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Silver Nanoparticles – Universal Multifunctional Nanoparticles for Bio Sensing, Imaging for Diagnostics and Targeted Drug Delivery for Therapeutic Applications

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1. Introduction

Nanotechnology is a multidisciplinary scientific field undergoing explosive development. Nanometer-sized particles offer novel structural, optical and electronic properties that are not attainable with individual molecules or bulk solids. Advances in nanomedicine can be made by engineering nanoparticles that are capable of targeted delivery of drugs. This leads toward the concept and possibility of personalized medicine for the potential of early detection of diseases and most importantly, molecular targeted therapy. Promoting nanotechnology for diagnosis, prevention and treatment is the focus of the recently developing multifunctional nanotechnology. Engineered nanoparticles have the potential to revolutionize the diagnosis and treatment of many diseases; for example, by allowing the targeted delivery of a drug to particular subsets of cells. However, so far, such nanoparticles have not proved capable of surmounting all of the biological barriers required to achieve this goal. Nevertheless, advances in nanoparticle engineering, as well as advances in understanding the importance of nanoparticle characteristics such as size, shape and surface properties for biological interactions, are creating new opportunities for the development of nanoparticles for therapeutic applications.

Silver nanoparticles as an arch product from the field of nanotechnology, has gained interest because of distinctive properties, such as good conductivity, chemical stability, catalytic , antibacterial activity, antifungal, anti-viral, anti-inflammatory (Mukherjee et al., 2001; Sondi and Branka, 2004; Chen and Schluesener, 2008). Silver-based medical products, ranging from topical ointments and bandages for wound healing to coated stents, have been proven to be effective in retarding and preventing bacterial infections (Chen, 2007). Improvements in the development of novel silver nanoparticles-containing products are continuously sought. In particular, there is an increasing interest towards the exploitation of silver nanoparticles technology in the development of bioactive biomaterials, aiming at combining the relevant antibacterial properties of the metal with the peculiar performance of the biomaterial.

Compared with larger particles of the bulk material nanoparticles exhibit completely new or improved properties based on specific characteristics such as size, distribution and morphology. Nanoparticles present a higher surface-to-volume ratio is relevant for catalytic reactivity and other related properties such as antimicrobial activity in silver nanoparticles.

Nanoenabled drug delivery has already been successful in delivering drugs to specific tissues within the body, and promises capabilities that will enhance drug penetration into cells, as well as other means to improve drug activity. A very promising prospect of nanoparticles is its use in targeted drug delivery and also “multi-targeting”, which is essential in the case of several diseases (Woodleand and Lu, 2005).

Recently, synthesis of silver nanoparticles has attracted considerable attention owing to their diverse properties like catalysis (Shiraishi and Toshima, 2000), magnetic and optical polarizability (Shiraishi and Toshima, 2000), electrical conductivity (Chang and Yen, 1995), antimicrobial activity (Sharverdi et al., 2007) and Surface Enhanced Raman Scattering (Matejka et al., 1992).

Recently it was shown that highly concentrated and nonhazardous nanosized silver particles can easily be prepared in a cost-effective manner and tested as a new type of bactericidal nanomaterial.

2. Synthesis of silver nanoparticles

The synthesis of metal nanoparticles is an expanding research area due to the potential applications for the development of novel technologies.

Silver nanoparticles have increasingly attracted more attentions because of their promising applications in the fields of catalysis (Musi et al., 2009; Shin et al., 2009; Tian et al., 2009) electronics, (Xia et al., 2003) sensing, (Guo et al., 2009; Zhao et al., 2009) and surface-enhanced Raman scattering, (Sun et al., 2009). For most applications, the properties of metal nanoparticles are determined by their size, shape, composition, and structure (Skrabalak and Xia, 2009; Xia et al., 2009). It is of great importance to prepare high quality silver nanoparticles with controllable chemical-physical properties.

Generally, nanoparticles are prepared by a variety of chemical and physical methods such as chemical reduction (Yu, 2007; Tan et al., 2002; Petit et al., 1993; Vorobvova et al., 1999), photochemical reduction (Vorobvova et al., 1999; Mallick et al., 2005; Keki et al., 2000; Pileni, 2000; Sun et al., 2001), electrochemical reduction (Liu and Lin, 2004; Sandmann et al., 2000), heat vaporation (Bae et al., 2002; Smetana et al., 2005) etc. These reagents could be inorganic such as sodium/potassium borohydrate, hydrazine and salts of tartarate, or organic ones like sodium citrate, ascorbic acid and amino acids capable of being oxidized. Various reagents have been reported to serve as stabilizing agent.

A number of reports adjusted the shape and size of silver nanoparticles using capping agents such as dendrimer, (Esumi et al., 2004) chitosan, (Murugadoss and Chattopadhyay, 2008) ionic liquid, (Zhang et al., 2009) and poly(vinylpyrrolidone) (PVP) (Sun and Xia, 2002), based on controlling the growth of silver nanoparticles through reaction confinement within the matrix or through preferential adsorption on specific crystal facets.

Most of these methods are extremely expensive and they also involve the use of toxic, hazardous chemicals which are not environmental friendly.

The biomedical applications of silver nanoparticle can be effective by the use of synthesized nanoparticles which minimize the factors such as toxicity and cost and are found to be exceptionally stable like other nanomaterials. Hence the development of better experimental

procedures for the synthesis of nanoparticles of different chemical compositions, sizes, shapes and controlled polydispersity is vital for its advancement (Bhattacharya and Mukherjee, 2008).

Recently, a number of inorganic nanomaterials have been synthesized by bioreduction processes employing different microorganisms. Nanocrystals of gold, silver and their alloys have been synthesized within cells of lactic acid bacteria (Nair and Pradeep, 2002), *Pseudomonas stutzeri* AG259, (Joerger et al., 2000; Klaus et al., 2001). In addition, eukaryotic organisms such as fungi have also been used to grow nanoparticles of different chemical composition and sizes like *Verticillium sp.* (Mukherjee et al., 2001); *Fusarium oxysporum* (Ahmad et al., 2003) and *Aspergillus flavus* (Vigneshwaran et al., 2003) and also with enzymes (Willner et al., 2006). On the other hand, to mimic natural biomineralization, even live plants have been studied as templates for silver nanoparticles synthesis (Sanghi and Verma, 2009).

Synthesis of nanomaterial such as silver, gold, platinum and palladium using plants or plant extracts (Shankar et al., 2004) have been suggested as possible ecofriendly alternatives to chemical and physical methods. Nanoparticles synthesis using plants can be advantageous over other biological processes because it eliminates the elaborate process of maintaining cell cultures and can also be suitably scaled up for large-scale synthesis of nanoparticles (Shankar et al., 2004). Bioreduction of gold and silver ions to yield metal nanoparticles using living plants, (Gardea-Torresdey et al., 2003; Gardea-Torresdey et al., 2005), Geranium leaf broth (Shivshankar et al., 2003), Neem leaf broth, (Shivshankar et al., 2004) Lemongrass extract (Shivshankar et al., 2005), Tamarind leaf extract (Ankamwar et al., 2005) and Aloe Vera plant extracts (Prathap et al., 2006), have been reported.

Kasthuri et al., (2009) adopted a bioreductive approach of anisotropic gold and quasi-spherical silver nanoparticles by using apiin compound. Kasthuri et al., (2009) synthesized the anisotropic gold and spherical- quasi-spherical silver nanoparticles using extract of phyllanthin at room temperature. Spent mushroom substrate (Vigneshwaran et al., 2007), *Gliricidia sepium* extract (Jae Yong Song and Beom Soo Kim, 2008; Raut Rajesh et al., 2009) and *C. zeylanicum* bark powder (Sathishkumar et al., 2009) were used to synthesize nanoparticles. Krishna raj et al., (2010) studied the rapid synthesis of silver nanoparticles using aqueous leaves extract of *A. indica* and evaluated its antibacterial activity against water borne pathogens such as *Escherichia coli* and *Vibrio cholerae*. Daizy Philip (2009) studied mushroom mediated green chemistry approach towards the synthesis of gold, silver and gold-silver nanoparticles. Synthesis of metallic nanoparticles using green resources like *Jatropha* (*J. curcas* latex) (Harekrishna Bar et al., 2009), Hibiscus, (Daizy Philip, 2010), *Ocimum tenuiflorum* (Kiruba Daniel et al., 2011b) and *Achyranthus aspera* (Kiruba Daniel et al., 2011c).

Silver nanoparticles can be synthesized and stabilized by peptides, proteins, DNA and chemical/biological polymers (Sengupta et al., 2009; Shemer et al., 2006). Several synthesis methods exist thus displaying different characteristics of the nanoparticles (Kiruba Daniel et al., 2010, 2011a 2011d; Nimroth Ananth et al., 2011)[Figure-1]

3. Characterization

Basically nanoparticles can be spectroscopically characterized on the basis of their sizes and the method can reveal the concentration of the synthesized nanoparticles too.

Nanoparticles are characterized by a variety of techniques such as dynamic light scattering (DLS), electron microscopy (TEM or SEM), atomic force microscopy (AFM), fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), powder X-ray diffraction (XRD), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), and magnetic resonance (NMR).

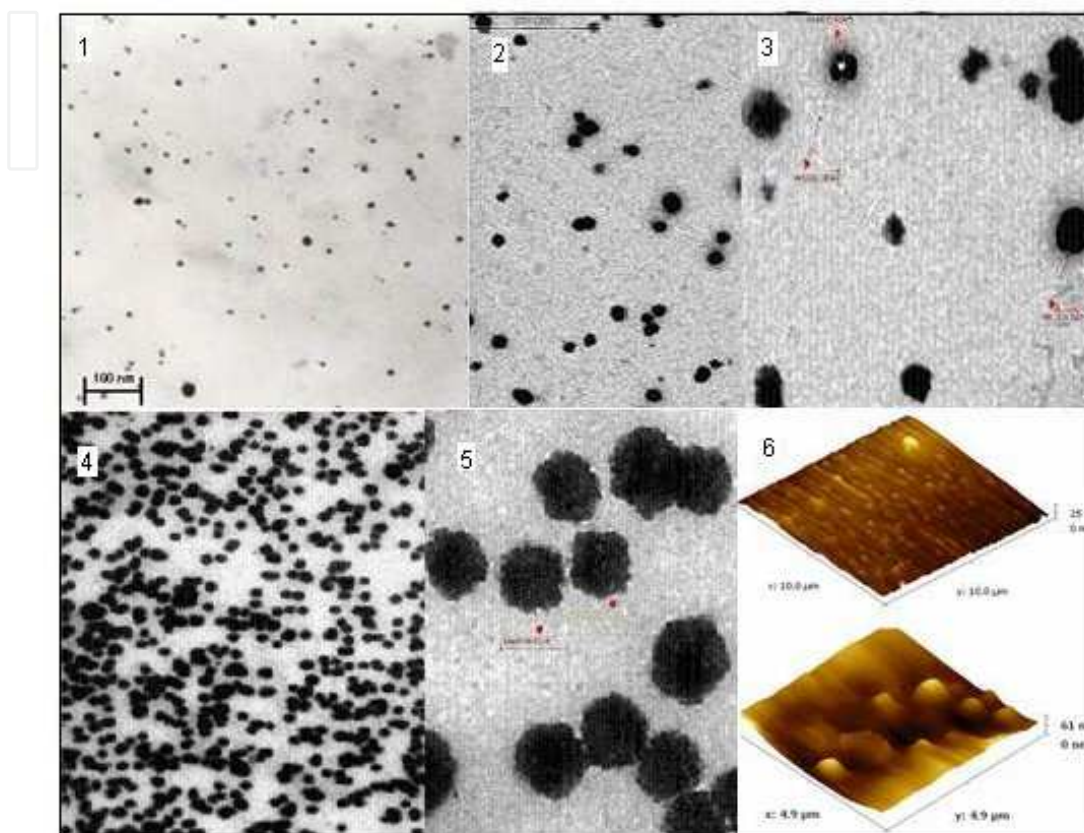


Fig. 1. Transmission electron microscopic pictures of Silver nanoparticles prepared using starch (1) , Plant extracts (2),(4) lower magnification , 3 & 5 higher magnification and atomic force microscopic picture of silver nanoparticles prepared using polyvinyl alcohol (top) and Bovine serum albumin (bottom)(6)

4. Structure and functional properties of nanoparticles

Most inorganic nanoparticles share the same basic structure. This consists of a central core that defines the fluorescence, optical, magnetic, and electronic properties of the particle, with a protective organic coating on the surface. This outside layer protects the core from degradation in a physiologically aggressive environment and can form electrostatic or covalent bonds, or both, with positively charged agents and biomolecules that have basic functional groups such as amines and thiols. Several research groups have successfully linked fluorescent nanoparticles to peptides, proteins, and oligonucleotides.

Of the three metals (silver, gold, copper) that display plasmon resonances in the visible spectrum, silver exhibits the highest efficiency of plasmon excitation (Kneipp et al., 2002). Moreover, optical excitation of plasmon resonances in nanosized silver particles is the most efficient mechanism by which light interacts with matter. A single silver nanoparticle

interacts with light more efficiently than a particle of the same dimension composed of any known organic or inorganic chromophore. The light-interaction cross-section for Ag can be about ten times that of the geometric cross-section, which indicates that the particles capture much more light than is physically incident on them (Esumi et al., 1997). Silver is also the only material whose plasmon resonance can be tuned to any wavelength in the visible spectrum.

The UV-Visible absorption spectrum of this preparation is given in Figure 2. The typical peak at 420 nm corresponds to the characteristic surface plasmon resonance of silver nanoparticles. Also, the plasmon band is symmetric which indicates that the solution does not contain many aggregated particles, a conclusion that agrees with the electron micrograph observation (below). It is well known that colloidal silver nanoparticles exhibit absorption at the wavelength from 390 to 420 nm due to Mie scattering (Kleemann, 1993). Hence, the band at 420 nm can be attributed to the property of Mie scattering. This may not include the protecting agent, because the Mie scattering responds only to the silver metal (Aoki, 2003). The plasmon bands are broad with an absorption tail in the longer wavelengths, which could be in principle due to the size distribution of the particles (Chalmers, 2002). Since the varying intensity of the plasmon resonance depends on the cluster size, the number of particles cannot be related linearly to the absorbance intensities (Klabunde, 2001).

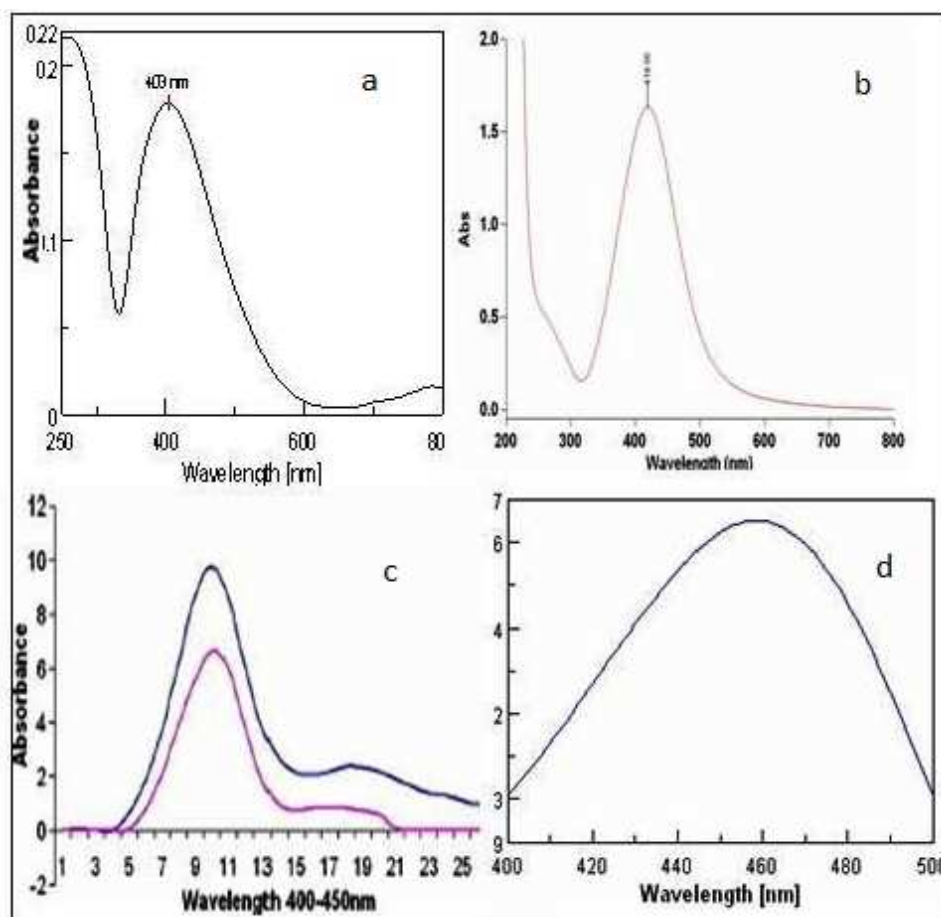


Fig. 2. UV-Visible spectral pattern of Clay stabilized(a), Starch stabilized (b), polyvinyl alcohol (Ag-PVA) and Bovine serum albumin (Ag-BSA) stabilized(c) and Plant extract stabilized (d) silver nanoparticles.

According to Mie's theory, only a single SPR band is expected in the absorption spectra of spherical nanoparticles, whereas anisotropic particles could give rise to two or more SPR bands depending on the shape of the particles. The number of SPR peaks increases as the symmetry of the nanoparticle decreases (Esumi et al., 2004; Murugadoss and Chattopadhyay, 2008; Zhang et al., 2009) [Figure-2].

5. Advantages of nanoparticles

- a. Longer shelf-stability
- b. High carrier capacity
- c. Ability to incorporate hydrophilic and hydrophobic drug molecules
- d. Can be administered via different routes
- e. Longer clearance time
- f. Ability to sustain the release of drug
- g. Can be utilized for imaging studies
- h. Increase the bioavailability of drugs
- i. Targeted delivery of drugs at cellular and nuclear level
- j. Development of new medicines which are safer
- k. Prevent the multi-drug resistance mediated efflux of chemotherapeutic agents
- l. Product life extension
- m. Does not involve higher manufacturing costs and decrease in the cost of formulation
- n. Does not involve use of harsh toxic solvents in the preparation process
- o. Does not trigger immune response and allergic reactions
- p. Tissues take only optimum concentrations nanoparticles and hence drug over dose does not occur

First-generation nanoparticles have been clinically translated as pharmaceutical drug delivery carriers for their ability to improve on drug tolerability, circulation half-life, and efficacy. Toward the development of the next-generation nanoparticles, researchers have designed novel multifunctional platforms for sustained release, molecular targeting, and environmental responsiveness.

6. Toxicity, immunological activity and pharmacodynamics *in vivo* and *in vitro* system

The lack of information regarding the toxicity of manufactured nanoparticles poses serious problems. Understanding the unique characteristics of engineered nanomaterials and their interactions with biological systems is key to the safe implementation of these materials in biomedical diagnostics and therapeutics and hence, the potential toxicity, the biological distribution and cellular uptake of silver nanoparticles were studied. For nanoparticles, like conventional chemical compounds, there are three main routes of exposure: inhalation, skin absorption and ingestion. It should be noted that nanoparticles have certain intrinsic properties (such as pinocytosis) that make it easy for them to enter cells. At the cellular level, nanoparticles can be found in various compartments, and even in the cell nucleus, which contains all the genetic information (Lovric et al., 2005; Asharani et al., 2009).

The animal study in swiss mice demonstrated that the silver nanoparticles were

1. non toxic, 2. showed no immune response. The silver nanoparticles were distributed in all organs (Figure 3 and 4) including liver and spleen that contained phagocytes similar to that

observed by Raynal et al., (2004); Bourrinet et al., (2006); Briley-Saebo et al., (2006); Chang et al., (2006) and Cai et al., (2007) in the case of iron oxide nanoparticles and AUNP-PEG nanoparticles because of the absence of renal excretion by glomerular filtration, as the size of the nanoparticles was larger (20 nm). In general, the spacing of cell membranes is in the range of 6 to 10 nm and the macromolecular contrast agents with a molecular size of less than 8 nm in diameter are cleared from blood by glomerular filtration and by tubular excretion of the kidney (Kobayashi et al., 2004) although the electrostatic charge properties of those particles also have a significant role in their ability to penetrate the glomerular basement membrane. Garnacho et al., (2008) have demonstrated enhanced accumulation of anti-ICAM/I125 ASM nanocarriers in the kidney, heart, liver, spleen and primarily the lungs both in wild type and ASM Knockout mice.

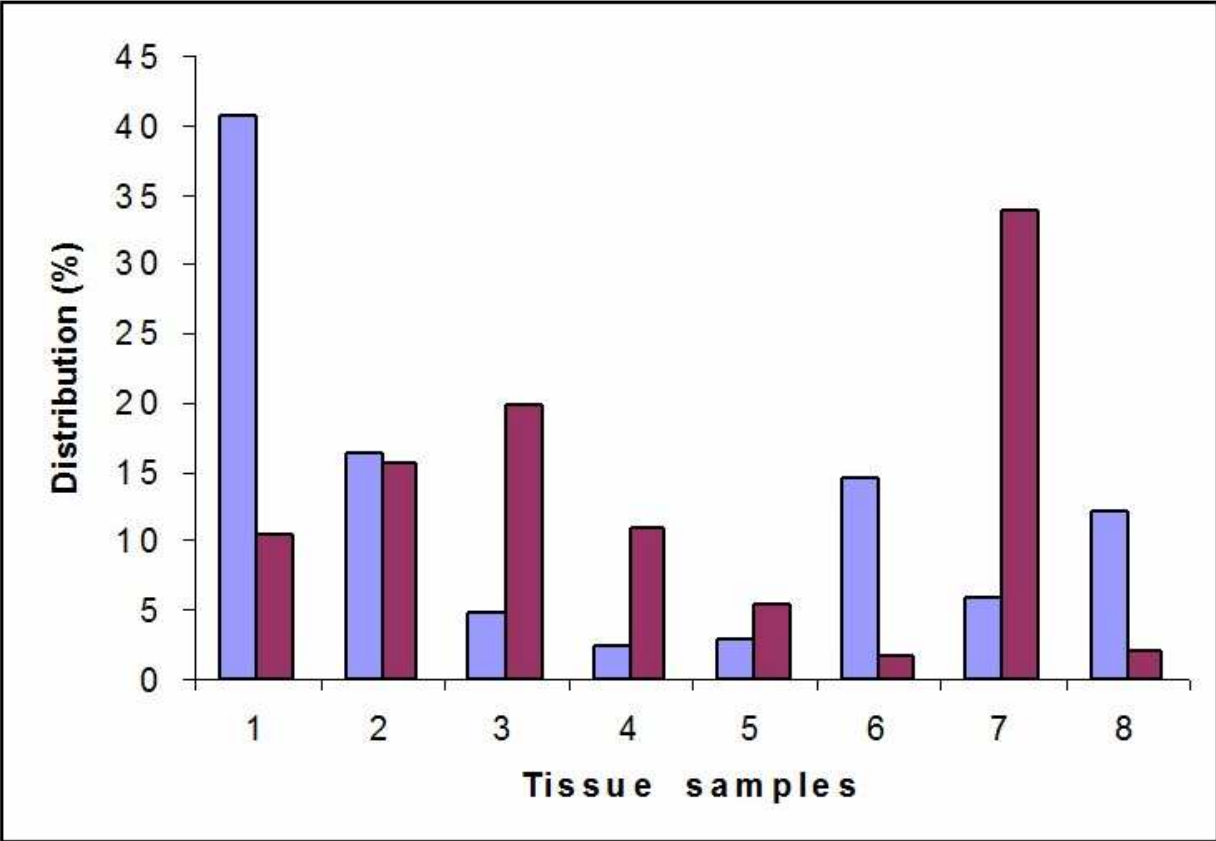


Fig. 3. Distribution pattern of Silver - polyvinyl alcohol / Silver - Bovine serum albumin nanoparticles in 1.Liver 2.Kidney 3.Spleen 4.Lungs 5.Heart 6.Intestine 7.Brain 8.Blood (420nm)

The presence of nanoparticles in the brain (Figure 5) indicated the penetration of nanosilver materials across the blood brain barrier (BBB) without producing apparent toxicity but upregulating the brain function by increasing the glutamine synthase activity of the brain that is important for neurotransmission and other activities. The nanoparticles were detected in the brain in UV-Visible analysis. To evaluate the potential effects of silver nanoparticles on brain neurophysiology, the level of glutamine synthase was tested. Approximately a two fold increase in the glutamine synthase activity was found. Glutamine synthase is the key enzyme responsible for the conversion of glutamate to glutamine and for

the detoxification of ammonia in the brain (Caroline et al., 1999). Reactive oxygen radicals are known to cause the reduction in specific activity of glutamine synthase (Friedman and McDonald, 1997). The higher glutamine synthase activity indirectly showed the low level of free radicals.

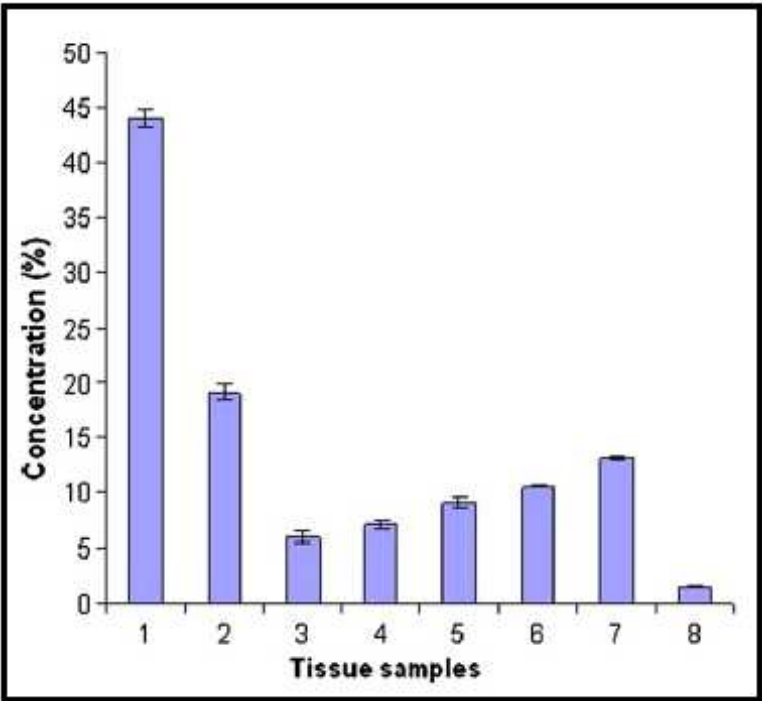


Fig. 4. Concentration of immuno-precipitated Silver – Bovine serum albumin(Ag-BSA) nanoparticles with rabbit antiBSA antibody in 1. Liver 2.Kidney 3.Spleen 4.Lungs 5.Heart 6.Intestine 7.Brain 8.Blood of mice as per the UV-visible spectrum pattern.

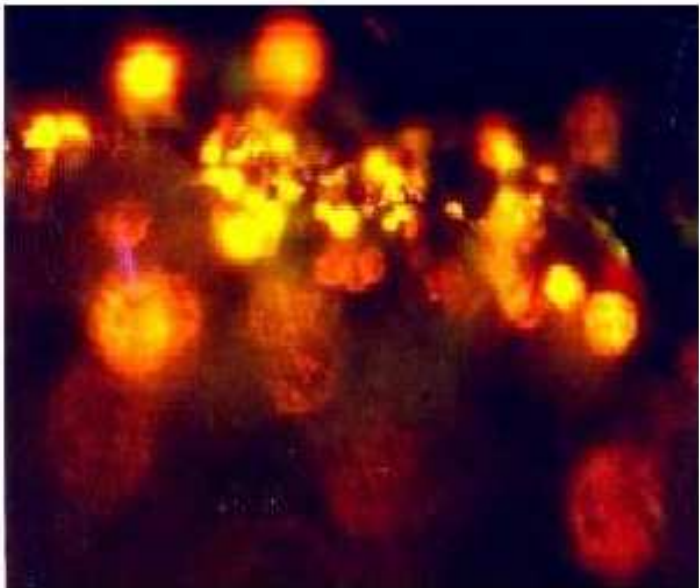


Fig. 5. Fluorescent microscopic images of Silver-Starch treated rat brain cells in suspension.

The silver nanoparticles were observed in other tissues especially in lungs at saturation with 5mg dose and no increase in uptake was observed in lungs when 20mg of silver nanoparticles were given revealing that the lung attained saturation at exposure to 5mg or less than that of silver nanoparticles. Increased half-life of silver nanoparticles in blood observed in this study was also reported earlier by Kobayashi et al., (2004) for AUNPs-PEG. Hainfeld et al., (2006) showed that the blood half-life of ultra small particles was increased by the redirection of the elimination pathways from reticulo-endothelial system to the mononuclear phagocyte systems with reference to gold nanoparticles. The lower concentration of silver nanoparticles particles in the spleen may be the reason for the less immune response.

7. Applications

Nanomaterials are at the leading edge of the rapidly developing field of nanotechnology. Their unique size-dependent properties make these materials superior and indispensable in many areas of human activity.

Living organisms are built of cells that are typically 10 μm across. The proteins are a typical size of just 5 nm, which is comparable with the dimensions of smallest man made nanoparticles. This gives an idea of using nanoparticles as very small probes that would allow unraveling and studying all physiological mechanism at the cellular machinery without introducing too much interference. Understanding of biological processes on the nanoscale level is a strong driving force behind development of nanotechnology.

A list of some of the applications of nanomaterials to biology or medicine is given below:

- Fluorescent biological labels - Drug and gene delivery - Bio detection of pathogens - Detection of proteins - Probing of DNA structure - Tissue engineering,- Tumor destruction via heating (hyperthermia) - Separation and purification of biological molecules and cells - MRI contrast enhancement - Phagokinetic studies and to use nanoparticles as biological tags.

8. Antimicrobial activity

Silver has long been known to exhibit a strong toxicity to a wide range of micro-organisms [5]; for this reason silver-based compounds have been used extensively in many bactericidal applications [6]. Silver compounds have also been used in the medical field to treat burns and a variety of infections. Several salts of silver and their derivatives are commercially employed as antimicrobial agents [7].

Silver nanoparticles exhibit a broad size distribution and morphologies with highly reactive facets. The major mechanism through which silver nanoparticles manifested antibacterial properties is by anchoring to and penetrating the bacterial cell wall, and modulating cellular signaling by dephosphorylating putative key peptide substrates on tyrosine residues. The antibacterial effect of nanoparticles is independent of acquisition of resistance by the bacteria against antibiotics.

Recently it was shown that highly concentrated and non hazardous nanosized silver particles can easily be prepared in a cost-effective manner and tested as a new type of bactericidal nanomaterial.

It was hypothesized that the exposed sulfur-bearing residues of the glycoprotein knobs would be attractive sites for nanoparticles interaction but the mechanism underlying the

HIV-inhibitory activity of silver nanoparticles are fully elucidated recently by Elechiguerra et al., (2005). They have done several assays like antiviral activity of silver nanoparticles against various HIV-1 strains, virus adsorption assays, cell-based fusion assays, a gp120/CD4 capture ELISA, time-of-addition experiments, virucidal activity assays with cell-free and cell-associated HIV-1 virus. From these assays, authors come into conclusion that the silver nanoparticles possess anti-HIV activity at an early stage of viral replication, most likely as a virucidal agent or viral entry inhibitor.

Drugs with the ability to dissolve have much stronger efficacy, however many drugs are insoluble. In order to compensate, drugs often need to be administered in higher doses. This increases the possibility of bacteria and other organisms mutating as the high doses make it easier for them to build resistance to the drugs. This leads to treatments becoming obsolete and the need for new medicines to be developed.

Recent data has shown that in some cases, low concentrations of insoluble drugs in a nanoparticle form can be more active than previously thought, offering the potential to administer drugs in low dosages without reducing the effectiveness of the treatment. The new technology is allowing the scientists to develop new medicines by converting currently available drugs into a nanoparticle form.

9. Imaging

One of the greatest values of nanotechnology will be in the development of new and effective medical diagnostics and treatments (i.e. nanomedicine). The ability to image cellular migration *in vivo* could be very useful for studying inflammation, tumors, immune response, and effects of stem cell therapy. Imaging to deliver fluorescent imaging agents to cells--the tiny spheres could help explain how some biological materials such as peptides are able to enter cells.

However, various imaging contrast agents were conjugated to these nanoparticles and results showed the feasibility of tumor imaging using these nanoparticles. Importantly, therapeutic agents can be conjugated or encapsulated to nanoparticles through surface modification and bioconjugation of the nanoparticles. Nanoparticles have been used in experimental paradigms to label and track transplanted human mesenchymal stem cells, neural stem cells, hematopoietic cells, Schwann cells, olfactory ensheathing cells, and oligodendrocyte precursors among others. Several promising cellular transplantation therapies for central nervous system diseases and injury are currently entering human clinical trials. There are many promising research directions that require concerted effort for success. Foremost is the design and development of nanoparticles with mono-, dual- or multiple functions, allowing detection, diagnosis, imaging, transport and controlled release of cargo, and cell destruction. Greater efficacy of lower doses of drugs and destruction of solely the cancer cells could be achieved by selective targeting of unique surface signatures of tumor cells.

Silver was chosen here instead of the traditional gold for several reasons. Silver exhibits slightly stronger and sharper plasmon resonance peaks than gold. This differential implies that silver would provide slightly better absorption of light and thus, stronger photoacoustic signal. Silver is also used in a host of biomedical applications as an antibacterial agent. Some of the most recent advances include silver coated catheters or other orthopedic implant devices. Silver has been shown *in vitro* to be more cytotoxic than gold, especially where the concentration of the silver ion exceeds 5 mg/ml, but silver toxicity is highly debated and it

is shown as low concentration as 16-20 ng is sufficient for its antibacterial activity without any toxicity (Kiruba Daniel et al., 2010, 2011 a, b, c, d, and Nimroth Ananth, 2011) [Figure-6].

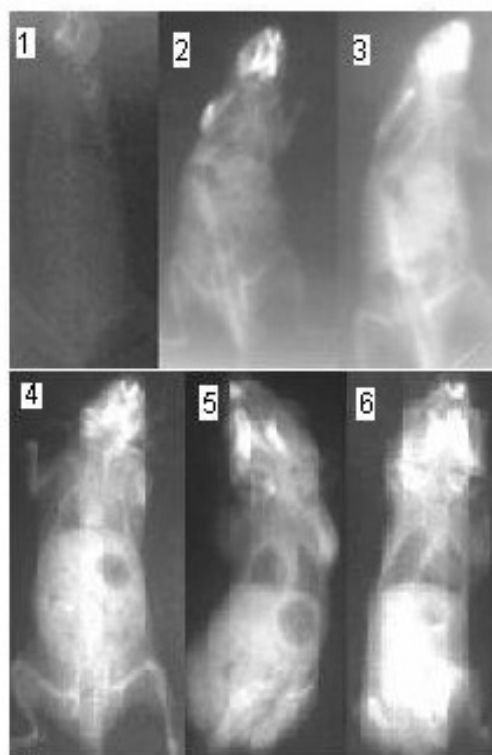


Fig. 6. The whole body X-ray of control mice (1), Silver – polyvinyl alcohol nanoparticle (2) and Silver – Bovine serum albumin nanoparticle injected (3) mice and Drug treated mice (4-6).

10. Multifunctional nanoparticles

Nanoparticles are emerging as promising candidates for various biomedical applications such as enhanced resolution magnetic resonance imaging, drug delivery, tissue repair, cell and tissue targeting and transfection, etc especially for *in vivo* applications, such as drug delivery.

Nanoparticles have a further advantage over larger microparticles, because they are better suited for intravenous delivery. The smallest capillaries in the body are 5–6 mm in diameter. The size of particles being distributed into the bloodstream must be significantly smaller than 5 mm, without forming aggregates, to ensure that the particles do not form an embolism. Nanoparticles can be used to deliver hydrophilic drugs, hydrophobic drugs, proteins, vaccines, biological macromolecules, etc. They can be formulated for targeted delivery to the lymphatic system, brain, arterial walls, lungs, liver, spleen, or made for long-term systemic circulation. Four of the most important characteristics of nanoparticles are their size, encapsulation efficiency, zeta potential (surface charge), and release characteristics.

In practice, silver and gold nanoparticles are the most commonly used nanoparticles for diagnostics and drug delivery. The unique chemical properties of colloidal silver make it a promising targeted delivery approach for drugs or gene specific cells.

11. Biosensor

In order to interact with biological target, a biological or molecular coating or layer acting as a bioinorganic interface should be attached to the nanoparticle. Examples of biological coatings may include antibodies, biopolymers like collagen, or monolayers of small molecules that make the nanoparticles biocompatible. In addition, as optical detection techniques are wide spread in biological research, nanoparticles should either fluoresce or change their optical properties.

A tight control of the average particle size and a narrow distribution of sizes allow creating very efficient fluorescent probes that emit narrow light in a very wide range of wavelengths. This helps with creating biomarkers with many and well distinguished colors. The core itself might have several layers and be multifunctional. For example, combining magnetic and luminescent layers one can both detect and manipulate the particles. Organic molecules that are adsorbed or chemisorbed on the surface of the particle are also used for this purpose. One group is aimed at attaching the linker to the nanoparticle surface and the other is used to bind various moieties like biocompatibles (dextran), antibodies, fluorophores etc., depending on the function required by the application.

12. Protein biosensor

Proteins are the important part of the cell machinery and structure, and understanding their functionalities is extremely important. Surface-enhanced Raman scattering spectroscopy is a well-established technique for detection and identification of single dye molecules. Antibodies are attached to the metal nanoparticles, and the antigen recognition is monitored via the change of light absorption when this binding event occurs.

Silver nanoparticles functionalized with bioreceptors (BSA) for biosensing applications were attempted. Upon binding of proteins to the silver particles, changes in both the intensity and the wavelength of the particle were observed. It can be used for biosensing using silver nanoparticle coated with any protein or any antibody, based on a resonance enhancement. Furthermore, this novel approach is promising as an alternative for conventional biosensing techniques [Figure 2] Nimroth Ananth et al.2011)[Figure-7 and 8].

13. Genosensors/diagnostic agent

The nanoparticles are coated with hydrophilic oligonucleotides containing a Raman dye at one end and terminally capped with a small molecule recognition element (e.g. biotin). Moreover, this molecule is catalytically active and will be coated with silver in the solution of silver (I) and hydroquinone. After the probe is attached to a small molecule or an antigen it is designed to detect, the substrate is exposed to silver and hydroquinone solution. A silver-plating is happening close to the Raman dye, which allows for dye signature detection with a standard Raman microscope. Apart from being able to recognize small molecules this probe can be modified to contain antibodies on the surface to recognize proteins. When tested in the protein array format against both small molecules and proteins, the probe has shown no cross-reactivity. Not only is the absorbance originating from plasmon resonances of the particles influenced by the dielectric properties of molecules attached to the nanospheres but also the inter band absorption of the particles changes [Figure-9]. This change in absorption can be very large when adhered molecules are at resonance (inter band

transitions). In addition, the presented type of biosensing can be a cost-effective and easy to use alternative to conventional biosensing techniques.

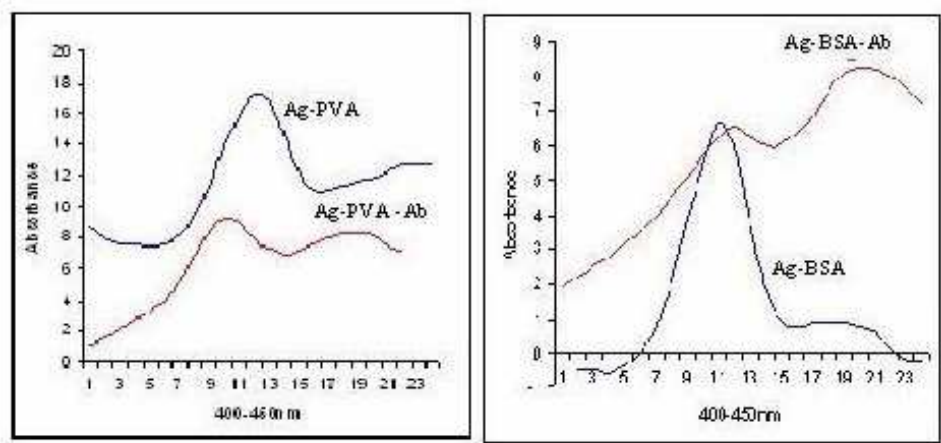


Fig. 7. Fluorescence Spectrum of Silver - polyvinyl alcohol and Silver - Bovine serum albumin nanoparticles with mice(3) and without antibody binding .

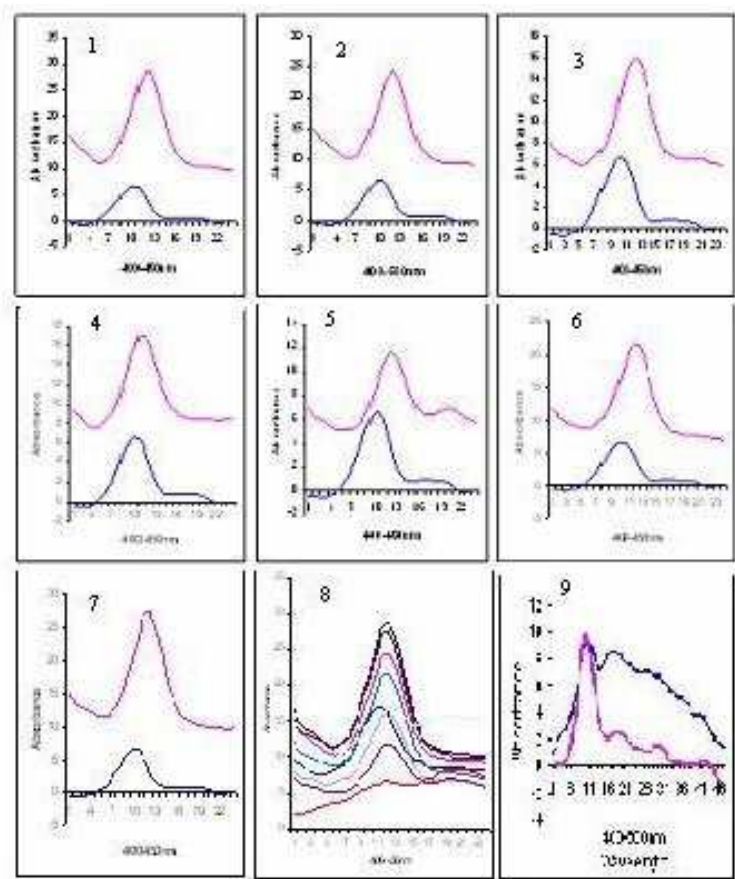


Fig. 8. UV-vis absorption pattern of Silver - Bovine serum albumin with (pink) and without (blue line) antiBSA in the visible region (400–450 nm) in different tissue samples 1. Liver 2.Kidney 3.Spleen 4.Lungs 5.Heart 6.Intestine 7.Brain 8.Comparitive pattern of all tissues 9. Positive control.

Applications of DNA-conjugated nanostructures have shown improvement in not only size, but also performance. For example, noncomputational tiling arrays have been used as molecular scale circuit components (He et al., 2009) either by the chemistry between DNA and molecular electrodes (He et al., 2009), or by the use of gold beads (Martin et al., 1999). Nano mechanical devices have also been created that undergo conformational change due to environmental change, (Mao et al., 1999; Chen et al., 2004; Liu et al., 2007) strand displacement, (Yan et al., 2002) such as the nano walker, (Sherman & Seeman, 2004; Shin & Pierce, 2004) or enzymatic activity, (Yin et al., 2004; Park et al., 2002). Lastly, the optical properties brought about by aggregation and network formation can be used as a tool in DNA-detection. Some examples include the diagnosis of genetic diseases, RNA profiling, biodefense, (Kushon et al., 2003; Lockhart and Winzeler, 2000; Hill et al. 2000; gene chips, (Lipshutz et al. 1999) detection of UV damage, (Jiang et al. 2007) and single-molecule sequencing, (Austin et al. 1997) including the use of nanopores, (Branton et al. 2008; Storm et al. 2003; Gerland et al. 2004). Our study is only one type of many novel biosensors developed using SPR technology [Figure-8].

14. Cancer treatment

Nanotechnology has become an enabling technology for personalized medicine in which cancer detection, diagnosis, and therapy. The promises of nanotechnology in cancer research lie in the potential to overcome the drawbacks such as side effects and toxicity to healthy cells that come across in the current cancer treatment (surgery, radiation, and chemotherapy).

Rational design of nanoparticles requires the knowledge of tumor-specific receptors that would allow endocytosis of nanoparticles, tumor-specific biomarkers that facilitate identification of cancers, and tumor-specific homing proteins and enzymes that can permit selective uptake into cells or accumulation in tumor micro environments.

Several nanobiotechnologies mostly based on nanoparticles, have been used to facilitate drug delivery in cancer. As tumor architecture causes nanoparticles to preferentially accumulate at the tumor site, their use as drug delivery vectors results in the localization of a greater amount of the drug load at the tumor site; thus improving cancer therapy.

Nanotechnology has tremendous potential to make an important contribution in cancer prevention, detection, diagnosis, imaging and treatment. It can target a tumor, carry imaging capability to document the presence of tumor, sense pathophysiological defects in tumor cells, deliver therapeutic genes or drugs based on tumor characteristics, respond to external triggers. Gene delivery offers the potentials to (a) replace missing or defective genes; (b) deliver genes that catalyze the destruction of cancer cells; (c) cause cancer cells to revert back to normal tissue, (O'Connor et al., 2006).

Nanoshells are layered colloids with a nonconducting nanoparticle core covered by a thin metal shell, whose thickness can be changed to precisely tune the plasmon resonance. Proteins that bind only with tumor cells can be attached to the surface, creating tumor-seeking nanoparticles. By tuning the shells to strongly absorb 820 nm NIR light, where optical transmission through body tissue is optimal and harmless, low-power extracorporeally applied laser light shone at the patient induces a response signal from injected nanoshells clustered around a tumor. Increasing the laser power to a still moderately low exposure heats the nanoshells just enough to destroy the tumor without harming healthy tissue. On exposure to 35 W/cm² NIR light, human breast carcinoma cells

incubated with nanoshells *in vitro* undergo photothermally induced morbidity. Cells without nanoshells display no loss in viability. Likewise, *in vivo* studies under magnetic resonance guidance reveal that exposure to low-dose (4 W/cm^2) NIR light in solid tumors treated with nanoshells incur a temperature increase of $37.4 \pm 6.6^\circ\text{C}$ within 4-6 minutes. The tissue displays coagulation, cell shrinkage, and loss of nuclear staining, indicating irreversible thermal damage. Controls treated without nanoshells demonstrated significantly lower temperatures and appeared undamaged. Miniscule beads coated with gold are also Nanoshells. By manipulating the thickness of the layers making up the nanoshells, scientists can design these beads to absorb specific wavelengths of light. The most useful nanoshells are those that absorb near-infrared light, which can easily penetrate several centimeters of human tissue. The absorption of light by the nanoshells creates an intense heat that is lethal to cells.

Researchers can already link nanoshells to antibodies that recognize cancer cells. Scientists envision letting these nanoshells seek out their cancerous targets, then applying near-infrared light. In laboratory cultures, the heat generated by the light-absorbing nanoshells has successfully killed tumor cells while leaving neighboring cells intact. To achieve tumor-targeted drug delivery, nanoparticle systems must address technical and biological concerns that influence their distribution.

15. Gene/Drug delivery

Gene delivery systems are used in the field of gene therapy to introduce foreign DNA encoding therapeutic protein sequences into cells. Several gene delivery systems have been developed to promote gene expression either *in vitro* or *in vivo*. Among them, viral methods are well known and can be extremely efficient (viral vectors were used in the first human gene therapy test), but the safety (including the immunogenicity and the risk associated with replication-competent viruses) and production issues of viral vectors have stimulated efforts toward the development of nonviral gene delivery systems such as cationic lipids, polymers and other mechanical and electrical methods. Among the nonviral gene delivery systems, novel biocompatible polymers have gained increasing attention and been examined for their properties as gene carriers. Although the use of polymeric gene carriers may overcome the current problems associated with viral vectors in safety, immunogenicity and mutagenesis, they are usually inefficient and toxic. Inefficient endosomal release, cytoplasmic transport and nuclear entry of plasmids are currently the limiting factors in the use of polymers for effective plasmid-based gene therapy.

Gene expression detection can provide powerful insights into the chemistry and physiology of biological systems. Better understanding of the molecular mechanisms underlying biological processes can be achieved by comparing gene expression between cells in different states or between cells from different tissues. Furthermore, an abnormally expressed gene can be used as a new drug target or as a genetic marker for diagnosis.

A major requirement for gene therapy is the efficient transport of DNA through the cell membrane by processes that are not well defined. Because potentially a large number of different genes need to be transported, and different types of organs and tissues whose cells need to be targeted for genetic therapy of different diseases, a broad range of gene delivery technologies is necessary for effective treatments.

Development of efficient gene therapeutics would depend largely on the availability of vectors that allow an efficient and selective delivery of therapeutic genes to target cells with minimal toxicity (Wagner et al., 2004; Wang and Yuan, 2006; Niidome and Huang, 2002). Because potentially a large variety of very different genes need to be delivered and many types of organs and tissues that cells need to be targeted for the therapy of different diseases, an immensely broad range of gene delivery technologies is foreseen to be necessary to cater for all the conceivable applications and treatments, (Lawson, 2006; Glover et al., 2005; Larin et al., 2004).

Silver nanoparticles have increasingly attracted more attentions because of their promising applications in the fields of catalysis, (Musi et al. 2009; Shin et al. 2009; Tian et al. 2009) electronics, (Xia et al. 2003) sensing, (Guo et al., 2009; Zhao et al., 2009; Nimroth Ananth et al., 2011) and surface-enhanced Raman scattering (Sun et al., 2009) etc.

DNA has particular advantages to produce silver nanomaterials, (Shemer et al., 2006; Sengupta et al., 2009) because of its unique self-assembly and mechanical properties, as well as the high affinity with silver cations. As silver cations prefer to associate with heterocyclic bases rather than balance negative charges of the phosphate backbone, (Eichhorn, 1973) it is intriguing to investigate the influence of particular DNA structures on the formation and the properties of silver nanoparticles.

The nanoparticles are usually coated with hydrophilic and biocompatible polymers/molecules. Clays are naturally occurring aluminosilicate materials composed primarily of alumina, silica and water with small amounts of metal cations such as Ca^{2+} , Fe^{3+} , K^{+} , Mg^{2+} and Na^{+} also present, (Izatt et al., 1971). Clays have interesting chemical and physical characteristics, e.g., montmorillonite has a high modulus, high cation exchange capacity, a large surface area to mass ratio, and the ability to form stable dispersions in aqueous solutions (Marzilli, 1977).

The unique features of clays have led to their widespread use in materials developed for the automotive, medical, food and cosmetics industries (Marzilli, 1977). In addition, clays have been used successfully as vectors for delivery of DNA into cells in recent experiments (Shamsi and Geckeler, 2008). The concept of green nanoparticles preparation using α -D-glucose as the reducing agent was first reported by Raveendran et al., (2003) where starch played the role of stabilizer. Soluble starch, the amylose component of starch, is a linear polymer formed by the α -(1-4) linkages between D-glucose units and adopts a left-handed helical conformation in aqueous solution. In this report, the aldehyde terminal of soluble starch is used to reduce silver nitrate while the starch itself stabilized the silver nanoparticles. Temperature accelerates the reduction process by aldehydes. The extensive number of hydroxyl groups present in soluble starch facilitates the complexation of silver ions to the molecular matrix while the aldehyde terminals helped in reduction of the same (Pinnavaia and Beall, 2000).

Synthesis of silver nanoparticles using citrate and poly lysine was also reported earlier. Organics like sodium citrate, ascorbic acid and amino acids capable of being oxidized also used as alternate methods, (Rivas et al., 2001; Zhu Shiguo et al., 2002). All the silver nanoparticles preparations showed partial size of 20-25nm.

Plasmid pCDNA-GFP was studied in terms of their degree of adsorption on montmorillonite, silver nanoparticles stabilized with montmorillonite clay, starch, citrate, polylysine and multiwalled carbon nanotubes [Figure 7].

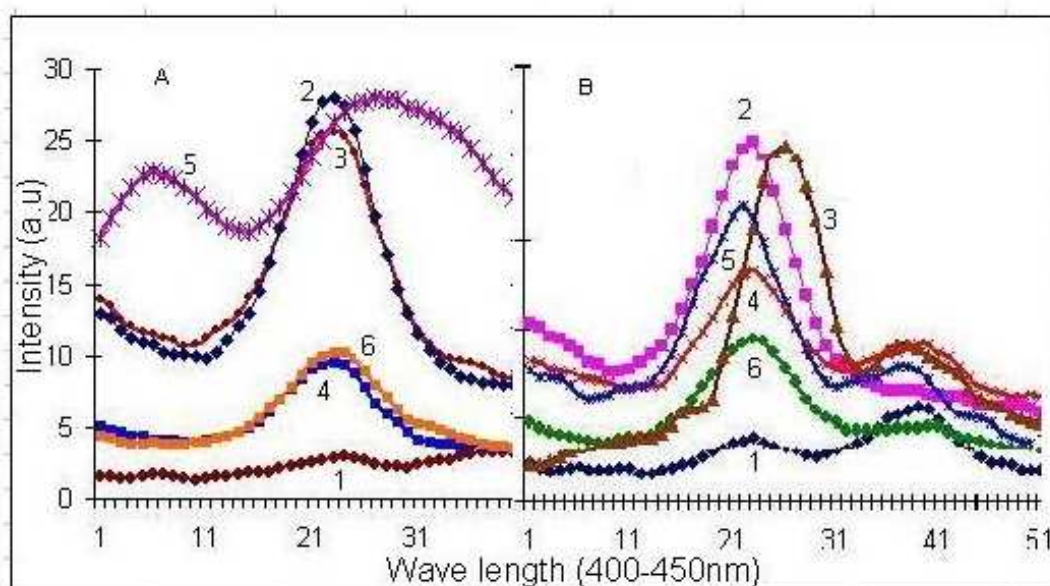


Fig. 9. The fluorescence spectrum (400-500nm) of control and plasmid DNA functionalized nanopreparations. 1. clay 2. silver- clay 3. silver-starch 4. silver-citrate 5. silver-poly lysine nanoparticles 6. Multiwalled carbon nanotubes.

DNA molecules are net negatively-charged, and they can adsorb to net positively-charged surfaces, such as the edges of clay minerals (Nath et al., 2007) as well as to net negatively-charged surfaces, such as the surfaces of clays, by electrostatic bridges with the water of hydration of charge-compensating cations (Paul et al., 2010). Under acidic conditions (generally below pH 5), DNA becomes positively charged by protonation of adenine and cytosine, followed by guanine, and by protonation of the negative charges of phosphate groups. This protonation produces cationic groups in the DNA molecule that can bind to negatively-charged sites on clays. The location and strength of the acidic groups of DNA determine the interaction between clay and DNA. Super coiled plasmid DNA interacts by a low number of strongly acidic groups, presumably located at the maximum of bending of the double strand where a high charge density exists. Linear chromosomal molecules appear to attach on the clay surface and edges, as demonstrated by previous observations, through acidic groups distributed along the DNA molecules.

Citric acid forms only two bonds with silver (1 0 0) because of the geometry mismatch. Migration of a hydrogen atom within citric acid activates the electrons of the carboxyl oxygen and provides additional binding affinity towards silver (1 1 1). The preferential binding energy of citric acid to silver (1 1 1) promotes crystal growth along the silver (1 0 0) surface (Rivas et al., 2001). Cationic Poly-L-lysine interacts with DNA cooperatively at high sodium chloride concentrations and in excess of DNA, and produces DNA particles with various structures, depending upon the concentration of monovalent ions in the medium (Zhu Shiguo et al., 2002).

Cationic carbon nanotubes are able to condense DNA to varying degrees, indicating that both nanotube surface area and charge density are critical parameters that determine the interaction and electrostatic complex formation between functionalized carbon nanotubes with DNA. Upon the addition of divalent metal ions super coiled plasmid DNA forms relatively stable complexes with carbon nanotubes due to chelation. The degree of binding

and tight association between DNA and nanotubes is a desirable trait to increase gene expression efficiency *in vitro* or *in vivo* (Khanna et al., 1998).

Transfection efficiency of these nanoparticles was then assessed on liver cells *in vitro*, using a plasmid containing a fusion of an enhanced green fluorescent protein (pCDNA-GFP) reporter gene [Figure-10]. The intensity was measured and transfection efficiencies were compared [Figure-11]. These results implied that this gene vector based on silver nanoparticles prepared with starch and clay as stabilizing agents could be a promising gene delivery system. Differences in the levels of gene expression were correlated with the structural and biophysical data obtained for the various products including multiwalled carbon nanotube -DNA complexes to suggest that large surface area leading to very efficient DNA condensation is not necessary for effective gene transfer.

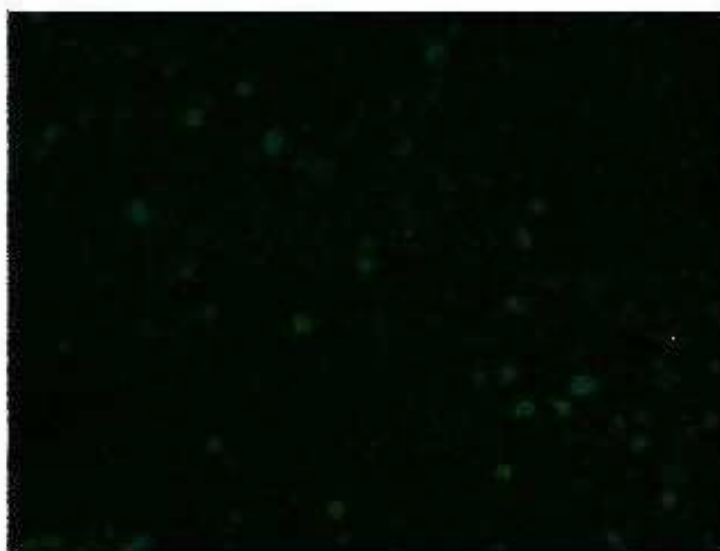


Fig. 10. Transfection of Liver cells with Silver -starch functionalized with pCDNA-GFP.
1. Cells under phase contrast microscope 2. Cells under Fluorescence microscope.

16. Therapeutics

Nanoparticles based diagnostics and therapeutics hold great promise because multiple functions can be built into the particles. Among noble-metal nanoparticles, silver nanoparticles have received considerable attention due to their attractive physicochemical properties and the strong toxicity that to a wide range of microorganisms.

Therapeutics and protection of ornamental gold fishes against red spot and white spot diseases was attempted. The results demonstrated the uptake of nano particles by fish via the gills and body surface, and a cure within 7days with a weight gain and without showing any toxicity. The starch stabilized silver nanoparticles could penetrate all tissues including the brain through BBB. The fishes showed resistance to re infection and hence life time protection can be given to diseased fishes at very low concentration (0.016ng/ml) by simple bathing method. This is the first report on silver nanoparticle therapy against protozoan and fungal infections in fishes [Figure-12] (paper communicated).

Surface modification of metal nanostructures can create multifunctional materials potentially very useful in many application fields and consequently, Silver has been used as therapeutic molecule.

Silver nanoparticles offer a wide range of surface functional groups allowing conjugation to multiple diagnostic and therapeutic agents. Multifunctional nanostructures could be used for simultaneous targeting, imaging and treatment, a major goal in nanomedicine.

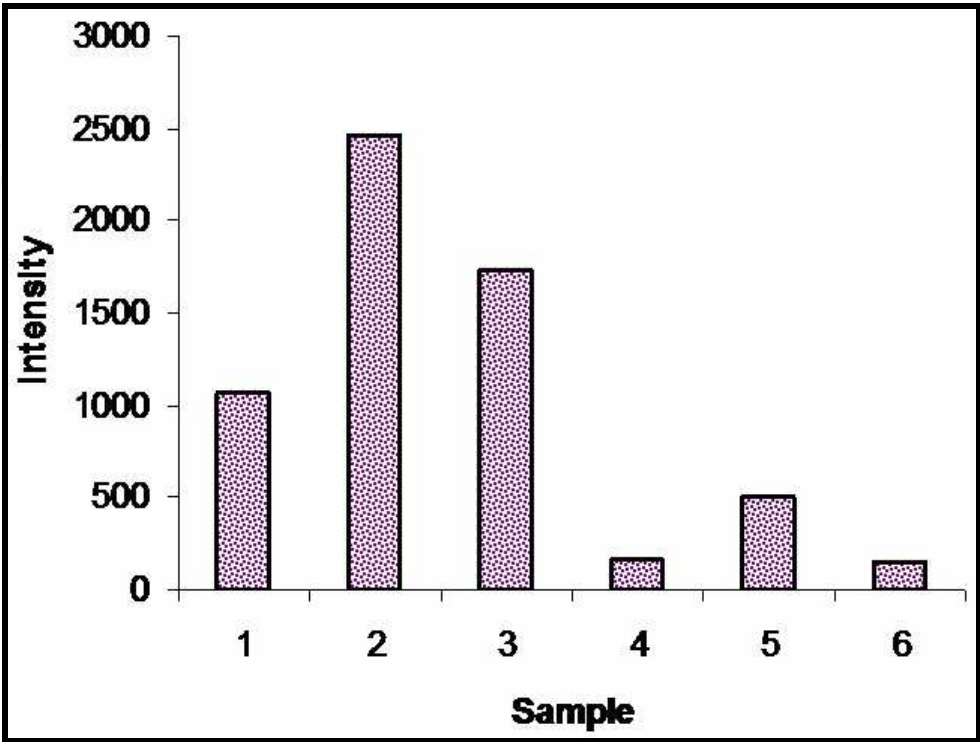


Fig. 11. Gene expression pattern of (GFP intensity) plasmid DNA functionalized nanopreparations. 1. clay, 2. silver- clay, 3. silver-starch, 4. silver-citrate, 5. silver-poly lysine nanoparticles, 6. Multiwalled carbon nanotubes.



Fig. 12. Red Spot diseased fish before(1) & after treatment (3) White Spot diseased fish before (2) and after treatment (4) Silver nanoparticle treatment.

17. Development and commercialization of nanomaterials

Drug delivery techniques were established to deliver or control the amount, rate and, sometimes location of a drug in the body to optimize its therapeutic effect, convenience and dose. Combining a well established drug formulation with a new delivery system is a relatively low risk activity and can be used to enhance a company's product portfolio by extending the drug's commercial life-cycle. Although not exhausting, this is a representative selection reflecting current industrial trends. Many companies are involved in the development and commercialisation of nanomaterials in biological and medical applications.

Most companies are developing pharmaceutical applications, mainly for drug delivery. Most major and established pharmaceutical companies have internal research programs on drug delivery that are on formulations or dispersions containing components down to nano sizes.

Most of the companies are developing pharmaceutical applications, mainly for drug delivery. Several companies exploit quantum size effects in semiconductor nanocrystals for tagging biomolecules, or use bio-conjugated gold nanoparticles for labelling various cellular parts. A number of companies are applying nano-ceramic materials to tissue engineering and orthopaedics

Colloidal silver is widely used in anti-microbial formulations and dressings. The high reactivity of titania nanoparticles, either on their own or then illuminated with UV light, is also used for bactericidal purposes in filters. Enhanced catalytic properties of surfaces of nano-ceramics or those of noble metals like platinum are used to destruct dangerous toxins and other hazardous organic materials.

Nanotechnology is the application of nanoscience. Nanotechnology is being seen as a science having potential to create many new materials with specific properties and devices with wide ranging applications in medicine, electronics and energy production. A lot of research is being carried out in all the branches of science which is expected to result in revolutionary progress in the field of nanoscience and nanotechnology. Already many nanotechnology based industries have come up with products like flat plate display unit using the concept of electron field emission by carbon nano tubes; devices using antimicrobial activity of nano-silver, water purification, crease free textile material, nano sensors and nano probes etc are in the market. The near future nanotechnology based products being envisaged are fuel cell, hydrogen storage, solar cell, super capacitors, lithium battery, microwave absorption, bullet proof jackets, drug delivery, diagnostic devices etc. The desire to be part of the global market, nanotechnology is diversifying into many innovative new fields which have generated lots of hope and hype. Research & Development with an eye on commercialization efforts of this young technology are continuing unabatedly across the globe.

Sustained world class R&D through funding multidisciplinary research and development is the prerequisite. Infrastructure availability is crucial to assist businesses, especially small companies that cannot afford the cost of nanotechnology instrumentation, equipment and facilities. There should be cooperation between university and industry. This will suffice the need of basic science innovations, expensive laboratories, and for highly trained workers.

18. Future opportunities and challenges

Nanotechnology has received much attention from scientists and journalists in the last few years raising hopes of revolutionary developments in a wide range of technologies on an

increasingly small scale, dramatic improvements to standards of living, and solutions to a variety of environmental, medical and communications problems.

Silver nanoparticles have already been applied as drug delivery systems with great success. Nanoparticles provides massive advantages regarding drug targeting, delivery and release and with their potential for combine diagnosis and therapy and one of the major tools in nanomedicine. These are many technical challenges in developing the following techniques:- virus- like systems for intracellular systems, architecting of biomimetic polymers, control of sensitive drugs, functions of active drug targeting, bioresponsive triggered systems, systems interacting with the person (body smart delivery), nanochips for nanoparticle release, carriers for advanced polymers for the delivery of therapeutic peptide / proteins.

As it stands now, the majority of commercial nanoparticle applications in medicine are geared towards drug delivery. In biosciences, nanoparticles are replacing organic dyes in the applications that require high photo-stability as well as high multiplexing capabilities. There are some developments in directing and remotely controlling the functions of nano-probes, for example driving magnetic nanoparticles to the tumour and then making them either to release the drug load or just heating them in order to destroy the surrounding tissue. The major trend in further development of nanomaterials is to make them multifunctional and controllable by external signals or by local environment thus essentially turning them into nano-devices.

19. Biosafety

Silver nanoparticles have been shown to damage brain cells (Hussain et al., 2006), liver cells (Hussain et al., 2005) and stem cells (Braydich-Stolle et al., 2005). Even with prolonged exposure to colloidal silver salt deposits of metallic silver under the skin cause skin diseases like argyria or argyrosis (Chen et al., 2007). Silver nanoparticles at 10 ug/ml and above concentration showed dramatic changes like necrosis and apoptosis of cells. Silver at 5-10 ug/ml, drastically reduced mitochondrial function and cell viability.

Silver metal and silver dressings, when used in reasonable has no negative effects on the human body and it has a natural antimicrobial (Margaret et al., 2006; Sarkar et al., 2007) towards many pathogens such as bacteria (Hill and Pillsbury, 1939; Zhang and Sun, 2007), viruses, fungi, yeast etc. New silver coated catheters are used because they stop the infections that were common place with the old ones. To protect us from food poisoning, silver particles are now being put in cutting boards, table tops, surface disinfectants and refrigerators. Silver is woven and impregnated into fabrics to kill bacteria that cause body odor.

In vivo tests have been completed, both injected and ingested at silver levels as high as 5000 milligrams per kilogram of a 32 part per million product. LD-50 tests have also been completed at a level of up to 200 times the normal adult dosage. Cellular or cyto-toxicity tests have also been completed on both the 10 ppm and also the 22 ppm products on both human epithelial cells and also on African green monkey cells. The products were found to be completely safe; they did not hurt the human or monkey cells in any way, shape or form.

20. Environmental safety

Silver nanoparticles will grow to biologically far less active clumps even if one dumps 27 liters of 20 ppm colloidal silver on each ton of soil. Because of the low concentrations in which silver nanoparticles based products are sold, the total amount which could be

released in any part of the environment would still be expected to be very low. Silver nanoparticles are not water soluble, and therefore, silver colloids will not release silver ions into the environment. Silver nanoparticles do not last as nanoparticles in nature for very long, but grow to harmless clumps of silver metal which has existed in nature from the beginning of our planet.

Silver nanoparticles based diagnostics and therapeutics hold great promise because multiple functions can be built onto the particles. The potential applicability of these silver nanoparticles in the present approach is simple, sensitive and selective for the versatile applications related to diagnostics and therapeutics. The usage of silver nanoparticles is safe to consumer health and environment.

21. References

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Drug discovery and development process aims to make available medications that are safe and effective in improving the length and quality of life and relieving pain and suffering. However, the process is very complex, time consuming, resource intensive, requiring multi-disciplinary expertise and innovative approaches. There is a growing urgency to identify and develop more effective, efficient, and expedient ways to bring safe and effective products to the market. The drug discovery and development process relies on the utilization of relevant and robust tools, methods, models, and validated biomarkers that are predictive of clinical effects in terms of diagnosis, prevention, therapy, and prognosis. There is a growing emphasis on translational research, a bidirectional bench to the bedside approach, in an effort to improve the process efficiency and the need for further innovations. The authors in the book discuss the current and evolving state of drug discovery and development.

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