

Nanocarriers-Mediated Drug Delivery Systems for Anticancer Agents: An Overview and Perspectives

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Abstract: Nanotechnology has been actively integrated as drug carriers over the last few years to treat various cancers. The main hurdle in the clinical management of cancer is the development of multidrug resistance against chemotherapeutic agents. To overcome the limitations of chemotherapy, the researchers have been developing technological advances for significant progress in the oncotherapy by enabling the delivery of chemotherapeutic agents at increased drug content levels to the targeted spots. Several nano-drug delivery systems designed for tumor-targeting are evaluated in preclinical and clinical trials and showed promising outcomes in cancerous tumors' clinical management. This review describes nanocarrier's importance in managing different types of cancers and emphasizing nanocarriers for drug delivery and cancer nanotherapeutics. It also highlights the recent advances in nanocarriers-based delivery systems, including polymeric nanocarriers, micelles, nanotubes, dendrimers, magnetic nanoparticles, solid lipid nanoparticles, and quantum dots (QDs). The nanocarrier-based composites are discussed in terms of their structure, characteristics, and therapeutic applications in oncology. To conclude, the challenges and future exploration opportunities of nanocarriers in chemotherapeutics are also presented.

Keywords: nanomaterials, anticancer agents, recent advances, multidrug resistance, chemotherapy

Overview

Cancer is a group of disorders causing abnormal cell growth and can spread to other body parts. Globally, cancer-associated death rates come second after the deaths related to cardiovascular system diseases and are considered the most critical global health issue. Due to this prevalence, cancer therapy has become a joint dialogue among health-care providers and researchers.¹ As stated by IARC (International Agency for Research on Cancer) worldwide, a total of 14.1 M cases were reported in 2012, and 82% (8 million) of those cases were reported from underdeveloped countries. This geological difference in cancer frequency can be explained by many aspects, including age factor, number of screening tests, early diagnosis, and accessibility of quality treatment, and occurrence of risk factors. Similarly, according to the world health organization (WHO), the number of cancer patients will increase up to 22 M within the next twenty years.²

Due to the massive impact of this deadly disease, researchers worldwide are focused on developing different novel carrier systems to deliver anticancerous agents at the target sites without producing harmful effects on healthy tissues.

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The outcome of therapy is determined by the nature of cancer, the malignant tumor area, and its progression stage. Different strategies, including immunotherapy, hormone therapy, surgery, chemotherapy, and radiotherapy, are used to treat cancer. Among these, chemotherapy is considered the prime choice for the eradication of cancerous cells. However, the conventional delivery systems for chemotherapy have some limitations, including toxic side effects of the chemotherapeutic agents on fast-growing healthy cells and other side effects like nausea, vomiting, fatigue, hair loss, and even death in extreme cases. Another main obstacle in the management of tumors is the development of multidrug resistance (MDR). The cancerous cell develops resistance and escapes from the effects of chemotherapeutic drugs.^{3–6} To overcome chemotherapy's limitations, the researchers are developing new nanotechnology-based advances in drug delivery systems for significant developments in oncotherapy by delivering anticancer agents at higher concentrations to targeted sites.^{7,8} Nanocarriers have been emerged and exploited as a new tool for cancer treatment to reduce numerous precincts of conventional drug delivery systems.⁹ Researchers are enthusiastically working to improve the treatment options for the management of malignant tumors. They have trialed nanotechnology-based drug carriers as useful cancer management applications, which further lead to nano-drug carriers (10–100 nm) impending as a distinct therapeutics for cancer treatment. The potential use and efficacy of various nano-drug carriers for anticancer agents are much higher than normal ones.¹⁰ Nanocarriers offer multiple benefits over conventional drug delivery systems like increased plasma half-life, improved biodistribution, and targeted delivery of a drug to tumor microenvironment through endothelial layers. These nanocarrier-based drug delivery systems are being used against various types of cancerous tumors containing tissues.

Various nanocarrier preparations have been designed to improve therapeutic efficacy and reduce toxic side effects. Nanocarriers prospect a continuous, direct, and controlled drug release to the malignant cells selectively with augmented drug localization and cellular uptake. Nanoparticles can be automated to identify malignant cells and give discriminating and precise drug transfer, evading contact through the normal cells. Additionally, various drawbacks, including systemic toxicity, low oral bioavailability, decreased solubility, narrow therapeutic

indices, and chemoresistance, have been overcome with the advancement of nanocarrier-based DDS.^{11–13}

Nanotechnology has become a vast field for biomedical applications and nanocarriers such as polymeric nanoparticles, micelles, dendrimers, solid lipid nanoparticles, quantum dots, and magnetic nanoparticles with substantial physical and chemical properties along with the nano-sized effect.¹⁴ The outcomes of various cancer research studies have generally acknowledged that nanoparticle-based drug delivery systems (DDS) with boosted bioavailability and minimum side effects embrace auspicious anticancer effects compared to free drugs.^{15–17}

Different types of nanocarriers have been successfully adopted in various nanomedicine. Nevertheless, their transformation to medical oncology remains inadequate. Engineered nanoparticles possess advanced applications that include gene delivery,¹⁸ site-specific targeted drug delivery system,¹⁹ as well as agents in magnetic resonance imaging to enhance diagnostic possibilities,²⁰ or to design and develop new imaging methods.²¹ Nanocarriers possess distinctive properties such as quantum effects, a high ratio of surface to volume, and an ability to carry therapeutically active compounds to the targeted site due to their nano size.²² This review focuses on polymeric nanoparticles, having unique identifying properties incorporated by various strategies that distinguish them from previous anticancer drug delivery systems. It also describes nanoparticles inside the cells, illustrating many successful research pieces about using different approaches to remove the side effects of conventional therapies with tailored cancer treatment.

Consequently, the current writing piece is about nanotechnology developments, concentrating on nanocarriers for anticancer drug delivery. It also describes the differences in the polymeric nanoparticles, micelles, dendrimers, solid lipid nanocarrier, quantum dots, and magnetic nanocarriers. Finally, the current challenges and future perspectives have been highlighted.

Precincts of Conventional Drug Delivery Systems

The delivery of chemical antineoplastic agents used as chemotherapy for local and metastatic tumors is associated with many drawbacks. The major problem related to chemotherapy is the lack of selectivity of the malignant cells; these chemotherapeutic agents have similar cytotoxic effects on the normal healthy cells. Therefore, the long-

run clinical use of such chemotherapeutic agents causes severe toxicity to normal healthy cells. Chemotherapeutics delivered via the conventional delivery systems can induce severe cytotoxic effects to healthy cells due to the high volume of distribution of the drugs, which are low molecular weight and are cleared quickly.²³

The chemicals with low therapeutic index administered in high concentration due to low bioavailability or early excretion from the body can lead to dose-dependent systemic side effects.²⁴ Poor solubility of chemotherapeutic agents is another problem; low solubility makes it challenging to formulate a drug delivery system. Paclitaxel is an example of such a low solubility drug, which has limited application in chemotherapy. Low water solubility can lead to embolization of blood vessels when administered through the intravenous route.^{25,26} Furthermore, the tumor cells also develop resistance to chemotherapeutic agents. The interstitial fluids of tumor cells develop high hydrostatic pressure, leading to an outward convective interstitial flow that can remove the therapeutic agents from the tumor cells.^{27,28}

Conventional drug delivery systems for the chemotherapeutic agents come across hurdles in the course of drugs' passage to the malignant tumor. The drug's physicochemical properties, comprising the surface composition, particle size, particle charges, demonstrate a substantial role in drug transportation to the site of action.²⁹ Additional steepchases involve the pathophysiological tumor

heterogeneity, which constrains an unvarying drug delivery into the whole tumor mass. Acidic tumor microenvironment causes dilapidation of the acid-sensitive drugs.

Various Types of Nanocarrier-Based Drug Delivery Systems

If at all possible, for anticancer drugs to be significantly effective, they should initially, be capable of breaching over the obstructions in the body and targeting the anticipated tumor tissues with insignificant forfeiture of their volume or activity in the blood circulation. Subsequently, after attaining the target site, chemotherapeutic agents should have the capacity to eradicate the tumor cells without distressing healthy cells. These two rudimentary tactics are also connected with enhancements in patient endurance by increasing the accumulation of chemotherapeutic agents inside the tumor microenvironment and dropping dose-limiting toxicities all together. Progressively, nanocarriers give the impression to have the prospective to propitiate both of these necessities for effective drug carrier systems.

Various novel nanocarrier-mediated drug delivery systems to deliver the chemotherapeutic agents at targeted sites are currently in practice. The structural representation of different nanocarriers-based delivery systems is illustrated in Figure 1.³⁰ Some important nanocarriers include polymeric nanoparticles, liposomes, polymeric micelles, carbon nanotubes, dendrimers, solid lipid nanoparticles,

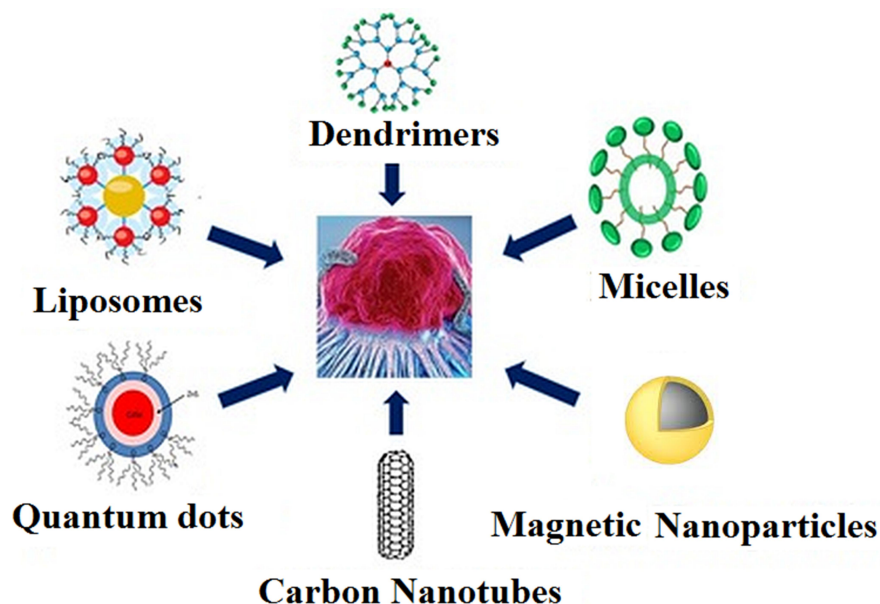


Figure 1 Various types of nanocarriers used to treat the malignant tumors.

magnetic nanoparticles, and quantum dots. These nanocarriers are discussed in the following sub-sections.

Nanocarriers Developed from Polymer

Various types of polymers are being employed for the preparation of nanocarriers; the active therapeutic agents are either physically entangled with polymeric matrix or bounded covalently with polymers.³¹ The prepared polymeric systems could be like a capsule, amphiphilic, or complicated branched macromolecule. Both natural and synthetic polymers are used for the development of nanocarriers.

Micelles-Based Delivery Systems

Micelles are constructed with the amphiphilic block copolymers, and their well-designed properties are based on the nature of copolymers, which mount up to form a nano-sized core/shell construction in hydrophilic-buffered media. The hydrophobic cavity of micelles acts as a reservoir for lipophilic drug molecules and outer hydrophilic shell help the micelle stability in an aqueous environment, and these

properties make micelles suitable for intravenous administration.³² Micelles can be enriched with drug molecules by using two methods, chemical covalent attachment method and physical encapsulation methods.^{33,34} Recently, the first polymeric micelles formulated with paclitaxel known as Genexol-PM, are cremophor-free polymeric micelle-formulated paclitaxel. Micelles formulation of paclitaxel has been undergone a clinical trial for advanced refractory malignancies. Another class of micelles being developed is the multifunctional polymeric micelles decorated with steering ligands, imaging and therapeutic agents,³⁵ and will turn out to be conventional amid numerous models of the micellar preparation soon. Recently, a research group established the novel drug delivery system of ursolic acid-loaded polymeric micelles (UA-PMs). The results shown in Figure 2 depict that formulation UA-PMs considerably improved the cell-growth along with inhibiting cell-migration properties against the human hepatocellular carcinoma cells HepG2 while displayed no toxicity to both human normal liver cell line L-02 in vitro and the normal

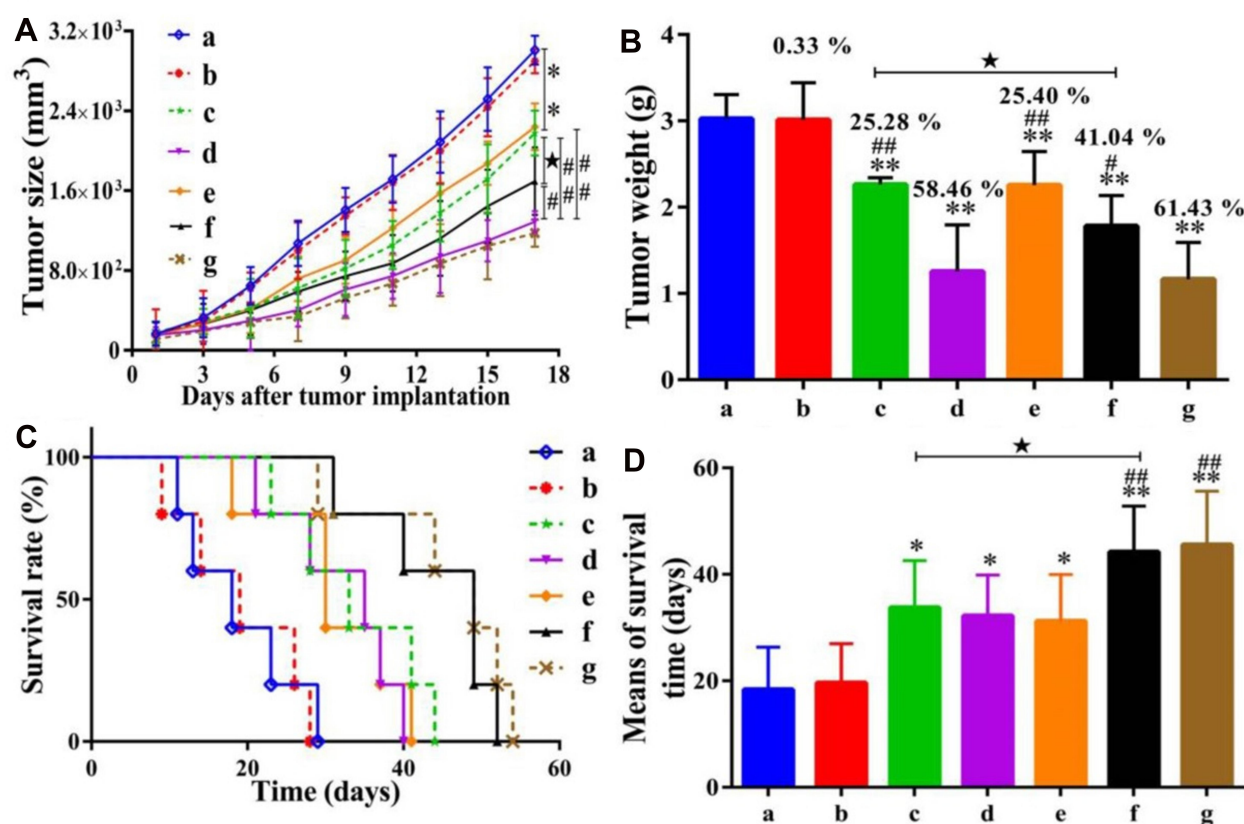


Figure 2 Determination of the antitumor activity of UA-PMs on H-22 xenograft model. The mice induced with the H-22 tumor were treated with different formulations. Outcomes measured the significant changes in the volume of tumor-induced in mice (A), changes in the weight of tumor (B), a curve showing the time of survival for the tumor-bearing mice (C), mean of the survival time (D) and weight of mice. Data are shown as the mean \pm SD in each group ($n=5$). Significant differences were observed between treated groups and saline (* $P < 0.05$, ** $P < 0.01$), treated groups and 5-FU group (## $P < 0.05$, ### $P < 0.01$), UA and UA-PMs (* $P < 0.05$) at the concentration of 50 mg/kg. Adapted from Zhou M, Yi Y, Liu L, et al. Polymeric micelles loading with ursolic acid enhancing antitumor effect on hepatocellular carcinoma. *J Cancer*. 2019;10(23):5820. Creative Commons.³⁶

Kunming mice *in vivo*. Additionally, the study revealed that UA-PMs could rescind the tumor development of H22 xenograft and lengthen the existence interval of the tumor-bearing mice.³⁶

Nanoparticles Developed from Polymers

Natural polymers like albumin, heparin and chitosan are used to create nanoparticles for the targeted transport of nucleotide-based drugs, oligonucleotide drugs and proteins. In recent times, nanometer-sized paclitaxel-loaded nanoparticles have been trialed in clinics for the treatment of metastatic mammary gland tumors.³⁷ In addition to breast tumor-related, these nanoparticles have been evaluated for the management of other types of malignancies together with non-small-cell lung cancer are at Phase II trial, progressive non-haematologic malignancy trials are at Phase I and pharmacokinetic trials.³⁸

A group of researchers has developed polymeric nanoparticle-based delivery systems with ultra-high drug loading glutathione sensitive heterodimeric multifunctional prodrug. The significantly fascinating property of the prodrug-loaded nanoparticles is enabling the quantitative pharmacokinetic imaging, which helps in monitoring the distribution of drug within the tumor cells by PET imaging. As illustrated in Figure 3A–D, polymeric nanoparticles loaded with prodrug and isotopes showed significantly improved drug distribution within tumor. PET imaging confirmed significantly higher quantities of the drug for 28 hrs. As compared with HPPH, the momentous tumor accumulation of CPT-ss-HPPH was verified by *ex vivo* bio-distribution evaluated via γ -counting of excised organs (Figure 3C).³⁹

Lipid-Based Drug Carriers

Among the lipid-based nanoparticulate formulations, liposomes were initially designed in 1965; liposomes were the foremost nanocarriers employed in nanomedicine field.⁴⁰ Nowadays, many liposomes based formulations are approved for clinical applications, and hundreds are in clinical and preclinical developments. The liposomes are superb drug delivery systems due to their easy degradation inside the body and additionally their property to encapsulate hydrophilic agents inside the aqueous environment and lipophilic agents in outer lipid layers. Further, to enhance the stability of liposomes, polyethylene glycol (PEG) is coated on the surfaces of liposomes.⁴¹ Pegylated liposomes demonstrated the reduction in the distribution volume of dox from 1000 L/m² in the free drug form to 2.8 L/m² by limiting the

dissemination inside the plasma. Likewise, liposomal drug delivery limits the highest drug concentrations within the tumor cells and reduce the pooling of drug in other tissues.⁴² At present, quite a lot of antitumor agents are being formulated within these novel lipids based drug delivery systems with different methods approaches. There are few essential liposomal delivery systems loaded with anticancer agents like doxorubicin (Doxil, Myocet) and daunorubicin (DaunoXome). Both have been approved for the treatment of mammary gland tumors and AIDS-linked Kaposi's melanoma.⁴³ In addition to these approved formulations, numerous anti-tumor formulations based on liposomes are at present being considered in clinical trials. The immunoliposomes seems to be the next generation of liposomal drugs, which selectively convey the drug to the anticipated sites of action.⁴⁴

Nanoparticles Developed from Solid Lipids

Nanoparticles developed from solid lipids are typically spherical, nano-sized (10 to 1,000 nm) colloidal carriers of natural or synthetic lipid-based drug delivery system. It is acclaimed that solid lipid nanoparticles are biocompatible and have a low toxicity profile. In contrast to polymeric or inorganic nanoparticles, lipid-based nanocarriers are less toxic and biocompatible.^{45,46} Solid lipid nanoparticles (SLNs) hold a solid core of the lipid matrix that can dissolve the lipophilic molecules. The term lipid is used generally in a vast sense and includes triglycerides, partial glycerides, PEGylated lipids, fatty acids, steroids, and waxes.⁴⁷ The lipid core is balanced by using surfactants, as shown in Figure 4. The amount of emulsifier used depends on administration routes and is more limited for parenteral administrations.^{48,49} In this drug delivery system, small-sized lipid core, surfactants and drugs are present in appropriate ratios showing some unbeatable properties that make them superior over other existing drug carriers. These SLN-based preparations have some unique characteristics, including high drug loading, and increased drug stability. These formulations have better feasibility of hydrophilic and lipophilic drug incorporation. Generally, SLNs are highly compatible owing to their composition similarity from physiological lipids. Exceptional ability to incorporate drugs into nanocarriers and size-dependent properties of SLN makes them an ideal candidate to develop novel therapeutic prototypes for drug delivery and targeting. SLN has the potential to enhance the efficiency of pharmaceuticals, nutraceuticals, and other materials. In comparison to phospholipids and biodegradable polymers, solid lipids are economical. Compared to

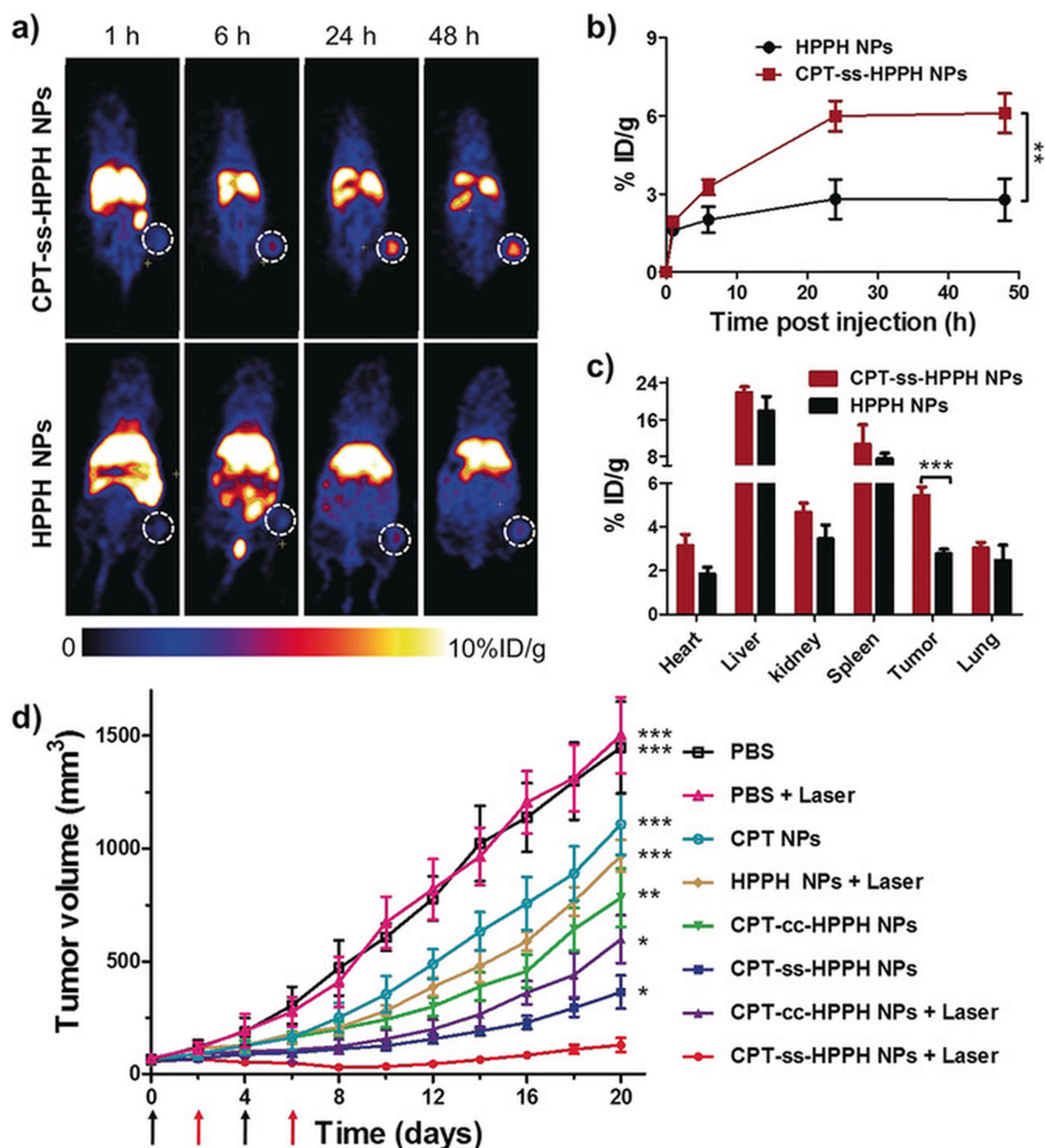


Figure 3 Heterodimeric multifunctional prodrug loaded NPs facilitated effective drug distribution to tumor and synergistic tumor chemotherapy and photodynamic therapy. **(A)** PET images showing the whole body of tumor-induced mice. Accumulation of NPs in tumors has been marked with white circles. **(B)** Quantification of the drug in tumor measured from decay-corrected PET images ($n=3$). **(C)** Ex vivo drug dissemination quantified by γ -counting of excised tissues at 48 h after the injection ($n=3$). **(D)** The volume distribution of tumor under the influence of treatment ($n=5$). Black arrow is a sign of intravenous injection of drugs, while red arrow reflects laser irradiation. Asterisk signs indicate the significant differences between CPT-ss-HPPH NPs and the other treatments. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. * $p < 0.001$. Adapted with permission from Zhang F, Ni Q, Jacobson O, et al. Polymeric nanoparticles with a glutathione-sensitive heterodimeric multifunctional prodrug for in vivo drug monitoring and synergistic cancer therapy. *Angewandte Chemie Int Edition*. 2018;57(24):7066–7070. © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.³⁹

traditional colloidal carriers, SLNs have superior cellular uptake and can improve the solubility and bioavailability of drugs.^{50–53}

Applications of SLN

In the recent past, SLN has emerged as a novel DDS for cancer research, including drug delivery,⁵⁴ diagnosis, and

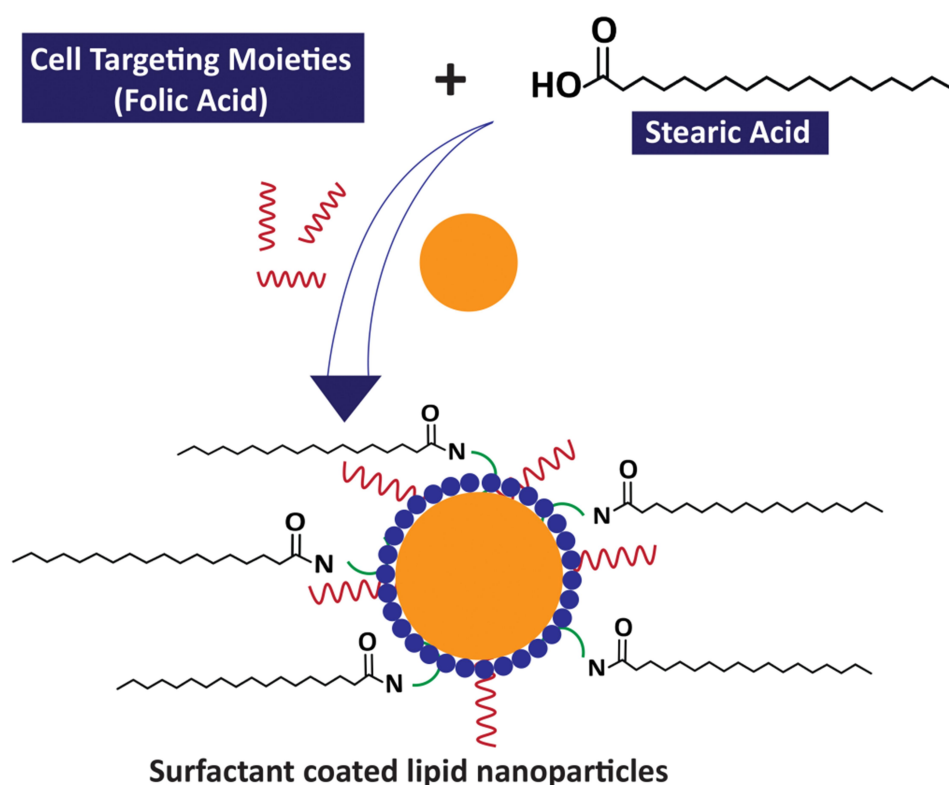


Figure 4 A schematic illustration of surfactant coating of solid lipid nanoparticles.

targeting.^{55,56} SLN, either single-handedly or in conjunction with other molecules, is extensively used in medicines, biomedical applications, bio-imaging, and photo-thermal therapy.⁵⁷ Anticancer agents are delivered with improved selectivity, and activity is enhanced when delivered via novel SLNs. The SLNs-based delivery system also has the potential for cellular-based drug directing by altering cellular signaling and gene expression.⁵⁸ Besides, SLNs are also deliberated as appropriate substitute carriers for par-enteral delivery,⁵⁹ gene delivery,⁶⁰ pulmonary delivery,⁶¹ and topical and transdermal delivery.^{62,63} In this review, we will only discuss chemotherapeutic applications.

As a substitute to current conventional drug carriers (liposomes, colloidal systems, and polymeric and solid lipid nanoparticles), SLN has been developed as a new type of colloidal drug carrier system suitable for drug targeting applications. In the last decade, SLNs hold great potential for attaining the goal of targeted and controlled drug delivery, which currently draws the interest of researchers worldwide. SLN is a strategic vehicle for tumor targeting because of their passive targeting properties by the enhanced permeability and retention (EPR) effect. Stealth shielding is the additional advantage that avoids

uptake by the reticuloendothelial system, thus prolonged the circulation time of the nanoparticles.^{64–66} Fundarò et al prepared doxorubicin-loaded stealth and non-stealth SLN by microemulsion template method to compare the pharmacokinetics and tissue distribution of doxorubicin-loaded SLN with commercially available doxorubicin solution.⁶⁷ DOX-SLNs increased the concentration of DOX in the brain and CSF of rats, but low uptake of SLN by RES organs. Stealth SLN-based formulation showed an increase in half-life, AUC, and peak plasma concentration (7-fold). Up to 24 hours, prolonged circulation time was also achieved with an improved DOX formulation in DOX incorporated stealth SLNs.⁶⁷

Sukumar et al reported the antitumor efficacy of SLNs by fabricating with variable proportions of stearic acid, lecithin, and phosphatidylserine. The SLN used in this work encapsulated phospho-sulindac was evaluated in human lung cancer xenograft models.⁶⁸ Lung cancers are usually labeled as mutations in the p53 gene, resulting in loss of mutational repair and tumor-suppressor function, inhibition of apoptosis, increased tumor angiogenesis, cell proliferation, and increased drug resistance.⁶⁹ SLNs are biodegradable, non-viral vectors that have gained increasing attention as

promising colloidal carrier systems to treat early endobronchial cancer. SLN have shown their advantage over other carriers by their increased stability, no immunogenicity, and their controlled-release ability.^{70,71}

Aiming at drug delivery, SLNs are developed to improve therapeutic delivery to target the cancerous cells by different mechanisms, including active targeting by external modification of SLNs, passive targeting leads to the malignant tumor microenvironment and provisions of co-delivery.⁷² SLNs can integrate various drug moieties and have recognized a suitable vehicle in different types of tumors (ie, lung, liver, breast, colon, and brain). SLNs have the potential to be used as a carrier for chemotherapeutic agents, corroborating their ability to improve pharmacokinetics and physicochemical stability of the integrated drugs. The lipid nature and nano size of SLNs also influence the drug's pharmacokinetics through its specific uptake and distribution profile.^{73–76} In a study, nanoparticles developed via lipid hybridization loaded with cisplatin demonstrated higher uptake of the drug within the cell and significantly improved tumor growth inhibition in the ovarian cell line.

Additionally, pharmacokinetic and toxicity evaluation carried out in rabbits showed a controlled release behavior and provided these nanocarrier's safety profile.⁷⁷ In contrast to other nanocarriers, SLN offers the possibility of a sustained-release due to its solid matrix. Owing to the smaller size and larger surface area, SLN-based DDS shows increase solubility and improved bioavailability.^{78,79} Furthermore, owing to the property of crossing the blood-brain barrier (BBB), SLN moved into the central nervous system and trapped by the cells more efficiently than larger molecules and, therefore, could be used as effective transport and delivery systems.⁸⁰ Bartsch et al reported that SLNs could work as an efficient drug delivery system to deliver antisense oligonucleotide (AS-ODN) to liver endothelial cells in-vitro and in-vivo by stabilized lipid-coated lipoplexes.⁸¹

Today, researchers are continuously developing new nanocarriers to deliver therapeutic agents and imaging agents for cancer therapy and diagnosis, respectively. Exploring solid lipid nanocarriers promises the most exciting advances in lipid-based drug delivery to offer new hopes to address some of the most confounding illnesses for substantial signs of progress in cancer treatment and diagnosis. To date, several publications explained lipid-based carriers for lymphatic metastasis. In the course of lymph node metastasis, cancer cells first reach the SLN via

lymph flow. For efficient SLN biopsy, cancer cells must be identified with high sensitivity in the SLN allied to the tumor site. In a study,⁸² Paliwal and colleagues developed SLNs for methotrexate delivery to the lymphatics. SLN being a lipid-based carrier retains a solid-state at physiological temperature. Results show a tenfold increase in lymphatic uptake after oral administration compared to methotrexate alone.⁸² In another study, Lu et al indicated that SLN of size <100 nm is an ideal delivery system for chemotherapeutic agents against breast cancer and lymph node metastases. These SLN formulations showed sustained release with high drug targeting to the lymph nodes and a strong affinity to tumor tissue diagnosis.⁸³

Quantum Dots

Nano-sized semiconductor quantum dots are among the novel strategies used in the treatment of different types of cancer. Water solubility and biocompatibility of quantum dots are improved by surface modification. It further helps the QDs to be used as fluorescent probes with targeting molecules.⁸⁴ Quantum dot nanocarriers possess exceptional features like to have broad and robust absorption spectra and have unique optical and chemical properties. Semiconductor quantum dots can be used as photosensitizers.^{85,86} They show resilience to chemical degradation, pH changes, and have high thermal stability. QDs being an absorber of high-energy photons (X-rays and gamma rays) act as a radiosensitizer.

QDs are made up of a core and a shell or cap.⁸⁷ A QD core includes various metal complexes, for example, noble metal, semiconductors, and magnetic transition metals. As, group III–V sequences QDs comprises of indium arsenate (InAs), indium phosphate (InP), gallium arsenate (GaAs), and gallium nitride (GaN) metalloid cores, while group II–IV sequences QDs has cadmium–selenium (CdSe), zinc sulfide (ZnS), zinc–selenium (ZnSe) and cadmium–tellurium (CdTe) cores. Cadmium contained semiconductors are the main component of quantum dots with noble optical characteristics. However, cadmium is probably harmful, and the toxicity studies of these cadmium-containing quantum dots in human living cells are comprehensively not evaluated yet. Consequently, exploration for non-toxic ingredients with comparable targeting and optical properties are of advanced concern.

Applications of QDs

QD-based nanocomposites have now become an exciting topic for research in the oncology field. QD nanomaterials

are usually tiny in size, however, with wide-ranging application potentials in different fields. The excellent characteristics of carbon-based quantum dots, including low toxicity profile and biocompatibility empower remarkable biomolecule, drug delivery, bio-sensing, and bio-imaging applications.

High accuracy is required for effective cancer treatment through ionizing radiations to reduce exposure and toxicity to adjacent healthy cells. Some research has recently been dedicated to fabricating photosensitizer-based quantum dots that yield free radicals upon visible light immersion. Although visible light is harmless, the strategy is still appropriate to cure only superficial lumps.^{88,89} Various research invitations have revealed that QD-conjugated oligonucleotide sequences (attached through surface COOH groups) are targeted to connect with DNA or mRNA.^{90,91} Bio conjugated QDs are also considered for the site-specific gene as well as drug delivery in cancer. Targeting moieties, such as antibodies,⁹² high-molecular-weight dextran,⁹³ aptamers,⁹⁴ peptides,⁹⁵ or folate,⁹⁶ can then be combined with QDs.

Quantum dots, an emerging product of nanotechnology, can be used for biomedical and investigational imaging. Their extraordinary photo-physical characteristics and, at times, multifunctional faces are appropriate for several biological applications. QDs characterize the emerging application for cancer imaging with their unique and stable fluorescence, absorption and emission spectra and negligible photo-bleaching, and stable fluorescence.^{97,98}

Although neurosurgery and radiotherapy have achieved significant advancement, yet the diagnosis of cancer patients with malignant gliomas has not shown any progress for the last decades. QDs show repetitious phases of excitation and fluorescence and a very narrow array of emission spectra. So the QDs are highly used in multiplexed imaging, in which several intensities and colors are united for small-molecules, genes coding protein libraries. For in-vivo studies, QDs are most widely used nowadays in sentinel lymph node mapping, localizing, and targeting tumors. As an alternative to radionuclide imaging procedures, optical imaging is now evolving as a new technique. The study's findings highlighted new paradigms and might be helpful for early diagnosis and therapy, including imaging-guided surgery. Researchers concluded that peptide-labeled NIR QD has the potential for in-vitro, ex-vivo tumor cell staining, and in-vivo tumor mass imaging.^{84,91}

QDs have great potential for management as well as in the detection of cancers. Semiconductor quantum dots and

nanocomposites made up of lipids, polymers, or metals have been developed with exciting cancer therapy applications and early detection. Presently only a few data are available regarding the application of QDs in whole-body imaging. QD-based multifunctional probes give excellent sensitivity for synchronized cancer molecular imaging and targeted therapy by their brightness. QD imaging technique has to turn into the most favorable tool for detecting cancer early due to its exceptional biomedical imaging performance.⁹⁹ Concurrent targeted DD and dual-mode tumor tissue imaging using near-infrared fluorescence and NMR spectroscopy.¹⁰⁰ Gao and coworkers fabricated PEGylated quantum dots and then conjugated them with the anti-HER2 antibody and localized them in specific tumor cells.¹⁰¹

QDs have been encapsulated in lipid-based micelles for biological imaging applications.¹⁰² Lipid nanoparticles can simply be fabricated in bio-conjugation of several targeting moieties with a variety of functional groups (SH, NH₂, biotin, COOH, and maleimide) presented in phospholipids.¹⁰³ The latest studies reported the preparation of lipodots; here, the QDs were incorporated in phospholipid vesicle bilayer. These folate-targeted lipodots are exploited for lymphoma cells targeting with overexpressed folate receptors, whereas colon carcinoma cells with not upregulated folate receptors did not respond to lipodots treatment.¹⁰⁴

Owing to their unique characteristics and properties, QDs are considered an efficient drug delivery system. QDs have the advantage of high specific surface area because multiple attachment sites are available for drug targeting; they can also easily cross the cell membranes. In this section potential of QDs as a delivery vehicle, connection with different ligands, and further improvements are also discussed. As an example, Olerile et al co-loaded chemotherapeutic drug paclitaxel (PTX) carrying SLN along with (CdTe/CdS/ZnS) QDs, and the results displayed higher drug loading and encapsulation efficacy with a tumor growth inhibition rate of 77.85%.¹⁰⁵ Another example is graphene QDs-based carboxymethyl cellulose hydrogel films were reported by Javanbakht and colleagues.²³ In this work, nanocomposite hydrogel films were used as a delivery vehicle for doxorubicin (DOX). The results showed a sustained and pH-dependent release of DOX.¹⁰⁶ Graphene-based QDS was developed as a DDS for the anticancer drug, methotrexate (MTX). GQDs were used as a cap with the polypyrrole mesoporous (PPy/mSiO₂) core. PPy core is

responsible for efficiently transforming near-infrared light into heat and acting as a photo-thermal agent. Near-infrared light-triggered the drug release from the delivery vehicle by increasing the temperature of the system. Consequently, this increased temperature of nanocomposites leads to H-bonds breakage between graphene QDs and mSiO₂. GQDs also improved the encapsulation efficiency of MTX in the PPy/mSiO₂.¹⁰⁷

Dendrimers

Dendrimers are nanometer size drug delivery systems developed from the synthetic polymeric macromolecules, and dendrimers are constructed of manifold prominently branched monomers that project externally starting from the central core as shown in Figure 1. Dendrimer-based drug delivery systems possess a lot of unique properties since they have modifiable surfaces, monodisperse size, hydrophilic internal cavities and multivalences.¹⁰⁸ Polyamidoamine dendrimers conjugated with cisplatin are famous for being used as scaffold systems.¹⁰⁹ The only changeable external characteristic of dendrimers enables these unique systems to be concurrently conjugated with several molecules make them unique multifunctional drug delivery systems.¹¹⁰

Applications of Dendrimers

Amid the vast assortments of NPs available, dendrimers offer numerous benefits. Dendrimers because of their branched structures can encapsulate and conjugate particular type of drug molecules. A widespread variety of dendrimers used is the polyamidoamine (PAMAM) dendrimers, appropriate for numerous biomedical, biotechnological, regenerative medicine and tissue engineering applications.¹¹¹ Polydiamine dendrimers are constructed of alkyl diamine inner core and peripheral branches of tertiary amine.^{112,113} The flexibility in the dendritic structure of dendrimers makes them perfect drug transporters in biomedical applications.¹¹⁴

As dendrimers hold a high density of functional surface molecules, they are straightforwardly conjugated with quite a lot of targeting agents for the pernickety supply of chemotherapeutics to the tumor tissue. Additionally, they encompass voids present in the core for encapsulation of lipophilic macromolecule, allowing them to transport highly hydrophobic drugs.¹¹⁵

Adding of stimuli response properties to the dendrimers make them versatile and release the drug loads in response to some specified triggers. These specified triggers can be internal from the tumor environment like acid,

enzyme, and redox potentials or it can be induced from the external like light and temperature.¹¹⁶ In the latest work, integrated by Nigam et al for the treatment of cervical cancer, iron oxide NPs were merged with Generation 2 (G2) PAMAM dendrimers and encumbered with doxorubicin (DOX). Consequently, an amalgamation of the magnetic chemotherapy and hyperthermia was evaluated on HeLa cancer cells.¹¹⁷ When exposed to a flashing current magnetic field, the outcomes displayed improved cell death as a consequence of the lethal synergistic effect of DOX and high temperatures. Remarkably, the combinatorial treatment abridged the cancer cell viability from 100% to 3.6%.¹¹⁷

Another research group conjugated folic acid to PAMAM dendrimer NPs for targeting the tumor cells.¹¹⁸ The outcomes disclosed insignificant harmfulness to non-cancerous MRC9 lung fibroblast cells, as well as the capability of dendrimer nanoparticles for targeted co-delivery of siRNA and chemotherapy agents together in the lung cancer cells. The dendrimers developed for targeting the breast tumor cells showed boosted in vitro cellular toxicity as compared with non-targeted dendrimers. The altered dendrimers displayed extraordinarily reduced relocation of BT-549-Luc breast cancer cells. Another research report confirmed the prospective utility of lactoferrin (LFC131) conjugated dendrimer for breast cancer therapy and metastasis. Galactosamine (Gal) is amongst the limited selective ligands used for targeting HCCs due to its high binding attraction to asialoglycoprotein receptors (ASGPRs) over-expressed in HCC. In the latest work, Yousef et al concocted a nanoscale G4 PAMAM dendrimer NP attached to Gal and laden with the potent anticancer curcumin derivative as a platform for targeted drug delivery to HCC. Astoundingly, in an in vivo xenograft model, cytotoxicity assays in HCC cell lines showed that curcumin derivative was more potent as a chemotherapeutic anticancer agent than the currently in use Doxorubicin, Sorafenib and Cisplatin chemotherapeutic agents.¹¹⁹ It has been pronounced that dendrimers have the magnetism to cross the blood-brain barrier after systemic administration.¹²⁰ Liu et al utilized united chemo- and gene-therapy tactic for effective glioma treatment and established a DOX-loaded dendrigraft poly-L-lysine dendrimer surface modified with tumor necrosis factor associated apoptosis-inducing ligand (TRAIL) for the tumor-targeting explicitly of a specific peptide.¹²¹

Colorectal cancer is the third maximum detected cancer in the world. Despite notable progress in treatment,

CRC still leads to significant morbidity and mortality.¹²² Therefore, a research squad established nanotechnology-based cell recognition and apprehension technique.¹²³ Refined anti-Slex (aSlex) antibody and FITC labeled-second antibody (IgG/IgM-FITC) were employed for the amalgamation of aSlex-coated dendrimer conjugates. By exploiting this coating, dendrimers would interment to saliva acidifying Louis oligosaccharides X (Sialyl Lewis X, Slex, a type II carbohydrate antigen for mediating the colorectal cancer metastatic process). By this technique, the colorectal cancer cells were not only captured in artificial blood samples but controlled in cell activity by the conjugates, which means, there was a specific interaction between antigen and antibody (existing in dendrimers).

Another study reported the incorporation of gold nanoparticles with dendrimers; the purpose of this research was to explore the theranostic competency of curcumin-loaded dendrimer-gold hybrid structures. The acquired consequences established higher cellular uptake, internalization and cytotoxicity of curcumin-loaded, gold nanoparticle-loaded dendrimers in comparison with blank nanoparticles in C26 and HT29 colorectal cancer cell lines. Besides, the developed structure functioned as an effective antitumor therapy and accurate computed tomography imaging of C26 tumor-bearing mice due to gold accumulation.¹²⁴

Carbon Nanotubes

Carbon nanotubes are mostly being applied biological fields as a sensor for diagnostic purpose and for detecting the DNA, proteins and discriminating different types of proteins from serum samples and help in the delivery of vaccines and proteins.¹²⁵ These delivery systems pose some health dangers because of the insoluble nature in all kinds of solvents. Nevertheless, by the chemical changes in these tubes and attaching some functional groups make them water-soluble, and enable them to be used for delivery of lots of active therapeutics like, proteins, peptides, nucleic acids and other active moieties. Most interesting delivery systems have been developed by incorporating an antifungal agent (amphotericin B) and by combining the antitumor agents like methotrexate along with fluorescent agents. Research studies carried out with the drugs attached with nanotubes showed more effective internalization of drug molecules compared to free drug molecules.¹²⁶ Similarly, human serum albumin has been attached with single-walled nanotubes for efficient loading of anticancerous compounds. The delivery systems showed significantly improved drug delivery

inside the cells, up to 80% in breast cancer cells. The high binding capacity of PTX with HAS leads to the enhanced drug loading on SWNT-based drug delivery systems. These functionalized nanotubes displayed the most increased growth inhibition activity in MCF-7 breast cancer cells.¹²⁷ The manifold covalent functionalization on the exteriors of carbon nanotubes permits them to convey more than a few drug molecules at once, and this approach offers a dynamic improvement in the management of cancer.

Applications of Carbon Nanotubes

Carbon nanotubes gain as mesmerizing nanocarriers for copious diagnostic and therapeutic applications for the reason that of elastic and conductive characteristics.^{128,129} CNTs generally exist in two forms: as Single-wall (SWCNTs) and Multi-Walled Carbon Nanotubes (MWCNTs) devouring benefits over globular nanoparticles for delivery applications.¹³⁰ Carbon nanotubes with special characteristic badge advanced drug loading and imaging agents, which are amiable with multiple biological systems, confirmed by organized in vitro and in vivo studies. Platinum drugs can be conveyed via CNTs in three diverse modes: i) the drug can be loaded into the CNT cavity, ii) the drug attached directly to the CNT surface-functionalized with a carboxylic acid or amine groups, or iii) the drug can be linked through the use of a chemical tether. Furthermore, the internal and external planes of the CNTs were couturier with various functional groups, conjugates, targeted ligands or attaching PEG-like polymers to enhanced biocompatibility.¹³¹

Recently, Bianco et al¹³² have emphasized the degradability of functionalized CNTs by oxidative enzymes. It suggests a new perception for its implication in the field of medical applications. The authors showed that monofunctionalisation, bi-functionalization, and tri-functionalization of CNTs provided high biocompatibility and translocated directly into the cytoplasm of cells. Non-degradable CNTs can be amassed in several organs and tissues.¹³² Furthermore, Allen et al efficaciously reconnoitred the degradation of pristine and oxidized SWCNTs with the help of oxidative enzyme horseradish peroxidase (HRP) as a catalytic agent.¹³³ Lippard et al described earlier that Pt (IV) prodrug conjugated with soluble SWCNTs revealed successful delivery of CDDP using toxic dose on selective intracellular reduction.¹³³ The same research group developed SWCNT-Pt (IV) complex with targeting molecules, containing a folate derivative (FA) at an axial

position. The authors demonstrated the SWCNT–Pt (IV)-FA efficacy over human cells, including choriocarcinoma and human nasopharyngeal carcinoma cells.

Moreover, Bhirde et al prepared the oxidized SWCNTs functionalized firstly with cisplatin followed by conjugation with epidermal growth factor (SWCNT–CDDP–EGF) for specific targeted drug delivery against squamous cancer cells. As a result, an increase in the EGF affinity towards cell surface receptor can selectively enter and kill the targeted cancer cells. Similarly, in-vitro studies were conducted on HNSCC cell lines (HN-13) using SWCNT-Qdot-EGF and SWCNT-Qdot as controls. Confocal microscopy and Qdot luminescence confirmed SWCNT-Qdot-EGF conjugates rapid internalized to HN-13 cells, whereas negligible uptake happened for SWCNT-Qdot control due to low levels of EGFR.¹³⁴ Hampel et al break new ground by filling up opened CNTs with Pt-based drug using wet chemical approach method where capillarity are the driving force for Carboplatin (CP) to enter the inner cavity.¹³⁵ Drug loading can be altering according to change in temperature. However, just about 30% (w/w) of CP was encumbered on the MWCNTs at the temperature of 90°C. Moreover, CP inside MWCNTs was scrutinized using EDX, EELS, XPS and found platinum (Pt^{2+}) existing at oxidation state that point out the CP complex is very stable.¹³⁶

Magnetic Nanoparticles

Magnetic particles are nanostructures of size ranges from 1–100 nm. MNPs usually contain a central magnetic core and a surface coat adjacent to the functional coat. Magnetic particles are assembled of pure metals such as iron,¹³⁷ cobalt,¹³⁷ nickel,¹³⁸ and manganese,¹³⁹ Mostly used in biomedical applications are iron oxide nanoparticles.^{140,141} Depending on magnetic characteristics, nanoparticles are classified as paramagnetic, ferromagnetic, diamagnetic, ferro-magnetic, anti-ferromagnetic and super-paramagnetic materials.¹⁴² Diamagnetic materials are repelled in the magnetic field applied externally; thus, it results in zero magnetic moments in the absence of an external magnetic field. However, paramagnetic materials in the absence of a magnetic field do not retain their magnetic properties and thus forms a weak magnetic moment. Ferromagnetic materials will remain magnetized even when the external magnetic field is absent due to unpaired electrons. Their domains line up in magnetic field direction resulting in a massive magnetic moment. Anti-ferromagnetic materials result in zero magnetization

because magnetic moments have opposite moments and equal magnitude. Ferri-magnetic materials have a net spontaneous magnetic moment because they consist of two different ions in which the opposing moments are unequal. Super-paramagnetism acts as a paramagnet in magnetic field presence^{143,144} Various magnetic nanoparticle features, like coating, size, and type of core material, all influence the biocompatibility or toxicity of magnetic nanoparticles. Ni and Co magnetic nanoparticles are susceptible to acid erosion and oxidation, and thus, they are considered toxic. In contrast, iron oxide nanoparticles are used extensively in biomedicine applications for several years because of their high chemical stability, mechanical hardness and magnetic properties in the radio frequency region. To enhance the efficacy of magnetic nanoparticles, various novel strategies of coating [with surfactants, inorganic materials (like silica, gold), polymers, and biomaterials] and functionalization are needed to enhance biocompatibility or to avoid phagocytosis by RES.^{143,145}

In research work, iron oxide nanoparticles (IONP) loaded with doxorubicin were conjugated with recombinant human IGF1 as a targeting ligand. The influence of theranostic IONPs was assessed in a tissue-derived xenograft model, acquired from an orthotopic human pancreatic cancer patient.¹⁴⁶ The outcomes of the study were that the nanoparticles based IGF1-IONPDOX formulation proficiently besieged to pancreatic tumors and were measurable by optical imaging and MRI, as displayed in Figure 5. Repetitive administration of IGF1-IONPDOX accomplished to break the barrier in the tumor stromal membrane that hinders the drug permeation, resulted in a reduction of tumor size and inhibited the growth of the human pancreatic tumor.¹⁴⁷

Applications of Magnetic Nanoparticles

MNPs have paid attention from the last decades and appear to be an extremely suitable candidate for drug delivery. Applications of MNPs as a targeted drug delivery significantly rely on different aspects related to the size and magnetism of the biocompatible nanoparticles.¹⁴⁴ MNPs can be used to overcome traditional DDS issues and deliver the API to the anticipated target area, sustaining the nanoparticles at a particular position during the drug release when joined with an exterior magnetic field.¹⁴⁸ Consequently, MNPs, by binding with ligands, chemotherapeutics, or other drugs and antibodies, have been successfully used as drug carriers. Docetaxel is a lipophilic chemotherapeutic agent, which needs an

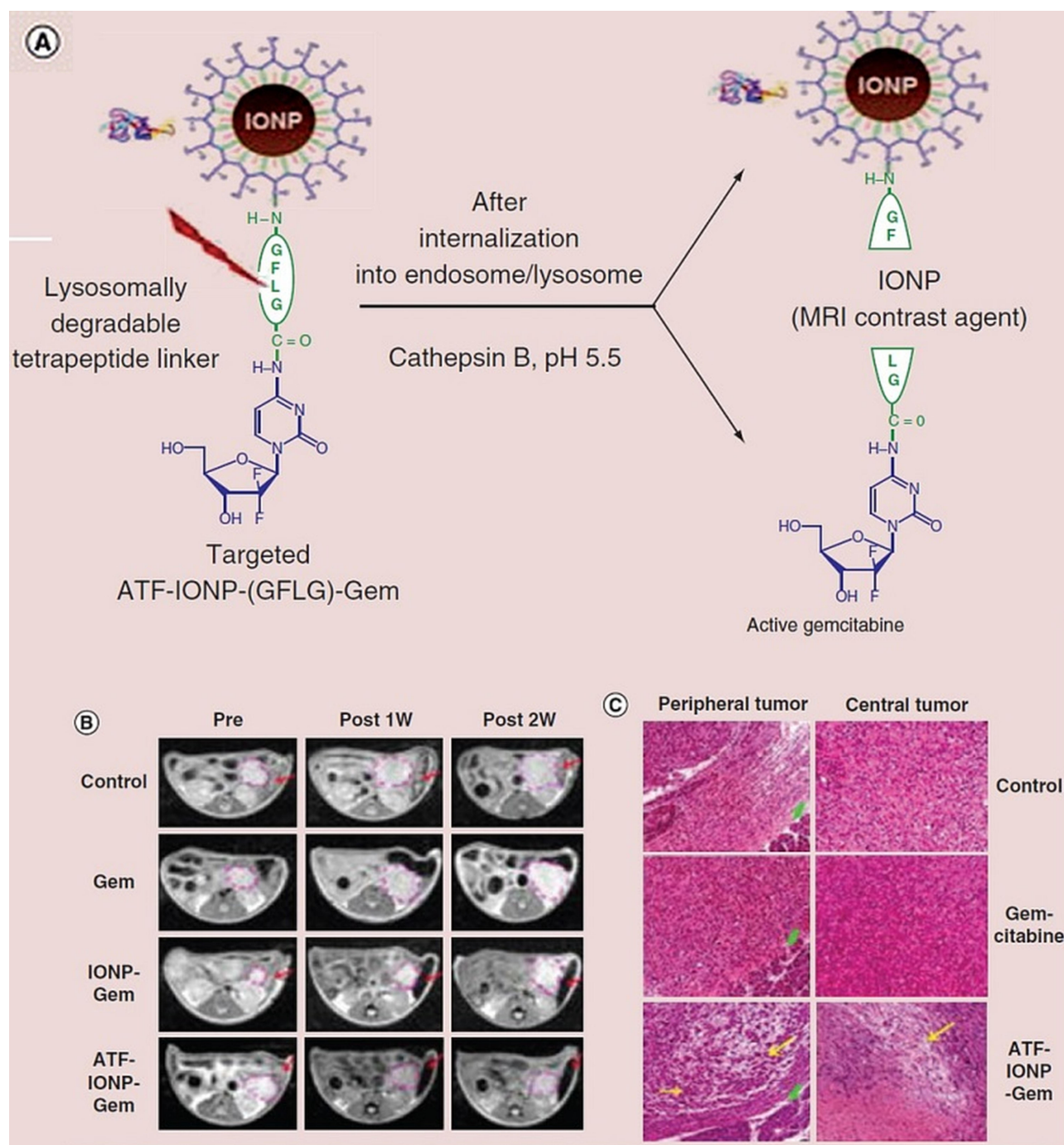


Figure 5 Magnetic resonance imaging of iron oxide nanoparticles based chemotherapy. **(A)** Scheme of development of gemcitabine conjugated iron oxide nanoparticles. **(B)** MRI observation of the therapeutic response of controlled released gemcitabine. **(C)** Histologic staining endorses the targeted therapeutic of pancreatic tumor. Adapted with permission from Lee GY, Qian WP, Wang L, et al. Theranostic nanoparticles with controlled release of gemcitabine for targeted therapy and MRI of pancreatic cancer. *ACS Nano*. 2013;7(3):2078–2089. Copyright © 2013, American Chemical Society.¹⁴⁷

appropriate drug delivery system to increase its antitumor action. Iron oxide nanoparticles grafted with single-chain antibody and β -cyclodextrin for ovarian cancer dual-targeting therapy developed by Huang et al proved the pronounced perspective of combining chemotherapeutic agents with antibodies in the breast carcinoma.¹⁴⁹ In

addition, Aires et al fabricated a novel multi-functionalized iron oxide MNP by using the combination of antibodies and gemcitabine derivatives.¹⁵⁰ A combination of anti CD44 antibody and chemotherapeutic drugs was used to select CD44-positive cancer cells to improve the therapeutic efficiency of gemcitabine.

In medicine, magnetic nanoparticles are used as diagnostics and therapeutic tools. When used as a diagnostic agent, they possess both in-vivo and in-vitro applications like detection of various biomolecules,¹⁵¹ immobilization, purification,¹⁵² cell separation,¹⁵³ and may serve as a contrast agent in MRI,¹⁵⁴ or gene transfer.¹⁵⁵ Magnetic nanoparticles provide skeletal or anatomical and metabolic/functional particulars with a high temporal and spatial resolution.¹⁵⁶ It utilizes a high magnetic field to line up the nuclear magnetization of hydrogen atoms in the body to which later on radiofrequency.¹⁵⁷ Pulse is put in that changes the lining up or alignment of nuclei. When the radio-frequency pulse is distant or removed, nuclei “relax” back to their original state. It provides three-dimensional high spatial resolutions and favorably contrasts differentiation between various soft tissues. Different contrast agents like MNPs and paramagnetic chelates were developed for MR imaging.¹⁵⁸ The spatial resolution of 10–100 μm with no imaging depth extremities is offered.¹⁵⁹ MNPs are also used in photoacoustic imaging technique where they monitor the progressing diseases and tumors. In this technique, light energy is used as a source of excitation, and it ascertains all ultrasonic sound waves generated from the target. PA imaging explains subsurface tissue structures and functional changes with resolution up to 100 μm .¹⁶⁰ Optical imaging in-vivo depends on photons monitoring that was emitted from florescent agents in the near IR region.¹⁵⁸ It has a capability to pass through various biological tissues. Fluorescent molecules absorb light at a particular wavelength and emit back the light at longer wavelengths.¹⁵⁹ They were used in the molecular screening of different surface-based diseases.

Conclusion

Reviewing the significant complications of cancer concluded that a pivotal approach is needed for active treatment modalities for cancer. Traditional therapies, including chemotherapy, radiotherapy, and surgery, are still considered adequate, but due to specific side effects to the healthy body tissues, additional work for some advancement in cancer treatment modalities is the need of the hour. Nanocarriers-based approaches play a dynamic role in biomedical applications, particularly in drug delivery of chemotherapeutics. Versatile modifications are brought together to overcome conventional chemotherapy's limitations and reduce the toxicity in different nanocarriers. This review summarized the polymeric-based nanoparticles, magnetic nanoparticle, lipid-based carriers, dendrimers and quantum dots mediated drug delivery systems for anticancer agents that hold

promising therapeutic outcomes. We also discussed the applications of these few important groups of nanocarriers in cancer drug delivery, drug targeting and cancer diagnosis. So based on the current review, it might be suggested that the nanocarriers developed from the healthy cells friendly biomaterials conjugated with tumor cells markers for the targeted and increased drug delivery at the site of action are better than the conventional nanocarrier systems.

Future Perspectives

However, there are still many challenges for nano-drug delivery systems to be successfully pragmatic for a suitable alternative to conventional chemotherapy for chemotherapeutics. The nanocarriers' toxicity, especially for QDs, is a significant obstacle for the development of a successful antitumor drug delivery system. Research is still going on to diminish the toxicity of existing nanocarriers and explore the advanced nanocarriers with a lower toxicity profile. Cadmium contained semiconductors are the main component of quantum dots with noble optical characteristics. However, cadmium is probably harmful and the toxicity studies of these cadmium containing quantum dots in human living cells are comprehensively not evaluated yet. Consequently, exploration for non-toxic ingredients with comparable targeting and optical properties are of advance concern.

Similarly, carbon nanotubes also hold promising future in the delivery of anticancer drugs, the manifold covalent functionalization on the exteriors of carbon nanotubes permits them to convey more than a few drug molecules at once, and this approach offers a dynamic improvement in the management of cancer.

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Disclosure

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