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Review Article

A Review- Emerging Use of Nano-Based Carriers in Diagnosis and Treatment of Cancer-Novel Approaches

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Abstract

Keywords

Nonomedicine,
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Oncology

Despite intensive research efforts, cancer remains one of the leading causes of death in the world. Many new methods and techniques have been developed in order to improve diagnosis and treatment, often promising in the beginning, but with limited results during the course of their application. In recent years, there has been an unprecedented expansion in the field of nanomedicine with the development of new nanoparticles for the diagnosis and treatment of cancer. Nanoparticles have unique biological properties given their small size and large surface area-to-volume ratio, which allows them to bind, absorb, and carry compounds such as small molecule drugs, DNA, RNA, proteins, and probes with high efficiency. Their tunable size, shape, and surface characteristics also enable them to have high stability, high carrier capacity, the ability to incorporate both hydrophilic and hydrophobic substances and compatibility with different administration routes, thereby making them highly attractive in many aspects of oncology. The expansion of novel nanoparticles for drug delivery is an exciting and challenging research field, in particular for the delivery of emerging cancer therapies, including small interference RNA (siRNA) and microRNA (miRNAs)-based molecules.

Introduction

Early in the 21st century, control of cancer is considered to be a major public health issue ^[1]. Despite intensive research efforts over past few decades, cancer remains one of the leading causes of death in the world. Many new methods and techniques have been developed in order to improve diagnosis and treatment, often promising in the beginning, but with limited results during the course of their application.

Nanotechnology is a relatively new branch of science that studies tools and devices of size 1 to 100 nm with various functions at the cellular, atomic and molecular levels ^[2]. Tumor blood vessels have several abnormalities compared with physiological vessels, such as a relatively high proportion of proliferating endothelial cells, an increased

tortuosity and an aberrant basement membrane formation. The rapidly expanding tumor vasculature often has a discontinuous endothelium, with gaps between the cells that may be several hundred nanometers large ^[3, 4]. Macromolecular transport pathways across tumor vessels occur via open gaps (interendothelial junctions and transendothelial channels), vesicular vacuolar organelles and fenestrations. However, it remains controversial which pathways are predominantly responsible for tumor hyperpermeability and macromolecular transvascular transport ^[5]. Colloidal nanoparticles incorporating anticancer agents can overcome such resistances to drug action, increasing the selectivity of drugs towards cancer cells and reducing their toxicity towards normal cells.

The accumulation mechanism of intravenously injected nanoparticles in cancer tissues relies on a passive diffusion or convection across the hyperpermeable tumor vasculature. Additional retention of the colloidal particles in the tumor interstitium is due to the compromised clearance via lymphatics. This so-called “enhanced permeability and retention effect” results in an important intratumoral drug accumulation that is even higher than that observed in plasma and other tissues^[6]. Controlled release of the drug content inside the tumoral interstitium may be achieved by controlling the nanoparticulate structure, the polymer used and the way by which the drug is associated with the carrier (adsorption or encapsulation).

Current research has therefore focused on developing more efficient local drug delivery or drug-targeted therapies to overcome these obstacles. New therapies are being designed to deliver chemotherapeutic drugs to the tumor at higher concentrations with minimal damage to normal tissues. Examples include drugs conjugated with monoclonal antibodies that bind to molecular targets that are solely expressed on cancerous cells. This allows the drug to be specifically directed to the tumor while limiting its exposure to normal cells that do not significantly bind with the attached antibody. Nevertheless, studies have shown that only 1 to 10 parts per 100,000 of intravenously administered monoclonal antibodies reach their parenchymal targets in vivo, with similar limitations noted for molecular imaging agents.^[7, 8, 9] A new emerging strategy to overcome these problems is to use nanoparticles for drug delivery, tumor therapy, and tumor follow-up using different imaging modalities.

In recent years, there has been an unprecedented expansion in the field of nanomedicine, with the development of new nanoparticles for the diagnosis and treatment of diseases such as cancer. Nanoparticles have unique biological properties given their small size, allowing them to have a surface area-to-volume ratio that is larger than that of other particles. Their large functional surface area allows them to bind, absorb, and carry other compounds such as small molecule drugs, DNA, RNA, proteins, and probes. Furthermore, their tunable size, shape, and surface characteristics enable them to have high stability, high carrier capacity, the ability to incorporate both hydrophilic and hydrophobic substances, and compatibility with different administration routes, thereby making them highly attractive in many aspects of medicine. Although the design (ie, shape and size) and material from which nanoparticles are made will ultimately determine their physicochemical properties, nanoparticles in general are relatively stable over large ranges of temperature and pH. However, the lack of biodegradation and slow dissolution rates of some nanoparticles raises concern over their safety, especially for long-term administration. Nanoparticles can be categorized into those made from biological-like materials (ie, phospholipids, lipids, dextran, and chitosan), carbon-based materials (ie, carbon nanotubes), and inorganic nanoparticles (ie, those based on metals, metal oxides, and metal sulfides), which also include semiconductor nanoparticles (ie, quantum dots [QDs]). Depending on the composition, their interaction with cells will be quite different.

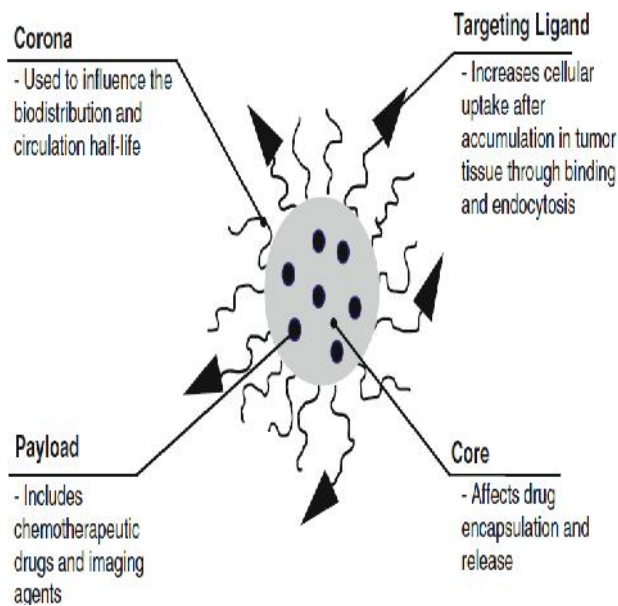


Fig. 1 Schematic of physicochemical structure of nanoparticle platforms for drug delivery, including core, corona, payload, and targeting ligand

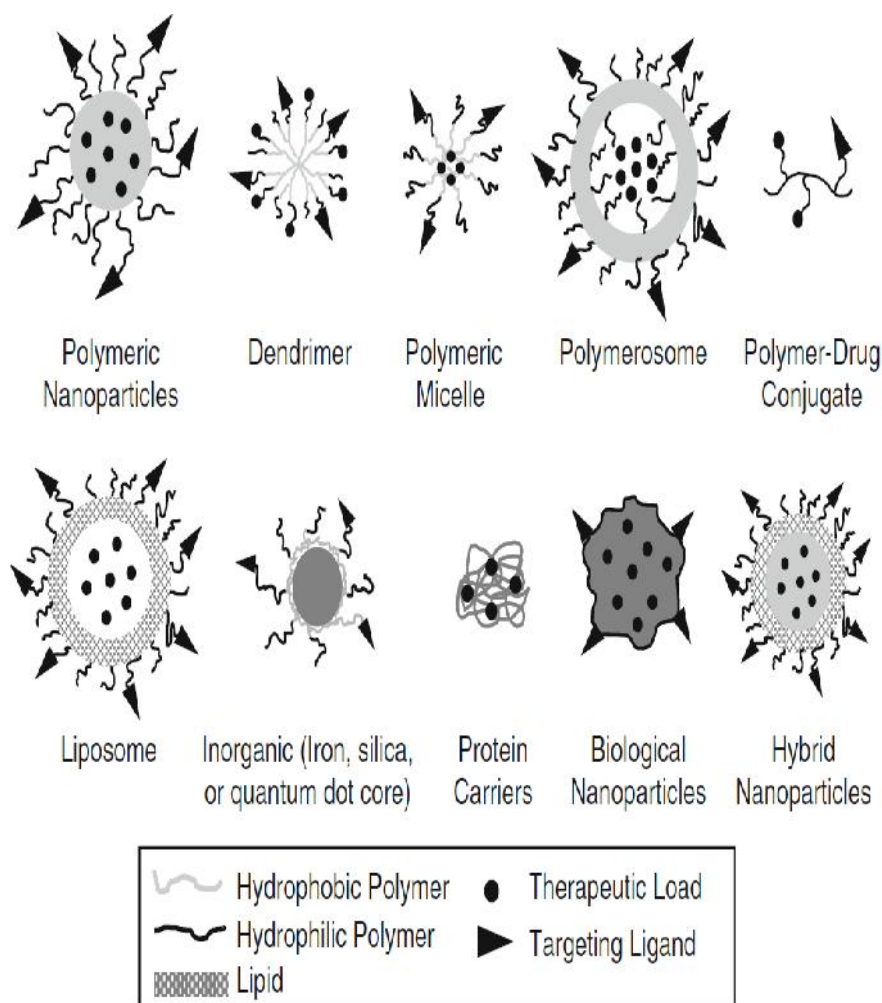


Fig. 2 Nanoparticle platforms for drug delivery. Nanoparticle platforms are characterized by their physicochemical structures, including polymer–drug conjugates, lipid-based nanoparticles, polymeric nanoparticles, protein-based nanoparticles, biological nanoparticles, and hybrid nanoparticles.

Nanoparticles as Carriers for Drug Delivery

Drug delivery is one of the major areas in which nanotechnology is helping revolutionize the treatment of cancer. Nanoscale complexes currently being developed consist of 2 main components: the nanoparticle itself, which is used as the carrier agent, and the chemotherapeutic drug.^[10] The drug can either be adsorbed, dissolved, or dispersed throughout the nanoparticle complex or, alternatively, it can be covalently attached to the surface. In addition to engineering nanoparticles for drug delivery, chemotherapeutic drugs themselves can also be formulated at a nanoscale level. For nanoparticle–drug complexes to be effective in delivering their payloads directly to cancer cells in living subjects, they must fulfill certain criteria:-

- ✓ The nanoparticle must be able to bind or contain the desired drug(s).
- ✓ The nanoparticle–drug complex must remain stable in the serum to allow systemic delivery of the drug.
- ✓ The nanoparticle–drug complex has to be delivered to tumor cells (either by receptor-mediated interactions or via the EPR effect), thereby reducing any unwanted complications from nontargeted delivery.
- ✓ The nanoparticle must be able to release the drug once at the site of the tumor.
- ✓ The residual nanoparticle carrier should ideally be made of a biological or biologically inert material with a limited lifespan to allow safe degradation.

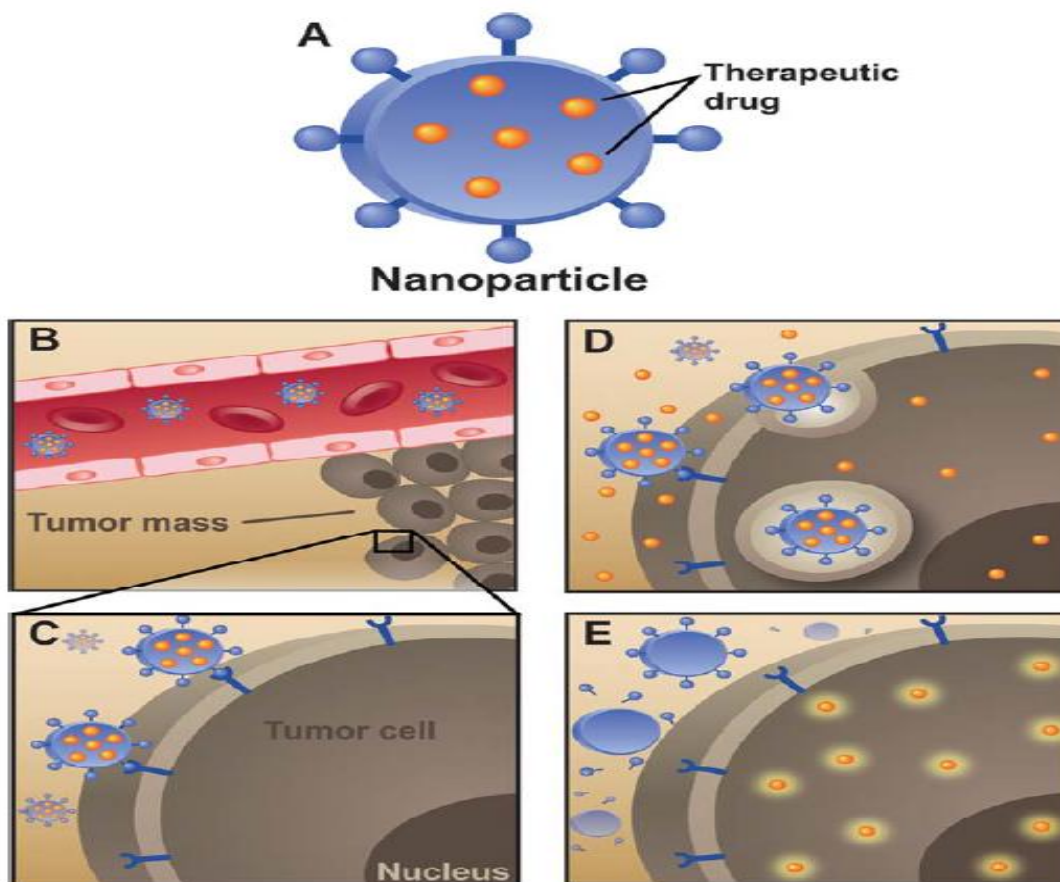


Fig. 3 The Criteria Nanoparticles Need to Fulfill to Be Effective Carriers for Chemotherapeutic Drugs. (A) The nanoparticle carrier must bind or contain the desired chemotherapeutic drug(s). (B) The nanoparticle-drug complex must remain stable in the serum to allow for the systemic delivery of the drug. (C) The nanoparticle-drug complex must be delivered only to tumor cells.

(D) The nanoparticle must be able to release the drug once at the site of the tumor. (E) After drug delivery, the residual nanoparticle carrier must be safely degraded.

The Nanoparticle-Drug Complex

Liposomes

Liposomes and particularly nanoliposomes are one of the most used delivery systems for small molecules, peptides, small and long nucleic acids, and proteins^[11]. Liposomes were the first nanoparticle platform applied in medicine since Bangham described them in 1961^[12, 13]. Nanoliposomes are nanometric (30–100 nm) versions of liposomes formed by exoptaneous self-organization of phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol and phosphatidylserine, and other molecules such as cholesterol^[14, 15, 16]. Importantly, many of the lipids used for liposome preparation are major components of naturally occurring bilayers^[17].

More recently, maturation in liposome synthesis and drug-encapsulation processes have yielded precise control over combinatorial drug dosing in liposomes. By adjusting the lipid composition, drug concentration during lipid film hydration, liposome incubation process and incubation time, Mayer *et al.* Were able to load several combinations of drugs into liposomes at comparable and adjustable molar ratios^[18]. *In vivo* pharmacological studies with these liposomes revealed that the initial loading molar ratios of different drugs were well maintained in the circulation for up to 24 h. This work makes a significant stride in bridging the gap between *in vitro* design and characterization and *in vivo* oncological evaluations. It has been well documented in *in vitro* studies that the molar ratio governs whether two drugs can act synergistically, additively or antagonistically^[19, 20, 21, 22]. For instance, the combination of camptothecin and doxorubicin shows synergistic activity against glioma cells at a molar ratio of 1.5:1 and strong antagonism at 5:1^[23].

However, in clinical studies drug administration has been an afterthought and different drugs are administered based on their maximal tolerated dose. By overcoming the dissimilar pharmacokinetics of different drug molecules, ratiometric liposomal formulations enable simultaneous delivery of multiple drugs to the target site at a predetermined and optimal molar ratio. This technology has yielded several products that are currently in clinical trials. For example, CPX-351 is a 5:1 cytarabine and daunorubicin dual drug-loaded liposome that is currently under Phase II clinical trial for the treatment of acute myeloid leukemia [24]. In murine models bearing HL-60B human leukemia cells, administration of CPX-351 extended the median survival time to 43 days from the 30 days of saline-treated mice. In comparison, ratio-matched free-drug cocktail treatment showed no increase in median survival time compared with saline even at 1.5-fold the dosage of CPX-351 [25]. Moreover, CPX-1, a 1:1 irinotecan and floxouridine liposome currently under Phase II trial for colorectal cancer treatment, also exhibited superior anticancer activity in various human tumor xenograft murine models compared with liposomal irinotecan or liposomal floxouridine alone and free-drug cocktail treatment [26]. It is also worth noting that liposomal co-delivery of irinotecan and floxuridine at an antagonistic ratio showed a poorer response compared with liposomal irinotecan, suggesting that the drug-ratio effect commonly observed *in vitro* can be faithfully translated to *in vivo* by liposomal co-encapsulation of multiple drugs. These liposomal platforms could bring a

Currently, around fifteen liposomal-drug formulations for different conditions are in clinical use [27]. For cancer treatment, some examples include, DaunoXome liposomal daunorubicin) for blood tumors, Doxil and Lipod-dox (PEGylated liposomal doxorubicin) for ovarian and breast cancers, and for Kaposi's sarcoma patients [28]. Nab-paclitaxel (Abraxane) represents one of the new strategies to overcome the solvent-related problems of paclitaxel, and was recently approved by the US Food and Drug Administration (FDA) for pretreated metastatic breast cancer patients [29]. Additionally, several liposomal formulations are in different clinical trial phases. For, example, nanoliposomal CPT-11, a Phase I study, is used for patients with recurrent high-grade gliomas [30]. CPT-11 is a multi-component liposomal formulation containing a camptothecin derivate and a topoisomerase-I inhibitor [31]. Other liposomal drug formulations include, SPI-077 (liposomal cisplatin for solid tumors), CPX-351 (cytarabine: daunorubicin for acute myeloid leukemia), Lipoplatin (cisplatin for non-small cell lung cancer), ThermoDox (a thermosensitive doxorubicin for hepatocellular carcinoma, and other advanced cancers), and Stimulax (an anti-MUC1 cancer vaccine for non-small cell lung cancer). In addition, Yakult Honsha Co., Ltd. developed IHL-305, a PEGylated liposome containing irinotecan [32]. IHL-305 is currently in a phase I study for advanced solid tumors [33].

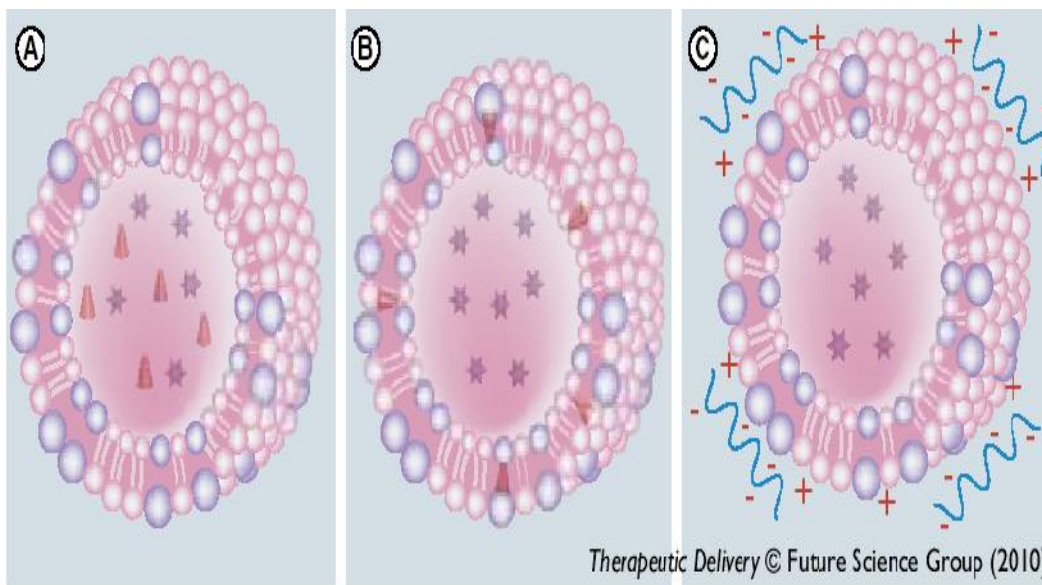


Fig. 4. Liposomal platforms for co-delivery of multiple drugs. (A) Co-encapsulation of multiple hydrophilic drugs (cones and stars); **(B)** co-encapsulation of lipophilic (cones) and hydrophilic drugs (stars) and **(C)** co-delivery of hydrophilic drugs (stars) and oligonucleotide drugs such as siRNA (curved lines).

Formulation Drugs	Drugs	Indication	Status	Refernces
CPX-351	5:1 cytarabine and daunorubicin	Acute myeloid leukemia	Phase II	34
CPX-1	1:1 irinotecan and floxuridine	Colorectal cancer	Phase II	35, 36
CPX-571	7:1 irinotecan and cisplatin	Small-cell lung cancer	<i>In vivo</i>	37
Liposomes co-encapsulating 6-mercaptopurine and daunorubicin	6-mercaptopurine and daunorubicin	Acute lymphocytic leukemia	<i>In vitro</i>	38
Liposome co-encapsulating quercetin and vincristine	1:2 quercetin and vincristine	Breast cancers	<i>In vitro</i>	39
Cationic liposome co-encapsulating siRNA and doxorubicin	Doxorubicin, MRP1-targeted siRNA and BCL2-targeted siRNA	Lung cancer	<i>In vitro</i>	40
Transferrin-conjugated liposomes co-encapsulating doxorubicin and verapamil	Doxorubicin and verapamil	Leukemia	<i>In vitro</i>	41

Polymeric nanoparticles

Polymeric nanoparticles are colloidal solid particles prepared from biodegradable polymers such as chitosan and collagen or non-biodegradable polymers such as poly(lactic acid) (PLA) and poly(lactic co-glycolic acid) (PLGA) [42,43,44,45,46]. Their small size (50–300 nm) allows these particles to penetrate capillaries and to be taken up by the cells, increasing the accumulation of the drug at the target site of action [47]. The majority of these compounds are formulated through a spontaneous self-assembly process using block polymers of two or more polymeric chains with different hydrophilicity [48]. They are considered promising nanocarriers for drug delivery because they can improve the specificity to the target site of action by changing their physicochemical properties and pharmacokinetics [49, 50]. The stability of PLGA nanoparticles can be further improved by coating them with PEG [51]. For example, Danhier et al. used paclitaxel-loaded PEG-PLGA-based nanoparticles grafted with RGD peptide, and found that the target nanoparticles reduced tumor growth more efficiently, and prolonged survival times of mice, compared with non-targeted nanoparticles [52]. A different very promising polymeric nanoparticle is the chitosan based-nanoparticles [53, 54]. Chitosan is a natural polymer obtained by the partial N-deacetylation of chitin, the second most abundant

polysaccharide in Nature [55, 56]. Doxorubicin (DOX)-loaded chitosan nanoparticles, and DOX-loaded anti-human growth factor receptor 2 (Her2)-surface modified chitosan nanoparticles have been proposed [57, 58]. A modified PLGA nanoparticle containing chitosan through physical adsorption and chemical binding methods has also been described [59]. However, more in vivo studies are needed to demonstrate the efficacy and safety of PLGA and chitosan nanoparticles as drug carriers.

Many approaches have been taken to co-encapsulate multiple therapeutic agents into a single polymeric nanoparticle. Presently, these approaches can be divided into three major categories, as follows:

- ✓ Directly encapsulating multiple drugs into the hydrophobic polymeric core;
- ✓ Incorporating an additional media compartment to the nanoparticle, usually on the particle surface, to create a separate partition for drug loading;
- ✓ Covalently conjugating multiple drugs to the polymer backbone before nanoparticle synthesis.

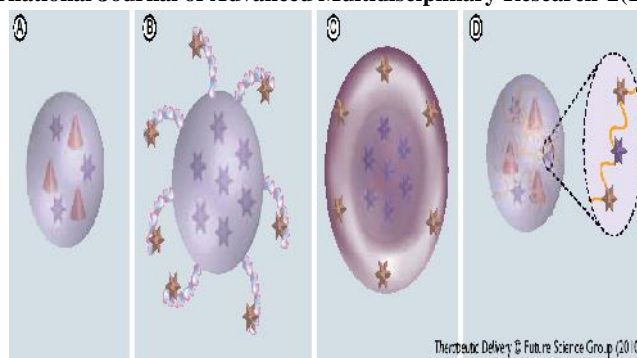


Fig. 5. Polymeric nanoparticle platforms for co-delivery of multiple drugs. (A) Bare polymeric nanoparticle for co-encapsulation of multiple hydrophobic drugs (cones and stars); (B) oligonucleotides modified polymeric nanoparticle with hydrophobic drugs (interior stars) entrapped inside the particle and hydrophilic drugs intercalated in the oligonucleotides (exterior stars); (C) lipidcoated polymeric nanoparticle with drugs entrapped in the polymeric core (interior stars) and lipid envelope (exterior stars) respectively; and (D) polymeric nanoparticle with multiple drugs covalently conjugated to the polymer chains (cones and stars).

Table 2. Polymeric nanoparticles and polymer–drug conjugates for combination cancer therapy.

Formulation Drugs	Drugs	Indication	Status	Refernces
HPMA–Gem–Dox	Gemcitabine and doxorubicin	Prostate cancer and various cancer types	<i>In vivo</i>	60
Poly(ethylene glycol)–poly(aspartate hydrazide) block copolymers–Dox–WOR	Doxorubicin and phosphatidylinositol-3 kinase inhibitor (Wor)	Breast cancer and various cancer types	<i>In vitro</i>	61
Combretastatin–doxorubicin nanocell	Combretastatin and doxorubicin	Lung carcinoma, melanoma and various cancer types	<i>In vivo</i>	62
Cationic core-shell nanoparticles.	Paclitaxel and Bcl-2-targeted siRNA	Breast cancer	<i>In vitro</i>	63
PDMAEMA–PCL–PDMAEMA-based cationic micelles	Paclitaxel and VEGF siRNA	Prostate cancer and various cancer types	<i>In vitro</i>	64
Nanoparticle–aptamer bioconjugates	Doxorubicin and docetaxel	Prostate cancer and various cancer types	<i>In vitro</i>	65
Poly(lactic-co-glycolic acid) nanoparticle co-encapsulating vincristine and verapamil	Vincristine and verapamil	Breast cancer	<i>In vitro</i>	66
Polyalkylcyanoacrylate nanoparticles co-encapsulating doxorubicin and cyclosporin A	Doxorubicin and cyclosporin A	Various cancer types	<i>In vitro</i>	67

Dendrimers are a novel class of nanoparticles that are emerging as a drug-delivery vehicle for cancer therapeutics. They are highly branched globular macromolecules that are synthesized in a stepwise and iterative fashion. The structure of dendrimers can be defined by an initiator core, layers of branched repeating units and functional end groups on the outermost layer. The unique properties of dendrimers make them a desirable platform for concurrent delivery of water soluble and insoluble drugs. Dendrimers offer enormous capacity for solubilization of hydrophobic compounds, and can be modified with guest molecules [68].

Dendrimers have shown enormous potential as anticancer drug delivery systems [69]. For example, Barker and coworkers produced dendrimers conjugated with fluorescein (FITC) and folic acid (FA) for imaging and therapeutic purposes [70]. In this study, dendrimers were linked with complementary DNA oligonucleotides to produce clustered molecules that target cancer cells overexpressing high-affinity folate receptors [71]. Limited number of preclinical or clinical studies of dendrimers as drug carriers is currently available. Thus, it is not possible to make any conclusions about the safety and/or efficacy of dendrimers for human use [72].

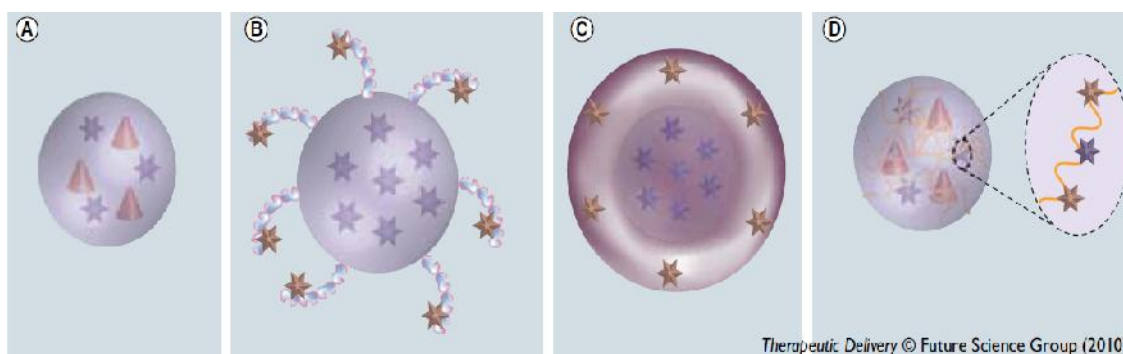


Fig. 6. Polymeric nanoparticle platforms for co-delivery of multiple drugs. (A) Bare polymeric nanoparticle for encapsulation of multiple hydrophobic drugs (cones and stars); (B) oligonucleotides modified polymeric nanoparticle with hydrophobic drugs (interior stars) entrapped inside the particle and hydrophilic drugs intercalated in the oligonucleotides (exterior stars); (C) lipidcoated polymeric nanoparticle with drugs entrapped in the polymeric core (interior stars) and lipid envelope (exterior stars) respectively; and (D) polymeric nanoparticle with multiple drugs covalently conjugated to the polymer chains (cones and stars).

Table 3. Dendrimers and other nanoparticles for combination cancer therapy.

Formulation	Drugs	Indication	Status	References
Generation-3 poly(l-lysine) octa(3-aminopropyl)silsesquioxane dendrimer	Doxorubicin and siRNA	Glioblastoma	<i>In vitro</i>	73
Generation-5 poly(propyleneimine) dendrimer with ethylenediamine core	Methotrexate and all- <i>trans</i> retinoic acid	Leukemia	<i>In vitro</i>	74
Generation-4 polyamidoamine dendrimers	Methotrexate and all- <i>trans</i> retinoic acid	Leukemia	<i>In vitro</i>	75
Oil nanoemulsion coencapsulating paclitaxel and curcumin	Paclitaxel and curcumin	Ovarian cancer	<i>In vitro</i>	76
Mesoporous silica nanoparticles	Doxorubicin and Bcl2-targeted siRNA	Ovarian cancer	<i>In vitro</i>	77

Quantum dots (QD) are small (2–10 nm) colloidal fluorescent semiconductor nanocrystals composed from 10–50 atoms of groups II–IV or III–V of the periodic table [78, 79, 80]. Their structure consists of a metalloid crystalline core and a shell that protect the core and renders the QD available for *in vivo* applications [81]. The size and shape of quantum dots can be controlled precisely, properties that determine their absorption and light emission [82]. One of the most valuable properties of QD is their fluorescence spectrum, which make them optimal fluorophores for biomedical imaging [83, 84,85]. Fluorescent QD can be conjugated with bioactive moieties or specific ligands (e.g., receptor ligands and antibodies) [86]. QD are stable for months without degradation or alteration [87]. QD are mostly used as long-term, high-sensitivity and multicontract imaging agents for detection and diagnosis of cancer *in vivo* [88]. Other examples of QD applications include transistors, solar cells, and quantum computing. Nevertheless, because they are composed of hazardous heavy metals, it is important to be cautious about their toxicity [89].

Fullerenes

Carbon nanotubes and buckyball clusters belong to the fullerenes, a family of structures composed entirely of carbon [90]. Carbon nanotubes are carbon coaxial graphite sheets of less than 100 nm rolled up into cylinders [91]. They can be classified in to two categories based on their structure: single-walled carbon nanotubes (SWNT) (one graphite sheet) or multi-walled carbon nanotubes (MWNT) (several concentric graphite sheets) [92]. They have been applied in biology as biosensors for detecting protein and DNA, diagnostics, and carriers [93]. This type of nanoparticle is insoluble in several solvents, provoking toxicity problems and some health concerns. However, they can be chemically modified to make them soluble in water, and functionalized so that they can be linked to active molecules such as nucleic acids, proteins, and therapeutic agents [94]. They have unique electronic, structural, and thermal characteristics that made them appropriate vehicles for drug delivery systems [95]. Liu *et al.* used single-walled carbon nanotubes (SWNT) chemically functionalized with PEG-paclitaxel (SWNT-PEG-PTX) in a xenograft breast cancer mouse model [96]. They observed higher tumor uptake of PTX and higher ratios of tumor to normal-organ PTX uptake for SWNT-PEG-PTX compared to taxol and PEG-PTX [97]. They also showed effective *in vivo* delivery of SWNT-PEG-PTX with higher tumor suppression efficacy and minimum side effects than taxol [98]. Due to their physicochemical properties, carbon nanotubes have additional applications in the computer, aerospace, electronics, and other industries [99,100]. Buckyball fullerenes have been tested *in vitro* as carriers for conventional anticancer agents (i.e. fullerene-paclitaxel conjugates) [101] and nucleic acids [102].

However there is striking evidence that fullerenes can cause oxidative damage to cellular membranes, and thus, toxicity [103,104]. The *in vivo* efficacy and safety of fullerenes require further studies.

Metal-Based Nanoparticles

Metal-based nanoparticles of different shapes, sizes (between 10 to 100 nm) have also been investigated as diagnostic and drug delivery systems. Most common metallic nanoparticles include gold, nickel, silver, iron oxide, zinc oxide, gadolinium, and titanium dioxide particles [105]. The large surface area of metallic nanoparticles enable the incorporation of high drug doses [106, 107, 108]. Qian *et al.* demonstrated the utility of gold-based nanoparticles in human cancer cells and in xenograft tumor mouse models. They reported the use of biocompatible and nontoxic PEG-gold nanoparticles for *in vivo* tumor targeting which were spectroscopically detected by surface-enhanced Raman scattering (SERS) [109]. Even though metallic nanoparticles are biocompatible and inert vehicles, a significant fraction of metal particles can be retained and accumulated in the body after drug administration, possibly causing toxicity [110]. Therefore, the use of metallic nanoparticles for drug delivery is a concern.

Conclusions

This review has demonstrated many different applications for which nanoparticles are being used in the fight against cancer. Although some nanoparticles have not been successful when being clinically translated, several new and promising nanoparticles are currently in development and show great promise, thereby providing hope for new treatment options in the near future. However, all newly developed nanoparticles, whether they are used as carriers for drugs, therapeutic agents, or imaging agents, will need to be thoroughly characterized physiochemically, pharmacologically, and immunologically before they can be approved for use in humans. The distribution of nanoparticle size, uniformity, and consistency between batches also needs to be tightly regulated. In addition, their high surface area-to-volume ratio, surface reactivity and charge will dramatically alter their chemical and physical properties, resulting in them possessing unexpected toxicities and biological interactions. Although several studies have investigated the toxicity associated with specific nanoparticles, the results are highly variable, [149, 150, 151] which can be attributed, in part, to the different shapes, sizes, and chemical preparations of nanoparticles as well as the type of human cell line studied. Hence, short-term and long-term toxicity studies will also need to be undertaken in both cell culture and living animal models before they can gain FDA approval for clinical trials. Nevertheless, with our continued drive to cure cancer and our determination to understand the molecular mechanisms that drive this disease to allow its early detection, nanotechnology provides hope in developing new ways to diagnose, treat, and follow patients with cancer in the 21st century.

TRADE NAME	DESCRIPTION OF NANOPARTICLE	CANCER TARGETED BY THE NANOPARTICLE	PHASE OF DEVELOPMENT	References
Abraxane	Albumin-bound paclitaxel	Metastatic breast cancer	Approved	111
Doxil	Liposomal doxorubicin	HIV-related Kaposi sarcoma, metastatic breast and ovarian cancer	Approved	112
DaunoXome	Liposomal daunorubicin	HIV-related Kaposi sarcoma	Approved	113, 114
Myocet	Liposomal doxorubicin	EGFR2-positive metastatic breast cancer	Approved	115
DepoCyt	Liposomal cytarabine	Intrathecal lymphomatous meningitis	Approved	116
Marqibo	Liposomal vincristine sulphate	Acute lymphoblastic leukemia	Approved	117, 118
Oncaspar	Polymeric PEG-L-asparaginase	Acute lymphoblastic leukemia	Approved	119
Zinostatin stimalamer	Copolymer styrene maleic acid-conjugated neocarzinostatin	Unresectable hepatocellular carcinoma	Approved	120, 121
Resovist	Carboxydextran-coated SPIO	MRI contrast agent for imaging hepatocellular carcinoma	Approved	122
Genexol-PM	Polymeric methoxy-PEG-poly(D,L-lactide) paclitaxel	Metastatic breast cancer	Approved	123
NanoTherm	Aminosilane-coated SPIO	Local ablation of glioblastoma multiform	Approved	124, 125
Xyotax	Poly-L-glutamic acid (poliglumex) conjugate with paclitaxel	Ovarian cancer and NSCLC	Phase 3	126
NKTR-102	PEG micelle with irinotecan	Breast and colorectal cancer	Phase 3	127
Mepact	Liposomal muramyl tripeptide phosphatidyl ethanolamine	Nonmetastatic resectable osteosarcoma	Phase 3	128
ThermoDox	Liposomal nanoparticle with thermal release of doxorubicin	Hepatocellular carcinoma	Phase 3	129

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CRLX-101	Cyclodextrin-PEG micelle with camptothecin	Lung and ovarian cancer		138-54
NKTR-102	PEG micelle with irinotecan	Ovarian cancer	Phase 2	131
Genexol-PM	Polymeric methoxy-PEG-poly(D,L-lactide) Paclitaxel	Non-small cell lung, pancreatic, bladder and ovarian cancer	Phase 2	132, 133, 134, 135
CRLX-101	Cyclodextrin-PEG micelle with camptothecin	Renal cell carcinoma	Phase 1	136
Docetaxel-PNP	Polymeric nanoparticle formulation of docetaxel	Advances solid malignancies	Phase 1	137
NanoTherm	Aminosilane-coated SPIO	Pancreatic and prostate cancer	Phase 1	138,139
Cyclosert (CALAA-01)	siRNA targeting M2 subunit of ribonucleotide reductase in a cyclodextrin-PEG nanoparticle	Solid tumors	Phase 1	140, 141
SGT53-01	Transferrin-targeted liposome loaded with the p53 gene	Solid tumors	Phase 1	142, 143
MCC-465	Human antibody fragment-targeted liposomal doxorubicin	Metastatic stomach cancer	Phase 1	144
Aurimmune	Gold nanoparticle loaded with tumor necrosis factor	Solid tumors	Phase 1	145
AuroShell	Near-infrared irradiation with gold nanoshells (localized thermal ablation)	Head and neck cancers	Phase 0 (pilot study)	146,147
C-dots	PEG-coated SiO ₂	Melanoma	IND approved	148

Note- HIV indicates human immunodeficiency virus; EGFR2, epidermal growth factor receptor 2; PEG, polyethylene glycol; SPIO, superparamagnetic iron oxide; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PNP, polymeric nanoparticle; siRNA, small interfering RNA; IND, Investigational New Drug.

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