EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 7
137-142
Year: 2019

GOLD NANOSHELL: SYNTHESIS, CHARACTERIZATION, EXAMPLE ANDAPPLICATION IN CANCER THERAPY

Dr. Sonali Mahaparale[1]* and Vrushali B. Londhe[2]

[1]Head of Department of pharmaceutical Chemistry, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, 411044, Maharashtra, India.
[2]Department of Pharmaceutical Quality Assurance, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, 411044, Maharashtra, India.

***Corresponding Author: Dr. Sonali Mahaparale**
Head of Department of pharmaceutical Chemistry, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, 411044, Maharashtra, India.

Article Received on 28/04/2019 **Article Revised on 19/05/2019** **Article Accepted on 10/06/2019**

ABSTRACT
Cancer is the 2nd and 3rd leading cause of the death after heart disease and stroke in US and in developed countries resp. Although hyperthermia has been a method of a treatment of cancer for decades traditional way of heating tissues involve invasive catheters or whole body heating system. The use of nanoshells involves the NIR heating of nanoshells without harming healthy tissues. The GNSs are spherical, ranging from 10-200nm, which is composed of dielectric core covered by a thin gold shells & it possesses optical, physical & chemical properties. These GNSs shows cancer detection, cancer treatment, cellular imaging & medical biosensing in the previous method. [1] Here in the current method the customized the Lee-Meisel method, to prepare small & monodisperse AgNSs of diameter 17-25±4nm. [3] The example of fabricated nanoparticles which is mesoporous silica loaded doxorubicin covered with a thin layer of pegylated gold. The prepare GNSs were characterized by TEM, UV-VIS spectroscopy, FTIR, Raman spectroscopy, X-ray photodetection spectroscopy, & examine relative solubility in a variety of solvents. [1]

KEYWORDS: Self assembled monolayers (SAMs), surface Plasmon resonance (SPR), alkanethiol functionalization, sacrifial silver nanoparticles (AgNPs).

INTRODUCTION
Metallic nanoparticles are in studies from several years because of their attractive physical &chemical properties, their size& their applications such as catalysis, optics, information storage, biological & chemical sensing, surface Raman scattering, bionanomedicine, etc.[3] Nowadays, AuNPs have been synthesized in different shapes & sizes accordingly to their shape & sizes it names as nanosphere, nanorods, nanostars, nanotubes, nanocubes, nanodisks, nanowires, hollow nanogolf gold balls & nanoshells. The main feature of the NPs is that they shows their absorption peak depends upon their size & shape, so for their medical application it is desirable to develop NPs that absorb in the transparent window of biological tissues; NIR from 800-1200nm.[3]

In recent years, gold nanoshells have generated great interest because of their highly inert and biocompatible nature. GNSs are a spherical in shape which consist of dielectric core covered with a thin metallic shell which is gold. They are categorized in class of nanoparticles with tunable optical resonance. The gold nanoshells have the diameter typically ranges from 10-200nm.[1]

The optical resonance of these GNSs can be precisely& systematically varied over a region ranging from the near ultra-violet to the mid-infrared (IR) depending upon varying the relative dimension of the core & the shell.[1]

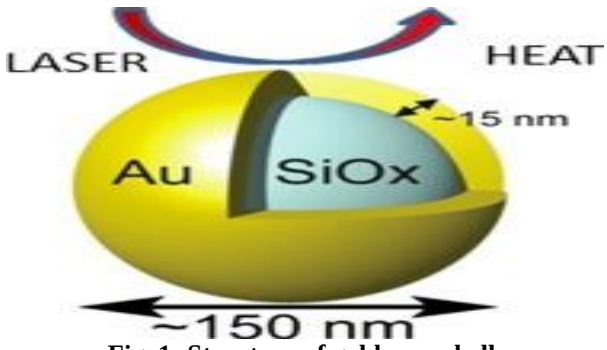

Fig. 1: Structure of gold nanoshell.

The metal colloid shows the surface Plasmon resonance (SPR) properties, which originate from collective oscillation of their conduction electrons in response to optical excitation. The SPR of the GNSs can be varied 100s of nanometer in wavelength from visible to IR

region, depending upon the change in relative dimensions of core & the shell.[1]

The AuNSs have been synthesized by various methods

1) Oldenburg etal, method synthesis the AuNSs with a silica core of diameter ~100nm & thickness 5-20nm.

2) Sun etal reports the method, it synthesized the hollow AuNSs of size about 50nm with an absorption peak that could shifted from 500-1200nm.

3) Polyvinylpyrolidone used as a capping agent & high preparation temperature is required; when wet-chemical synthesis method is used it produces highly polydisperse AuNSs & peak located around 800nm.

4) Liang etal method gives the hollow AuNSs of approx...60nm diameter using small cobalt nanoparticles as sacrificial template & it shows peak at 526-650nm.[3]

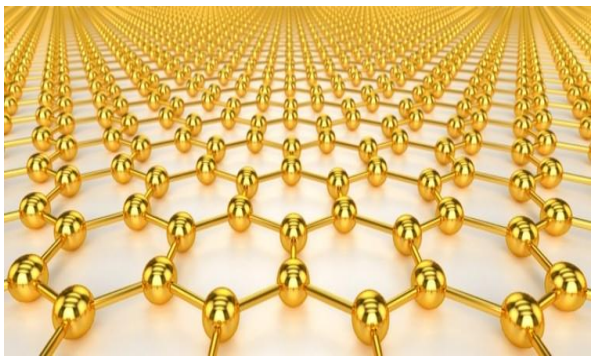

Fig. 2: Gold nanoshells

Preparation

1. Preparation of silica nanoparticles: Take a mixture of 3ml (30%) ammonia & 50ml of absolute ethanol & stir it vigorously, then add drop wise 1.5ml, 6.7 mmol tetraethyl orthosilicate ($Si(OC_2H_5)_4$) TEOS. The formation of silicon dioxide (SiO_2) nucleus from the TEOS monomer indicates the completion of reaction. Time required for the completion of reaction is determined by the time required to change the solution from clear to opaque white. The conc. of the silica nanoparticles should found to be $7x10^{12}$ particles per ml. by using TEM ,it shows that formed silica nanoparticle is spherical in shape & have the diameter approx.. 100nm.[1]

2. Functionalization of silica nanoparticle surfaces with 3-aminopropyltrimethoxysilane (APTMS): In 100ml of the vigorously stirred silica nanoparticle solution add small excess of the APTMS (approx. 50µl, 0.28 mmol) & allow it to react for 2hrs. When the solution is separate into two layers cease the stirring, the silica nanoparticles coated with APTMS precipitate at the bottom & clear solution of ethanol is at the top. The solution is gently refluxed for 1hr. to enhance the efficiency of covalent bonding between APTMS & silica nanoparticles. By centrifusing & redispensing in ethanol. The purification of APTMS coated silica nanoparticles is done. Then analyze these coated nanoparticles by TEM.[1]

3. Preparation of colloidal gold nanoparticles

A reaction mixture[A mixture of 45ml HPLC grade water, 0.5 ml NaOH & 1ml tetrakis (hydroxymethyl) phosphonium chloride solution (which is a mixture of 0.067mml of 80% THPC in water& 1ml of HPLC grade water] stir for 15min. Add quickly the 2ml (27mmol) of 1% $HAuCl_4$ in to the stirred solution. If we vary the volume of 1% $HAuCl_4$ solution, the size of the colloidal gold nanoparticles get varied. For Ex: if we add 1.5ml instead of 2ml then reduction in size occurs from 2-3nm. The nanoparticles are detected by the TEM. When the sample is dried then it shows the same color of Au55 clusters i.e. dark brown. Above procedure gives the gold nanoparticles which are 2-3nm in diameter in size. [1]

4. Attachment of colloidal gold nanoparticles to APTMS coated silica nanoparticles

Approximately 0.5ml, 7×10^{12} particles/ml APTMS coated silica nanoparticles solution dispersed in ethanol & add excess of gold nanoparticles (5ml 7×10^{14} particles/ml) & placed it in centrifuge tube. Centrifuge it for 2min. & allow to settle it for 2hrs. The red coloured pellets is settled at bottom when mixture centrifuge at 2000rev/min. Decant the supernatant & slightly red coloured pellets redispersed & sonicate in HPLC grade water. Redispersed the purified Au/APTMS/silica nanoparticles in 5ml of HPLC grade water which can then be used for further steps.[1]

5. Preparation of gold nanoshells

25mg (0.18mmol) of potassium carbonate ($K2Co_3$) is dissolved in 100ml HPLC grade water stir for 10min. & add 1.5ml (20mmol) solution 1% $HAuCl_4$ in water. Over a course of 30min. The solution changes from transparent yellow color to a colorless. Inject the 200µl of Au/APTMS/silica nanoparticles solution to a 4ml of vigorously stirred colorless solution & add 10µl formaldehyde (0.36mmol) to this solution. After 2-4min. solution turns into colorless to blue which indicates the formation of nanoshells. The formed nanoshells should be centrifuged & redispersed in HPLC grade water until use.[1]

6. Adsorption of alkanethiols onto gold nanoshells

Three separate alkanethiols solution in ethanol are prepared i.e. dodecanethiol, hexadecanethiol & octadecanethiol. 25ml of each thiol solution & 25ml of bare gold nanoshells which is dispersed in ethanol add separately into a flask & stir or 1 night. After that these nanoshells are dispersed & centrifuged in ethanol for 5min. to remove any unreacted reagents. [1]

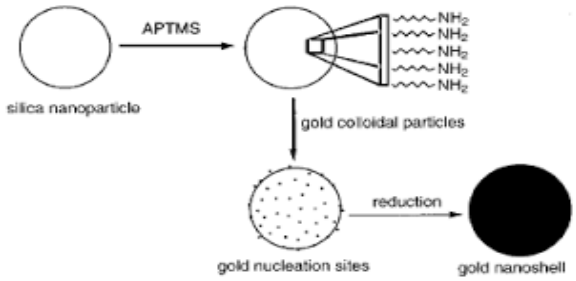

Fig. 3: Synthesis of gold nanoshells.

Recent Lee- Meisel method for the preparation of extremely small & monodispersed AuNSs: In this method, AgNSs is used as a sacrificial agent for the preparation of the extremely small& monodispersed AuNSs.[3]

1. AgNP synthesis

i) Seed solution: the mixture of 1% NaCit (trisodium citrate dehydrated) 2ml & 7.6ml water heated at 70^0c whole stirring for 15min. 200ml of 4^0c $NaBH_4$ 0.1% solution & 170µl of 0.1% $AgNO_3$ is added at the same time & stir it for 60min. & obtained 4nm diameter nanoparticles.[3]

ii) Growth of $AgNO_3$: 400µl of 1% NaCit solution & 16ml of water mixed in a RBF, boil & stir for 15min. while stirring & heating the solution for 60min. add 2ml of seed solution & 340µl of 1% $AgNO_3$ solution & the resulting solution kept at the room temperature in dark.[3]

2. AuNS synthesis: Deposition of gold layer on AgNPs involves the formation of K-gold solution (potassium – gold) & mix with the AgNPs & K-gold solution. [3]

i) K-gold solution: Add 110ml of water & 0.0025gm K_2CO_3 in RBF which is covered from light & while stirring at RT for 30min. 200µl 1% $HAuCl_4$ solution& kept the resulting solution for 12hrs. At 4^0 c before use.[3]

ii) Gold deposition: when we add K-gold solution in the AgNP solution at different volume ratios then different shell thickness of AuNSs will obtained. When we add K-gold solution in a 5ml of AgNPs with different ratios like 1:0.1, 1:0.2, 1:0.4, 1:0.6, 1:0.8, 1:1, 1:1.2, & stir at RT for 5min. then each solution shows different color depending upon the thickness of the nanoshells. The resulting solution repeatedly centrifuge at 6000g for 10min. at RT.[3]

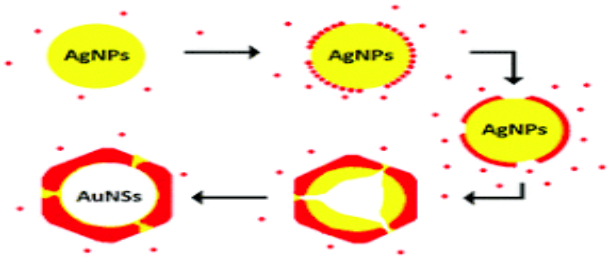

Fig. 4: Synthesis of extremely small gold nanoparticles.

Characterization

1. **Analysis by TEM:** Analysis of gold nanoshells by Transmission electron microscopy provides the morphological information, continuity of gold layer over the core, diameter of the nanoparticles, thickness of the gold over the core of silica.[1]

2. **EX:** JEOL JEM-2010 electron microscope operating at a bias voltage of 200kv.[2]

3. **Solubility of self-assembled monolayer-coated gold nanoshells:** To get an information about the formation of SAMS on their surfaces solubility of metal nanoparticles in various solvents can be used. The alkyl chain of alkanethiol based SAMS extend outward from the nanoparticles, increasing their solubility in nonpolar aprotic solvents (ex: hexane) but in not in water; in contrast, bare gold nanoparticles are soluble in water but insoluble in non-polar aprotic solvents. Alkenthiol-treated nanoshells are add into water, centrifuged it, decant the solvent, & redisperse them into following solvents; pentane, hexane, benzene, CCl_4, CH_2Cl_2, THF< ethanol & water. The test becames positive only if,first alkanethiols treated nanoparticles do not redispersed in water, second, even if they redisperse in CCl_4& ethanol, nanoshells should precipitate from these solvents after few hrs. Third, if the alkanethiol treated nanoshells are redispersed in pentane, hexane, benzene, CH_2Cl_2& THF, they should remain dissolved in solution even after 48hrs. [1]

4. **Analysis of X-ray photoelectron spectroscopy**
For X-ray photoelectron spectroscopy, a PHI5700 X-ray photoelectron spectrometer equipped with a monochromatic A1 K2 x-ray source (hv= 1486.7eV) incident at 90^0 relative to the axis of a hemispherical energy analyzer.[2] This analysis method provides atomic composition of the SAM & the underlying substrate as well as information related to the nature of the S-Au interactions. Spectroscopy should show only the presence of C,S,& Au. There is no silicon or oxygen should detect, it indicates complete coverage of the silica core by the overlying gold shell. [1]

5. **Analysis by FTIR:** FTIR analysis provides information related to the structure of SAMs on flat surfaces & on the surface of nanoparticles. The FTIR data were collected using a Nicolet MAGNA –IR 860 spectrometer. [2] FTIR shows the order & packaging of the alkyl chain extending away from the surface. For ex: characteristic bond positions and intensities for the C-H symmetric & antisymmetric stretches, which can offer insight into the conformational order & orientation of the alkyl chains of SAMs. Polyethylene use as a useful liquid &/or crystalline model for the methylene backbones of hydrocarbon SAMS. When dissolved in solution, the antisymettric {-(CH_2)-} bands & the symmetric (-CH_2-) bands appear at 2928cm^{-1} & 2856cm^{-1} resp. In crystalline form, the antisymmetric & symmetric bands appear at 2920cm^{-1} & 2850cm^{-1}. resp. [1]

6. Analysis by RAMAN spectroscopy

Analysis done by Nicolet Magna IR 560 ESP.[2] the symmetric bands are weak or almost unpredictable by FTIR, little information can be gleaned by IR analysis of the C-C region while RAMAN spectroscopy can readily detect symmetrical bonds, such as for those found in C-C backbones of SAMs. For alkanthoils SAMs analysis of thye C-S and S-H bonds by RAMAN spectroscopy provides structural and chemical insight into the interaction between the adsorbate & the underlying metal substrate. When chemisorption of gold, the S-H bond of alkanethiol is cleaved, upon examination of symmetric (S-H) band in free thiol & thiol nanoshell samples, the absorption step can be monitored. [1]

7. UV-Vis spectroscopic analysis

Analysis done by using Varian CARY 50 scan UV-Vis spectrometer over the range 300-1100nm. [2] Samples were dispersed in ethanol & loaded into a quartz cell for analysis. The position of the resonance is dictated by both the shell thickness & the size of the dielectric core. According to the rule of thumb,thick shells around small cores shows resonance in the visible region & thin shells around large cores shows resonance in the the medium in contact with the surface of the metal.[1]

Applications

1. Cell and phantom imaging

The optical properties of the gold nanoparticles show optical imaging of the cells & phantoms with a wide variety of contrast mechanisms. [5]

2. In vitro cancer detection & imaging: The cancer originate from a small number of malignant epithelial cells, nanoshells have ability to detect low numbers of malignant& precancerous epithelial cells. It detects the cancer at earliest stages, before any significant photogenesis, tumor formation & metastasis.[5]

3. Tissue welding: Nanoshells used to treat laceration in an emerging room setting.

Ex: Gabin etal have used nanoshells as an exogenous NIR absorber for welding deep tissue wounds. A nanoshells based solder (nanoshell + bovine serum album) applied to full thickness on rate incisions, incisions were irradiated with near infrared laser light for few minutes to initiate tissue welding. Healing results shows similar results with the suture treat control group until day 5, after that healing was shown to be better in the suture group.[1]

4. Biosensors: As biosensors nanoshells used for the sensitive detection of biosensors at the ng/ml level. [1]

5. Drug delivery: Drug release calculated by formula [4]

$$\text{Cumulative release (\%)} = \frac{\text{Amount of drug released}}{\text{Amount of drug in nanoparticles}} \times 100$$

A nanoparticle delivery system, consist of PEG coated gold nanoparticles loaded with the TNF-α was constructed to maximize the tumor damage & minimize the systematic toxicity of TNF-α. Local heating and nanoparticles based delivery of TNF-α on combination result in enhanced therapeutic efficacy. Nanoparticles when administered intravenously at the proper dosage and timing, it enhances the thermally induced tumor growth delay. Suppression of tumor blood flow as well as defect tumor perfusion. Suggested vascular damage mediated tumor cell killing. Following intravenous administration little to no accumulation in the reticuloendothelial system (ex: liver, spleen) or other healthy organ. [5]

Major application

To fight against cancer

Fig. 5: Gold nanoshells fighting with cancer.

Nanoshells can be designed to absorb light of different wavelength frequencies & generate heat.

When nanoshells administered intravenously it gets attached to the cancerous cells due to antibodies EGFR with the help of amine group which act as a catalyst. The nanoshells have ability to bind only EGFR receptor without disturbing cancerous cells.

When nanoshells attached to the cancerous cells, apply near infrared light which get absorbed by nanoshells, it creates an intense heat inside the nanoshells and get melts and burns the cancer cell and kills them without disturbing neighboring healthy cells.[7]

Example of gold nanoshells

Gold nanoshells of mesoporous silica loaded doxorubicin Doxorubicin hydrochloride is used for the treatment of different types of cancers, such as leukemia, breast cancer, ovarian cancer, various lymphomas, etc. It has disadvantages like cardiac toxicity, cardiomyopathy & congestive heart failure. [4]

Preparation method

A. Prepare mesoporous silica nanoparticles
B. Amino functionalization of mesoporous silica nanoparticles.
C. Prepare the seed solution and load the doxorubicin.

$$\text{Loading efficiency (\%)} = \frac{\text{Initial amt of doxorubicin} - \text{supernatant free amt of doxorubicin}}{\text{Initial amt of drug}}$$

D. Prepare pegylated gold nanoshells loaded with doxorubicin.[4]

The doxorubicin loaded nanoshells are 170nm in diameter. These nanoshells are characterized by TEM, energy dispersive X-ray analysis, UV absorption spectroscopy, dynamic light scattering zeta potential measurement & small angle X-ray diffraction. [6]Upon intravenous administration of these nanoshells are targeted to the cancer cells inhibit the growth of subcutaneous Ehrlich carcinoma in vivo & provide combined cancer chemo-photothermal therapy. Upon exposure of NIR radiations, the light energy converts into heat & affect the release rate of doxorubicin & kills the cancer cells photothermally. [4]

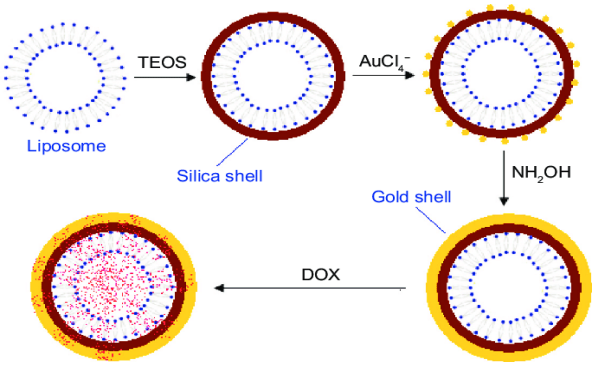

Fig. 6. Formation of DOX loaded gold nanoshells.

CONCLUSION

Here, we provide the simple & novel method for the synthesis of smallest gold nanoshells to date. Determined the various physical properties, which are important for their applications in biomedicine. These are monodispersed have negative charge, smallest average size i.e. 17-25±4nm. Cancer is easily treated with these gold nanoshells, when it is administered intravenously & exposed with NIR. It kills the cancer cells without disturbing healthy cells. The study provides the simple method for preparation of doxorubicin loaded mesoporous silica, & this formulation provides two oncological modalities: photothermal therapy& chemotherapy. This passively targeted nanocarriers has capability to convert NIR laser to heat which not only induced tumor cell damage but also triggered drug release with high therapeutic efficiency.

REFERENCES

1. N.Jadhav, M. Karpe, V. Kadam.GOLD NANOSHELLS: A REVIEW ON ITS PREPARATION CHARACTERISATION AND APPLICATIONS. Wjpps, 2014; 3(12): 1679-1691.
2. T. Pham, J. B. Jackson, N. J. Halas, and T.R. Lee.Preparation and Characterization of Gold Nanoshells Coated with Self-Assembled MonolayersLangmuir, 2002; 18(12): 4915-4920.
3. A.L. Duran-Meza, etal. Synthesis and characterization of extremely small gold nanoshells, and comparison of their photothermal conversion capacity with gold nanorods. Nanoscale, 2016; 8: 11091-11098.
4. N. Elbialy, N. Mohamed, A. S.Monem. Synthesis, characterization and application of gold nanoshells usingmesoporous silica core.Microporous and Mesoporous Materials, 2014; 190: 197–207.
5. P.Dron,S. Chaudhary, R. Shah and J. Sen.Gold Nanoshell: The Advancing Nanotechnology to Fightagainst Cancer.BBB. 2013; 023(34): 2347-2353.
6. W. Congyu,Y. Cong, W. Maoquan, A gold nanoshell with a silica inner shell synthesized using liposome templates for doxorubicin loading and near-infrared photothermal therapy. International journal of nanomedicine, 2011; 6: 807-813.
7. M. Nithyapriya and C.Chellaram. Gold Nanoshell: The Advancing Nanotechnology to FightAgainst Cancer.Indian Journal of Innovations and Developments, 2012; 1(8): 43-45.
8. D.V. Leff, L. Brandt, J.R. Heath. Synthesis and characterization of hydrophobic, organically-soluble gold nanocrystals funtionalized with primary amines. Langmuir, 1996; 12(20): 4723.
9. R.S. Ingram, M.J. Hostetler, R.W. Murray. Poly-hetero- ω- funtionalized alkanethiolatestabilized gold cluster compounds. J. Am. Chem. Soc., 1997; 119(39): 9175.
10. M.J. Hostetler, J.J. Stokes, R.W. Murray. Infrared spectroscopy of three dimensional selfassembled monolayers: N- alkenethiolate monolayers on gold cluster compounds. Langmuir, 1996; 12(15): 3604.
11. S.Francisco,R. Fernando, etal .Gold nanoshells: Contrast agents for cell imaging by cardiovascular optical coherence tomography. Nanoresearch, 2018; 11(2): 676-685.
12. T. S.Hauck & W.C. Chan. Gold nanoshell in cancer imaging and therapy: towards clinical application. Nanomedicine, 2(5): 735-738.
13. D.Zhan, J.Y. Li, X.C.Wang, H.X.Yue, etal. Preparation and evaluation of doxorubicin hydrochloride liposomes modified by poly (2-ethyl-2-oxazoline)-cholesteryl methyl carbonate Acta Pharmaceutica Sinica, 2015; 50: 1174-1179.
14. S.Huo, H. Ma, K.Huang, J.Liu, T.Wei, S. Jin, etal. Superior penetration and retention behavior of 50 nm gold nanoparticles in tumors Cancer Research, 2013; 73: 319-330.
15. E.A.Azzopardi, E.L. Ferguson andD.W.Thomas. The enhanced permeability retention effect: a new paradigm for drug targeting in infection Journal of Antimicrobial Chemotherapy, 2013; 68: 257-274.
16. S.Xing, X.Zhang, L. Luo, W. Cao, etal. Doxorubicin/gold nanoparticles coated with liposomes for chemo-photothermal synergetic antitumor therapy. Nanotechnology,2018 29(40).

17. M. Das, K.H. Shim, etal. Review on Gold Nanoparticles and Their Applications Toxicol. Environ. Health. Sci. 2011, 3(4), 193-205.
18. L.A. Porter, J. David, S.L. Westcott, M. Graupe, R.S. Czernuszewicz, N.J. Halas, T.R. Lee. Gold and silver nanoparticles functionalized by the adsorption of dialkyl disulfides. Langmuir, 1998; 14(26): 7378.
19. C.S. Weisbecker, M.V. Meritt, G.M. Whitesides. Molecular self-assembly of aliphatic thiols on gold colloids. Langmuir, 1996; 12(16): 3763.
20. S.R. Johnson, S.D. Evans, S.W. Mahon, A. Ulman. Alkenethiol molecules containing an aromatic moiety self-assembled onto gold clusters. Langmuir, 1997; 13(1): 51.
21. R.G. Nuzzo, F.A. Fusco, D.L. Allara. Spontaneously organized molecular assemblies. 3. Preparation and properties of solution adsorbed monolayers of organic disulfides on gold surfaces. J. Am. Chem. Soc., 1987; 109(8): 2358.
22. Y.-S. Shon, S. Lee, Jr., R. Colorado, S.S. Perry, T.R. Lee. Spiroalkanedithiol- based SAMs reveal unique insight into the wettability and frictional properties of organic thin films. J. Am. Chem. Soc., 2000; 122(31): 7556. www.wjpps.com 2014; 3(12): 1690.
23. M. Brust, J. Fink, D. Bethell, D.J. Schiffrin, C.J. Kiely. Synthesis and reactions of funtionalised gold nanoparticles. J. Chem. Soc., Chem. Commun., 1995; 16: 1655.
24. D.V. Leff, L. Brandt, J.R. Heath. Synthesis and characterization of hydrophobic, organically-soluble gold nanocrystals funtionalized with primary amines. Langmuir, 1996; 12(20): 4723.
25. R.S. Ingram, M.J. Hostetler, R.W. Murray. Poly-hetero- ω- funtionalized alkanethiolatestabilized gold cluster compounds. J. Am. Chem. Soc., 1997; 119(39): 9175.
26. M.J. Hostetler, J.J. Stokes, R.W. Murray. Infrared spectroscopy of three dimensional selfassembled monolayers: N- alkenethiolate monolayers on gold cluster compounds. Langmuir, 1996; 12(15); 3604.
27. L.R.Hirsch' S R.J. Stafford, J.A. BanksonN.JHalas, etal. Nanoshell–mediated Near–infrared Thermal Therapy of Tumors Under Magnetic Resonance Guidance. Proc Natl Acad Sci USA. 2003; 100: 13549-13554.
28. L.A. Porter, J. David, S.L. Westcott, M. Graupe, R.S. Czernuszewicz, N.J. Halas, T.R. Lee. Gold and silver nanoparticles functionalized by the adsorption of dialkyl disulfides. Langmuir, 1998; 14(26): 7378.