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A Review on Multifunctional Nanoshells and Its Therapeutic Applications

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ABSTRACT: Nano shells are a kind of spherical nanoparticles which consist of a silica dielectric core covered by a thin metallic shell (mostly gold). These are novel classes of nanoparticles that exhibit novel properties which differ from other drug delivery systems. They exhibit collective excitation/oscillation i.e. oscillate simultaneously and are termed as Nanoshell Plasmon. Optical response/surface plasmon resonance is highly dependent upon the dimensions of the core that can be tuned by bringing about simple adjustments in the thickness of the shell so that the properties of NS can also be altered to the desired range. These are being proved to be multifunctional particles in various fields which include-optical, biomedical imaging, target therapy, gene delivery, tissue welding, drug delivery systems, therapeutic applications in general as well as cancer imaging and treatment in particular. Mechanism of action is through electro-chemical detection and these NS are known as biomarkers (detect infected cells/tissues).

KEY WORDS: Nano shells, Multifunctional, Surface plasmon resonance, Dielectric core, Cancer therapy, Biomarkers.

I. INTRODUCTION:

Definition of Nanoparticles: The particles of size less than 1micrometer or size ranging between 1-100 nanometers are known as nanoparticles. These are not detected by the human eye and can exhibit prominently varying physical and chemical properties.

Definition of Nanoshells: It is a spherical nano-particle that consists of a dielectric core covered by a thin metallic shell (specifically gold) whose size ranges from 10-40nm in diameter and common SPR peak from 500-600nm.

Nanoparticles covered with thin metallic shells, mostly gold and carrying a dielectric core4 are termed as nano shells. They exhibit collective excitation or oscillations which are referred as Nano Plasmonic. Nanoshells plays a vital role in diagnosis and extends its application even in therapy of many disease conditions.[1] The mechanism by which they act is by electrochemical detection, in which firstly the standard electrode is coated with chitosan, a complex sugar, followed by coated with gold nano-particle such that it provides electrical conductivity, a phenomenon responsible for adhering the cancer cells.[2]

SYNTHESIS OF NANOSHELLS

The steps involved in the synthesis of nanoshells are:

Synthesis of the dielectric core material followed by surface functionalization with terminal amine groups to facilitate the attachment of gold/silver colloids.

SYNTHETIC METHODS OF PREPARATION OF NANOSHELLS: [3-9]

1) Reduction of HA $_4Cl_4$ silver nanoparticle templates.
2) Surfactant assisted seeding method.
3) Single step deposition-precipitation seeding.
4) Sonochemical gold seeding method.
5) Sandwiched gold seeded shell synthesis.
6) One pot synthesis.
7) Templated galvanic replacement of silver nanoparticle.
8) Sacrificial galvanic replacement of cobalt nanoparticles.

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9) Electrochemical synthesis.
10) Sacrificial template method.
11) Standard lithographic method.

1. Explanation of Reduction of HA $_4$Cl $_4$ onto silver nanoparticle templates method:

An aptamer-AS1411- which is selective towards the nucleolus with a terminal thiol group has been conjugated to hollow gold nanoshells (HGNs).This step is followed by surface fictionalization of synthesized nanoparticles in order to attain affinity to the tumour cells, thus allowing the selective drug delivery to the targeted site.

2. Explanation of surfactant assisted seeding method:

Silica nanoparticles are primarily synthesized.3-amino propyl tri ethoxysilane (APTES) as a linker is condensed onto their surface that provides desired NH_2 groups which could link to gold. After separation of organosilane functionalized silica nanoparticles, gold colloidal solution is added to the mixture. Immediately after the binding of gold nanoparticle seeds to silica nanoparticles, excess seeds are removed.

3. Explanation of single step deposition-precipitation seeding method:

This method is widely used to form supported nano-particulate gold catalysts for carbon monoxide formation at low temperatures. Deposition-precipitation forms gold seeds on silver nanoparticles directly. Their surface is subsequently decorated with APTES as a linker. These silica nanoparticles with terminal amine groups are then seeded with Au $(OH)_3$ nanoparticles.

There are a wide range of applications of nanoshells like

APPLICATIONS OF NANOSHELLS:

1. As mediators of photo thermal cancer therapy.
2. Cancer detection, treatment, research.
3. Optically controlled micro fluidic valves.
4. In first stage clinical trials as therapeutic agents in the treatment of head and neck cancers.
5. Medical biosensing.
6. Cellular imaging.
7. Whole blood immunoassay.
8. Modulated drug delivery.
9. Optical imaging contrast agents.
10. Gold encased nanoshells have been used to convert light into heat, enabling destruction of tumours by selective binding to malignant cells.
11. Nanoshells can be embedded in hydro gel polymers containing drugs.
12. Used as a waterproof coating for wood, metals etc.

MULTIFUNCTIONAL NANOSHELL IN DIAGNOSIS AND THERAPY:

BIOMARKER AND BIOSENSING:

Nano shells exhibit varied functions, where the role in contrast imaging has become certain due to its nature of being a biomarker, it can selectively identify the infected tissue. In addition to this, they extend their role in biosensing the presence of chemical and biological agents such as drugs, viruses etc. where it exhibits the signal characteristic to viruses and thereby detect their presence or absence[2]. VIPER utilizes the peptide fusion tag (coil E) which forms alpha helical hetero dimer with the protein of interest by conjugating with the labelled probe (coil R) resulting in the formation of labelled protein that enables the study of intracellular proteins. The hollow gold nanoshells aids in the internalization of labelled probe [10]

HEAVY METAL POISONING

As the mercury poisoning is the common heavy metal poisoning in most of the people working in coal-based power plants. The measure of mercury level in urine can be one of the best ways of the diagnosis, since the mercury is excreted through the kidneys.[11]

DETECTION OF TUMOUR CELLS

The gold nanoshells have relatively varied thickness of core and outer shell, which enable them to absorb and scatter the light over a broad region i.e. UV-IR, thereby facilitating the detection of tumor cells in optical coherence tomography imaging study. Apart from detecting the specific Ag on the cancer cell, a nano shell conjugated with HER-2 antibody destroys the specific HER -2 antigens that are over expressed on the breast tissue [12]. Similarly, it includes the detection of prostate specific antigen, where the presence of intracellular pores in the cancer cells, allows the passive transport of nano shells - conjugated with antibodies with no difficulty. Furthermore, the prostate cancer cells are destroyed due to the heat released by nanoshells.[13] There is a

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large number of macrophages observed in plagues, which further gets ruptured and enhances the risk of stroke. The nano clusters work more efficiently in destroying the macrophages than the original gold nano particles, as these nano clusters exhibit luminescence property due to decreased thickness of gold coating in them. [14]

SELF-REPAIRING MECHANISM

Most of the traditional nano structured shells gets affected by cell division and lose their coating, therefore new technique called self-repairing mechanism has been evolved by nano shells, where bio-hybrid aggregates are dispersed in PBS in the first step, followed by shake it gently at room temperature after adding the aggregates to clean cell solution, thus nano shell exhibits cell protection phenomenon. [15]

PHOTOTHERMALLY BASED DRUG DELIVERY

As it is clear that gold nano shell possess multifunctional ability, it is used in photothermally based drug delivery system when it is conjugated with protein avidin after incorporating the shell with temperature responsive poly iso propyl acrylamide-co-acrylic acid hydrogel, which is responsible for exhibiting plasmon resonance at 800, that ultimately indicates its role in biomedical application as it is considered as the important spectral range [16]. Melanin shows its beneficial effects in revealing the deep imaging system whereby PEG-melanin nanoparticles are used in photoacoustic imaging and diagnosis of certain signals at the tumor site. They act as antioxidants and improve the condition of brain damage to ischemic stroke caused by reactive oxygen species [17] .Gold nano shell stimulates the inflammation of some complex that is activated by the toll like receptors and release of pro-inflammatory mediators for generation immune response , stimulation of inflammation of some complex results in apoptosis of the tumor cell. [18]

PHOTOACOUSTIC AGENT IN IMAGING

Gold nanoshells when conjugated with the tumor specific ligands, they act as a best photoacoustic agent in imaging the melanomas and other cancers. Nano shell when combined with anti-chemokine core receptor antibody, it helps in understanding the mechanism of T-IIV infection since the chemokine core receptor is an important for virus attachment to host cel1[19] In the same way nano shell conjugated with anti VCAM antibody helps in detection of adhesion molecule on the endothelial cells VCAM-l overexpression in atherosclerotic lesion, one of the factor i.e, epidermal growth factor overexpression is certain in most cancer ,therefore use of nano shell conjugated with anti EPGR antibody can detect the EPGR antigen in the cancer cells specifically oral epithelial cancer can be diagnosed by looking at the sharp plasmon resonance exhibited at the absorption band.[20 , 21]

DETECTION OF METABOLITES

Usually, the metabolites in the body are detected by laser desorption ionization (mass spectroscopy), using plasmonic gold nanoshells. Nonetheless, recent studies indicate that use of silver plasmonic nanoshells has been considered as the best option due to their quick and selectivity characteristics, thus evolving their role in detection of small metabolites in biofluid [21, 22]. At times high intensity ultrasound was used as ablation therapy and MRI was used for the detection. During this process there was a report of patient discomfort. In order to avoid such discomfort,a sensitizing agent biodegradable perfluoropentacene nano shell was synthesized to replace the use of MRI and results in mechanical ablation of tumor. [23]

METAL ION DETECTION

Metal ion homeostasis is vital in the living cell for proper functioning of the body, whereby the detection of metal ions becomes important which can be carried out by DNA enzymes due to their enzymatic reaction in presence of metal cofactors . Nevertheless there is disadvantage too as they react with extracellular metal ions and cleave its substrate prior to their entry to desired location. Therefore nano shell that can absorb near infrared light is utilized for metal ion detection that can control the DNA enzymes activity resulting in dehydration of DNA -active DNA- cleavage and the cleaved product exhibits fluorescence helps in Zn+2 detection. [22]

Nanoshell Acts Against Trustuzumab Resistance By Triple Way (Immunotherapy+Gene+Thermal Therapy)

As we know the breast cancer cells over express the JWR-2 receptors, trustuzumab is administered that specifically targets these receptors, the studies reveal that most patients exhibit resistance to this drug. To overcome this gold carrier drug system where it includes the combination of small inference RNA that targets L-

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IER-2, immunoadjuvant oligo deoxynucleotides containing cytosine and guanine (CPG) that modulates immune system in order to kill the cancer cells were incorporated. Apart from this gene therapy of SiRNA and immunotherapy there was thermal therapy of gold nanoshells resulting in synergistic killing activity of tumor cells. [17, 24]

NANOSHELL FOR CONTROLLED DRUG DELIVERY

Nano shell is prioritized among other nanoparticles due to its characteristic features of low toxicity. Optical resonance properties and biocompatibility[25] .Its optical properties leads to the thermal ablation of tumors by penetrating deep into tissues. They also exhibit the phenomenon of efficient drug delivery due to the above properties for example, hollow gold nanoshells when conjugated with doxorubicin it binds to HDLM 2 lymphoma cells aids in release of doxorubicin to act specifically on target cells. Instead of using the cytotoxic drugs alone they are conjugated with ligands (nano shell) forming as nano-complexes for maintaining sustained drug release, by enhancing the specific target tissue binding capacity. [26]

NANOSHELLS AS CARRIERS

Nanoshells acts as a carrier for most of the hydrophobic drugs for example paclitaxel, where nano shell is synthesized by alkylated derivative of hyaluronic acid ,nevertheless this is degraded by hyaluronase enzyme over expressed in the breast cancer cell, therefore the hydrophobic drug is entrapped in this after adding a biodegradable polymer to form polyelectric multilayer films which promote the release of paclitaxel at the specific tissue due to slight degradation of the derivative by the enzyme.[27]

II. CONCLUSION

From the content mentioned above it is clear that nanoshells have drawn a lot of attention in the field of sensing and therapy in the last few years due to their intriguing physical properties which include optical & surface plasmon resonance which can be tailored during the synthetic methods. Shape controlled synthesis of Nanoshells has resulted in the practical advancement in their utilization in various fields. There are various synthetic methodologies which have met their own challenges. It has applications in various disciplines of pharmaceutical sciences & technology, diagnosis, biosensing, engineering. Based upon the collaborative effort of expertise personnels world wide regarding the research on nanoshells, it was compiled that there are developments in this field at present as well as in future. As per the significant potential presented by the nanoshells in resolving key aspects, it is trusted that the synthetic evolution continues & new methodologies will be developed.

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