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Gold Nanoparticles: Applications in Photo-Thermal Therapy (PTT)

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Abstract

Nano-technology has entered the field of medicine in recent decades and many of the nanomaterials developed have already had a high impact on health care. Among nanomaterials, gold nanoparticles (GNPs) are receiving significant attention because their unique physical, chemical, and biological properties are quite different from the bulk of their counterparts. In this article, after a brief historical overview, the applications of Nano-gold and the methods of its preparation are reviewed, this review particularly deals the use of GNPs in photo thermal therapy.

Keywords: Friction stir processing, Tool rotation speed (TRS), transverse speed (TS)

1. Introduction

GNPs, also named as gold colloids, have attracted increasing attention due to their unique properties in multi-disciplinary research fields. Daniel et al., [2004], Sardar et al., [2009] Although. GNPs are defined by tiny size, significant quantities of GNPs are likely required in commercial and industrial applications. Gold Nanoparticles (GNPs) has advantageous optical, chemical and physical properties which make it suitable for novel biomedical applications. The biocompatibility, resistance to the oxidation, photo-bleaching immunity and high-contrast properties of Nano gold have been used to diagnose and treat diseases. Delfino et al., [2013]. The applications of GNPs in medicine are preferably accompanied with organic ligands attached to its surface to obtain novel imaging, diagnostic and therapeutic properties. The attachment or conjugation of GNPs produces highly stable nanostructures, Hassan et al., [2017] and also provides a platform to transport and deliver drugs selectively. The optical properties of gold based nanostructures are very sensitive to their size, composition, morphology, surrounding environment properties, inter-particle distance and surface properties.

2. Methods of Preparation GNPs

2.1 Physical methods

Laser ablation method is used to produce gold nanoparticles by using the pulsed laser irradiation of gold target in water in the absence of any additives, at (532 nm, 10 ns, 10 Hz), or (266 nm) wavelengths. Choi et al., [2006]. Inert gas condensation can be used for the preparation of gold nanoparticles. In this method, the gold nanoparticles as soon as they are formed rapidly collide with inert gas in a low-pressure environment and thus smaller and controlled nanoparticles are formed. The advantage of these methods is the narrow particle size distribution of the produced gold nanoparticles, while its limitation is the need for expensive equipment. Other physical methods such as thermolysis of gold(I) complex at 180^{o}C for 5 h under nitrogen atmosphere Yamamoto et al., [2003] radiolysis of gold salts in aqueous solution using c-irradiation-induced reduction in the field of a 60Co c-ray source , Henglein et al., [1998] Dawson et al., [2000] photochemistry, e.g. in the $HAuCl_4$ solution containing certain amounts of protective agent and acetone, the colloidal gold particles with an average diameter of 5 nm (r=0.86) were prepared by UV 300 nm irradiation , Mallick et al., [2001] and sono-chemistry using ultrasound-induced reduction of gold salts in aqueous solution Chen et al., [2007] have been used to prepare a variety of gold nanoparticles.

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2.2 Chemical methods

Emulsification procedure produces gold nanoparticles but with a wide distribution of particle diameters. Pal et al., [2007] Nanogold particles are prepared by reduction of the gold ions in the presence of a dispersant in order to avoid excessive gold agglomeration. Frens et al. Frens et al., [1973]. Initially introduced a sodium citrate reduction of $HAuCl_4$ for the synthesis of stable gold nanoparticles. In addition there are other reductants such as sodium borohydride Wagner et al., [2008] stannous chloride Vasˇkelis et al., [2007] and ascorbic acid. Sun et al., [2009] Amine-containing molecules for example, branched poly (ethyleneimine) (PEI). Note et al., [2006] third-generation poly(propyleneimine) dendrimer (PPI-G3) in the presence of sunlight Luo et al. [2008] azacryptand at room temperature Lee et al., [2007] amino acid, Selvakannan et al. [2004] polysaccharide Huang et al., [2004] gallic acid Wang et al., [2007] alcohols, chitosan Shih et al., [2009] or other organic compounds are also used as a reductant for the synthesis of Nano gold (see figure 1).

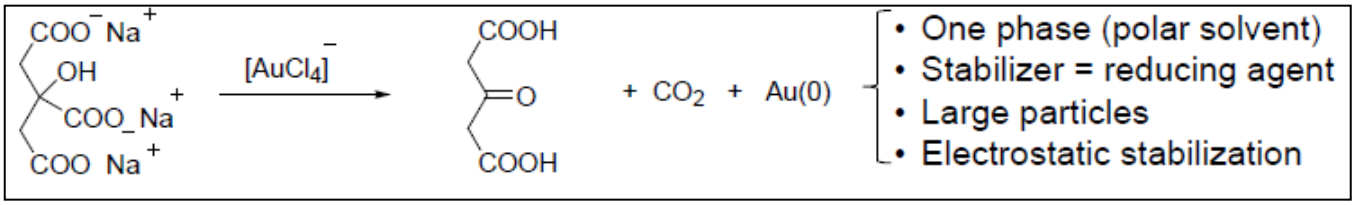

Figure: 1 Synthesis of gold nanoparticles using Turkevich method

There are several reported modified chemical methods including seed-mediated growth where small particles produced by other techniques like irradiation were exploited as seeds and fresh Au(III) ions were reduced onto the surface of the seed particles by reducing agents like ascorbic acid, Jana et al., [2004] use of reverse micelles which involves reduction of $HAuCl_4$ in sodium bis (2-ethylhexyl) sulfosuccinate /isooctane reverse micelles system using reducing agents like ascorbic acid, Chiang et al.,[2000] phase transfer reactions as a representative reaction in a novel water–cyclohexane two-phase system, the aqueous formaldehyde is transferred to cyclohexane phase via reaction with dodecylamine to form reductive intermediates in cyclohexane; the intermediates are capable of reducing gold ions in aqueous solution to form gold nanoparticles in cyclohexane solution at room temperature. Esumi et al., [2000], Haifeng et al., [2005]. In addition to previous methods, Brust–Schiffrin synthesis (BSS) of gold nanoparticles has emerged as a major breakthrough in the field for its ability to produce highly stable thiol functionalized nanoparticles. (see figure 2).

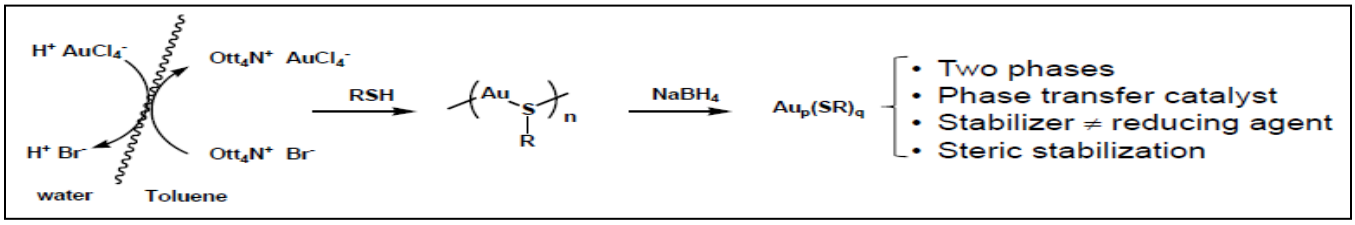

Figure 2: synthesis of gold nanoparticles using BSS method.

In view of these two methods, it was reported that the chemical methods are still the preferred method for the preparation of gold nanoparticles than physical method.

2.3 Application of GNPs

The range of applications for gold nanoparticles is growing rapidly, these applications include

2.3.1 Electronics

Gold nanoparticles are designed for use as conductors from printable inks to electronic chips. As the world of electronics become smaller, nanoparticles are important components in chip design. Nanoscale gold nanoparticles are being used to connect resistors, conductors, and other elements of an electronic chip.

2.3.2 Photodynamic Therapy

Near-IR absorbing gold nanoparticles (including gold Nano shells and Nano rods) produce heat when excited by light at wavelengths from 700 to 800 nm. This enables these nanoparticles to eradicate targeted tumors. When light is applied to a tumor containing gold nanoparticles, the particles rapidly heat up, killing tumor cells in a treatment also known as hyperthermia therapy.

2.3.3 Therapeutic Agent Delivery

Therapeutic agents can also be coated onto the surface of gold nanoparticles. De Chae et al., [2008]. The large surface area-to-volume ratio of gold nanoparticles enables their surface to be coated with hundreds of molecules (including therapeutics, targeting agents, and anti-fouling polymers) (see Figure 3).

2.3.4 Sensors

Gold nanoparticles are used in a variety of sensors. For example, a colorimetric sensor based on gold nanoparticles can identify if foods are suitable for consumption. Other methods, such as surface enhanced Raman spectroscopy, exploit gold nanoparticles as substrates to enable the measurement of vibrational energies of chemical bonds. This strategy could also be used for the detection of proteins, pollutants, and other molecules label-free.

2.3.5 Probes

Gold nanoparticles also scatter light and can produce an array of interesting colors under dark-field microscopy. The scattered colors of gold nanoparticles are currently used for biological imaging applications. Also, gold nanoparticles are relatively dense, making them useful as probes for transmission electron microscopy.

2.3.6 Diagnostics

Gold nanoparticles are also used to detect biomarkers in the diagnosis of heart diseases, cancers, and infectious agents. They are also common in lateral flow immunoassays, a common household example being the home pregnancy test.

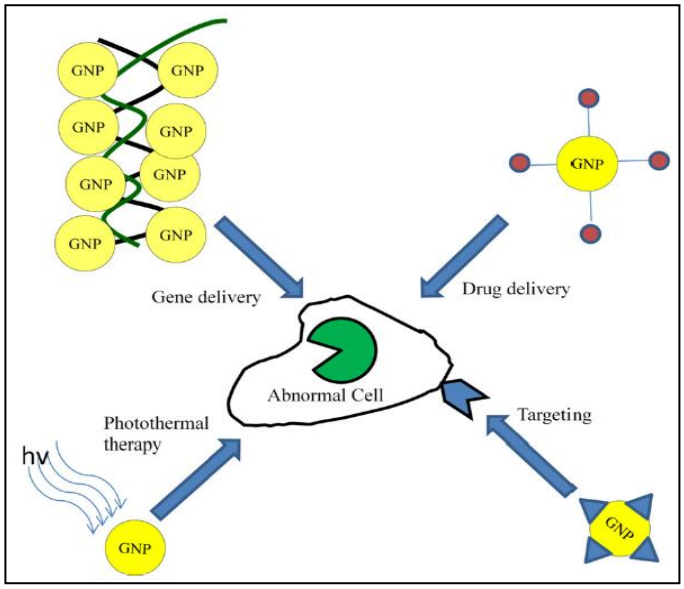

Figure 3: Various applications of gold nanoparticles in therapy

2.3.7 Catalysis

Gold nanoparticles are used as catalysts in a number of chemical reactions. Huang et al., [2009]. The surface of a gold nanoparticle can be used for selective oxidation or in certain cases the surface can reduce a reaction (nitrogen oxides). Gold nanoparticles are being developed for fuel cell applications. These technologies would be useful in the automotive and display industry.

2.3.8 Enhanced photo-physical properties of gold nanoparticles

When matter is exposed to light, a number of processes can occur.

- The light can be absorbed.
- The light can be scattered at the same frequency as the incoming light (Mie or Rayleigh scattering).
- The absorbed light can be re-emitted (i.e., fluorescence).
- The local electromagnetic field of the incoming light can be enhanced, thus enhancing any spectroscopic signals from the molecules at the material surface, that is, surface-enhanced spectroscopy, such as surface-enhanced Raman scattering.

In the case of gold nanoparticles, all these processes are enhanced strongly owing to the unique interaction of light with the free electrons in the metal particles. When gold nanoparticles are exposed to light radiation, the electric field of the light causes the collective oscillation of the conduction-band electrons at the surface of the particle, with respect to the ionic core of the nanoparticle. The coherent oscillation of the metal free electrons in resonance with the electromagnetic field is called the surface Plasmon resonance (SPR). A theoretical and experimental discussion of the SPR can be found in earlier and recent literature. Link et al., [2003]For gold Nano spheres, this resonance occurs in the visible spectral region at approximately 520 nm, which is the origin of the brilliant red color of the nanoparticles in solution. For gold Nano rods, the free electrons oscillate along both the Nano rod long and short axis, Huang et al., [2007] resulting in a stronger resonance band in the near infrared (NIR) region and a weaker band in the visible region (similar to the Nano spheres), respectively. Link et al., [2005]. The excitation of the SPR results in the enhancement of the photo physical properties of gold nanoparticles. Figure 4 summarizes the major optical processes that occur on the interaction of light with gold nanoparticles, which we discuss in detail in the following sections.

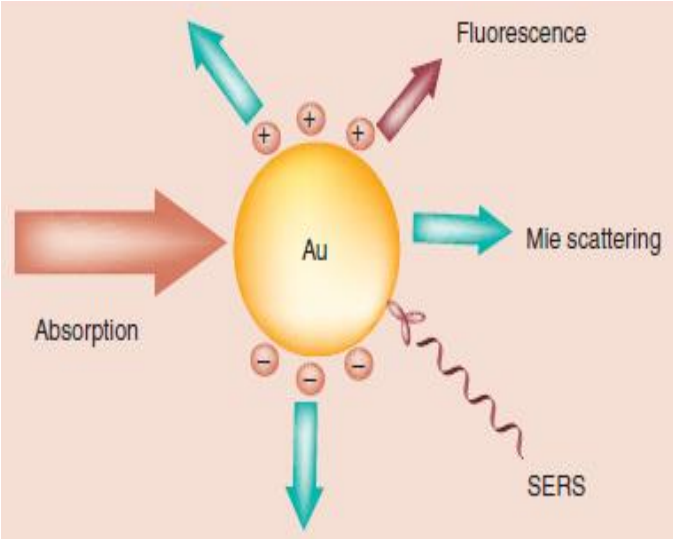

Figure 4: Important optical processes resulting from the interaction of light with a gold nanoparticle, viz. light absorption, Mie scattering, surface-enhanced luminescence and surface-enhanced Raman scattering from adsorbed molecules.

3. Photo thermal therapy using gold nanoparticles

Photo thermal cell damage is a promising direction in both tumor therapy Kennedy et al., [2011] and the therapy of infectious diseases, which has been intensively developing. The essence of this technique is as follows: gold nanoparticles reach their absorption maximum in the visible or near-infrared region and become hot when irradiated at the corresponding light wavelength. If they are located inside or around the target cells (which can be achieved by conjugation of gold particles with antibodies or other molecules), these cells die.

Thermal exposure has been used in tumor therapy since the 18th century. To do that, both local heating (using microwave, ultrasound, and radio radiation) and hyperthermia of the entire organism (heating to 41–47°C for 1 h) Huang et al., [2008] were applied. Upon local heating to 70°C, the duration of the procedure can be reduced to 3–4 min. Local and general hyperthermia result in irreversible cell damage caused by the disruption of the cell's membrane permeability and protein denaturation. Healthy tissues are also clearly damaged in this process. All this imposes considerable restrictions on the application of this method.

The revolution in cancer thermotherapy was triggered by the use of laser radiation, which made controlled and directed damaging of tumor tissues possible. Minton et al., [1965]. The combination of laser radiation with fiber-optic waveguides gave excellent results and was named interstitial laser hyperthermia. The disadvantages of laser therapy include the low selectivity associated with the necessity of using powerful lasers for the efficient stimulation of tumor cell death.

In 2003, GNPs were applied for the first time as agents for photo thermal therapy; Hirsch et al., [2003] it was latter proposed to refer to this kind of therapy as plasmonic photo thermal therapy (PPTT). A new method for selective damaging of target cells, which is based on the use of 20–30 nm gold Nano spheres radiated by 20 ns laser pulses (532 nm) in order to create local warming-up, was described in. Pitsillides et al., [2003]. The sandwich technology consisting in labeling T- lymphocytes with GNP conjugates was used for the pulse photothermy in the model experiment. The use of GNPs for the photo thermal therapy of chemotherapy-resistant types of cancers seems to be the most promising direction. As opposed to photosensitizers (see below), GNPs appear unique because the cells retain their optical properties under certain conditions for a significant amount of time. Successive irradiations with several laser pulses allows to control cell inactivation using a method that is not traumatic, while the use of the nanoparticles, properties to simultaneously scatter and absorb radiation makes PPTT possible using optical tomography. Loo et al., [2005]

Further development of PPTT and its introduction in clinical practice will depend on how successful scientists will be in solving a host of problems, the most significant ones being 1) selecting nanoparticles with the optimal optic properties; 2) increasing the contrast of nanoparticle accumulation in a tumor and decreasing overall potential toxicity; and 3) elaborating methods for delivering optical radiation to the targets and searching for alternative irradiation sources, which would combine high permeation ability with the possibility of GNP heating.

The first requirement is determined by the coincidence of the spectral position of the maximum of the Plasmon absorption resonance and the bio tissue transparency window in the near-infrared region (700–900 nm). The summarizing theoretical analysis of the photo thermal efficiency of GNPs depending on their size, shape, structure, and degree of aggregation has been published. It was shown that although gold Nano spheres are inefficient in the near-infrared range, their aggregates can be very efficient at appreciably small interatomic distances (below 10% of their diameter). Such clusters form both on a cell's surface and inside cells. Lapotko et al., [2007] Data on the amplification of PPTT due to clusterization were obtained. Lapotko et al., [2005] In particular, it was ascertained Huang et al., [2007] that small aggregates consisting of 30 nm particles enable the destruction of cancer cells at an intensity lower than that in the particle-free control by a factor of 20.

The parameters of gold Nano shells and Nano rods that are optimal for PPTT were determined. Harris et al., [2006] Today, a number of studies have been published in which the application of gold Nano rods, Huff et al., [2007] Nano shells, Loo et al., [2005] and a relatively new class of particles – gold-silver Nano cages Petrova et al., [2006] – for PPTT is described. The results of a comparison of the efficiency of heating Nano rods, Nano shells, and Nano cages are provided in Terentyuk et al., [2009].

Three fundamental things should be kept in mind in connection with the optimization of the parameters of a particle. First, intrinsic absorption is not the only parameter

determining the efficiency of PPTT. Lapotko et al., [2009] The rapid heating of nanoparticles or clusters results in the formation of vapor bubbles, Hleb et al., [2008] which can cause cavitation cell damage upon irradiation with visible or near-infrared light. Zharov et al., [2005]. The efficiency in the formation of vapor bubbles considerably improves upon the formation of nanoparticle clusters. It is possible that it is this effect, instead of the enhanced absorption, that determines the larger extent of cell damage, other conditions being equal. Finally, irradiation of nanoparticles by high-intensity resonance nanosecond IR pulses may result in the destruction of particles as early as after the first pulse. In a series of studies, Lukianova et al., [2013] and refs. There in) focused their attention on the fact that the heating of GNP and their destruction may result in an abrupt decrease in the photo-thermal efficacy of "cold" particles tuned to the laser wavelength. The use of femtosecond pulses does not solve this problem because of the low energy supplied; therefore, it is necessary to accurately control the retention of nanoparticles' properties for the selected irradiation mode.

We shall now turn our attention to the second issue connected with the problem of targeted delivery of nanoparticles into the tumor. This issue has two significant aspects: increasing the contrast in the desired bio target and decreasing the side effects conditioned by the accumulation of GNPs in other organs, primarily in the liver and spleen (see below). Two delivery strategies are typically used. The first strategy is based on GNPs conjugation with PEG, and the second one is based on GNPs conjugation with antibodies to certain marker proteins of tumor cells. PEG is used to enhance the bioavailability and stability of nanoparticles, resulting in the increase in time of their circulation in blood flow. Citrate-coated gold Nano spheres and CTAB-coated Nano rods and Nano shells are characterized by low stability in buffer saline solutions. Upon conjugation of nanoparticles with PEG, their stability increases considerably, preventing salt-induced aggregation.

The question of the efficacy of targeted delivery of nanoparticles into the tumor has recently resurfaced as the subject of investigation and discussion. Huang et al., [2011] In experiments with liposomes labeled with anti-Her2-antibodies Kirpotin et al., [2006] and GNP labeled with transferrin, Choi et al., [2010] it was shown that functionalization improves the penetration of nanoparticles into cells; however, the contrast of particle accumulation in the tumor does not improved considerably. The bio distribution and localization of gold Nano rods labeled with three types of probe molecules, including the (1) scFv-fragment of EGFR antibodies; the (2) N-terminal fragment of the peptide recognizing the urokinase plasminogen activator receptor (uPAR); and the (3) cyclic RGD-peptide recognizing the $\alpha_v\beta_3$-integrin receptor have been studied [50]. It appears that all three types of ligands fail to significantly improve the contrast of particle accumulation in cell models and in the tumor upon intravenous administration, but they do have a considerable effect on extracellular distribution and intracellular localization. Therefore, a conclusion can be made that in the case of PPTT, the direct introduction of particles into the tumor can be more efficient than intravenous administration.

The last important question associated with modern PPTT has to do with the efficient delivery of radiation to the bio target. Since the absorption of bio tissue chromophores in the visible region is lower by two orders of magnitude than it is in the infrared region, the use of IR radiation dramatically reduces the no target thermal dose and increases the deep tissue penetration of the radiation. Nevertheless, the penetration depth typically does not exceed 5–10 mm; Tuchin et al., [2009] therefore, it is necessary to search for alternative solutions. The first approach consists in using impulse (nanoseconds) modes of radiation instead of continuous ones, which allow to increase the intensity of the irradiation without additional side effects. The second approach consists in using fibre-optic devices for endoscopic delivery of the radiation or delivery inside the tissue. The advantages and drawbacks of this approach are evident. Finally, radiation with deeper penetration, such as radio radiation, Hainfeld et al., [2004] can be used for hyperthermia.

GNPs conjugated with antibiotics and antibodies have also been used as photo thermal agents to inflict selective damage to protozoa and bacteria. Pissuwan et al., [2007], Zharov et al., [2006]

4. Conclusion

Plasmon photo thermal laser therapy of cancer using GNP was first described in 2003 and recently moved into the stage of clinical approval. The actual clinical success of this technology will depend on how quickly several urgent problems can be solved: (1) developing efficient methods for the delivery of radiation to tumors inside the organism using fibre-optic technologies or no optical heating methods; (2) elaborating methods for delivering conjugates to tumors, enhancing the contrast and uniformity of accumulation; and (3) developing methods for controlling the in situ photo thermolysis process.

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