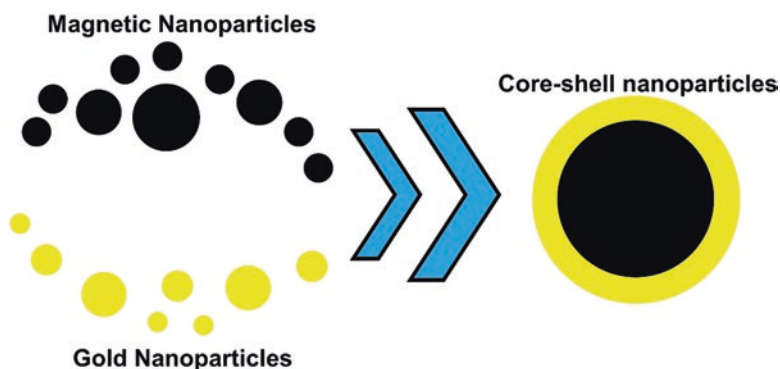


Chapter 2

Literature Survey on Magnetic, Gold, and Core-Shell Nanoparticles



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2.1 Synthesis, Properties, Surface Functionalization, and Applications of Nanoparticles

2.1.1 Magnetic Nanoparticles (MNPs)

2.1.1.1 Synthesis and Properties

Magnetic materials at nanoscale possess various biomedical applications due to their unique physical properties at the cellular and molecular levels of the biological interface. They are an efficient theranostic agent since they are considered to be good for therapeutic purposes, as well as for MR contrast imaging [1, 2]. They have been exploited for the diagnosis and treatment of cancer [3], cardiovascular diseases [4], and neurological diseases [5]. The size, shape, surface charge, surface chemistries, and composition can be tailored for such NPs so that their magnetic properties are improved and hence can be used proficiently for the theranostic purpose, both in vivo and in vitro [6].

As a contrast agent, such MNPs have been commercially used since they enhance the proton relaxation of specific tissues, serving as MR contrast imaging agents. The commercially available materials are Lumiren® and Gastromark® for bowel contrast imaging, Endorem® and Ferridex IV® for liver/spleen imaging, etc. [7]. As a treatment agent, these NPs have been utilized as a magnetic drug-targeting agent [8] as well as an active targeting agent [9, 10]. Other NPs possess the defect of lack of targeting strategies; hence, when they are biodistributed systemically after conjugating with drugs, they are intrinsically inefficient to reach towards their target. But MNPs can be targeted towards cancer cells due to the external magnetic field. This reduces the deleterious side effects and drug dosage due to the synaphic delivery of drugs.

Magnetic nanomaterials possess the ability to penetrate the magnetic field through human tissue and manipulate in such a way that they can be exploited for medicinal purposes [11]. The material's magnetic property is symbolized by its magnetic susceptibility (χ) that is the ratio of induced magnetization (M) to the applied magnetic field (H). At a nanoscale of the order of tens of nanometers, ferri or ferromagnetic materials possess a large single magnetic domain having a large magnetic moment. In the presence of an external magnetic field, this single magnetic domain having a magnetic moment is aligned parallel to H . But at high temperatures (blocking temperature T_B) (37 °C) and in the absence of an external magnetic field, thermal fluctuations can stimulate free rotation of the particles, thus leading to a loss in net magnetization. Hence this superparamagnetic property, which renders NPs without any remnant magnetization after the removal of external fields, helps them to maintain their colloidal stability and prevents any agglomeration with the vascular proteins. Moreover, these superparamagnetic particles possess individual magnetic domains and their coupling interactions lead to higher magnetic susceptibilities.

Superparamagnetism is a favorable property but the reduction of size also comes with a disadvantage, that as the size of the particle decreases, the surface-to-volume ratio increases leading to manifestations of surface effects, that is, spin canting,

noncollinear spins, that affect the overall magnetic properties [12]. Recently, there have been reports in which magnetization of iron oxide NPs (Fe_3O_4 and Fe_2O_3) has been increased by doping them with ions such as cobalt, manganese, zinc, nickel, and iron itself. MnFe_2O_4 is nontoxic in vitro and has higher magnetic susceptibility than iron oxide NPs. Both cobalt and nickel ferrites, though they possess in vivo toxicities, possess unique MR imaging properties. Furthermore, iron oxide NPs are also coated with Fe, where iron oxide acts as a core and Fe as a shell so that the magnetization value increases from 30 to 50 emu/g for plain iron oxide NPs to $\text{Fe}/\text{Fe}_3\text{O}_4$ CSNPs having 102 emu/g. In another instance, Pt, Au, and Ag have been used for coating the surface of iron oxide NPs. FePt has been used to bind DNA and protein on its surface [13, 14], while $\text{Au}/\text{Fe}_3\text{O}_4$ CSNPs have been utilized to improve the biocompatibility of iron oxide NPs and bind anticancer drugs for delivery inside cancer cells [15] (Fig. 2.1).

2.1.1.2 Surface Functionalization

MNPs need to be functionalized by surface ligands such as polymeric coatings, metallic coats such as silica or gold, liposomes, and micelles since individually they are toxic and tend to be easily recognized and cleared out by the reticuloendothelial system (RES) before reaching their target. The effectiveness of MNPs is increased

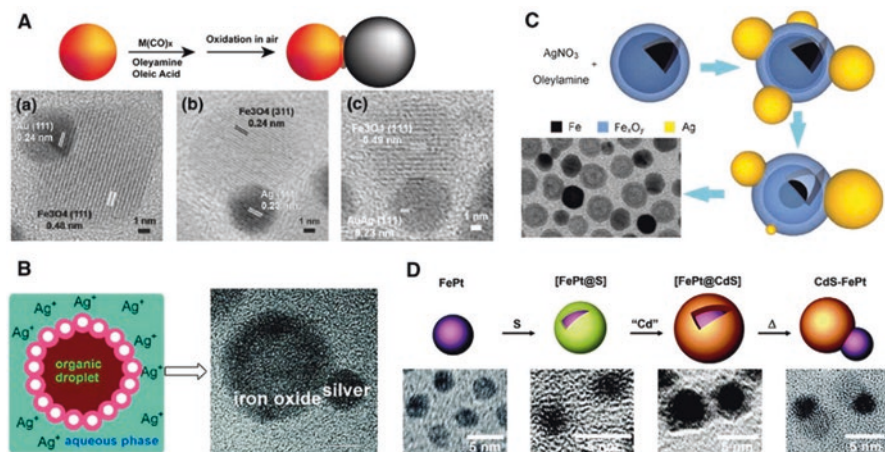


Fig. 2.1 (A) Schematic illustration of the growth of metal-oxides dumbbell MNPs on pre-made metal NPs and HRTEM images of (a) Au- Fe_3O_4 , (b) Ag- Fe_3O_4 , and (c) Au, Ag- Fe_3O_4 MNPs. (Reproduced with permission from [16] Copyright 2010 American Chemical Society.) (B) Schematic illustration of the growth of Ag-hollow Fe_3O_4 dumbbell MNPs in the aqueous phase. (Reproduced with permission from [17] Copyright 2010 American Chemical Society.) (C) Schematic illustration of the growth of Ag-hollow Fe_3O_4 dumbbell MNPs in organic phase. (Reproduced with permission from [18].) (D) Schematic illustration of the growth of FePt-CdS dumbbell MNPs. (Reproduced with permission from [19] Copyright 2004 American Chemical Society)

by improving their stealthiness by surface functionalization, thus increasing their retention time in blood circulation, so that there is the maximum probability of MNPs reaching their target [20–22].

2.1.1.3 Applications

2.1.1.3.1 Delivery of siRNA/DNA

The delivery of genes is unfavorable due to inefficiencies in their transfection, short half-life in blood, being nonspecific, as well as deprived diffusion through cell membranes [23, 24]. This can be overcome by conjugating MNPs with antisense oligodeoxynucleotides (ODNs), which is also known as magnetofection. This has been successfully optimized for in vitro applications and now is being tested for in vivo applications [25, 26]. A dendrimer-tethered MNPs has been used to transport antisense surviving ODNs to breast and liver cancer cells [27]. Researchers have demonstrated that positively charged polyamide amine-coated MNPs, when complexed with ODNs, can downregulate the surviving gene, as well as protein, in 15 min. This consequently led to the inhibition of cellular growth.

MNPs after surface functionalization act as an important vehicle for delivery of small interfering RNA (siRNA) [28]. There are a plethora of cationic polymers which are coated onto the surfaces of MNPs, along with polyethyleneimine-coated MNPs which have been utilized for the delivery of siRNA. There are reports on NIFR-labeled MNPs, which are covalently bound with siRNA, that can silent GFP production in a GFP-expressed xenograft in a tumor mouse model. The report confirms the in vivo tumor uptake of such MNPs conjugates due to EPR effect, which can be used for MR imaging purposes. The future endeavor is to exploit such conjugates for therapeutic purposes [29, 30].

2.1.1.3.2 Delivery of Drugs

Chemotherapeutic agents possess the most disadvantageous effects of nonspecificity and augmented side effects to healthy tissues. This can be circumvented by utilizing MNPs due to magnetic targeting and site-specific delivery of therapeutic cargoes [31–33]. To make it simple, the process involves attachment of an anticancer drug on to prefunctionalized MNPs. This conjugate on intravenous injection was followed by application of an external magnetic field gradient to target the NPs on the pathological site. Due to a hyperthermal effect, the drugs are released onto the desired site. But the execution of such a simple process has been complicated by physicochemical parameters such as field strength and geometry, hemodynamic shear force, and depth of the tumor tissue, which play a pivotal role in drug delivery [34]. MNPs attached to epirubicin have reached early clinical trials which have been targeted to tumors. Patients tolerate such conjugates, but the most challenging task is the occurrence of embolization of blood vessels; due to limited field penetration

into tissues, such conjugates cannot be used *in vivo*. There is no proper control of drug diffusion after release and toxicity of MNPs. For the comprehension of the effects of MNPs, there is a creation of a mathematical model, which takes care of the hydrodynamics of the blood vessels, particle volumes, magnetic field strength, etc. This model proves that magnetic drug targeting could be useful only on the targets which are close to the surface of the body [35–37]. This study inspired attachment of mitoxantrone on the surface of starch-coated MNPs in VX2 squamous cell carcinomas on the hind limbs of New Zealand White rabbits. It was demonstrated that such conjugates could completely eradicate tumors after 35 days of treatment [38, 39]. In other instances, traditional drugs such as etoposide, doxorubicin, methotrexate, and cisplatin have been either attached to MNPs or encapsulated inside polymer functionalized MNPs for the treatment of malignant prostate and breast tumors [40–42]. Moreover, there are reports in which poly(ethyl-2-cyanoacrylate) (PECA)-coated MNPs are attached to two different types of drugs, that is, hydrophobic cisplatin and hydrophilic gemcitabine. This helps in controlled release of cisplatin due to its hydrophobicity and rapid release of gemcitabine due to its hydrophilicity [43].

2.1.1.3.3 MR Imaging

MR imaging is a significant technique which employs contrast agents like SPIONs to clearly distinguish between healthy and pathologically different tissues/cells. Recently the various developments in MR imaging have implemented *in vivo* scanning even at a very high resolution [44]. To visualize and track cells by MR imaging, it is vital to magnetically tag cells. Recently, Tat protein-derived peptide sequences have been used for internalizing a various marked proteins into cells [45]. The tagging of MNPs with cells does not affect its normal mechanisms like viability, differentiation, or even the proliferation of CD34⁺ cells. The research evidence shows that the transgene expression can be envisaged by MRI *in vivo* [46]. The researchers have attached human holo-transferrin to MNPs and demonstrated the receptor level increment on the surface of the cell which causes noticeable changes in MR imaging signals. These SPIONs are almost nontoxic when administered *IV*, which is confirmed from various clinical use [47], and as the MNPs has highly biodegradable, which allows multiple imaging of transgene expression for a prolonged time. Therefore, this new field in MR imaging opens a provocative area for establishing additional and innovative strategies for imaging the different gene expressions in deep organs [48].

MNPs have been widely employed to reveal apoptosis by MR imaging [49]. The posttreatment of tumor cells *in vivo* shows changes in MR image contrast which reflect the cell morphological appearance due to apoptosis [50]. The C2 domain—synaptotagmin I, binds to cell membranes (especially to anionic phospholipids), which binds to the apoptotic cells plasma membrane this can be evaluated by both confocal microscopy and flow cytometry. Therefore, the administration of C2-SPIONs can significantly increase the image contrast of a tumor where apoptotic

cells are high in number. This method paved the way for both in vitro and in vivo detection of apoptotic cells after the chemotherapy [51].

Thus, this MR imaging technique can detect apoptosis at an early stage after the posttreatment which is advantageous over other methods like magnetic resonance spectroscopy (MRS) and radionuclide method with high spatial resolution. Due to various advantages over other contrast agents, recently SPIONs has been clinically approved by FDA as a MR imaging blood pool agent [52].

2.1.1.3.4 Hyperthermia

Magnetic hyperthermia is one of the currently employed therapies for treatment of cancer by exposing cancer cells/tissues under alternating magnetic field (AMF). It is due to the production of heat caused due to magnetic hysteresis loss by MNPs when subjected to AMF. The heat generation completely depends on the MNPs nature and AMF parameters. MNPs are injected in the tumor region and placed within an AMF which will heat up to a certain temperature depending on the various parameters like magnetization of MNPs and AMF strength. Cancer cells are prone to die/damage when the temperature is as high as 43 °C, but the normal cells can survive even at higher temperatures. The size of the MNPs plays an important role in producing heat inside the cancer cells [6].

Many research work using MNPs for hyperthermia has already been carried out as a therapeutic agent for various types of cancers by evaluating with animal models [53] or using in vitro cancer cell lines [54]. Choosing optimum AMF and MNPs size even very small quantity is enough to produce required amount (order of a tenth of milligram) of heat in a specific site which leads up to cell necrosis/apoptosis. The research has shown that hyperthermia augments cell cytotoxicity by chemotherapy and chemo hyperthermia with brain tumor cell lines, which were confirmed by various hyperthermia studies with multimodel rat, rabbits, and dogs [55]. Using interstitial microwave antennas, it is evaluated that a maximum tolerable dose for dog's normal brain is around 44 °C for 30 min.

Modified aminosilan MNPs showed increased differential endocytosis specifically into glioblastoma cells in vitro [56]. This study shows a tenfold increased uptake by glioblastoma cells. And these modified aminosilan-type NPs were also taken up by cancer cells lines like prostate carcinoma cells in vitro. This shows that the MNPs size and surface is very important for the endocytosis process into the cancer cells. And also dextran coated magnetite (DM) are employed for hyperthermia of oral cancer hyperthermia. This NPs suspension was injected into the tumor and heated up to 43–45 °C by an AMF of 500 kHz. The results suggested that the growth inhibition of tongue carcinoma in the 4-time heating group when compared to the control group. And also, the survival rate was higher in the heated groups than in the control [57].

Furthermore, combined therapies of hyperthermia and gene may be possible in the near future. For example, using magnetite cationic liposomes (MCLs) combined with TNF- α gene therapy driven by the stress-inducible promoter was employed for

hyperthermia for the first time. In nude mice, MCLs induced cell necrosis in the tumor area on heating under an AMF. The produced heat stress resulted in an increase of TNF- α gene expression when compared with that of the non-heated tumor. This combinational treatment completely arrested the growth of tumor in an animal model over a month period, proving it to be a potential candidate for future cancer treatment [58].

2.1.2 Gold Nanoparticles (GNPs)

2.1.2.1 Synthesis and Properties

GNPs have been exploited as a theranostic agent as they possess unique capability of binding amine ($-\text{NH}_2$) as well as thiol ($-\text{SH}$) functional groups [59–62]. They act as a paradigm for drug or gene delivery vehicles since they can synaptically interact with miscreant cells and possess decreased systemic toxicity, improved efficacy, effective biodistribution, and clearance of therapeutics [63]. They have attracted biomedical scientists for synthesizing different sizes (in the range of 1–100 nm) and shapes (including spherical, rods, cuboids, CSNPs, and much more) [64–66] of GNPs. The biomedical applications of such NPs are size as well as shape-dependent as gold nanorods, gold nanoshells, and other gold nanostructures, when injected into the body, can absorb NIR light since the body tissues possess high transparency towards NIR light. Gold nanostructures aid in drug/gene release as well as PTT when exposed to NIR. There are different strategies for binding drugs or genes to drug-delivery vehicles, but GNPs efficiently tether via covalent linking. This is possible either by amino linkage or thiol linkage between GNPs and therapeutic agents. Smaller-sized GNPs (5 nm) exhibit large optical absorption due to SPR, while larger NPs (10–100 nm) scatter exorbitantly, but they can absorb light only in the visible region. The biological tissues are less transparent to visible light as compared to near-infrared light, hence gold nanorods and nanoshells are synthesized which possess strong SPR in the near-IR region. Gold nanorods are synthesized using a surfactant known as CTAB as a capping agent. But due to the inherent toxicity of CTAB, several groups are exchanging it with controlled surface chemistries. Gold nanoshells possess a spherical dielectric core having a thin gold layer acting like a shell [67].

2.1.2.2 Surface Functionalization

GNPs are functionalized via thiol moiety, but this proves to be conditionally advantageous. Thiol groups have the tendency to be exchanged with the solution, which is a limitation, but in certain cases when inside the cells due to high levels of glutathione in the cytoplasm it can also be useful for drug release by means of exchange reaction [68]. Glutathione partially displaces the thiol group on the

surface of NPs, thus causing the release of covalently bound drugs. The stability of NPs can be enhanced if the system is made more complex, in the sense that multiple thiols can be grafted onto the single NP, making it more stable [69, 70]. A cyclical disulfide can also be used for multiple binding points in a multidentate fashion with GNPs increasing the binding energies. Hence exploiting 1,2-dithiane end group, thioctic acid, and in situ dithiocarbamate has shown an efficient way of grafting onto a GNPs surface [71, 72]. This refers to thiol groups which are considered to be covalently stronger as compared to amine groups. In cases where weaker binding forces are needed, such as noncovalent ones especially for drug release purposes, NPs can attach or trap molecules via amine groups. If efficient drug release is the desire of a biomedical scientist, then only GNPs tethered to amines can accomplish this role since bond strength between gold and the amino group is 66 kcal/mol as compared to 47 kcal/mol for thiols [73]. GNPs are proficient vehicles for delivery of DNA/RNA or drugs for traversing through the cell membrane. The entry of nucleotide inside the cell is restricted due to its negative charge, hence through thiol linkage, they can interact with GNPs and traverse through the membrane via the above-explained mechanisms. There are certain drugs which are toxic to normal cells and cannot enter the miscreant culprits, such as bacteria or cancer cells, due to resistance against them. GNPs, nanorods, or nanoshells can tether such drugs and then via a targeted mechanism using antibodies or certain molecules, they can enter inside the cells synaptically.

2.1.2.3 Applications

2.1.2.3.1 Delivery of siRNA/DNA

GNPs are considered to be an efficient system for delivery of either DNA or RNA for gene silencing and consequently for therapeutic purposes. Mirkin et al. [74] demonstrated that a dense layer of ssDNA molecules can coat the surface of citrate stabilized spherical NPs via thiol linkers and hence can be exploited for gene silencing. Though ssDNA possess high negative charge density, the NP-ssDNA conjugate could not prevent the internalization into the cells. Moreover, the conjugates are protease and nuclease-resistant. The tethering of complementary DNA to the ssDNA immobilized NPs becomes stronger since there is a staunch dense packing of DNA around the NPs leading to increased efficiency for gene silencing applications [69]. In another instance, instead of regular DNA, chemically modified nucleic acids, known as locked nucleic acids (LNA), were used which have the advantage of being more stable and enhanced complementary DNA binding capacities. They also efficiently tether GNPs. Hence, tailor-made DNA for desirable functions is the requirement so that we can apprehend and predict the NP conjugate structures and their functions [75]. The stability of such DNA functionalized GNPs can be correlated to the salt concentration and curvature of the NP surface [76]. DNA packing density decreases as the size of the NPs increases to 60 nm, reaching a plateau near the packing density of ssDNA on a flat substrate. Spherical NPs acted like a

paradigm based on which ssDNA attachment on rod-shaped NPs was possible with complete accuracy.

Furthermore, similar to ssDNA, even RNA attachment was possible and was then demonstrated by Mirkin et al. [77]. Anti-firefly luciferase siRNA was conjugated to GNPs and their gene knockout potential was noted and compared with the regularly used cationic lipid transfection agents [78]. Nuclease-free synthesis of GNPs was possible through diethyl pyro-carbonate treatment and autoclaving since RNA is highly susceptible to nucleases. This treatment is possible only for the citrate-capped spherical GNPs and not for gold nanorods since at high temperatures they tend to reshape into spherical ones. This kind of coupling between GNPs and siRNA is considered to enhance the stability of such conjugates in serum eightfold as compared to bare siRNA. Such conjugates are resistant to degradation from many physiological RNA cleavers.

2.1.2.3.2 Delivery of Drugs

Controlled release of drugs is an important criterion for designing a good drug delivery system. Other parameters, such as high surface area, tunability, and decreased physiological side effects, are playing a critical role in deciding whether the delivery system can be used for delivering the drugs. There are many antibiotics which have gained resistance against microorganisms and are sometimes toxic to host cells. GNPs have come to the rescue of such drugs and have been conjugated with them for transforming resistant bacterial cells to sensitive ones. Moreover, this conjugation has also led to a reduction in the toxicity of host cells. Notably, vancomycin is the antibiotic to which Enterococci and gram-negative bacteria such as *Escherichia coli* have become resistant (Fig. 2.2). Such strains have been tested after conjugating vancomycin with GNPs via thiol linkage which showed very good activity against both bacterial strains. The modus operandi of such particles is due to multivalency since multiple drug molecules on a single NP led to the increased binding to the D-Ala-D-Ala moieties at the terminal position [79–81].

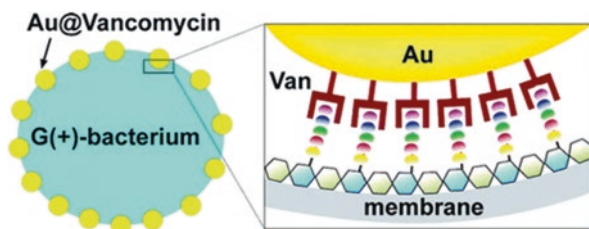


Fig. 2.2 Illustration of a possible multivalent interaction between a Van-capped Au nanoparticle (2) and a VanA genotype VRE strain (hexagons: glycosides; ellipses represent the amino acid residues of the glycanpeptidyl precursor with different colors: L-Ala (yellow), D-Glu (orange), L-Lys (green), D-Ala (blue), and D-Lac (purple) (Reprinted with permission from [81] Copyright 2003 American Chemical Society)

Table 2.1 Summary of gold nanoparticle–drug conjugates for bactericidal applications showing the drugs which have been studied, any extra treatment which is required, the attachment chemistry to the gold surface, the type of bacteria tested, and the corresponding references (*Adapted from the reference [85]*)

Drug/treatment	Attachment	Tested against	References
Vancomycin	Thiol	VRE, gram-negative	Gu et al. (2003) [81]
Vancomycin/photothermal	Thiol	Gram-positive, gram-negative, VRE, MRSA, PDRAB	Huang et al. (2007) [91]
Ampicillin, streptomycin, kanamycin	Amine	Gram-positive, gram-negative	Saha et al. (2007) [236]
Cefaclor	Amine	Gram-positive, gram-negative	Rai et al (2010) [212]
Toluidine blue O / photosensitization	Thiol	Gram-positive	Gil-Tomas et al. (2007) [84]

The orientation of vancomycin is very critical for enhancing the binding with bacteria. Hence covalent tethering between GNPs and vancomycin is an important method to be exploited. Moreover, bis(vancomycin) cystamide has been exploited to surface functionalize NPs since they can absorb near-IR wavelengths of light maximally [82, 83]. GNPs can also be utilized for binding a variety of bacterial types such as vancomycin-resistant Enterococci (VRE) and meticillin-resistant staphylococcus aureus (MRSA) strains. Once such NPs are bound to resistant strains, they can cause photothermal destruction with maximal efficiency. This method is even nontoxic for nonbacterial cells, which was determined by the MTT assays with human epidermoid carcinoma epithelial cells. Instead of antibiotics, photosensitizers such as toluidine blue O (TBO) were also covalently attached to tiopronin-functionalized GNPs, that were highly stable [84]. There was a fourfold decrease in the minimal inhibitory concentration (MIC) when irradiated with white light or laser light when TBO-functionalized GNPs are used in comparison with free TBO. In another instance, many anticancer drugs have been utilized for their attachment with GNPs, since they tend to exhibit systemic side effects and are non-specific, affecting normal cells too. The chemotherapeutic drugs such as cisplatin, paclitaxel, tamoxifen, and doxorubicin are a few examples of this class. GNPs have proved to be advantageous in the sense that after their attachment with anticancer drugs, the conjugate is less toxic with increased specificity towards cancer cells as compared to free drug. Table 2.1 summarizes GNP-drug conjugates for bactericidal applications.

2.1.2.3.3 Plasmonic Photothermal Therapy (PPTT)

Currently, the most widely employed technique to treat cancer and some infectious disease are photothermal therapy (PTT) which can damage the cells [86]. The main principle behind this method is as follows: GNPs have a capability of maximum

absorption in the visible or near-IR region, so when it is excited with the corresponding light source which causes vibrations of atoms in GNPs and produces enough heat. So, when GNPs are injected into the human body to treat cancer cells the NPs produce heat which kills or damage the cells. This thermal treatment can be produced by both local heating (with Mw, ultrasonic) and general hyperthermia [87]. Therefore, both local and general hyperthermia leads to irreversible damage to the cells. The thermal cancer treatment is a big revolution, which enabled controlled injury to tumor region to be achieved.

GNPs were started for PTT use in 2003 [88, 89]. Afterward, it was called as plasmonic photothermal therapy (PPTT) [87]. In the beginning for selective damage to target cells researcher employed 20 and 30 nm GNPs irradiated with a laser pulse to produce local heating [90]. The unique GNPs are able to hold their optical properties inside the cells for quite a long time under certain conditions. So, successive irradiation with pulsed laser controls the cell inactivation by means of nontraumatic mode. Specifically, a cluster of small 30 nm GNPs produces more heat at low laser power than the free individual particles [91]. Usually, the gold nanoshell and nanorod are best suited for PPTT [92]. In the recent years, the number of research publications dealing with the application in PPTT is increasing especially of gold nanorods [93–95] and nanoshells [96–99].

But to avoid GNPs toxicity in the liver and spleen and its side effects in other organs, the surface functionalization is carried out. Usually, there are two delivery strategies:

- Conjugation of GNPs to polymer coating
- Conjugation with antibodies to target only cancer cells

The commonly used polymer for drug delivery is PEG; this is because it acts to increase the bioavailability, NPs stability and prolonging the circulation time in the bloodstream by less accessible to the immune system. This method is called passive and in the active version where antibodies are used [100, 101]. The active delivery method is more reliable and effective, because of employing antibodies to a specific tumor, most commonly used antibodies are epidermal growth factor receptor (EGFR) and its types [102, 103] as well as tumor necrosis factor (TNF) [104]. Because of this multifunctionality, the GNP conjugated with antibody can be used for both diagnosis and PPTT [105, 106]. For example, liposomes functionalized GNPs labeled with anti-Her2 [107] and transferrin [108] shows increased penetration of NPs into cancer cells. Finally, GNPs with SPR property shows a promising candidate for PPTT of cancer and other diseases.

2.1.2.3.4 Photodynamic Therapy (PDT)

To treat cancer using photosensitizers at a specific wavelength of visible light is known PDT method [109]. Usually, photosensitizers are injected into the human body intravenously, but sometimes contact and oral administration are also done which will accumulate in tumors regions. Then the tumor region is irradiated using laser light at a specific wavelength of which dye can absorb. Therefore, the substance produces highly

active radicals which will induce necrosis and apoptose the tumor cells or tissues [110]. The major drawbacks of using photosensitizer in PDT is that they remain in the human body for a longer time, thus leaving the patient tissues highly sensitive to light. It is notable [111] that some of the metallic NPs can be employed as an effective fluorescence quenchers. Recently [112, 113] it is shown that the plasmonic particle can enhance the fluorescence intensity by placing at an optimal distance from the metal. This concept improved the efficiency of PDT. Therefore, several investigations have been carried out for drug delivery by coating GNPs with a layer of polymer [114–117]. And to improve the entry of photoactive material, the surface of GNPs have been modified using peptides and proteins [118, 119]. Recently, composite NPs made of MNPs with gold nanoshell (CSNPs) with PEG coating along with impregnation of photodynamic dye and antibodies has been employed for effective PDT [120]. Finally, GNPs attached with photodynamic dyes can also be used as an antimicrobial effect has been reported [121–123].

2.1.3 Core-Shell Nanoparticles (CSNPs)

Core-shell nanoparticles are captivating huge attention than other NPs because it comprises more than one material which exhibited new and improved properties (Fig. 2.3) [124–126]. Since these NPs have emerged at the verge between materials chemistry and other fields, such as biomedical, pharmaceutical, optics, and catalysis [127]. CSNPs are highly functional materials with modified properties. The fascinating properties arising either from core or shell can be ultimately different. The properties can also be modified by altering the constituting materials of core and shell or their ratios [128]. These CSNPs are widely explored especially because it can be manipulated easily to meet the requirements of different application [65, 129]. The true goal of designing CSNPs is for the following possibilities:

- Surface modification
- Increase the functionality
- Stability

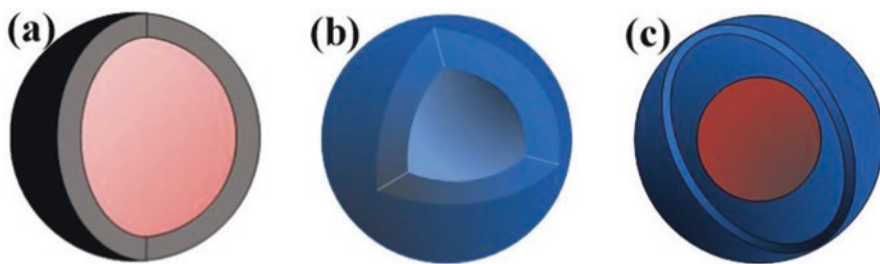


Fig. 2.3 General classification of CSNPs based on material-type and properties of their shells (Adapted with permission from reference [141])

CSNPs are widely used in different fields like biomedical [130, 131] and pharmaceutical applications [129]. In case of biomedical field, CSNPs are majorly used for

- Bioimaging [132, 133]
- Controlled drug release [134, 135]
- Targeted drug delivery [6, 134, 136]
- Cell labeling [137, 138]
- Tissue engineering applications [139]

The CSNPs are classified into three types (Fig. 2.4), such as:

1. Core-shell
2. Hollow core-shell
3. Rattle core-shell nanostructures

But, as this thesis is purely concentrated only on CSNPs. So, the various synthesis methods, characterization techniques, and applications will be discussed in detail below.

2.1.3.1 Design of Core-Shell Nanomaterials

The CSNPs are a class of nanocomposite which contains an inner core shielded with one or more shells of different other materials. Therefore, CSNPs can exist in different amalgamations [127]. The properties of CSNPs are mainly correlated with the materials used for the synthesis of core, shell, and also related to the interface layer. Thus, it offers potential opportunities and capabilities for manipulating properties by controlling the chemical compositions and sizes of the core and shell [142, 143].

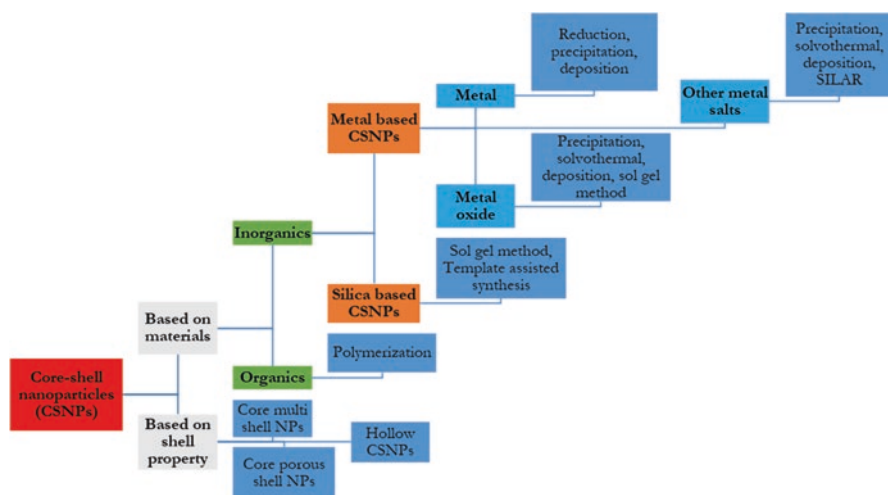


Fig. 2.4 Types of multifunctional nanomaterials (Reproduced with permission from reference [140])

The synthesis and selection of the material for CSNPs are completely dependent on the application type. Therefore, designing CSNPs are generally dependent on the final application. For example, in the case of drug delivery application, the core material could possess magnetic property, and the shell can be made of either polymer or porous silica [144]. Similarly, for nanocatalysts, the core comprises Fe_3O_4 or Fe_2O_3 , while the shell is a metal nanocluster [145]. The morphology, size, etc. of a core material predicts the architecture of CSNPs. For designing a multifunctional system for performing various therapies and imaging of cancer cells [146], the magnetic core with a porous silica shell can be encapsulated. Finally, GNPs can be formed as a subsequent shell around the silica shell, which can be employed as a multifunctional structure for imaging, drug delivery, and photothermal therapy.

As a matter of fact, the design of CSNPs is merely dependent on the type of core and its size. For example, multifunctional CSNPs where MNPs are used as core for MR imaging in which the core size is a deciding factor because when the magnetic core size is lesser than 50 nm it will possess weak magnetic forces in the scanner and MNPs larger than 300 nm will obviously get trapped in the lungs and liver causing side effects or toxicity [147]. Therefore, in most of the cases, functionalization is considered to be a crucial process for designing the shell. Commonly, the gold shell is fabricated around the magnetic cores using thiol groups as functional linkers which aid for attaching gold nanoclusters for the formation of shell [148]. Thus using above strategies various CSNPs architectures are constructed using the nature of the core and shell materials (Fig. 2.5) [149].

2.1.3.2 Fabrication Techniques of Core-Shell Nanomaterials

2.1.3.2.1 Core Materials

The applications of CSNPs are dependent on the material selection of core and shell. Usually, the core is composed of metals, metal oxides, QDs, and polymer. Many types of research have been carried out for synthesizing CSNPs using metal

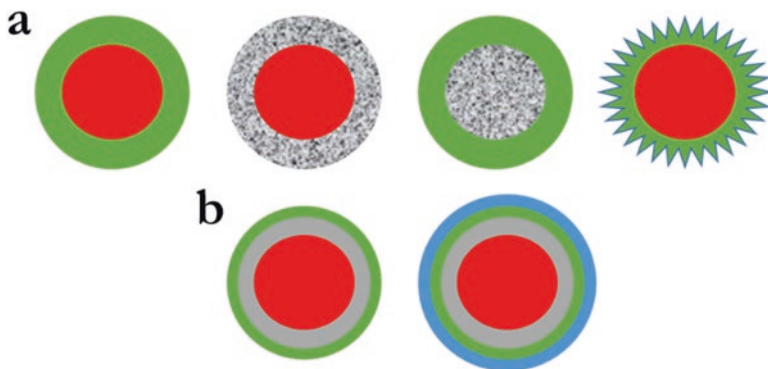


Fig. 2.5 Different CSNPs structures with (a) porous core and shell, (b) different core-multiple shell structures (Adapted with permission from reference [140])

oxides [150], Au [151], Ag [152], Co [153], Fe, and polymer cores [154] for various applications. For example, metal oxide NPs used for photocatalytic, drug control release and delivery applications. Additionally, Au noble metal nanocores have been used for nanocatalysis and PTT. QDs for bioimaging and diagnostics. Iron, cobalt, manganese, and gadolinium [155] core NPs play important roles in MR imaging [156]. Furthermore, Fe-based MNPs exhibiting as a potential candidate as a multi-functional nanosystem for therapy, imaging, and diagnosing [157].

2.1.3.2.2 Shell Fabrication

There are several synthesis approaches for forming nanoshell on the core NPs. Mostly, core NPs are synthesized first and then shell NPs are made. This is because the core NPs (substrate/matrix) surfaces provide nucleation sites for the shell atoms to nucleate on it. Various techniques for coating different types of shell materials are as follows:

2.1.3.2.2.1 Metal-Oxide Shell

Formation of metal-oxide shell on the core materials lead to produce a wide spectrum of properties. For example, metal-oxide shell on MNPs generates interesting semiconducting and magneto-optical properties. Although the various types of metal-oxides are used for shell formation, silicon dioxide (SiO_2) is still widely employed for shell formation using sol-gel approach, which involves hydrolysis and condensation of the tetraethyl orthosilicate (TEOS). Some of the examples are Au@SiO_2 [158], Ag@SiO_2 [159] (Fig. 2.6), and Pd@SiO_2 . However, a much understanding of the shell formation process is necessary for controlling the size or thickness of metal-oxides on to the cores NPs [160].

2.1.3.2.2.2 Noble Metal Shells

Noble metal shells coating onto NPs has gained its strong place in the research topic as it results in peculiar characteristics and versatile applications. Currently, the most important synthesis methods for coating noble metal is the reverse micelle technique which is usually carried out by varying the metal salt ratio to the amount of reducing agent. This method has been widely used to form metal shells around MNPs such as Co and Fe NPs [161–163]. Another method is the thermal decomposition method at high temperatures [164]. For example, Pd shell coating onto Ni Core using oleylamine at an elevated temperature [165]. In the case of Au coated MNPs by thermal decomposition, MNPs were synthesized first in the presence of oleic acid and oleylamine mixture. After that, Au shell was introduced by chloroauric acid (HAuCl_4) reduction. Additionally, silver (Ag) shell was constructed around the CSNPs by adding silver nitrate (AgNO_3) in the presence of reducing agent. Au coated MNPs not only provide the dual functionality of the magnetic and plasmonic properties but also long-term stability. So, it possesses great platform for both therapeutic and diagnostic applications [166].

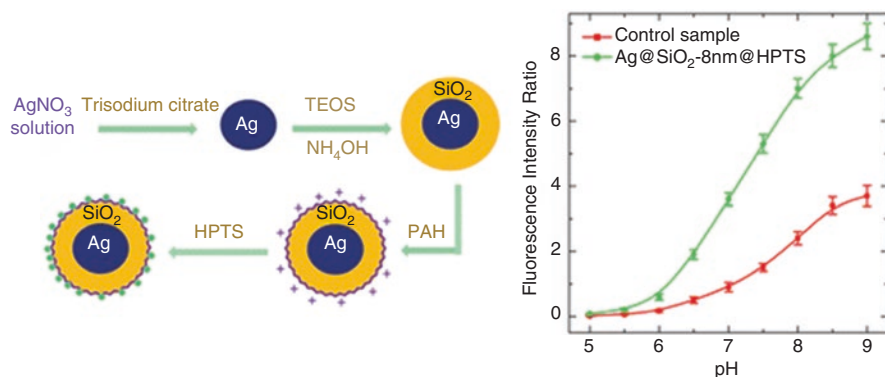


Fig. 2.6 Scheme of the proposed formation process and TEM images of a SiO_2 shell around a Ag nanocore (Reprinted with permission from reference [159] Copyright 2013, American Chemical Society)

2.1.3.2.2.3 Dense Shells

The shell formation on the core is usually dense or solid. This type of dense shell is usually made of silica or alumina, and sometimes with carbon. The silica or alumina shell will show a hydrophilic character and carbon shows a hydrophobic character. These dense shells are widely used for coating MNPs which can be utilized for biological applications. However, in the recent years, polymer shells are coated homogeneously on the core NPs which provides stealth mechanism to the core and found to be more suitable candidates.

2.1.3.2.2.4 Mesoporous Shells

The formation of dense shells around NPs provides protection, insulation, and multifunctionality. But, the novel opportunities can be obtained using the mesoporous shell because it can hold different moieties and dissipates it in and out from the core. This mesoporous shell diameter ranges from 2 to 15 nm, depending on the surfactant used. CTAB has been widely employed to form mesoporous silica shells around different types of cores. For instance, amino functionalized Si shell has been fabricated around silica cores [167], and MNPs [168] using anionic surfactants. Mesoporous shells with a pore size of 7 nm have also been fabricated using a Pluronic P123 surfactant [169].

2.1.3.3 Characterization Techniques for Core-Shell Nanoparticles [141]

Here, some of the important characterization techniques employed for CSNPs are discussed in brief: In the case of CSNPs, the combination of the core, shell, and surface functionalization plays crucial effects on their properties and applications.

So, in order to describe the properties of CSNPs, it is mandatory to elucidate, i.e., the size, shape, surface characteristics, and existence of dopants.

XRD is a method used for evaluating the crystal phases of various materials, including CSNPs. Particularly for CSNPs, it is an important tool which can shed light on the presence of CSNPs. This can even detect the separated phases of core and shell simultaneously.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis were usually carried out to determine the size, shape, and homogeneity of the CSNPs. But, in the case of SEM, it uses only secondary electrons so it generates only a surface image, which is very difficult to distinguish the CSNPs structure with SEM analysis.

HRTEM aids in the simultaneous analysis of both lattice fringes and interplanar atomic spacings of CSNPs which clearly distinguish the core and shell. Additionally, EDS (accessory to TEM instruments) can serve as a powerful technique for determining the elemental distribution in a specified region. In the case of HAADF-STEM, which is one of the most important analytical methods to confirm the formation of CSNPs, regions with a larger atomic number are determined by brighter contrast in images. Therefore, using this Z-contrast images one can analyze the element distribution visually.

The unique optical properties are exploited which is exhibited by noble metals. So, plasmonic and absorption properties of various NPs used to synthesize CSNPs are characterized directly or indirectly by several spectroscopic methods. UV-Vis spectroscopy is the most widely used spectroscopic methods for the analysis of different NP types. In the case of organic type CSNPs, IR spectroscopy was used for the identification of the various organic moieties present in the CSNPs.

Another most important technique for studying the CSNPs surface characteristics is Raman spectroscopy. And also, surface enhanced Raman spectroscopy (SERS) is used for investigating CSNPs incorporated with SERS active metals like Cu, Au, and Ag.

2.1.3.4 Applications of Core-Shell Nanoparticles

CSNPs have major advantages in the field of biomedical and electronics. Some of the different applications are as follows:

2.1.3.4.1 Biomedical Applications

CSNPs have got a variety of exciting applications in the field of biomedicine which have been developed by researchers over the past few decades. Some of them are mentioned below:

2.1.3.4.1.1 *Drug Targeting and Delivery*

For drug delivery and targeting, CSNPs are designed with exceptional properties:

- At first, the drug is encapsulated with the help of surface functionalization along with a linker for specific targeting to cancer cell.
- Then these CSNPs will reach the target cell site and disintegrate the drugs which are attached on to the surface acting like a drug cargo.

The drug release from the CSNPs will be triggered heat, light, pH, or ion concentration. By further attaching the fluorescent material, these CSNPs, which can be considered either as sensors or to track the drug delivery to a specific site. Generally, MNPs made of superparamagnetic Fe, Ni, and Co are often used to design the core with suitable shell coatings for in vivo drug release and sensor applications [170, 171]. Presently, MNPs with polymer CSNPs are typically employed for drug delivery, cell labeling, separation [172, 173], and tumor delineation [174]. This is due to their biocompatibility with living cells, so MNPs@polymer and MNPs@SiO₂ are often used over bare MNPs for drug delivery applications [175, 176].

2.1.3.4.1.2 *Bioimaging*

There are different types of molecular bioimaging techniques used for both in vivo and in vitro specimens. But, CSNPs comprising both QDs and MNPs are synthesized for dual-mode of optical and MR imaging simultaneously [174, 177, 178]. These CSNPs use either QDs or dye-doped QDs. However, QDs shows a high level of toxicity which can be minimized by coating them with appropriate materials to form a CSNPs for utilizing in vivo optical imaging applications [179, 180].

For bioimaging, both fluorescence and photoluminescence properties are also used by incorporating lanthanide metal group. Usually, lanthanide metals show good luminescence, so with well-designed biocompatible shell, these materials can be possibly utilized for the imaging and detection. By choosing right lanthanide dopants such as Er, Yb, or Tm, the emission spectra can be shifted to green, blue, or red wavelengths with increased intensity [181–183].

2.1.3.4.1.3 *Sensors*

Sensors are compact devices which assess and quantify a physical property and transfer it into a signal, which can be interpreted by a different instrument. The biomacromolecules like DNA, RNA, glucose, cholesterol, etc. can be detected using NPs-based sensors for in vivo applications. Currently, MNPs coated with metal, silica, and polymers are used for bioanalytical sensors [184–186]. One of the big research breakthroughs is the detection of tumor cells in in vivo using Au/Ag CSNPs [187]. And damaged DNA can be detected using MNPs-based sensors such as Fe/Fe₂O₃ CSNPs [188], where the MNPs surface is functionalized with cytochrome P450, myoglobin (Mb), and hemoglobin (Hb) to mimic in vivo toxicity [189].

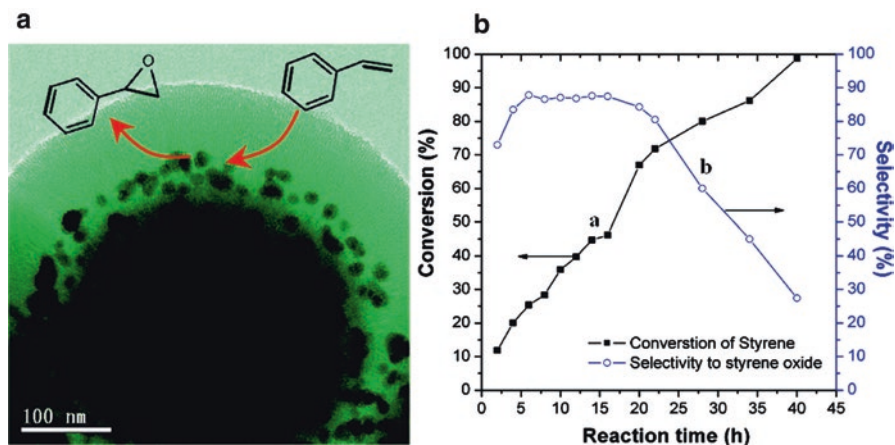


Fig. 2.7 (a) TEM image and (b) the conversion of styrene and selectivity of styrene oxide over multifunctional $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Au@mSiO}_2$ double CSNPs as a highly integrated catalyst system (Reprinted with permission from reference [145] Copyright 2010, American Chemical Society)

2.1.3.4.2 Catalytic Applications

The MNPs properties are greatly influenced by surface coating with functional materials like noble metals, semiconductors, etc. [190, 191]. For example, MNPs-based catalyst has been fabricated $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Au@m-SiO}_2$ double CSNPs considered as integrated catalysts for the catalytic reduction of 4-nitrophenol and styrene epoxidation (Fig. 2.7). Furthermore, $\text{Au@Fe}_2\text{O}_3$ with SiO_2 was employed for the catalytic conversion of CO to CO_2 whose conversion is more efficient when compared to uncoated Au@SiO_2 [192]. This proves that MNPs incorporation plays a vital role in conversion efficiency in catalysis. And bimetallic CSNPs [193], such as Au/Pd [194] and Au/Ag [195], are currently employed majorly in catalytic reactions.

2.1.4 Gold Coated Magnetic Nanoparticles (MNPs@Au)

Gold coated magnetic nanoparticles (MNPs@Au) have been highly recognized by material scientists and efficiently used in various fields. To be specific, effectively employed in biomedicine, including MR imaging [196], targeted drug-delivery [197], etc. The main reason behind the usage of MNPs@Au in many sectors is because these CSNPs are highly versatile; both magnetic and plasmonic properties can be highly tuned/tailored depending on the applications by modifying CSNPs size, shell, morphology, and surface functionalization. This thesis is completely devoted to MNPs@Au, so it is necessary for us to discuss various synthesis methods, surface modification, and finally some of the biomedical applications which are represented as follows:

2.1.4.1 Synthesis of MNPs@Au

As discussed earlier, the MNPs@Au synthesis involves two main processes:

1. Iron/iron oxide core is synthesized first
2. Then subsequent of Au shell coating is done

The previous sections explain the various methods and surface functionalization of MNPs and GNPs. So, we have discussed some of the major challenges involved in the synthesis of MNPs@Au below.

2.1.4.2 Challenges in Au Shell Formation

Some of the challenges faced by researchers in the formation of Au shell around the iron oxide core are as follows [198]:

- When MNPs are coated with Au layer it is necessary to ensure that the NPs are completely protected without exposing the core NPs.
- To accurately control the thickness of the Au shell.
- To characterize the synthesized MNPs@Au morphologically.

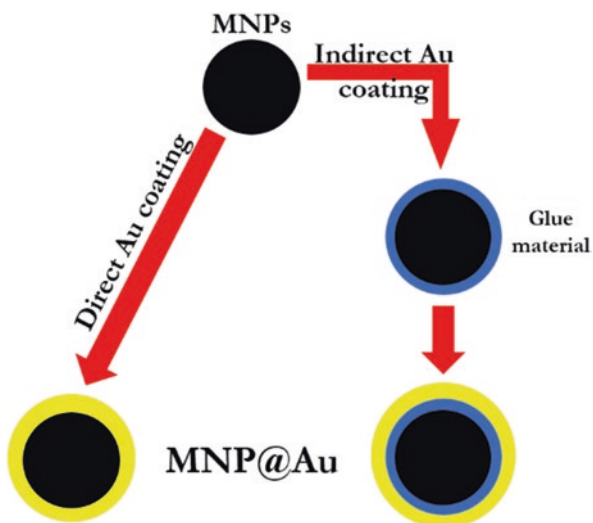
2.1.4.3 Formation Mechanism of MNP@Au

The formation of MNP@Au using Au shell can be of two types (Fig. 2.8), which is as follows:

Direct coating—Au shell is formed directly on the MNP surface.

Indirect coating—glue material is used onto MNP surface and then Au shell is formed.

Fig. 2.8 Illustration representing direct and indirect routes for gold shell coating



2.1.4.4 Direct Au Coating

In the case of direct Au coating, sodium citrate method is widely used technique for the synthesis of Au shell onto the surface of MNP core. In this technique, the Au seeds are prepared by using HAuCl_4 precursor solution in the presence of sodium citrate, by mixing with MNPs under vigorous stirring [199, 200]. Here, sodium citrate acts as a both reducing agent and also as a capping agent, so it provides NPs stability by preventing MNPs aggregation. The formation of MNP@Au is confirmed by a change of reaction solution color from faint brown to burgundy [201, 202].

For instance, when the MNPs are synthesized using thermal decomposition at high temperatures using organic compounds such as oleic acid and oleylamine, the gold shell is formed by reduction of HAuCl_4 in the presence of chloroform. This technique produces thick Au shell and to make it water-soluble, sodium citrate and CTAB are employed. To increase the Au shell size, gold precursor along with ascorbic acid and CTAB is used. This direct coating provides a fine control of both shell thickness and smoothness [166, 203].

2.1.4.5 Indirect Au Coating

MNP@Au CSNPs can be obtained by indirect Au coating by employing a glue layer in between the MNPs core and the outer GNPs shell which provides enough stability during the formation of CSNPs and also for other biomolecule functionalization.

Researchers developed poly-L-histidine as the glue material for CSNPs synthesis. The MNPs were synthesized using oleic acid capping and were dispersed in chloroform. So, to make MNPs water-soluble their surface was modified using an amphiphilic polymer with a carboxylic acid. The pol-L-histidine was added to the reaction mixture which adsorbs onto the amphiphilic polymer via electrostatic interactions. Finally, HAuCl_4 is reduced onto the chelating agent with hydroxylamine forming the Au shell [204].

In a different study, a polymer poly(cyclotriphosphazene-co-4,4'-sulfonyldiphenol) (PZS) was used as the glue material. The MNPs were coated with PZS layer and then Au seeds were added which get adsorbed on the PZS surface by reduction of HAuCl_4 by sodium borohydride (NaBH_4) [205].

Silica has been widely used as a glue material for CSNPs synthesis [206]. Firstly, the MNPs were synthesized by coprecipitation method, then it is coated with a silica shell through the sol-gel technique. Secondly, Si coated MNPs were formed with three layers of positively charged polyelectrolytes, to ensure a smooth and uniform NPs surface. Later, negatively charged Au seeds using HAuCl_4 and ascorbic acid as the reducing agent were formed. The finally formed Au shell was about 30 nm thick by this process [207].

2.1.4.6 Surface Functionalization of MNPs@Au

The surface modification/functionalization of MNPs@Au is a crucial step which plays an important role for their use in various fields like analytical chemistry and biomedicine. The functionalized MNPs@Au has the ability to express very high sensitivity, specificity, and biocompatibility *in vitro* or *in vivo*. For example, in the biosensor, drug delivery nanocargo development of where the functionalized MNPs@Au act as an active element. The process of functionalization on the surface of Au nanoshell behaves as a bridge between the molecules for targeting or delivery in the specific site. The great advantage of nanoshell is its versatility, so any kind of biomolecules can be attached to enzymes, proteins, DNA, RNA, drugs, etc. Additionally, the Au shell coating results in protecting the inner core from various environmental factors and also in the case of MNPs it prevents the aggregation which is the major drawback by means of electrostatic charge usually causing repulsion between MNPs.

2.1.4.7 Applications of MNPs@Au

Some of the potential applications of MNPs@Au ranging from biosensing to medical imaging and therapies are discussed.

2.1.4.8 Imaging

Some of the investigations compare MRI contrast agents like as-synthesized Au@MNPs, Feridex, dextran-MNPs which revealed similar r_2 values which confirm that the Au shell has no detrimental effect on the internal magnetic properties of the MNPs. But, Au@MNPs increase biocompatibility and long blood circulation time [16]. Other combination diagnostic techniques like MRI-CT, MRI-ultrasound imaging, and MRI-photoacoustic imaging employs Au@MNPs probes.

CT relies on the attenuation of X-rays [208]. MRI-CT-ultrasound imaging probe was designed based on 6.1 nm Au@MNPs with a sugar coating. The results showed that the Au shell enhances CT contrast, MNP core showed high T_2 -weighted MR imaging and also allowed the imaging extravascular regions using ultrasound, which was not achievable with the microbubbles which are currently in clinical use [209].

Photoacoustic imaging, where contrast is dependent on the absorption of light with the presence of contrast agents [189]. Au@MNPs nanoroses was synthesized which was found to possess a high r_2 relaxivity of $219 \text{ mM}^{-1}\text{s}^{-1}$ when compared to commercially available Feridex. Therefore, Au@MNPs offers a solid platform to be used in imaging technologies as a diagnostic tool adding several benefits to patients [210].

2.1.4.9 Hyperthermia

Hyperthermia therapy is used to treat superficial tumors by heat. This therapy offers an advantage of treating in a specific region or a whole body. MNPs and GNPs are commonly used candidates for hyperthermia to generate a cytotoxic environment to attack cancer cells [211].

For the MNPs-based hyperthermia, the AMF with the frequencies of kHz—MHz is applied. Heat would be produced by MNPs due to the Brownian and the Néel modes. For GNPs-based hyperthermia, the characteristic plasmon absorption in the NIR region which convert 100% absorbed NIR light into heat. But, the photo-induced hyperthermia can only treat shallow cancer but not in deeper tissues [212].

The Au-Fe_xO_y CSNPs possess both magnetic and photo-induced hyperthermia properties with many advantages:

1. This CSNPs can be used both for therapy and also for imaging at once.
2. As it is a combination of two different kinds of NPs, it can enhance tumor cell killing even at very small concentrations in the body.

2.1.4.10 Magnetic-Induced Hyperthermia

The magnetic-induced hyperthermia for Au-Fe₃O₄ CSNPs can be achieved even with the smaller oscillating magnetic field frequencies with 44–430 Hz. The heat generated by CSNPs are much higher when compared to MNPs alone under the same condition. This high heat generation purely depends on the higher magnetic anisotropy with the Au shell. Even though both Au-Fe_xO_y CSNPs and MNPs can be used for magnetic-induced hyperthermia for cancer therapy, but Au-Fe_xO_y CSNPs will drastically reduce the aggregation of MNPs under magnetic field [213].

2.1.4.11 Photo-Induced Hyperthermia

Au-Fe₃O₄ CSNPs are widely employed for combination therapy in photo-induced hyperthermia using Au NPs and for MR imaging using MNPs in several literatures [214–216]. The CSNPs are immobilized with an antibody which could specifically target cancer cells, and when NIR laser is applied which could cause the cancer cell death. Au-Fe₃O₄ NPs can absorb in the NIR region, through which photo-induced hyperthermia can be achieved. Core/cluster/shell: Au@Fe₃O₄@SiO₂ NPs with anti-HER2 was designed. These NPs binds only to the HER2+ to target SKBR3 cells. Then, NIR laser is applied which will initiate cell death. The fluorescence images observed that the cells upon NIR laser irradiation were dead [217].

2.1.4.12 Drug Delivery

Functionalized Au-Fe₃O₄ dumbbell-shaped NPs with herceptin attached on MNPs and the cisplatin attached on the GNPs were used as a drug nanocargo. This multi-functional nanocargo can do multi-tasking work during therapy without disturbing each other. It is due to the difference in length, size and ligand thickness is quite large which may interfere with the each other's performance. The drug release profile was studied using dialysis tube at pH 7, in comparison to cisplatin release. There is a very low percentage of cisplatin is released in just 2 h. But the release has been increased when the pH is lowered which is close to endosomal pH. The viability of cells was evaluated with control and cisplatin, which indicated that the viability of the nanocomplexes was negligible for its therapeutic effect [218].

2.1.4.13 Gene Delivery

Gene therapy has become one of the great potential therapy for treating many diseases including cancer. But due to the low efficiencies of nonviral gene vectors, currently, this therapy is still limited [26]. MNPs-based "Magnetofection" has been used to overcome this drawback by associating gene vectors with the aid of a magnetic field [219]. Several research reports prove that MNPs improves the efficiency of viral and nonviral gene vectors up to several folds under the influence of magnetic field.

Usually, adenovirus and its linked viruses are the most efficiently tested for cancer gene therapy [220]. This vector's efficacy is highly dependent upon the coxsackie and adenovirus receptor (CAR) expression level of the target/cancer cell. If CAR level is low then it leads to poor gene transduction occurs. To overcome this, γ -Fe₂O₃@Au CSNPs is conjugated with adenovirus and introduced into the cells which increased the adenovirus gene expression over 1000 times. Furthermore, these CSNPs entered the cell directly, independent of any pathways. Thus, the γ -Fe₂O₃@Au CSNPs have a huge potential to increase adenovirus tropism and also enhances gene transduction efficiency [221].

2.1.4.14 DNA-Based Biosensors

Functionalized Au NPs are effectively employed for various DNA-based sensors. Au NPs are functionalized with thiolated oligonucleotides to recognize complementary DNA targets [222]. A 3-layer sandwich nanocomposite structure was designed based on SiO₂@Fe₃O₄@Au core/cluster/shell particles for sensing DNA [223]. These NPs were functionalized with 3' and 5' thiol-modified DNA strands, which were responsible for complementary hybridization with a target oligonucleotide of base pair mismatch. Usual aptamers are either DNA or RNA with specific identification of target biomolecules. But recently, due to the convenience of oligonucleotide functionalization via Au-S bonds an ultrasensitive aptasensor for thrombin was designed using Fe₃O₄@Au cluster/shell NPs [224].

2.1.4.15 Enzyme-Based Biosensors

The enzyme-based sensor combines the enzyme specificity and electrochemical techniques to be potentially used in diagnostics and monitoring. Au NPs have been extensively employed in modified electrodes because of their

- Electrical conductivity
- Biocompatibility
- Enzyme immobilization on Au NPs surface via Au-S bonds

Currently, Au@Fe_xO_y NPs were used to design enzyme-based sensors. Au@Fe_xO_y NPs can easily be immobilized onto the electrode surface under magnetic field. The Fe₃O₄@Au CSNPs is attached to the surface of a magnetic glassy carbon electrode (MGCE). Horse heart Mb was immobilized on CSNPs using cysteine. This modified electrode Mb-Fe₃O₄@Au-MGCE showed a good reduction performance of H₂O₂ [189].

And also, when Au NPs are attached with a fluorescence marker, the light emitted from dye will be quenched by Au NPs. So, this property is utilized for developing enzyme. For instance, flower-shaped Au@Fe₃O₄ CSNPs used as a template to design an optical probe containing a fluorescent dye Cy5.5-GPLGVRG-TDOPA on the MNPs surface and SH-PEG₅₀₀₀ onto Au NPs surface. This complex is quite efficient for in vivo tumor imaging [210].

2.1.4.16 Cell Sorting and Separation

MNPs-based separation has become the most widely employed techniques for biomarker purification, separation, and sorting. The usage of Au@MNPs efficiently improve the separation. For example, two hybrid Fe₃O₄@Au@Fe₃O₄ nanodumbbells and Fe₃O₄@Au necklace-like structures proved improved sorting and separation with tunable properties of both magnetic and optical [225]. Fe₃O₄@Au CSNPs are used for the purification of CD4⁺ lymphocytes from the spleen of mice [226]. Another investigation also used poly(diallyldimethylammonium chloride) coated Fe₃O₄ (PDDA@Fe₃O₄) NPs by the coprecipitation method for cell purification [227]. The 4-mercapto-phenylboronic acid-modified Fe₃O₄@C@Au CSNPs were synthesized and used for selective enrichment and separation of glycoproteins and glycopeptides [228].

2.1.4.17 Catalysis

Au NPs plays an important role in several catalytic processes [229–231]. Recently, Au@MNPs CSNPs were popularized to successfully demonstrate many catalytic effects for carbon-monoxide oxidation [232], hydrogen peroxide (H₂O₂) [233], reduction of nitrophenols [234] and H₂O₂ [235]. The Au@Fe_xO_y NPs enables good separation for recycling the nanocatalysts from the reaction mixture using an external magnet. Also, the Au@Fe₃O₄ nanocatalysts can be easily recycled and reused with a conversion efficiency of around 100%.

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