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Gold Nanoparticles: A Review

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Abstract

Gold nanoparticles are small gold particles with a diameter of 1 to 100 nm. Their characteristic surface Plasmon resonance feature aid indistinctive absorption and optical properties which can be characterized and can be useful in many biomedical applications. Gold Nanoparticles can be used as delivery vectors due to their high surface loading capacity of drug, gene, Protein or vaccine. The surface of Gold Nanoparticles can be modified by molecules such as polymers, Ligands, surfactants by conjugation increases its ability to cross the membrane and also helps in reduction of cytotoxic effect due to attraction to targeted areas. So, it can be used in Targeted drug Therapy by conjugating cancer drug molecules to these particles. Gold Nanoparticles absorbs certain wavelength of incident light and converts into heat which is transferred to cancer cells and leads to destruction of cells due to photothermal effect.

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INTRODUCTION

The particles which exist in nanometer range (i.e., 1 to 100 nm) are generally called as Nano particles. These particles are strong enough to hold their electrons such that they can produce Quantum effects and also have unexpected visible properties [1]. The Nanoparticles are beneficial both in material sciences and Biology due to their characteristic physical properties such as conductance, Uniformity and optical properties [2].

Gold nano particles are small gold particles with a diameter of 1 to 100 nm. They contain free electrons which conducts electricity when voltage is applied. These electrons have a tendency to absorb certain wavelength of light which inturn resonate on surface of gold Nanoparticles [3]. This Phenomenon is called as Surface Plasma resonance. Gold nanoparticles have capability to turn certain wavelength of light into heat, i.e., they can be heated up by Radio Frequency which in turn heat up the cancer cells and can destroy them [4].

Generally Bulk gold is yellow in color and is inert in nature where as gold nanoparticles are wine red in color and have Antioxidant property. Gold nanoparticles exist in different sizes ranging from 1 nm to 8 μm [Figure 1]. The color of Gold Nanoparticles mainly depends on its size. If size of Particle is large it appears more red in color for example 20 nm gold nanoparticle has a distinct wine red color [5].

They also exist in different shapes such as Nanorods, Nanospheres, Nano stars, Nano shell, Nanocluster, Nanocube, sub octahedral, decahedral, Multiple twined, Tetrahedral, Nanotriangles, Nanoprisms etc. [6]. Gold Nanorods are solid cylinders of gold of diameter up to 10 nm range whereas Gold nanospheres consist of gold coating over a silica core [7]. If thickness of gold coating changes the wavelength of light absorbed by these particles also changes [Figure 2].

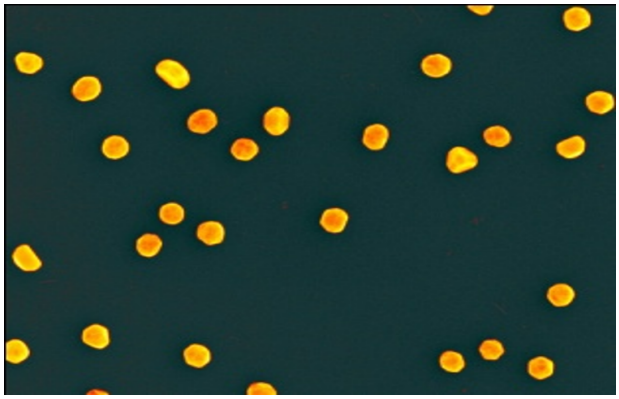

Figure 1: Color of Gold Nano Particles

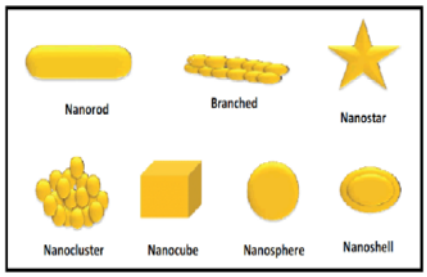

Figure 2: Shapes of Gold Nano Particles

Gold Nanoparticles have the tendency to attract towards cancer tumors when drug molecules are attached to these particles, so they can be opted for Targeted drug Therapy. The gold nano particles are stable under Physiological conditions and can be practically used as a Cytotoxic agent. They are highly resistant to bacteria and can prevent infections. They are also useful in treatment of Rheumatoid Arthritis and other autoimmune diseases.

Advantages of Gold Nanoparticles

1. Gold nanoparticles have unique optical, physical and chemical properties due to their size and shape.
2. Gold nanoparticles have high surface area which provides dense drug loading.
3. These particles are biocompatible and are readily available for conjugation with small Biomolecules such as proteins, enzymes, carboxylic acid, DNA, and amino acids.
4. Gold nanoparticles have controlled dispersity.
5. Due to small size and uniform dispersion they can easily reach to the targeted site in accordance with the blood flow.
6. They are non-cytotoxic to the normal cells.
7. When compared with other metal Nano structures these are easily synthesized and bioconjugated [8, 9].

Disadvantages of Gold Nanoparticles

1. The optical signal is very weak and is not as strong as quantum dot.
2. The Reticulo endothelial system also gets affected in the presence of Gold nano particles.
3. Its exposure leads to long term acute and chronic cytotoxicity.
4. Their arises a problems in case of Bio incompatibilities, *in vivo* kinetics and target drug delivery efficiency [10].

Metal Nanoparticles generally have the ability to color the glass. The colloidal gold has the property of staining the glass. In ancient times Romans used this technique to prepare Lycurgus cup in 4^{th} century. Depending on source of light, the color may be changed i.e. green color for Day light and Red color when illuminated from inside. In Middle Ages Solution of Colloidal gold salt is used to cure many diseases [11, 12].

In modern times Faraday accidentally observed Ruby red color solution when pieces of gold leaf are mounted on microscopic slides. He first prepared the pure sample of colloidal gold by reducing the solution gold chloride with phosphorous. Richard Adolf prepared the first colloidal gold in diluted solution [13].

Methods of Preparing Gold Nanoparticles

Turkevich Method

In this method, hot cholorauric acid is treated with sodium citrate to produces colloidal gold. Capping agents such as Citric acid and Tannic acid is added in order to inhibit particle growth and aggregation. They also act as reducing agents [Figure 3] [14].

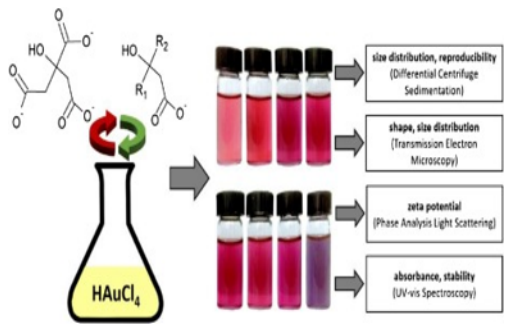

Figure 3: Procedure of Turkevich Method

Brust - Schiffrin Method

Gold Nanoparticles are produced in organic liquids such as Toluene. In this method, Tetra octyl ammonium bromide (TOAB) is dissolved in Toluene and to

this a solution of Chloroauric acid is added. In next step Sodium borohydride which acts as an Anticoagulant and reducing agent is also added. Gold Particles don't bind to TOAB which leads to aggregation of particles. This can be prevented by adding a binding agent like Thiol which will bind to gold nanoparticles and forms a solution [Figure 4] [15].

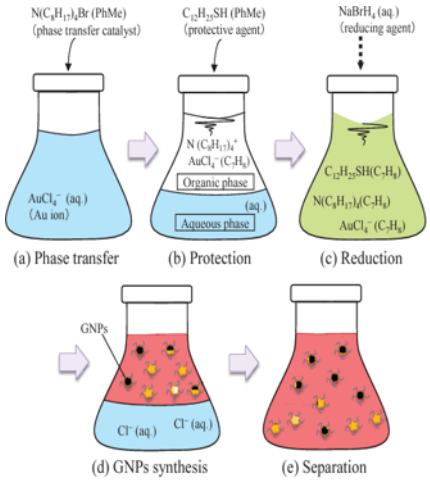

Figure 4: Procedure involved in Brust - Schiffrin Method

Perrault Method

This method uses Hydroquinone to reduce Chloroauric acid in aqueous solution that contains gold nanoparticles seed. The reduced Gold Nanoparticles settle on previously formed film of gold nanoparticles due to reduction of Chloroauric acid by Hydroquinone [16]. Sodium citrate acts as stabilizer to control the deposition of gold atoms onto the particles.

Martin Method

In these method, Monodisperse naked Gold Nanoparticles in water is produced by adjusting the Stoichiometric ratios of Sodium Borohydride, Sodium Hydroxide to Chloroauric acid to hydrochloric acid ions [17].

Even without stabilizer like citrate these particles are highly stable due to excess ions provided by Hydrochloric acid and Sodium hydroxide in solution.

Sonolysis

The ultrasound energy is used for the reaction of aqueous solution of chloroauric acid with glucose. In this reaction, hydroxyl radicals and Sugar Pyrolsis radicals acts as reducing agents [18].

Nano ribbons are obtained by this process which can bend at an angle greater than 90^{o}.

Spherical Gold Nanoparticles are obtained when glucose is replaced by Cyclodextrin [Figure 5].

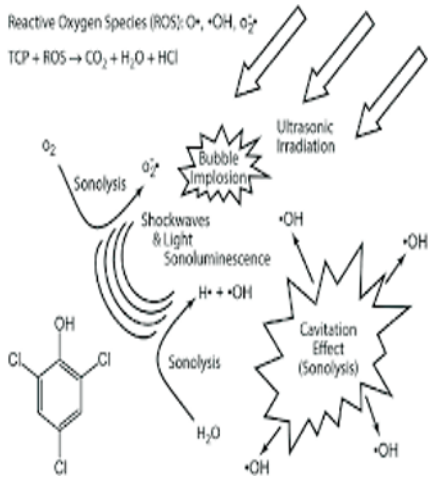

Figure 5: Procedure of Sonolysis

Block-Copolymer Mediated Method

This method involves three steps

1. Reduction of Gold salt ion by Block copolymer which results in formation of Gold clusters.
2. Adsorption of Block copolymer on Gold clusters.
3. Stabilisation of Gold Nanoparticles by Block co Polymer.

Examples of block co polymer are Poly –Methyl Phenyl Phosphazene

The stability of Gold Nanoparticles can also be increased by encapsulation technique by the use of Block copolymers such as Polystyrene and Poly Acrylic acid which interact with gold nanoparticles by hydrophilic and hydrophobic interactions [Figure 6] [19].

Synthesis of Spherical Gold Nanoparticles

It is most widely used method. In this method the reduction of aqueous chloroauric acid is done with sodium citrate [20]. By varying the amount of reactants, size of Gold Nano particles can be controlled. This method uses Metal precursor, Reductant and stabilizer. Citric acid acts as both stabilizer and reducing agent.

Synthesis of Gold Nanorods

It can be done by two general colloidal approaches such as seed-mediated method and seedless growth [21].

Seed Mediated Growth

In seed mediated growth, it already contains small sized gold seeds in a solution which is formed by reduction of chloroauric acid by sodium borohydride. In next step these seeds are added to silver

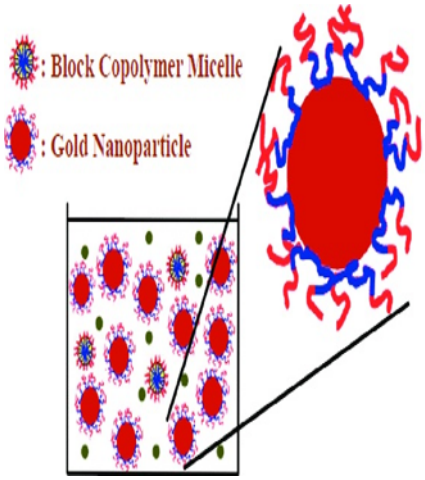

Figure 6: Block-Copolymer Mediated Method

nitrate solution containing L-Ascorbic acid which helps in further reduction [23]. Surfactant such as Hexadecyltrimethyl ammonium bromide helps in the growth of seeds in one axis forming Nanorods.

Seedless Growth Method

It is used to prepare Gold Nanorods of less than 5nm. To the growth solution, Sodium Borohydride is directly added which acts as a reducing agent that reduces Au^{3+} to Au. In this method PH and concentration of sodium Borohydride is adjusted to obtain Gold Nanorods.

Green Synthesis

In this method, the Biomolecules present in plant extract are used to reduce metal ions into Nanoparticles [22]. The plant extract is simple mixed with solution of metal salt at room temperature to produce the Nanoparticles. Examples of plant extract include Olive Leaf, Datura, Neem, *Cinnamom camphora*, Geranium leaf, Lemon grass, Aloe vera, *Catharanthus roseus* etc.

Characterization of Gold Nanoparticles

Ultra Violet Visible Spectroscopy

Gold Nano particles exhibits optical feature known as Localised Surface Plasmon Resonance (LSPR) which means when voltage is applied the cloud of free electrons oscillate on surface on gold nanoparticles between positive and negative charges. When a UV light is passed through a sample containing colloidal gold nano particles they absorb a specific wavelength of incident light in the visible region (i e 500nm-600nm). This absorbance can be measured by uv visible spectroscopy. The peak absorbance wavelength increases with particle diameter ie for uneven shaped particles it shifts to far red region of spectrum when compared with spherical particles [23].

Dynamic Light Scattering

This technique is used to measure Size and Size distribution of particles. When a Laser beam is passed through a sample suspension, the fluctuation of scattered light is analyzed to know the velocity of particles and Brownian motion. From this particle size can be inferred. The DLS can measure not only the physical size but also the coating associated with it and also the solvent layer of particle. The substances which are conjugated with Gold Nanoparticles are generally PEG, Proteins and oligonucleotides which increase the size of particle. So, this technique is useful to analyse the surface modification of Gold nanoparticles also.

Microscopic Imaging of Gold Nanoparticles

In this technique, the gold Nanoparticles are viewed in dark field microscopy. Because of strong Surface Plasmon Resonance and light scattering, the gold Nanoparticles can be visualized as bright spots under dark field microscope. The Spherical Gold Nanoparticles appear green whereas Gold Nano urchins appear red.

Gel Electrophoresis

It is an Analytical technique that separates the particles based on size, shape and charge. The distinct color of Gold nanoparticles enables us to visualize the migration of particles within the gel. In Agarose gel Electrophoresis, there will be alteration in migration pattern when we modify the surface with charged ligands or molecules such as Amine PEG, Carboxyl–PEG oligonucleotides. When protein molecules are conjugated with Gold nanoparticles, it results in increased particle size which leads to decrease in their Electrophoretic speed. This technique is also used to isolate pure Gold Nanoparticles.

Scanning Electron Microscopy

This technique is used to analyze the morphology of Gold nanoparticles. The Equipment mainly consist of Integrated X-ray energy dispersive Spectrometer and high resolution camera. In vortex motion, the Gold Nanoparticles are dispersed in Deutrium depleted water (DDW) and is placed on a carbon sticky conductive tape and is allowed to evaporate. Then the SEM images are recorded.

Transmission Electron Microscopy

The samples for TEM analysis are prepared by centrifugation method. The samples are subjected to centrifugation for 10 minutes and the supernantant liquid is discarded and wash the remains with distilled water. The final solution was placed on a carbon-coated copper grid and water is allowed to evaporate and the images are recorded.

Nanoparticles Tracking Analysis

In this technique, the light scattering and Brownian motion are used to obtain Particle size distribution. When laser beam is allowed to pass through sample, the light gets scattered by the particles. This scattered light is visualized by a 20 x magnification microscope onto which a mounted camera is placed. The camera can capture a video file of particles moving under Brownian movement by operating at approximately 30 frames per second. The Nanoparticle tracking software can determine the average distance moved by each particle in x and y plane, with the help of which we can determine Particle diffusion coefficient. From Stokes-Einstein equation, the diameter of particle can be known if sample temperature and viscosity can be known.

Applications Gold Nano Particles

Drug Delivery

Gold Nanoparticles generally conjugates with drug molecules such as Antibiotics and cancer cells by ionic or covalent bonding or by Physical adsorption [24]. For Example the carboxylic group present in Methotrexate drug combines with Gold Nanoparticles after overnight incubation is useful for cancer treatment. The surface of Gold Nanoparticles can be modified by using PEG. The use of Amphiphile polymer makes the gold Nanoparticles stable in Physiological conditions.

Gene Delivery

Gold nanoparticles can be used to deliver both RNA, DNA molecules, Plasmids. Gold Nanoparticles protect the nucleic acids by preventing degradation.

Protein Delivery

Gold Nanoparticles have been used for delivery of Insulin by Chitosan which is a non–toxic polymer that stabilize Gold Nanoparticles. These chitosan Gold Nanoparticles adsorb insulin molecule on their surface and is effective for Transmucosal delivery of Insulin. The Gold Nanoparticles can also be conjugated to Human serum or Albumin or Apo Lipoproteins [24]. The Protein conjugation of gold Nanoparticles results in reduced liver retention which in turn increases the specificity and efficiency of Nanoparticles in diseased target organs.

Vaccine Delivery

Gold Nanoparticles enable to deliver vaccines against Tick borne Encephalitis. Gene Gun technology has been used for epidermal delivery of DNA vaccines. In Gene gun technology, the gold Nanoparticles are coated with genes for delivery into the cells which is a biolistic technology used in genetic engineering.

Diagnosis

Gold Nanoparticles can be used for home pregnancy test. It uses Polystyrene spheres and 50 nm gold particles. When urine containing Human chronic gonadotropin comes in contact with this complex the Nanoparticles Coagulate into red clumps. This fluid when passed through a filter it will attire pink color to the filter paper [25]. When no color is obtained it indicates the absence of HCG and negative result for pregnancy. It is also used to detect Microalbuminuria in urine. When equal volumes of urine and Gold Nanoparticles are mixed if purple color appears it indicates microalbuminaria and grey color indicates absence of Microalbuminaria which means increased levels of albumin in urine.

Miscellaneous

When blood sample is mixed with Gold Nanoparticle solution it results in accumulation of these particles in white blood cells. Hence it is useful for cytotoxic drug treatment. The Polysaccharide obtained from kernel of Tamarindus not only stabilizes gold Nanoparticles but also has Anti tumor and Immuno modulatory effect [26].

CONCLUSION

Gold Nanoparticle helps to treat Multi drug Resistant Tumors by Targeted Photothermal treatment in combination with chemotherapeutic agent. When Tumor Necrosis Factor α is conjugated with PEG coated Gold Nano Particles it not only destroys the cancer cells but also reduces the toxicity. It also delays the tumor growth and decreases the blood flow to the tumor.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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