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# Review Article
# Multifunctional Nanomaterials for Multifaceted Applications in Biomedical Arena

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## Abstract

Nanotechnology is the technology having massive capacity in the areas of biology, biotechnology and medicine technology etc. It includes understanding and controlling materials ordinarily in the size range of 1-100 nm. Owing to their nanoscale effects and enhanced surface area. Nanomaterials have been explored as promising tools for the progression of medication and gene delivery, diagnostic biosensors and biomedical imaging. In contrast with their larger counterparts, nanomaterials have inimitable physicochemical and biological properties. These nanomaterials are at the leading edge in the field of nanotechnology. Numerous properties of the nanomaterials, for instance, size, shape, surface structure, chemical composition and charge significantly influence their interactions with biomolecules and cells. Nanoparticles with size-tunable light emanation have been utilized to create uncommon pictures of tumor destinations. Single-walled carbon nanotubes, having distanced across practically identical to the width of DNA atoms. They have exhibited a great potential as high-efficiency delivery conveyance transporters for biomolecules into cells. Thus, in this review, a brief account of the diverse types of nanosystems is discussed. The applications of various nanomaterials in the biomedical area have been explained in detail. The diverse applications of nanomaterials in drug delivery, gene delivery, etc. have been clearly discussed. Therefore, this review would help the readers to better understand different types of nanomaterials along with the diverse applications of these nanometers in the biomedical field.

Key words: Nanotechnology, nanomaterials, nanomedicine, biomedical applications

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## INTRODUCTION

The idiom "Nanotechnology" was first coined in 1974 in the Tokyo Science University by Norio Taniguchi. Nanotechnology was abbreviated to "Nanotech". It is the learning of manipulating materials on an atomic and molecular scale[1,2]. Nanotechnology deals with a dimension of 0.1 nm to 100 nm materials[3]. The concept of nanotechnology relates to Richard Feynman's lecture in 1959 at California Institute of Technology which was given on the topic, there's plenty of room at the bottom[4]. However, at that time the practical methods of implementing Feynman's ideas had not been discovered[5]. But, in 1982 with discovery of the Scanning Tunneling Microscope (STM)[6] and the Atomic Force Microscope (AFM) in 1986[7] paved the way milestone for the enlargement of nanotechnology. With the help of these two techniques, it becomes probable to observe structures on the atomic scale. The further increment in the development of nanotechnology was achieved by the Eric Drexler's book Engines of Creation, (1986)[8]. The main developments were, fullerene (1985)[9] and carbon nanotubes (1991)[10] for the nanostructures synthesis. The first application of nanomaterials in the treatment of cancer has been seen in 2003[11]. The various stages of development in the field of nanotechnology are tabulated in Table 1. Nanotechnology is an interdisciplinary branch of science, with combining elements of physics, chemistry and technical sciences. Nanotechnology is changing the direction of science by giving us a wide range of applications[12-14]. The application of nanomaterials can be historically traced back to even before the generation of modern science and technology. Michael Faraday explained how metal nanoparticles affect the color of church windows, in his paper in 1857[15].

Nanotechnology includes practical applications in medical and pharmaceutical sciences[16-20]. Nanotechnology is useful in medicine and related sciences. For example, in drug delivery on the cellular level, cell Bioimaging in the therapy of cancer, targeted therapy and in the regeneration of organs and tissues[21]. Figure 1 outlines the practical application of nanotechnology in pharmacy, medication and medical

Table 1: Periodical development of nanotechnology

| Year | Improvement in nanotechnology |
|---|---|
| 1959 | R. Feynman began the process |
| 1974 | The first-time nanotechnology term was utilized by Taniguchi |
| 1981 | IBM Scanning Tunneling Microscope |
| 1985 | "Bucky Ball" |
| 1986 | The first book "Engines of Creation" on nanotechnology published by K. Eric Drexler, Atomic Force Microscope |
| 1989 | IBM logo was made with individual atoms. |
| 1991 | First time Carbon nanotubes discovered by S. Iijima |
| 1999 | R. Freitas publishes first "Nanomedicine" book |
| 2000 | The National Nanotechnology Initiative was established |
| 2001 | Preparation and characterization of CNTs |
| | Feynman awarded for developing theory for nanometer-scale nanotechnology |
| 2002-04 | Prize was awarded to Feynman in the field of Nanotechnology |
| 2005-10 | 3D Nanosystems like robotics |
| | 3D, networking |
| 2011 | Era of molecular nanotechnology began |

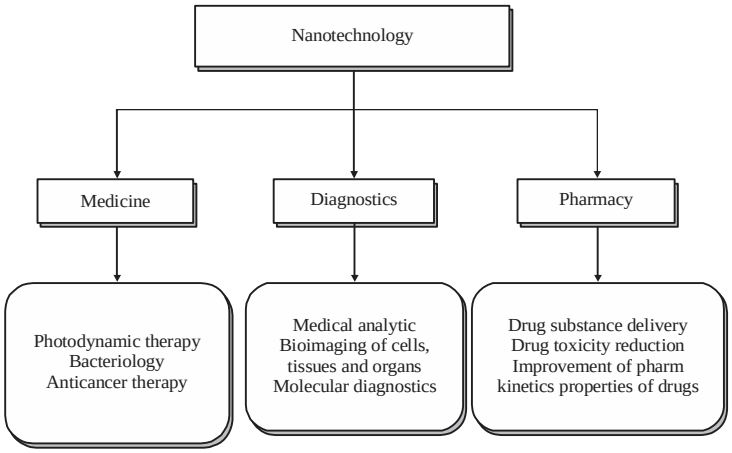


Fig. 1: Application of nanotechnology in medical science

diagnostics. Nanotechnology also useful in many diseases like Alzheimer's disease, cancer, cardiovascular diseases, diabetes, as well as different types of severe infectious diseases like HIV. Damaged tissues can be reproduced or doctored with the aid of nanotechnology. Superior biosensors can be synthesized by means of nanotubes with novel properties. These advanced nanomaterials are used for Astrobiology and help to study the origins of life. This technology also leads in stem cell research like Quantum dots have been employed for molecular imaging and tracking of stem cells, not-fluorescent carbon nanotubes, as well as fluorescent CNTs, have been used in the stem cell research[22,23]. In stem cell, research nanodevices have been used in imaging and tracking them. Nanodevices also have an application of basic science and translational medicine. Nanodevices also have been used for intelligent delivery, intracellular access and for the biomolecules sensing. Nanotechnology holds a big influence in tissue technology and stem cell microenvironment and has a promising potential for biomedical applications[24]. Nanotechnology contributes to the growth of every field of science.

## PROPERTIES

Enhanced relative surface area and quantum effects are the two important principal properties of nanomaterials, which distinguish theirs from other materials. Due to these extraordinary attributes of minute size and high surface area to volume ratio and the capacity of surface changes. Nanomaterials exhibit unique biological, magnetic and optical properties. The biological properties assist us to adjust processes taking place on a cellular stage. The electrical properties of the nanomaterials rely upon the diameter of the materials. These properties diverge between metallic to semiconducting materials. Nanomaterials have extremely high electrical conductivity, because of the fewer defects in the crystal. Nanomaterials have enhanced thermal conductivity, owing to the heavy vibration of covalent bonds. These have 10X higher thermal conductivity than the metal and this is because of fewer defects in the quartz. They are exceedingly solid and hold out extreme strain. Again, due to fewer defects in the crystal structures, materials do not fracture on bending[25].

## CLASSIFICATION

The classification of nanomaterials can be managed according to their chemical composition, dimensionality or application and part of the social system. Based on the structure type, nanomaterials can be divided into nanoparticles, nanotubes, dendrimers, quantum dots and micelle formations. Based on the chemical classification, nanomaterials can be either inorganic or organic. Organic nanomaterials include carbon structures (CNTs, fullerenes, graphene), dendrimers or polymer nanoparticles and an inorganic nanomaterial include metal oxide nanoparticles, semimetal oxides, metal nanoparticles and semiconductor quantum dots. Figure 2 outlines the classification of nanomaterials in terms of structure type and chemical composition.

Table 2: Nanomaterials based on different phases

| Phase | Examples |
|---|---|
| Single phase solids | Crystalline, amorphous particles and layers |
| Multi-phase solids | Coated particles, matrix composites |
| Multi-phase | Aerogels, colloids, ferrofluids |

Nanomaterials can also be classified by dimensions (0D, 1D, 2D and 3D) like nanorods, nanowires, tubes, fibers, platelets and particles and quantum dots. Nanomaterials can also classify based on phases, like single phase solids and multiphase solids (Table 2).

## BIOMEDICAL APPLICATION OF NANOMATERIALS

Different types of nanomaterials are used for biomedical applications. They may be dendrimers, liposomes, carbon nanotube, nanocrystals, nanoparticles, inorganic nanoparticles, metal-based nanoparticles and polymeric nanoparticles etc[26-33].

**Carbon Nanotubes (CNTs):** Ever since the discovery of carbon nanotubes (1991), they have been broadly utilized for the probable applications in the biomedical area. Owing to their capacity to conduct electricity with less resistance they can be utilized in devices and sensors. The tremendously high length-to-diameter ratio makes them suitable as nanocarriers[34,35]. While their outstanding spectroscopic properties make them attractive for photothermal therapy and/or for medical imaging[36]. In comparison to the other nanomaterials i.e., spherical ones, CNTs have extremely high absorption properties. The indomitable strength of CNTs because of the $sp^2$ character of the C-C bonds and owing to their very less density they are very light materials. Thus, CNTs can be precious materials for diverse of biomedical applications[37]. Various studies have been demonstrated the superb biocompatibility[38-40] and high capability of adequately functionalized CNTs to selectively target cells after intravenous injection[41]. The blend of these properties and their performance in biological systems makes carbon nanotubes as a fascinating nanomaterial for biomedical applications. The

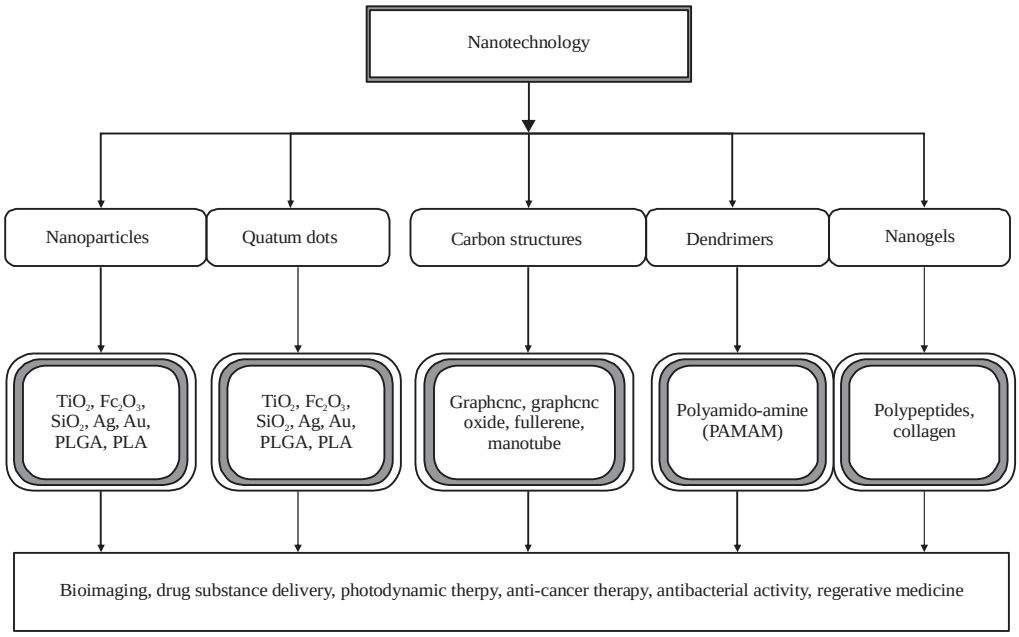


Fig. 2: Outline classification of nanomaterials in terms of structure type and chemical composition. [PLGA- poly (lactic-co-glycolic acid), PLA- polylactic acid, PAMAM- polyamide amine]

classification of CNTs can be done based on the number of their layers. Single-Walled Carbon Nanotubes (SWCNTs) are characterized as one-atom-thick sheets of carbon atoms. These sheets are associated by means of $sp^2$ bonds arranged in hexagonal structural and rolled up into a cylinder characterized by a high aspect ratio. Multi-walled CNTs (MWCNTs) can have rolled-up structures of multiple concentric sheets. The diameter SWCNTs has 0.4-2 nm and length up to 1 μm while the MWCNTs has the diameter from 2-100 nm and lengths up to several micrometres[42-44]. The syntheses of SWCNTs involve catalyst and generally have a higher amount of impurities and are more for defects during functionalization. The producer of MWCNTs can be achieved in the absence of a catalyst and is having a higher purity as well as fewer defects[45].

**CNT in cancer therapy:** The CNTs have been utilized as a therapeutic tool and as a diagnostic in the cancer treatment. Kesharwani *et al.*[46] thoroughly examined the utilization of diverse cell lines for the testing of CNTs. The most well-known model of anticancer drug that is utilized to show the capacity of new drug delivery systems is the Doxorubicin (DOX)[47].

Oxidized CNTs are usually favored, over pristine and other modified tubes, as drug vehicles. They contain surface carboxylic gatherings that allow the simple functionalization, specifically for the addition of passive and active targeting moieties. In addition, oxidized carbon tubes possess fewer impurities of metal and cross cell hindrances more productively because of their abbreviated size. The CNTs functionalized with Folic Acid (FA) and wrapped in hydrophilic polymers can enter cancer cells by means of energy-dependent mechanism mediated by the means of folic acid receptor[48-50]. This addition of FA with CNTs is effective on numerous human tumor cells. This is a well-organized approach to enhance the cellular uptake of drug loaded carbon tubes.

The functionalized carbon nanotubes along with the paramagnetic particles were reported by Chen *et al.*[51] for building up a drug delivery system, the proper conditions must be chosen. Cisplatin is extensively utilized as an anticancer drug that can be utilized against various distinctive strong tumors. With respect to DOX, cisplatin is a very high degree cytotoxic and requires specific delivery to diminish harmful impacts. With the assistance of DOX, cisplatin tranquillizes loads inside the CNT. Guven *et al.* encouraged the synthesized ultrashort carbon tubes for the delivery of cisplatin, which could avoid the reticuloendothelial system. Li *et al.*[52] worked on MWNTs which are capped with C18-coated GNPs, in this way the cisplatin molecules retain within MWNTs. Tan *et al.*[53] further worked on the coating of carbon tubes with a biocompatible polymer. These Functionalized tubes not only just benefits the general biocompatibility of the systems, but also synergistically improve the thermal properties of the nanocomposite[53].

**CNTs in tissue engineering and in bone regeneration:** Tissue engineering and regenerative medicine are innovative approaches in medical science. In future, for developing engineered artificial tissues for applications in replacement grafts and tissue models for *in vitro* disease studies and drug discovery[54-58].

Adhesion, differentiation, migration and proliferation, migration of cells within the ECM form the basis of tissue regeneration. Tonelli et al. reported the tissue engineering applications of CNTs. They focused on how these materials interact with osteoblasts with regeneration of bones, myocytes with regeneration of muscles and neurons for regeneration of neural tissue[59]. Many polymers and polymeric hydrogels have been used for matrix forming materials. On recent advances CNTs enhance the strength of matrices and increase the porosity of matrices[60], because of its high tensile properties. It was demonstrated by Li *et al.*[61]; that CNTs favor subsequent cell adhesion, migration and proliferation. Due to their nanostructure, enhanced surface area and high capacity to absorb proteins[61]. The CNTs with biodegradable polymers are effective for bone regeneration matrices. The CNTs with polymer matrices are also the system with biocompatibility together with controllable structure. Ciapetti *et al.*[62] demonstrated the disputable impact of the introduction of carbon tubes in PLLA/HA develop. PLLA scaffolds stacked with SWNTs indicated poor osteoconductive properties when tried *in vitro* with human bone marrow-derived mesenchymal stromal cells[62]. Hirata *et al.*[63] reported the PLLA polymer surface coated with MWNTS which enhanced cell attachment. This might be due to carboxylated groups, so more hydrophilic[63] and in this case, differentiation and migration were not affected. Strengthening properties of CNTs are more beneficial for bone regeneration. CNTs with surface characteristics were capable of favouring cell attachment, migration, differentiation and proliferation.

Shimizu *et al.*[64] reported first the significance of the nanotubes surface modification. These modified carbon nano tubes utilized in the induction of bone calcification and studies the underlying effects of CNTs on bone regeneration[64]. Oxidized MWNTs have surface carboxyl group attract $Ca^{2+}$ ions from physiological fluids. This enhanced the extracellular $Ca^{2+}$ concentration which serves to favors osteoblasts differentiation. This differentiated cell discharge alkaline phosphatase which advances calcification. Pan *et al.*[65] also developed an ideal weight ratio of CNT/ polymer that permits the synthesis of scaffolds with promising properties for biomedical applications[65].

**CNTs as biosensors:** Research in the field of biosensors is to synthesize cost effective sensors for the detection of glucose *in vivo.* Owing to the enhanced surface area, electrical conductivity and electrochemical stability, CNTs displayed a noteworthy application in electrochemical glucose[66]. The method utilized for the determination of glucose can be enzyme based or nonenzymic. Wang *et al.*[60] detailed the preparation of enzyme based detectors that utilized glucose oxidase (GOX) and glucose dehydrogenase (GDH). Electrostatic self-assembly method was employed for the synthesis of the sensor by Fu et al.[67]. The synthesized biosensor not only displayed enhanced sensitivity, fast response and less detection limit but also the improved stability. Because of the formation of strong covalent bonds in comparison with the non-photo-cross-linked biosensors.

Hoshino *et al.*[68] developed multilayer amperometric biosensors by the dry method. The developed sensor comprised of SWNTs, nano-thin plasma, the electron transfer mediator phenothiazine (PT), GDH and polymerized film (PPF). The synergy between CNTs and the electron transfer mediator increases the sensitivity to glucose and decreases the working potential.

Researchers have also synthesized biosensors which can detect other biomolecules and species. Hu *et al.*[69] prepared detector to identify concanavalin A (ConA), by immobilized D-glucose to MWNTs-polyanilin. The prepared sensors demonstrate a detection limit of 1 pM. This strategy can be employed in the development of fast, easy, cost-effective and miniaturized electrochemical biosensors for biological binding assays.

Chen *et al.*[70] synthesized an amperometric sensor, for the detection of hydrogen peroxide. The sensor comprised of MWNTs and bimetallic nanoparticles in a Nafion film. The proposed sensor could operate at reduced working potential achieving high sensitivity and quick amperometric response[71]. Cao *et al.*[72] prepared a luminal electrochemiluminescence biosensor, for the determination of A-1-fetoprotein. On integrating the enhanced specific surface area of MWNTs and conductivity of ionic liquids, Bai *et al.*[73] synthesized an electrochemical sensor. The integration of carbon tubes into biosensors has an influence on their stability, sensitivity and reproducibility by increasing their interfacial properties.

**Dendrimers:** Dendrimers are extremely branched synthetic polymers in nano range1-10 nm. The major advantages of the dendrimers are their control over the size, predictability and number of functional groups present for its amendments. This provides a greater chance of incorporation of drugs. Hence, it enables reproducible pharmacokinetics, which makes dendrimers an interesting drug delivery system for Photo. The action of dendrimer in drug delivery is shown in Table 3.

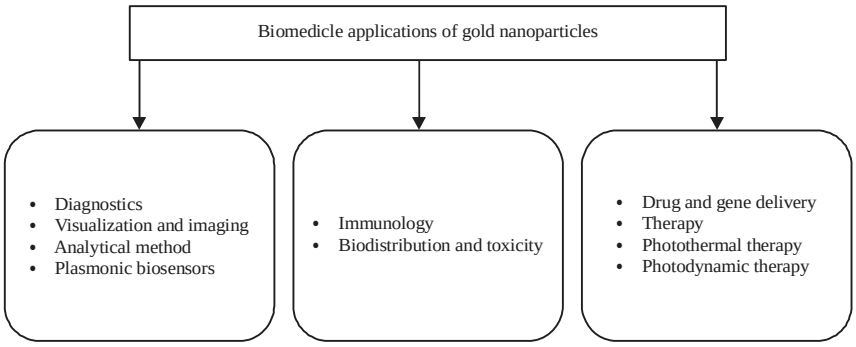


Fig. 3: Biomedical applications of GNPs

Table 3: Different therapeutic moieties studied using dendrimers platform

| Drugs | Pharmacology | Dendrimers type | Application | References |
|---|---|---|---|---|
| 10 hydroxycamptothecin | Anticancer | Carboxylated poly(glycerolsuccinic acid) | High toxicity | Morgan *et al.*[74] |
| 7 butyl 10 aminocamptothecin | Anticancer | G4.5 poly (glycerol succinic acid) COONa | Increased aqueous solubility and 16-fold increased cellular uptake | Morgan *et al.*[75] |
| Paclitaxel | Anticancer | Polyglycerol (G4 and G5) Increased aqueous solubility[30] | Increased aqueous solubility, enhanced | Ooya *et al.*[76] |
| | | G4 PAMAM | Cytotoxicity | |
| Methotrexate | | G2.5 and G3 PAMAM 24 fold increment in cytotoxicity[34] | 24 fold increment in cytotoxicity[34] | Gurdag *et al.*[77] |
| | | G5 PAMAM | G5 PAMAM Targeted delivery | |
| Doxorubicin | | G4 PAMAM | Improved cytotoxicity | Papagiannaros *et al.*[78] |
| Famotidine | | G5 PPI | Improved solubility | Kumar *et al.*[79] |
| Indomethacin | NSAIDs | G5 PPI | Improved solubility | Mutlu *et al.*[39] |
| Rifampicin | Antitubercular | Mannosylated PPI | Sustained release and targeted delivery | Dutta *et al.*[80] |
| Lamivudine | Anti HIV | Mannosylated PPI | Prolonged drug release up to 144 h | Dutta *et al.*[81] |
| Efavirenz | Anti HIV | PPI | Targeted delivery | Dutta *et al.*[81] |
| Furosemide | Diuretic | G4 PAMAM | Increased solubility and sustained release | Devarakonda *et al.*[82] |
| Etoposide | Anticancer | PAMAM | High loading capacity | Wang *et al.*[83] |
| Erythromycin | Bactericidal | | | |
| Antibiotic | G4 PAMAM | Sustained release and improved activity | Bosnjakovic *et al.*[84] | |
| Zidovudine | Anti HIV | G4 PPI | Targeted delivery | Gajbhiye *et al.*[85] |
| Ketoprofen | NSAIDs | PAMAM | Improvement of drug permeation through Skin | Cheng *et al.*[86] |
| Diflunisal | NSAIDs | PAMAM | Improvement of drug permeation through Skin | Zharov *et al.*[87] |

## Metal-based nanoparticles

**Gold Nanoparticles (GNPs):** The GNPs have found diverse applications in biomedical applications with high sensitivity diagnostic assay, drug and gene delivery, radiotherapy and photothermal therapy enhancement. Outline applications of GNPs are shown in Fig. 3. To make effective GNPs for the biomedical applications GNPs have also been functionalized. In 2003, GNPs were first used in photothermal therapy. Photothermal therapy with GNPs is also called as the plasmonic photothermal therapy[88]. Pitsillides *et al.*[89] reported the use of 20 and 30 nm gold nanosphere for selective damage to target cells. Khlebtsov *et al.*[90] reported that the effectiveness of GNPs for the photothermal therapy is based on the shape, size; aggregation extent and the structure of GNPs. Huang *et al.*[91] showed that 30 nm small aggregates of GNPs were capable of destroying cancerous cells.

**GNPs as a therapeutic agent:** The GNPs have been increasingly used for the direct therapeutic purposes. Abraham and Himmel[92] demonstrated the utility of gold nanospheres (GNSs) for the cure of rheumatoid arthritis. Tsai *et al.*[93] reported the utilization of gold colloid in treatment collagen-induced arthritis in rats. Further, Brown *et al.*[94,95] subcutaneously injected GNPs into rats with collagen and pristane-induced arthritis. The antiangiogenic property of GNPs is explained by Bhattacharya *et al.*[96] and Mukherjee *et al.*[97]. These GNPs mediate angiogenesis, together with that in tumor tissues and reduce tumor activity[98].

Table 4: Antitumor substances conjugated with GNPs

| Drugs | Particle size (nm) | Method of functionalization | Auxiliary substance | References |
|---|---|---|---|---|
| Paclitaxel | GNSs, 26 nm | Paclitaxel-SH | PEG-SH, TNF | Llevot *et al.*[103] |
| Methotrexate | GNSs, 13 nm | Physical adsorption | - | Paciotti *et al.*[104] |
| Daunorubicin | GNSs, 5nm,16 nm | 3-mercaptopropionic acid as a linker | - | Chen *et al.*[105] |
| Gemcitabicin | GNSs, 5 nm | Physical adsorption | Cetuximab | Li *et al.*[106] |
| 6-mercaptopurine | GNSs, 5 nm | Physical adsorption | - | Patra *et al.*[107] |
| Dodecylcysteine | GNSs, 3-6 nm | Physical adsorption | | Podsiadlo *et al.*[108] |
| 5-fluorouracil | GNSs, 2 nm | Thiol ligand | - | Azzam *et al.*[109] |
| Doxorubicin | GNSs, 12 nm | Physical adsorption | Folate-modified PEG | Agasti *et al.*[110] |
| Cisplatin | GNSs, 5 nm | PEG-SH linker | PEG-SH, Folic acid | Dhar *et al.*[111] |
| Oxaliplatin | GNSs, 30 nm | PEG-SH linker | PEG-SH | Patra *et al.*[112] |
| Kahalalide F | GNSs, 20, 40 nm | Physical adsorption | - | Brown *et al.*[113] |
| Tamoxifen | GNSs, 25 nm | PEG_SH as a linker | PEG-SH | Hosta *et al.*[114] |
| Herceptin | GNRs, | 11-mercaptoundecanoic acid as a linker | | Dreaden *et al.*[115] |
| B-Lapachon | GNSs, 25 nm | Physical adsorption | Cyclodextrin as a drug pocket, anti-EGFR, PEG-SH | Eghtedari *et al.*[116] |
| Prospidin | GNSs, 50 nm | Physical adsorption | - | Park *et al.*[117] |

Wang *et al.*[99] reported the PEG-coated gold nanorods (GNRs), they have the unique ability to induce tumor cell death and subsequently damage them.

**GNPs as drug carriers:** The GNPs have shown potential applications in medicines as well as targeted drug delivery[100,101]. The most popular objects for targeted delivery are antitumor preparations[102] and antibiotics. The GNPs have been complexes with a number of antitumor substances[103-117] which are shown in Table 4.

Gu *et al.*[118] reported a gold colloid with vancomycin. A gold vancomycin-colloid is effective toward various enteropathogenic strains of *enterococcus faecal*, *Enterococcus faecium* and *E. coli*. Rosemary *et al.*[119] reported a similar complex, which was synthesized by gold nanoshells and ciprofloxacin. This complex with gold nanoshells shows elevated antibacterial activity against *E. coli* bacteria. Selvaraj and Alagar further reported a conjugated colloidal gold complex with antileukemic drug 5-fluorouracil[120]. The gold colloid complex exhibited unexpectedly high antifungal and antibacterial activities against *A. niger, Aspergillus fumigates, E. coli* and *Pseudomonas aeruginosin*. With the help of GNPs, the antibacterial activity of the antibiotics is improved. Burgin et al. reported the synthesis of a stable composite of GNPs coated with antibiotic molecules which enhance antibacterial activity[121]. The GNP coated antibiotic composite had extra high antibacterial activity against *E. coli* and *S. aureus*. Nie *et al.*[122] reported GNPs complexed with tocopherol which has high antioxidant activity. Bowman *et al.*[123] reported the preparation of the conjugate of GNPs with TAK-779 which exhibits more prominent activity against HIV than the native preparation at the cost of the high local concentration. Finally, Chamberland *et al.*[124] reported a therapeutic effect of GNRs conjugated with antirheumatic drug etanercept.

**Iron oxide nanoparticles (IONPs):** Magnetic iron oxide nanoparticles have been in the limelight due to the exclusive properties stemmed from their exceptionally minute size and large specific surface area[125]. They have been broadly investigated in current years for the promising biomedical applications, such as drug delivery[126,127], immunoassay analyser[128,129], magnetic resonance imaging[130,131] and cancer hyperthermia[132]. For most of these applications, surface modification of iron oxide nanoparticles plays an important role in enhancing their hydrophilicity, biocompatibility and conjugation of bioactive functional groups. To this end, many materials have been employed to design stable surface coatings for iron oxide nanoparticles, such as polymers, surfactants, or inorganic shells[133,134].

**Magnetic Resonance Imaging (MRI):** The MRI drugs help to enlarge the contrast of the image between disease and the normal tissue to distinguish pathological and healthy tissues. A number of different contrast agents have been used for this function. Paramagnetic gadolinium chelates work as a contrast agent in MRI studies up to[135]. These MRI agents work by reduction of the longitudinal relaxation time ($T_1$ relaxation time) of water in tissues. While superparamagnetic iron oxide nanoparticles (SPIONs) enhance the specificity and diagnostic sensitivity due to their advanced properties. They have the capability to decrease both longitudinal relaxation time ($T_1$) and transversal relaxation time ($T_2$) and have the higher molar relaxivities[136]. The effectiveness of these particles can be further improved by the amendment of their surface. These modifications can be done with the help of biologically active antibodies, polysaccharides, proteins etc. The efficiency of these particles depends on their charge, size and coating properties of particles[137]. Yu *et al.*[138] developed a new contrast agent for MRI in cancer imaging. These particles increase the

permeability and retention effect of the coating, which helps in tumor determination. So, this MRI agent has high efficiency to deliver anti-cancer drugs to tumors also. Thus, this contrast agent is beneficial in both cancer imaging and therapy[138]. Yang *et al.*[139] further synthesis the multifunctional SPIONs. These are used for MRI or positron emission tomography (PET), targeted drug delivery and utilized for the cancer therapy[139].

**Gene and drug delivery:** The IONPs have also been utilized in gene and drug delivery *in vivo* and *in vitro*. Magnetic nanoparticles attach to therapeutic gene and these particles targeted towards the specific target via high gradient external magnets. This approach is known as magnetoreception. After reaching the specific target the gene release from the IONPs. The release of the gene with the IONPs cans possibly through the hydrolysis of the polymer which is coating around NPs and through the through enzymatic degradation[140]. Mah *et al.*[141] used Adeno-Associated Virus (AAV), cleavable heparin and green fluorescent protein attach to magnetic particles. These reported for the targeted delivery of DNA[141]. Lubbe *et al.* and Wilson *et al.* utilized IONPs for the delivery of epidoxorubicin[142].

Basuki *et al.*[143] reported the synthesis of IONPs with exceptional colloidal stability that is stabilized with functional polymers with a capability to attach DOX through a pH-onsite imine bond [143]. Laurent *et al.*[144] reported the IONPs covered the starch derivative and this can be further functionalized with phosphate groups which help in chemotherapy by targeting mitoxantrone to the tumor location[144]. In addition, SPIONs and quantum dots have also been used to accomplish targeted delivery of an anti-cancer agent[145]. Recently, Kebede *et al.*[146] reported the synthesis the composite of iron oxide with chitosan and loaded with insulin and investigated the use in type II diabetes through oral delivery[146]. The iron oxide-chitosan nanocomposite loaded with insulin can lower down the 51% blood glucose levels in mild diabetic, sub diabetic and severely diabetic rats. Shen et al. synthesized the similar composite of hybrid nanogels composed from SPIONs with chitosan and CdTe quantum dots[147]. Spherical hybrid nanogels, smaller than 160 nm, were used for insulin loading. These hybrid nanoparticles could be capable of both insulin delivery purposes and cell imaging. IONPs have been also used as biosensors to detect proteins[148], cells[149], nucleotides[150] and pathogens[151] in a biological sample. Perez *et al.*[152] reported avidin conjugated SPIONS for the successful detection technique for Green Fluorescent Protein (GFP)[152]. For detection of GFP, nanoparticles were first conjugated with avidin and then the biotinylated anti-GFP polyclonal antibody was attached to the nanoparticles surfaces. With this biosensor molecule, GFP can determine in less than 30 min. Tumor cells, progenitor cells, or stem cells can also be targeted by modification of IONPs with the functionalization[153,154].

**Graphene:** Graphene has $sp^2$ hybridized carbon atoms arranged in a 2D array. Graphene has many properties suitable for electronic, mechanical, optical and thermal applications[155,156].

Graphene has extensive biomedical applications, like drug and gene delivery, imaging and biosensing. The utilization of graphene and its derivatives such as graphene oxide are due its attractive properties like;

- High specific surface area, i.e., 2630 $m^2/g$
- High thermal conductivity, i.e., ~5000 W/m/K
- High electronic conductivity, i.e., 200,000 $cm^2 V^{-1} s^{-1}$
- Mechanical strength, ~1100 Gpa of graphene

In addition to the above exceptional properties, graphene and graphene oxide has intrinsic biocompatibility. It is cost effective and high production and facile biological/chemical functionalization of GO[157,158].

**Graphene and graphene oxide in drug delivery:** Graphite on vigorous oxidation produces graphene oxide by Hummers method[159]. The GO is a proficient nanocarrier for drug and gene delivery. Graphene oxide having 1-2 nm broad layer and size in the range of 1-100 nm is used for drug delivery[160-162]. The GO has exclusive structural features, like large and planar $sp^2$ hybridized carbon domain, enriched oxygen-containing groups, high specific surface area (2630 $m^2/g$) and. The GO has an outstanding physiological solubility and stability. The potential of loading drugs or genes via chemical or physisorption and biocompatibility. In addition to the reactive carboxyl and hydroxyl groups GO makes easy conjugation with a variety of systems. Systems like as polymers[163], biomolecules, DNA[164], protein[165-168], QD[169], iron oxide nanoparticles[170] and others[171]. Imparting GO multi-modalities and multi-functionalities for miscellaneous medical and biomedical applications. First-time Nanoscale Graphene Oxide (NGO) synthesized by Dai *et al.*[171] which was inspired by the ideas of CNT-based drug delivery. For the efficient delivery of water insoluble aromatic anticancer drug into cells, NGOs are the novel nanocarriers[172]. Depan *et al.*[173] also studied the pH-sensitive drug release behavior from different GO-based drug delivery systems[173]. The advance investigation of drug delivery by GO advantages from anticancer drugs to other drugs also for non-cancer diseases treatment[174]. Rana *et al.*[175] demonstrated the chitosan-grafted GO for the

anti-inflammatory drug, delivery i.e., Ibuprofen. To further improve the anticancer drug effect, Yang *et al.*[176] synthesized GO-$Fe_3O_4$ NPs hybrid which is a bio and magnetic-double targeting drug delivery mechanism[176].

**Graphene and graphene oxide in gene delivery:** Gene therapy is a new and shows the potential way to cure a variety of severe diseases. Diseases which are especially due to the genetic disorders like cancer, cystic fibrosis and Parkinson's disease[177]. For performing an excellent gene therapy, a gene vector plays an important role to defend DNA from nuclease degradation and helps to facilitate cellular uptake of DNA with very high transfection efficiency[178]. The most important problem in front of the growth of gene therapy is the need of safe and efficient vectors for the gene[169]. Liu *et al.*[176] studied the gene delivery using graphene oxide derivative with the polyethyleneimine (PEI)-modified i.e., PEI-GO. The GO hybrid with positively charged PEI and with the electrostatic interaction between cationic polymer and DNA. It allows for the condensation of plasmid DNA onto the surface of GO sheet. The transfection efficiency of GO-PEI-10K and GO-PEI-1.2K was also studied by Liu and co-workers. They compared the transfection efficiency with the free polymers of PEI-10K and PEI-1.2K, respectively[179,180]. The chitosan-functionalized graphene oxide (GO-CS) sheets were reported for the application for drug and gene delivery by the research group of Singapore. This work of this group shows that GO-CS sheets have a high drug payload and improved cancer cell killing ability of the CPT-loaded GO-CS as compared to the pure CPT[181].

**Graphene oxide in cancer:** Lu and colleagues studied the use of PEGylated GO first time in the photothermal therapy and *in vivo* tumor uptake. This study done with the help of xenograft tumor mouse models. The PEG-modified GO shows very high tumor uptake ability due to extremely efficient tumor passive targeting of graphene oxide caused by EPR effect[182,183]. Markovic *et al.*[184] reported the comparison of the photothermal anticancer activity of CNTs and NIR-excited graphene.

Zhang *et al.* synthesized the NGO-PEG-DOX for anti-tumor effect by the combination of chemo and photothermal therapies in both *in vitro* and *in vivo*. The combined experiment of both chemo-photothermal therapies exhibited synergistic effect which led to enhanced cancer killing effect as compared to photothermal or chemotherapy[185].

Huang and coworkers demonstrated the function of sulfonic acid and folic acid-conjugated graphene oxide laden with porphyrin photosensitizers for targeting PDT[186]. Tian and colleagues reported the GO loaded with a photosensitizer in the application of photo-thermally assisted photodynamic therapy. This combined treatment yields extraordinarily enhanced cancer-killing effect[187].

**GO-based antibacterial material:** Peng *et al.*[188] developed macroscopic freestanding GO and reduced graphene oxide (rGO) paper from their suspension by vacuum filtration technique. These GO papers show a very high antibacterial effect. Akhavan and Ghaderi[189] reported the antibacterial effect of nanosheets of graphene. These sheets show positive effect for both Gram-positive and Gram-negative models of bacteria in the form of nanowalls. These nanowalls are deposited on stainless steel substrates[189]. Liu *et al.*[190] reported the antibacterial mechanism of graphene and its derivative, graphite (Gt), graphite oxide (GtO), GO and rGO. GO, rGO, Gt and GtO are the order decreasing order of antibacterial activity[190].

**Nanocomposites:** Nanocomposites are the hybrid which formed by the composition of a polymer or copolymer in which the NPs spread over the matrix of the polymer. These are used for the applications of anti-HIV drug delivery. PLA/chitosan are considerably useful for the anti-HIV drug delivery applications[191]. Controlled releasing of the drug is the key factor for the drug delivery. Metal oxide nanocomposites are the appropriate e.g., for the capable transport system in the delivery applications[192].

**Polymeric nanoparticles:** Polymeric NPs have potential applications in drug delivery. Biodegradable polymers, such as poly(alkyl cyanoacrylates), polyesters, its copolymers and also the polysaccharides are useful for the drug delivery. Polysaccharides like polyglycolic acid, polylactic acid, poly(methylidene malonate), poly (ε-caprolactone) are utilized for drug delivery. Polymeric NPs are used in cancer for a delivery remedy to tumor cells with superior capability and decreased cytotoxicity on marginal tissues[193, 194].

**Inorganic materials:** Metals, metal oxides and metal sulfides are the inorganic nanomaterials utilized to synthesize innumerable nanomaterials with a different shape, size and porosity. The Si NPs have been widely used in a drug delivery system. Because of its acquired outstanding properties like high pore volume, tunable pore structures, physicochemical stability and high specific area. The Si NPs were also used for prohibited delivery of a variety of hydrophobic or hydrophilic active agents. The Si NPs have surface properties like surface

functionalization and PEGylation and can function as a drug delivery vehicle for cancer treatment. Douroumis[195] and Wu López *et al.*[196]. demonstrated delivery of methotrexate anticancer drug.

## CONCLUSION

Nanomaterials have been utilized as a promising tool in biomedical imaging, diagnostic biosensors and cancer therapy etc. Owing to the enhanced surface area and nanoscale effects, nanomaterials have distinct biological properties in comparison to their larger counterparts. The properties of nanomaterials significantly affect their interactions with biomolecules and cells. This is because of their small size, shape, surface structure, charge and solubility etc. There is a splendid upcoming to nanotechnology, by its converging with different technologies and the subsequent emergence of complex and innovative hybrid technologies. Science dependent advances are entwined with nanotechnology are as of now utilized to control hereditary material. Advance investigate in nanotechnology, can help explore its application in other areas. Medicine, regenerative medicine, stem cell research and nutraceuticals are areas which required further amendment by the nanotechnology innovations.

## SIGNIFICANCE STATEMENTS

This review focuses on the most relevant and popular nanomaterials. It explores the biomedical applications of nanomaterials such as CNTs, graphene etc. The review will facilitate the readers to know about the various nanomaterials and their utilization in severe diseases, for instance, cancer etc. in detail.

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