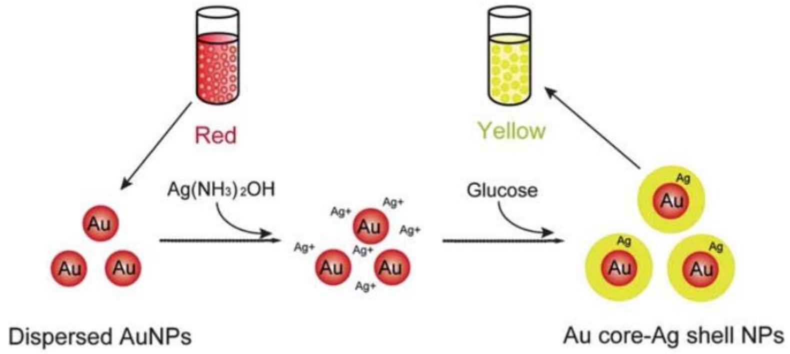

Figure 3. Schematic representation of AuNPs assisted silver mirror reaction.[10]

4. Application of gold nanoparticles in drug detection

At present, the drug problem has become a common serious problem all over the world. Common drug detection methods include hair detection, blood detection, urine detection, and saliva detection. But these technologies have certain flaws, Gold nanoparticles can improve these existing technologies to make detection faster and more accurate.

4.1. Gold Nano-Enhanced Raman Spectroscopy:

Raman spectroscopy is a kind of vibrational information that can explore molecules, which can be analyzed qualitatively or quantitatively. However, when the analyte concentration is low or the Raman scattering cross section is small, the signal intensity is weak and a clear spectrum cannot be obtained. SERS generally uses noble metals (Au, Ag) with nanoscale rough structure as the substrate. Under the excitation of incident light of a specific wavelength, plasmon resonance occurs on the surface of the substrate, causing an extremely strong local electromagnetic field, thereby significantly enhancing the Raman signal of the analyte molecules adsorbed on the surface of the substrate (up to 10 to the 14th power). times) to achieve highly sensitive detection and identification of trace analytes [11-12].

Raman spectrometers, which have also been well applied to SERS detection. While nanomaterials have different properties due to their nanoscale effect, some studies have developed a method for rapid detection of cocaine in urine using self-assembled two-dimensional gold nanoparticle films as SERS substrates. Mostowtt's et al.[13] team mixed cannabinoids with gold nanoparticles in an alkali-containing solution, and th nanoparticles polymerized under the action of the salt, resulting in spectral enhancement that was used to identify four chemically similar synthetic cannabinoids. Han et al.[14] uses the oil-in-water emulsion method to assemble the dispersed silver nanoparticles into spherical colloidal superstructure materials in the water phase. This superstructure material will generate SERS hot spots in three-dimensional space, and the use of three-dimensional hot spots can realize the quantitative detection of amphetamine drugs.

Gold nanoparticles can also modify sensors, which play an important role in drug detection, Yang et al.[15] constructed an AuNPs/ITO alkaline electrode sensor using AuNPs and ITO glass as substrates for the quantitative detection of ketamine in the hair of drug addicts. First, ketamine is electrostatically immobilized on the AuNPs/ITO electrode, and when the ketamine antibody specifically binds to the antigen on the alkaline electrode, an immune complex is produced, which blocks electronic communication and mass transfer, quenching Electrochemiluminescence signal for rapid identification of ketamine. In addition, gold nanoparticles are used for signal amplification, and an aptamer fluorescent sensor is designed for the hypersensitive detection of cocaine. Fei Wenjuan[16] used the dendritic polymer polyamidoamine (PAMAM) template method to synthesize CdS-PAMAM quantum dots (QDs) with uniform particle size and good dispersion, and construct electrochemical electrochemical based on CdS-PAMAM/gold nanoparticles (AuNPs) thin films. Luminescence (ECL) immunosensor is designed to combine sensitive electrochemiluminescence detection technology with highly selective immune response to establish a sensitive analytical method for drug detection with strong luminescent signal, good selectivity and high stability, and is compatible with other drugs. Compared with the analytical method, it has higher sensitivity and lower detection limit, and has a wider linear range and higher sensitivity than similar immunosensors.

5. Conclusions

In this work, the preparation methods of gold nanoparticles and their applications in biomedicine are summarized. Although the preparation method of AuNPs has been basically mature, it is still necessary to accurately control the size of AuNPs and improve their performance for various applications. The morphology and preparation of gold particles with uniform size and shape control are still the difficulties in the synthesis of AuNPs. In addition, these experiences are also valuable for the controllable preparation of other nano metal particles. The synthesis of nano gold composite and its applications in biomedical field would still be a key issue. Improving the accuracy and speed of detection should be a promising research direction that researchers need to make continuous efforts.

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