EXPERT OPINION

Advancement in multifunctional nanoparticles for the effective treatment of cancer

Mahfoozur Rahman, Mohammad Zaki Ahmad, Imran Kazmi, Sohail Akhter, Muhammad Afzal, Gaurav Gupta, Farhan Jalees Ahmed† & Firoz Anwar
†*Dreamz College of Pharmacy, Himachal Pradesh, India*

Introduction: Nanotechnology has gained wider importance for the treatment of various diseases, including cancer. Multifunctional or theranostic agents are emerging as promising therapeutic paradigms, which provide attractive vehicles for both image and therapeutic agents. Nanosystems are capable of diagnosis, specific targeted drug therapy and monitoring therapeutic response. Due to their well-developed surface nature, nanomolecules are easy to anchor with multifunctional groups.

Areas covered: The present review aims to give an extensive account on the progress of multifunctional nanoparticles throughout the blooming research with regards to their clinical application in cancer. This paper discusses graphene, a newly developed multifunctional vehicle in nanotechnology. Furthermore, it focuses on the development of tumor cells, the advantages of novel multifunctional nanoparticles over traditional methods and the use of nanoparticles in cancer therapy. In addition, patents issued by the US office are also included.

Expert opinion: Despite numerous advantages, multifunctional nanoparticles are still at an infancy stage. Many great achievements have been attained in this field to date, but many challenges still remain. A problem that limits the use of multifunctional nanoparticles is toxicity. If this toxicity can be overcome then the advancement in nanocomposite material science will be well on the way to a prospective treatment of cancer.

Keywords: dendrimer, gold nanoparticles, graphene, multifunctional nanoparticles, patents, quantum dots, silica nanoparticles, tumor cell

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1. Introduction

Cancer is a serious global health threat and in developed countries it is the second leading cause of cell death [1]. Cancer is a multistep process which involves numerous changes such as cells signaling and apoptosis to name a few [2,3]. The conversion of proto-oncogene to oncogene is responsible for development of abnormal immatured group of cells, which is responsible for tumor formation. Development of tumor and its increase in size changes the normal function of adjacent healthy cells. This results in initiation of apoptosis in healthy cells. The maximum size of most of the tumors is 2 mm^2. After achieving maximum size these cells move to other parts of body initiating the process of metastasis, which makes cancer incurable [4]. An illustration of tumor development from single cell to maximum size tumor is depicted in **Figure 1**. Cancer is a very complex disease due to its molecular heterogeneity (multiphenotype) and adaptive resistance found in various tumor cells, and this makes it more challengeable for its treatment. Conventional treatment approaches like surgery, radiation, biological therapies (immunotherapy) and chemotherapy; these have poor specificity, non-recognition

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Article highlights.

- Cancer is a serious and complex disease across the world. Multiphenotype and adaptive resistance found in various tumor cells makes it more challengeable for cancer treatment.
- In oncology research, theranostic nanomedicine (TNM) has garnered increasing attention in the treatment of cancer and has emerged as promising therapeutic paradigm.
- TNM is called an all-in-one system. It means mounting of different therapeutic function on single nanosystems, resulting in co-delivery of therapeutic agents and imaging function. Several TNMs have been discussed such as iron oxide nanoparticle (IONP), quantum dots (QD), silica nanoparticle, carbon nanotube (CNT), gold nanoparticle (GNP), dendrimer and graphene. All these multifunctional nanoparticles have integration of cancer research, therapeutic diagnosis and imaging.
- Stability and pharmacokinetic profile of TNM can be improved by using several polymer, dye, ligand, PH labile group, photosensitive, thermosensetive groups.
- So far, many TNMs have been approved by the FDA such as AMI-121, AMI-277, Feridex® and Combidex®.
- Recently, patents have been issued by the US office in this nanotechnological arena on TNM, due to their effectiveness found at different stages of clinical trials.
- One of the major limitations associated with TNM is toxicity. Advancement in nanocomposite materials science may overcome toxicity. In the future, TNM holds a great potential to be used as a therapy for cancer.

This box summarizes key points contained in the article.

of tumor markers, along with dose-related toxicity, targeted action, poor bioavailability, neurotoxicity and risk of damage to vital organs [5]. Hence, it is the need of the hour to develop new and innovative technologies that will help in prevention of adaptive resistance, identify tumor marker cells and micrometastases. Combination of nanotechnology with oncology is a new field of interdisciplinary research, comprising biology, chemistry, engineering and medicine (designing of materials at nanoscale levels to create products that exhibit novel properties), which have profound impact on disease prevention, diagnosis and their treatment [6]. Multifunctional nanoparticles are the novel technological innovations developed recently to fight against cancer. This is the most effective approach to recognize the molecular heterogeneity and adaptive resistance found in cancer cells. It reduces the problems associated with conventional therapy with respect to diagnosis, imaging and real-time controlled drug release, followed by reduction in toxicity and making treatment duration shorter [7,8].

2. Theranostic nanomedicines or multifunctional nanoparticles

It is an integrated nanotherapeutic system. The term theranostic nanotechnology means combination of individual technique to form a single nanoplatform by mounting therapeutic function on them. This is a combination of diagnostic test with targeted therapy at controlled rate, which co-delivers therapeutic agents and imaging functions (**Figures 2** and **3**). For successful development of theranostic nanomedicines (TNM), we must have deep knowledge regarding the materials science and nanocomposite materials like particle surface chemistry, noncovalent binding, electrovalent strategies, biospecific interaction, hydrophobic adsorption and safety. These combinations provide controlled and improved reproducibility of TNM [5]. Amorphous or semi-crystalline colloidal system which has 10 – 200 nm of particle size is best suited for TNM. It posses better optical, magnetic and thermodynamic properties [9], and is efficient in targeting high drug loading, high specificity on tumor cell. Further, it improves bioavailability, imaging cell sensitivity, reduces multidrug administration, high spatial resolution, tomographic capability, easy and early onset of detection and delivers selective therapeutic agents [9]. The function of TNM depends on different subunits as anticancer drug or tumor-targeting moieties [10]. These nano-based TNMs have four special properties that distinguish them from other cancer treatment options: i) the TNM can themselves have therapeutic (drug delivery, gene delivery, drug targeting and photothermal property), diagnostic and imaging properties (**Figures 2** and **3**). It further achieves synergistic effects by blocking different receptors; ii) TNM can be attached to multivalent different targeting ligand, which results in high affinity and specificity for different markers; iii) TNM can be made to carry multiple drug molecules that simultaneously enable combinatorial cancer therapy and iv) TNM can bypass traditional drug resistance, molecular heterogeneity and adoptive resistance mechanisms. TNM can achieve increased intracellular concentration by using both passive and active targeting strategies. This results in enhanced anticancer effects, reduction in systemic toxicity and minimum toxicity to normal cells [10,11]. Several TNMs have been employed as the carriers of diagnostic agents and drugs. Lukianova-Hleb *et al.* studied the optical generation and detection of plasmonic nanobubbles (PNBs) around gold nanoparticles (GNPs) in individual living cells, and evaluated the multifunctional properties of PNB [12]. Recently, much work has been reported and discussed about characteristics and biomedical applications of magnetic nanoparticles, and has concluded that it can simultaneously act as diagnostic molecular imaging agents and with therapeutic properties for different types of drug carriers [13]. Shim *et al.* reported that coated small-interfering RNA-encapsulating polyplexes attached to small GNPs via acid-cleavable linkages for the development of combined (theranostic) stimuli-responsive multimodal optical imaging and stimuli-enhanced gene silencing [14]. Several nanoparticles such as iron oxide, quantum dots (QD), silica nanoparticles, carbon nanotubes (CNTs), gold, dendrimer and graphene have been investigated as multifunctional nanoparticles. This review introduces multifunctional agents, in which a linkage between nanoplatforms and functional entities has been

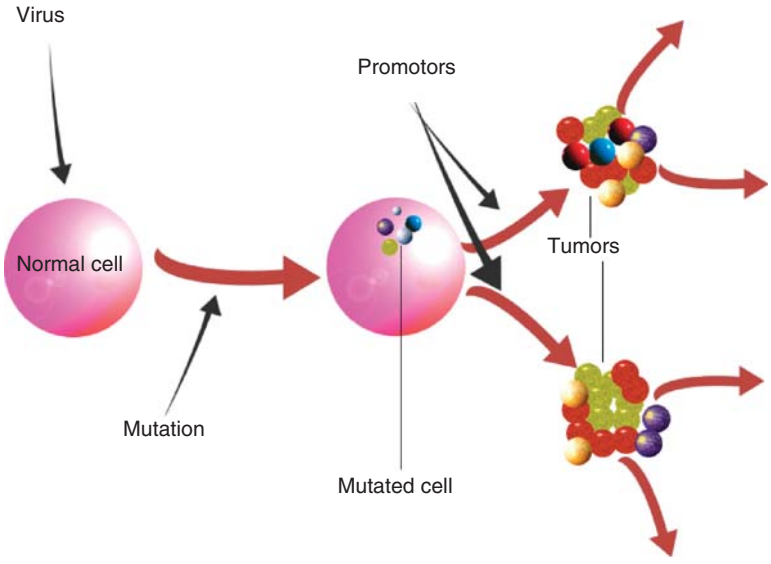

Figure 1. Tumor development.

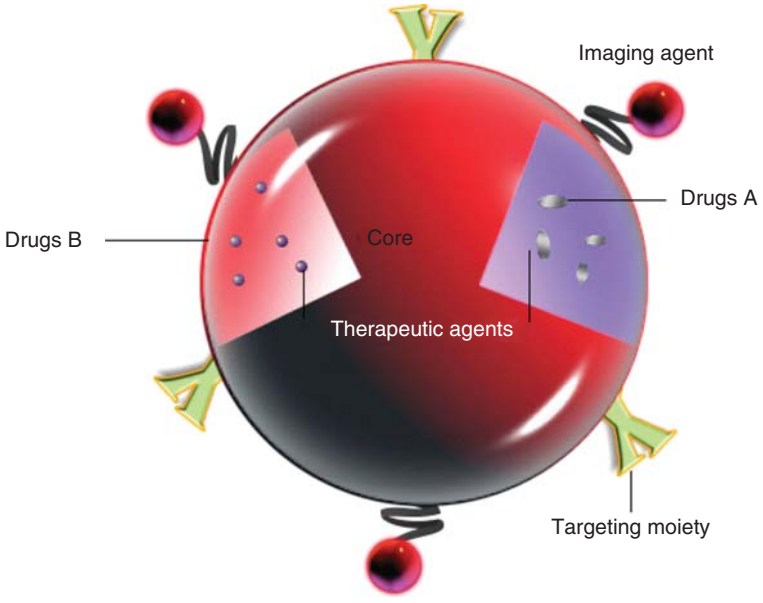

Figure 2. TNM have specific targeting agent, imaging agent, diagnostic agent and chemotherapeutic agent (drugs), all are in one platform system.

developed. It has been discussed in text and also summarized in Table 1.

2.1 Iron oxide nanoparticle

Iron oxide nanoparticles (IONPs)-based theranostic agents are a magnetite or hematite nanocrystals. They are used as contrasting agents for magnetic resonance imaging (MRI) and targeted drug delivery to the tumor cells [15,16]. Two types of iron oxides nanoparticles have been reported, namely supermagnetic iron oxide and ultra-small superparamagnetic iron oxide (SPIO). Among these, SPIO has superior action due to its biocompatible and biodegradable properties of iron, which can be recycled for iron metabolism via biochemical pathway. Many articles are available, where SPIOs have been used in combination with molecules and monoclonal antibodies to detect variety of cancers. They have also been used with peptides to target transferring and pancreatic receptor and augmented to image the cancer cell [17-22].

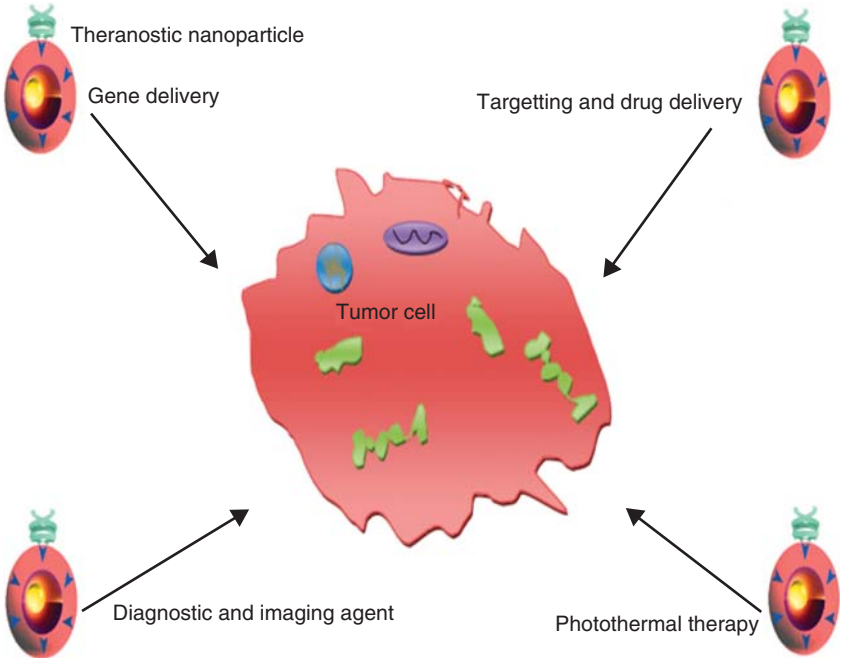

Figure 3. Various applications of multifunctional nanoparticles in therapy.

Table 1. Examples of different multifunctional nanoparticles [27,28,119].

Multifunctional nanoparticles	Target organs	FDA status
AMI-121 (SPIOs)	Gastrointestinal lumen	Approved
AMI-277 (SPIOs)	Blood node, lymph node	Approved
SHU 555A (SPIOs)	Spleen/liver	Approved
Feridex®	Spleen/liver	Approved
Combidex®	Lymph node	Stage III
DOX-TCL-SPION (DOX thermally cross-linked SPIOs)	Breast cancer and imaging	Approved

DOX: Doxorubicin; FDA: Food and Drug Administration; SPIO: Superparamagnetic iron oxide.

IONP synthesized by co-precipitation of Fe(II) and Fe(III) precursors and with advancement of high temperature decomposition method are utilized to synthesize them [23,24]. Co-precipitation techniques improve the colloidal suspendability of the particles. Generally, hydrophilic polymers such as PVP, polyaniline and dextran, are used during particle formation, which results in prevention of particle aggregation [23,25,26]. Several polymeric IONP as MRI contrast agents are available in market, like Feridex® particles (AMAG Pharmaceuticals, Inc., Cambridge, MA, US) for detection of liver and spleen lesions, and Combidex® is used at clinical trial III stage, where lymph node image is required [27,28]. In high temperature decomposition method, pyrolysis synthesis results in organic solvent by the temperature treatment, particle growth is carried in regular controlled fashion and particles have better crystallinity and higher magnetism than traditional method. Drug molecules can be easily coupled by appropriate coating on IONP [29]. Zhang and collaborators investigated this coupling effect on methotrexate (MTX). Similarly, multiple coupling of paclitaxel (PTX), herceptin antibody molecules on IONP already have been reported [30-33]. Jain *et al.* reported loading of doxorubicin (DOX) and PTX onto IONP by using oleic acid. Recently, Yu *et al.* reported that loaded DOX by using antibiofouling polymer-coated IONP showed better clinical pharmacokinetic and therapeutic effect than only DOX. Hyeon group [36] reported that many drug molecules which are smaller in size can be loaded on to hollow nanostructure by process of physical absorption such as loading of DOX on to hollow spindle shape of β-FeOOH nanoparticles which are made from $FeCl_3$ hydrolysis. Hollow IONP are made by controlled oxidation and etching of Fe particles. This combination targets the ErbB2/Neu-positive breast cancer cell and delivery of cisplatin at a controlled rate is obtained [34-37]. Presently, genes are delivered through nanoparticles-based delivery system which can antagonize abnormal gene regulation through target cell membranes [38].

2.2 Quantum dots

They are nanocrystals which are made of semiconductor materials. They have unique light-emitting properties that can be optimized by tuning their size and composition. They are classified into two parts: i) first generation of QD consist of

Cdse, CdTe and Pbs, changes of their size gave rise to nanometarials that lie in visible spectrum. Major limitations associated with these dots are their ineffective/limited tissue penetration. This was overcome by use of CdTe/CdSe, Cd3P2, InAs/ZnSe and InAs/InP/ZnSe and also by enhancing the quantum photoluminiscent properties. ZnS coats enhance the efficiency of QD nanoparticles. QDs are prepared by heating organometallic precursors in high boiling point organic solvent. Surfactants such trioctylphosphine (TOP) and trioctylphosphine oxide (TOPO) were used to control the particle growth (**Figure 4**) [39-43]. Alkyl groups present on QDs make them water insoluble, and thio group is attached to overcome this problem which forms disulfide linkage with core shell (ZnS) of QDs. Major limitation of such nanoparticles is fragile disulfide linkage. To strengthen this linkage and to improve the longevity of QD, DiHydroLipoic Acid (DHLA) oligomeric phosphines, cysteine-rich peptides and multidentate polymers were added [39,44-46]. First-generation QD-based drug delivery has innate toxicity due to release of Cd and lead. This toxicity leads to the development of second generation of QDs (InAs/InP/ZnSe), which are free from Cd and are potentially better carriers [39-41]. They were made water soluble by the addition of poly(ethylene glycol) (PEG)-10 and 12-pentacosadiynoic acid (PEG-PCDA) (**Figure 4**). Furthermore, QD nanostructure were stabilized by application of UV-irradiation, which cross-linked the coating shell and reduced the leakage of core materials from QDs. Recently, Bagalkot *et al.* investigated QD–aptamer (Apt)–DOX conjugated [42], which has been used for co-delivery of therapy and therapeutic agents (**Figure 5**).

DOX loading on QD surface by using A10 RNA results in controlled release of DOX which initiates therapeutic function and recovery of QD fluorescence (**Figure 5**). Yuan *et al.* reported that loading of MTX onto QD surface by the mechanism of physical adsorption induced photoluminescence quenching [42,43]. QDs are used as gene delivery vehicles, by mounting polymers such as lipofectamine and poly(maleic-anhydride-alt-1-decene), which result in more efficient delivery and reduce toxicity [44,45]. Matrix metallopeptidase 9 (MMP-9) is the main part of the blood–brain barrier and lies in the brain microvascular endothelial cell. Poly(diallyledimethyl ammonium chloride) (PDDAC) on QDs, which forms a complex with MMP-9-siRNA, can modulate the activity of MMP-9. This results in collagen I, IV and V expression and a decrease in endothelial permeability. QDs have unique properties like photostability, broad absorption spectra, narrow size, stable emission spectra and mounting of several agents on them. For these unique properties, they have great potential in photodynamic therapy as a photosensitizer. The mechanism involved is activation by light and transfer of unpaired electron state energy to near oxygen molecule. This generates reactive oxygen intermediate, which causes abnormal cell damage [46-48].

2.3 Silica nanoparticles-based theranostic agents

It is the most common biosafe material, used as surgical implant. Silica nanoparticles do not possess the potential for imaging, but they can be made theranostic by the application of broad range of imaging group and therapeutic functions on them. Hence, different moieties can be delivered through this multifunctional carrier. Generally, two techniques, hydrolysis and condensation are used for preparation of silica nanoparticles. Theranostic properties can be developed by mounting of aminopropylmethoxysilane (MPS) on tetraethylorthosilicate (TEOS). MPS acts as a co-precursor which brings amine or thiol group to the particle surface. During particle formation, organic dyes and GD-DTPA can be incorporated into silica particles matrix for developing the magnetic properties [49-51]. Sathe *et al.* and Koole *et al.* developed IONPs, Au NPs and QDs incorporated into single silica nanoparticles, resulting in dual core shell–shell nanoparticles in which better magnetic and optical properties were observed [52,53]. Roy *et al*. and Kim *et al.* reported the incorporation of hydrophobic photosensitizing anticancer drug like 2-devinyl-2-(1-hexyloxyethyl)pyropheophorbide (HPPH) into silica matrices which efficiently kills cancer cell. Moreover, photon absorbing dye such as 9,10-*bis* [4-(4-aminostyryl) styryl]anthracene (BDSA) can be incorporated to upconvert the near-infrared (NIR) light that can transfer the intraparticle energy to HPPH which activates the PDT function [54,55]. Some new changes have been developed in preparation, by using chemical and physical techniques to obtain mesoporous structure. In chemical process, at the particle stage development, an *N*-alkyltrialkoxysilane or other surfactants were mixed with precursors and then were incorporated into matrices; subsequently, surfactants were removed by post-synthesis solvent extraction or calcinations method to make a toxic-free preparation. In physical process, physical interaction plays important role through which many therapeutic molecules can be loaded. Mesoporous structure consists of accurate pore size, more than 100 channels are available that result in large surface area (900 m^2/g) and this inhibits premature drug release and makes them excellent reservoir for many therapeutic moiety in cancer drug delivery system. PTX when loaded on mesoporous structure and further capped with Au NPs along with QDs and IONPs observed better drug release profile [56-59]. Luminescent porous silica nanoparticles (LPSiNPs) preparation uses physical process which consists of single crystal silicon wafer porous silicon film, filtered through a 0.22 μm membrane filter. These luminescent porous nanoparticles can be used with many therapeutic drug molecules like DOX with a unique feature of self *in vivo* destruction and renal clearance within a short duration of time (**Figure 6**), rendering less chance of their entrapment into normal organ [60].

2.4 Carbon nanotube-based theranostic agents

CNTs are graphite-like structure and inert in nature. Its potential application in Raman and photocoustic imaging

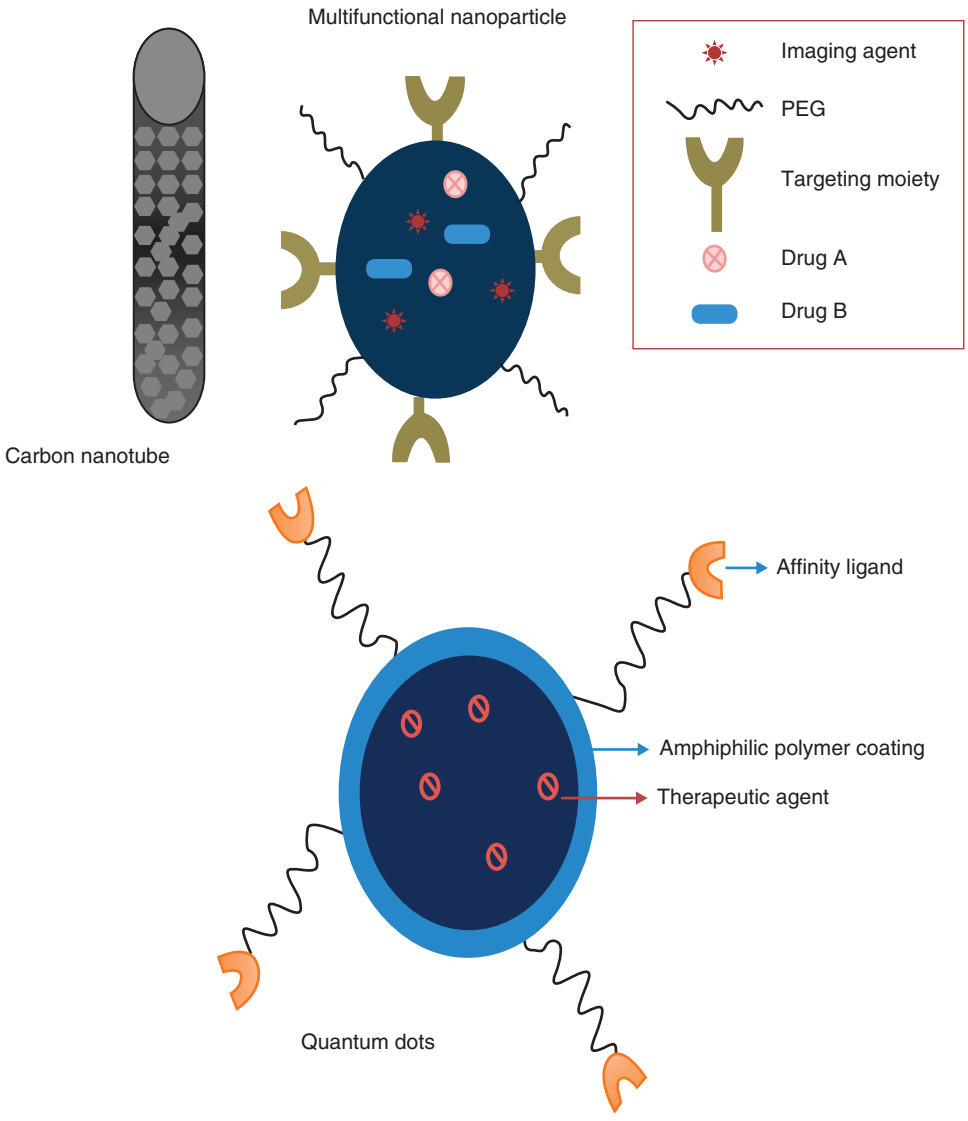

Figure 4. New synthetic methods have been developed to design multifunctional nanoparticles like carbon nanotube and quantum dots, QD nanoparticles, conjugated to a ligand by coating a polymeric layer, on which can encapsulate both therapeutic and imaging agents in a single nanoplatform system.

have also been under investigation as a drug carrier (**Figure** 4) [61,62]. Extreme oxidative conditions were developed to yield a defect on CNTs surface that can be used for mounting different therapeutic moieties on them. Single wall nanotubes (SWNTs) when refluxed with 2.5 M HNO_3 for 2 – 36 h with the interval of 30 min form water-soluble SWNTs, due to the presence of carboxyl groups on nanotubes surface. This is the site where several molecules can be conjugated by covalent bonding, recently one group called azomethineylide and its derivatives were incorporated onto surface by 1,3-dipolar cycloaddition mechanism [63-66]. Similarly, many moieties like PEGlyated phospholipids can anchor onto CNT surface, and they have shown better efficacy, better entrapment in spleen and liver without any degradation and toxicity [67].

CNTs have unique physical and surface properties, high loading drug molecule capacity and can also anchor the IONPs, AuNP on CNT surface but its non-biodegradability and impurity remain problems of concern. CNTs can be taken up by cells through endocytosis, passive diffusion or other mechanism that may depend on the nature of surface coatings. Prato *et al.* coupled MTX onto CNT by 1,3-dipolar cycloaddition, reports are available where multiple amines were used to load and deliver the DNA plasmid [70]. PTX when coupled on branched PEGylated CNTs, improved pharmacokinetics, stability and better tumor suppression. Moon *et al.* [71] investigated the use of CNTs as a photothermal therapy, where PEGylated SWNT and NIR irradiation, caused extirpate of tumor cells and no reoccurrence after 6 months was observed [68-71].

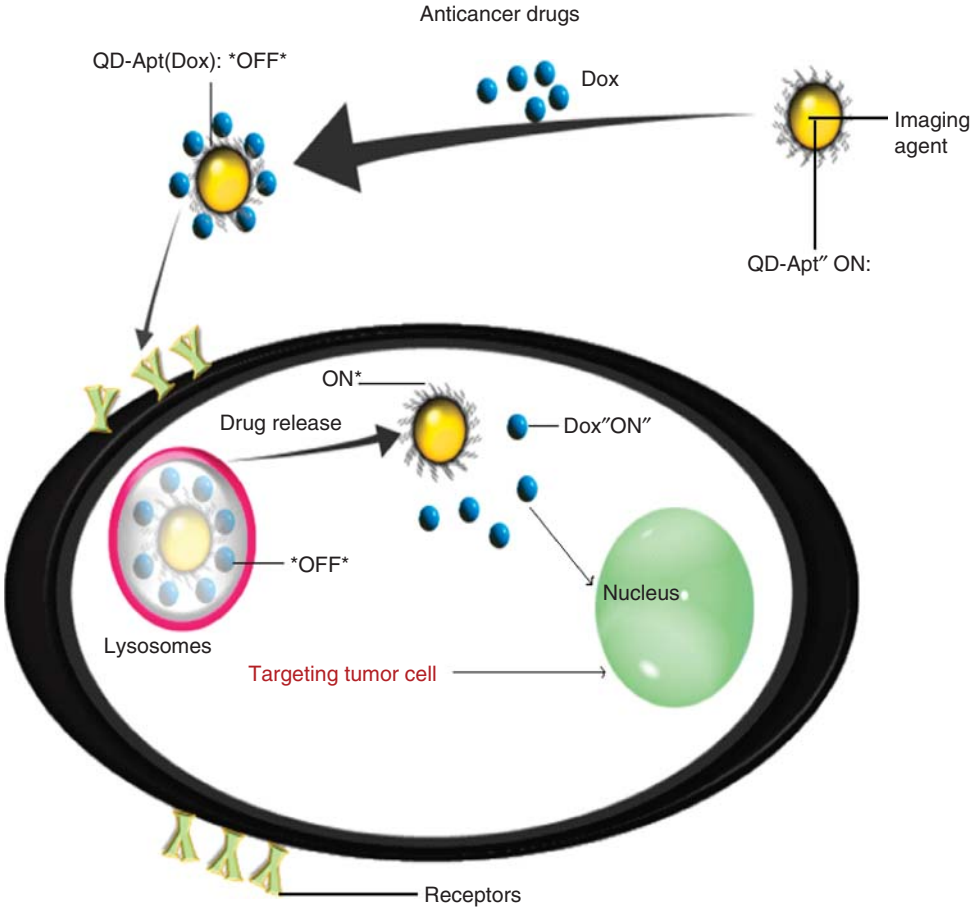

Figure 5. Building and working mechanism of QD–Apt–DOX nanosystems. Two steps are involved: first, CdSe/ZnS QDs are surface conjugated with the A10 PSMA aptamer. The intercalation of DOX within the A10 PSMA aptamer on the surface of QDs. This forms QD–Apt–DOX nanosystem, which quenches fluorescence from both QD and DOX ('OFF' state). Second, specific uptake of QD–Apt–DOX nanosystems into target cancer cell through endocytosis. Ultimately, release of DOX from the QD–Apt–DOX nanosystems induces the recovery of fluorescence from both QD and DOX ('ON' state), thereby sensing the intracellular delivery of DOX and synchronous fluorescent localization, resulting in killing of cancer cells.

2.5 Gold nanoparticles-based theranostic agents

GNPs have recently emerged as an attractive candidate for delivery of various functional groups into their targets sites [72,73]. The functional groups can be small drug molecules or large biomolecules, like proteins, DNA or RNA (vide post), etc. GNPs are inert, easy to prepare, non-toxic and efficient release of therapeutic agents from them gives a better alternate for effective therapy [74]. The unique properties make GNP to be investigated in various image-related areas, such as computed tomography (CT), photocoustic and surface-enhanced Raman spectroscopy. GNPs are available in various forms like spheres, cubes, rods, cages and wires [75,76]. Size and morphology of GNPs influence the properties of the products, as for example, 10 nm spherical Au NPs have some characteristic surface plasmonic absorption at around 520 nm. If particle size is increased from 48.3 to 99.4 nm GNPs, then there is a bathochromic shift of the particle, which shows absorption at the 533 and 575 nm, respectively. Further change in morphology of Au NPs to rod-like shape shifts the absorption to NIR region (650 – 900 nm). These properties make GNPs applicable as a photoacoustic image or mediators in photothermal therapy [75,77]. Multithiolated group by layer deposition method makes them more stable with high drug loading capacity for antibodies and other large molecules. Better therapeutic effects of PTX can be observed when drug is covalently coupled to 4-mercaptophenol using GNPs technique. Similarly, protein-based preparation have been used for loading onto Au NPs and TNF anchoring onto PEGylated Au NPs, and these all have better therapeutic efficacy and less toxicity when used as a single moiety [78-81]. In addition to Au-thiol chemistry on Au NPs, chitosan-based preparations are used when a reducing agent and coating materials are mounted to make Au NPs which are positively charged and highly efficient in nature. DOX conjugated onto the hydrophobic shell by covalently hydrazone linkage, resulted

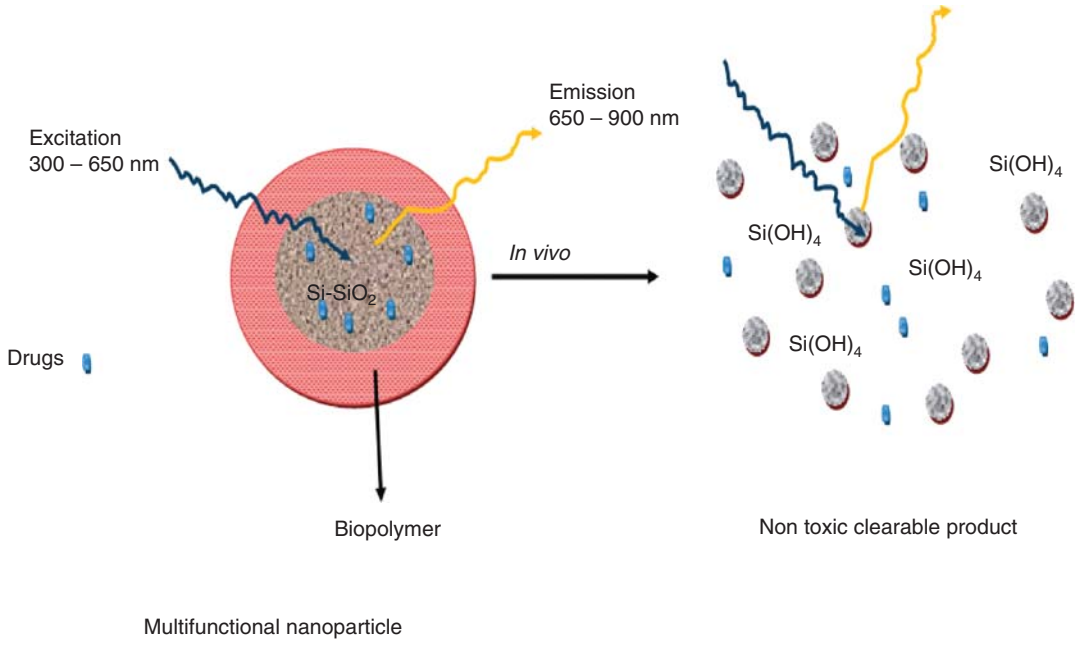

Figure 6. Illustrated structure and *in vivo* degradation of the silica nanoparticles.

in selective target and efficient drug delivery in controlled way and better image formation made new way to control the group of tumor [82,83]. GNPs have been mounted with alkylated quaternary ammonium compounds on plasmid DNA. Au NPs is a good candidate for photothermal therapy; because of their unique surface plasmon resonance, stability and biosafety, they are easily modified. Its accumulation in tumor cell results in conversion of light into heat, which kills cancerous cells. One of the demerits associated with Au NPs is the high cost of production, which diminishes its clinical application [84,85].

2.6 Dendrimer

These are the newer variety of nanocarriers which are stable, non-immunogenic and less than 5 nm in diameter. The application of therapeutic and diagnostic purposes in treatment of cancer including advances in the delivery of anti-neoplastic and contrast agent, neutron capture therapy, photodynamic therapy and recently in photothermal therapy is a matter of great importance. Due to their better elucidation and unique derivative properties Dendrimer have been synthesized with biocompatible retention, and better pharmacokinetic and targeted delivery properties are under research [86-88]. In dendrimer, drug can be incorporated with the help of polymers, either by non-covalent or covalent conjugation to form macromolecular products. Camptothecin was conjugated with poly(glycerol-succinic acid) to obtain its dendrimer, multiple drugs can be anchored to each dendrimer molecule [89]. Gurdag and Khandare, reported conjugation of MTX with polyamidoamine (PAMAM) by the release of carboxylic and amine group, which were beneficial in resistant CCRF-CEM human acute lymphoblastoid leukemia. PTX when conjugated by PEG or G4-PAMAM, results in homogeneous distribution intracellularly. This homogeneous distribution reduces the IC_{50} more than 10-fold when compared with free drug, further it increases plasma circulation time and also enhances tumor uptake due to enhanced permeability and retention (EPR) effect. Liposomal DOX has been complexed with G4-PAMAM for potential delivery in the breast cancer and showed highest efficacy against it [90-92]. Recently, Lee *et al.* reported conjugation of DOX through PEGylation with one side substituted by 2,2-*bis*(hydroxymethyl)propionic acid dendrimer, which conjugates the DOX by hydrazone linkage. This results in gradual release of increased DOX and short elimination half-life [92]. Target delivery of dendrimer, achieved by the conjugation of folic acid, peptides, monoclonal antibodies, which are highly capable of delivering multifunctional agents at targets are under investigation. Acetylated PAMAM dendrimers were conjugated to folic acid (for tumor targeting), drug MTX and a fluorescent label for its imaging [93,94]. The toxicity of 5-fluorouracil (5-FU) can be minimized by acetylation of this drug if conjugated to dendrimer. Starpharma (Prahran, Australia) formulated drug dendrimer-based microbicides (VivaGel), which are easy to administer and have improved the safety level of patients [95]. The unique architecture of dendrimers is the potential candidate for multivalent attachment of imaging probes and target moieties; therefore, it can be used as a diagnostic tool for cancer imaging and drug delivery stick to cancer cell.

2.7 Graphene

Graphene is a two-dimensional honeycomb monoatomic thick building block of a carbon allotrope (CNT, fullerene,

diamond) with a bond length of 0.142 nm. It was first prepared by peeling a single layer of grapheme using sticky tape and a pencil in 2004. At the global level, it has emerged as an exotic material of the 21st century, due to its exceptional high electron mobility at room temperature (250,000 cm^2/vs), exceptional thermal conductivity (5000 W/m/K) and optical and mechanical properties [96-98]. On behalf of its unique properties, electronic, optoelectronic devices, chemical sensors, nanocomposites and energy storage instruments can be designed easily. Hence, it can be used in the biological systems for detection of DNA, metal ion, protein, pathogen, design of cell/bacterial nanodevice, drug delivery carrier and drug targeting in cancer. Recently, researchers have developed an electrochemical aptasensor for label-free selective and sensitive detection of cancer cells which can be used for the treatment of cancers [99-101]. For early detection of carcinoma cells, perylene tetracarboxylic acid (PTCA) functionalized grapheme modified electrodes have been developed [102]. Over the past several years, scientists have used various methods for producing graphene, such as micromechanical exfoliation and epitaxial growth or chemical vapor deposition (CVD) epitaxial growth. The sticky tape and pencil method is like micromechanical exfoliation or peel-off method, which can be used successfully to produce pure and single-layered graphene sheet with a honeycomb lattice [103,104]. The major disadvantage associated with this is of small yield. Recently, graphene synthesized by chemical process is a new tool with advantages of scalable, high-volume production and ease of chemical modification [105].

Biologically compatible and biodegradable natural polymers, such as lignin and cellulose derivatives, have been employed to formulate stable graphene nanosheets, which can be used as loading platform for biomarkers and other multifunctional anticancer agents (**Figure** 7), such as adhesive-protein functionalized graphene nanosheet with the electrostatic assembly of various metallic NPs, for example, Au, Pt, Ag and Pd to name a few. Functionalized graphene nanosheets are very useful in identification of tumor cell at the early stage and eradication of cancer cell [106,107].

3. Possible improvement in characteristics of multifunctional nanoparticles

Stability and biocompatibility of TNM can be improved if various groups such as PEG, modified acrylic acid polymer, phospholipids micelles are attached to nanoparticles, this can improve in maintaining the drug level in blood. Aptamer (oligonucleotides), carbohydrates, folic acid and peptides may be attached to have specific target site [108]. Intracellular penetration peptides can be transferred through transactivating transcriptional activator (TAT) ligand, using positively charged moieties and cationic lipid polymers. This attachment improves pharmacokinetic and biodistribution properties of drugs. Different groups may be attached to TNM such as QDs, magnetic nanoparticles for better imaging [109-111]. For making the best stimulus, sensitive drug release property must be altered by attachment of pH labile, photosensitive, thermosensitive, magnetic sensitive and redox sensitive groups. These all, provide better control bioavailability and reduce the toxicity [112]. Silica-based TNM applicable for bioimaging, biosensing and releasing therapeutic drug is a good carrier of metals, drugs and fluorescent dye; further, it can be modified and different ligand or biomolecules can be attached [113,114]. Moreover, recently the conjugation of silica with dye fluorescein isothiocynate is used for imaging of human bone marrow stem cell [115,116]. Now core satellite composed of rhodamine dye, silica core and multiple satellites, made up of magnetic nanoparticles, when combined to human B1 antibodies, can be used as marker of neuroblastoma, lung carcinoma and Wilm's tumor if associated with polysialic acid. Mesoporous silicate TNMs can conjugate with different ligands and chemotherapeutic drug molecules, which are beneficial for diagnosis and treatment of various types of cancers [117,118].

4. Advancement related to patents

There is extensive support for the applications of multifunctional nanoparticles in biological system for the diagnostic and therapeutic uses. However, the use of multifunctional nanoparticles in cancer therapy has recently been reported by many nanotechnologists [119].

4.1 Patents on multifunctional nanoparticles

Possible cancer therapy and diagnostic techniques which are through multifunctional nanoparticles such as early detection of tumor and imaging of cancer cell along with therapeutic delivery of drug to the targeted tissues or cancer cell have already been or are being patented.

The US patent number 3177868 describes the biconjugated biocompatible QD, which targets the specific targeted moiety and it claimed that QDs emit electromagnetic radiation of UV region after soft X-ray treatment [120]. The US patent number 67485 describes the composition of semiconductor nanoparticles with polypeptides templates, which also includes cadmium selenide, cadmium telluride, zinc selenide, zinc sulfide and zinc tellurides. These particles have the properties to show multiple color luminescent system. This can be eminent approach for early tumor diagnosis and therapy. Moreover, iron oxide (Fe_2O_3/Fe_3O_4) nanoparticles have supermagnetic properties, which can serve as better contrast enhancement agents for MRI [121]. The US patent number 216239 describes the composition and evaluation of nanoparticles, which are made up of magnetic materials for targeting, diagnostics and therapeutic purposes and can be used for early detection of tumor cell and further for their treatment [122].

The US patent number 255403 describes the composition and production of fluorescent nanoparticles, which can act as markers, indicators and light sources [123]. It is used

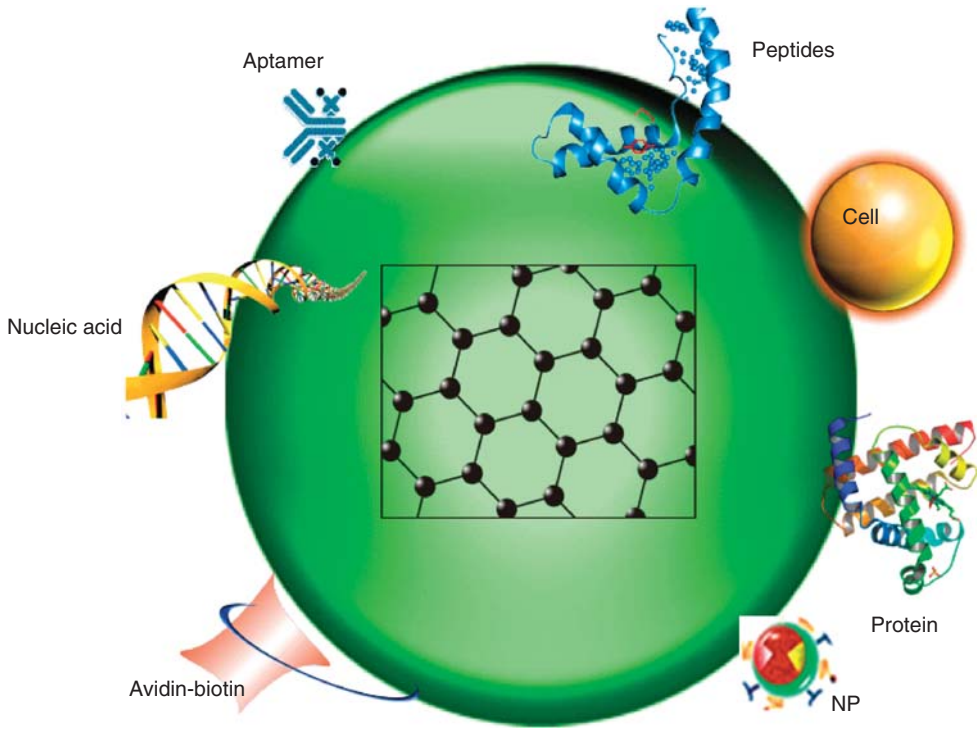

Figure 7. Graphene due to its unique properties can be functionalized with different moieties like peptides, proteins, aptamer, Avidin-Biotin, multifunctional nanoparticles and cells via the physical adsorption or chemical conjugation. This biosystem can be used to build up multifunctional biological platforms for medical applications.

for identification and location of the tumor cell and provides therapeutic action too. The US patents number 6,689,338 describes biconjugation of nanoparticles as radiopharmaceuticals, it is a combination of radio immunotherapy and radioimmunodetection agents and is used for diagnosis and treatment of cancer [124].

The US patent number 6165440 (entitled radiation and nanoparticles for enhancement of drug delivery in solid tumor) describes conjugation of nanoparticles to many bodies like antibodies, ligands as targeting molecules can enhance the targeting action to desired tissue for specific action [125]. The US patent number 6187823 describes conjugation of CNTs to molecules like carboxyl, amino group can enhance particular action [126]. The US patent number 6884478 informs that QD nanoparticles which have different diameters but same composition can emit a different wavelength for therapeutic action [127]. The US patent number 6843919 describes the aromatic structures like graphene for their MRI and NIR agents [128]. The US patent number 6001054 describes GNPs for enhancing the targeting action and better therapeutic effects of these nanoparticles [129]. The US patent number 6, 165440, describes interaction of metallic nanoparticles with electromagnetic pulse and ultrasonic radiation, which results in enhanced drug delivery in solid tumor. Ultrasonic waves-induced cavitations, resulting from perforation of cancer cell membranes, ultimately provide enhancement of drug delivery from blood to cancer cells [125].

5. Conclusion

The application of nanotechnology in the field of cancer biology has experienced exponential growth in the past few years. In this article, the authors have discussed some nanoplatforms that are currently under investigation to build multifunctional nanoparticles. All these nanoparticles have been previously studied for imaging; because of their unique optical or magnetic properties. Every nanoparticle has its own advantages and disadvantages. This review discussed the anchor role of target moieties onto nanoparticles to achieve multifunctional nanoparticles, in which integration of imaging and therapeutic function can be augmented where therapeutic molecule can be delivered to disease area and can use its imaging function to improve diagnosis and therapeutic response. It is too premature to say when one system with comprehensive feature will be available for human use.

6. Expert opinion

Cancer is a complex disease across the world. Tumor heterogeneity and adaptive resistance of malignant cells to drugs is a major challenge for treatment. Conventional treatment approaches used to remove cancer cells lies with several limitations. However, the growing of interdisciplinary science at the nanoscale gives an option for nanotechnology. Nanotechnology uses development in surface chemistry

of nanoparticles anchored with different functional moieties onto nanoparticles giving rise to multifunctional nanoparticles, which can be integrated in cancer research, imaging, diagnosis and therapeutics. Despite of all these advantages, multifunctional nanoparticles are still at an infancy stage. Many great achievements have been attained in this field but still many challenges remain. Currently, most of the multifunctional nanoparticles have been develop and have been approved by the Food and Drug Administration (FDA) and many are under clinical developmental stage. A problem that limits the use of multifunctional nanoparticles is toxicity. If this toxicity can be overcome then the advancement in nanocomposite materials science will be a prospective way to treat the threat of cancer.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Mahfoozur Rahman[1,4], Mohammad Zaki Ahmad[1], Imran Kazmi[2], Sohail Akhter[3], Muhammad Afzal[2], Gaurav Gupta[2], Farhan Jalees Ahmed[†3] & Firoz Anwar[2]
[†]Author for correspondence
[1]Dreamz College of Pharmacy, Himachal Pradesh, India
[2]Siddhartha Institute of Pharmacy, Dehradun, Uttarakhand, India
[3]Faculty of Pharmacy, Department of Pharmaceutics, Jamia Hamdard, Hamdard Nagar, New Delhi, 110 062, India
[4]Assistant Professor, Dreamz College of Pharmacy, Himachal Pradesh, 175036, India
Tel: +91 9625218477;
E-mail: mahfoozkaifi@gmail.com