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Active-targeted Nanotherapy as Smart Cancer Treatment

Katayoun Derakhshandeh and Abbas Hemmati Azandaryani

Additional information is available at the end of the chapter

Abstract

Drug delivery systems (DDS) can be designed to improve the pharmacological and therapeutic properties of drugs. Targeted drug delivery, sometimes called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in infective organs or cells, relative to others. Cancer is one of the major causes of mortality worldwide and innovative methods for cancer therapy are urgently required. Nanoparticles (NPs), by using active targeting strategy, can enhance the intracellular concentration of drugs in cancerous cells while avoiding toxicity in normal cells. Nanoparticles with bioscience are being actively developed for in vivo tumor imaging, bimolecular profiling of cancer biomarkers, and targeted drug delivery. The advantages of the targeted release system are the reduction in the frequency of dosages taken by the patient, having a uniform effect of the drug, reduction of drug side effects, and reduced fluctuation in circulating drug levels. In this chapter, we focus on targeted drug delivery systems integrated from nanobiotechnology.

Keywords: Targeted drug delivery, Nanobiotechnology, Nanocarrier, Active targeting, Cancer therapy

1. Introduction

Currently, maximizing the safety and efficacy of drug therapy is the main goal of pharmaceutical scientists and physicians. To this end, drug targeting is the best approach. This subject is critical for some diseases such as cancer treatments, which involve a balancing act between the destruction of cancerous and healthy tissues, including damage to the immune system and highly replicating cells.

Newly developed nanotechnological methods as active targeting carrier in the medical treatment have increased attention [1–4].

Active targeting involves attaching different ligands such as antibodies, biological proteins, peptides, sugars, and vitamins or a specific ligand to the drug or drug delivery system, which meet and form a complex with cell receptors and cause the drug to accumulate in the target cells.

Specifically, "targeting" can be categorized into three levels:

- First-order targeting: When the delivery is to a specific organ, for example, drugs may be targeted to the liver because of its leaky or fenestrated vasculature or loose junctions; the drug is not released in other tissues because of their nonleaky vasculature.

- Second-order targeting or cellular targeting: When a drug delivery system releases the drug to a particular cell within an organ or a tissue.

- Third-order or subcellular targeting: When the delivery is to distinct cell types with biological barrier transport, for example, epithelial cells or cells of the lung-associated lymphatic tissue. A good example is the delivery of genes. The delivery system carries the gene, enters specific cells and releases the gene intracellularly. This is the third order and the most sophisticated type of targeting.

Traditional targeting activities can also be grouped into passive and active targeting [5]. Drug delivery systems that have been developed to be used as targeting carriers include micelles, nanoparticles, polymeric conjugates, and liposomes. NPs protect the drug from premature degradation, prevent drugs from interacting with the biological environment, and enhance the absorption of drugs into a selected tissue. Nanoparticle technologies may improve the therapeutic index of drugs by enhancing their efficacy and/or increasing their tolerability in the body. Nanoparticles could also improve the bioavailability of water-insoluble drugs, carry large payloads, as well as enable the development of novel classes of bioactive macromolecules (e.g., DNA and siRNA) [4–8]. Thus far, over two dozen nanotechnology products have been approved by the US Food and Drug Administration (FDA) for clinical use, and many are under clinical and preclinical development [9].

In our studies, we focused on targeted drug delivery systems integrated from nanobiotechnology. Nanoparticles, by using active targeting strategies such as folate, monoclonal antibodies (mAbs) and aptamer ligands can enhance the intracellular concentration of drugs in cancerous cells while avoiding toxicity in normal cells. Nanoparticles with bioscience are being actively developed for in vivo tumor imaging, biomolecular profiling of cancer biomarkers, and targeted drug delivery. Nanoparticles remain in the blood circulation for a longer time and can passively accumulate at target sites after the systemic administration because of leaky tumor vasculature and poorly developed lymphatic drainage (the enhanced permeation and retention (EPR) effect).

In this chapter, we focus on explaining anticancer agents loaded in different nanoparticles and how they could be targeted to different tissues especially to solid tumors by attaching specific ligands [6–8].

2. Nano drug delivery

Drug delivery systems such as lipid-, polymer-, liposome-, dendrimeric-, or biomacromole-cule-based nanoparticles can be designed to improve the pharmacological and therapeutic properties of drugs administered parenterally or by other routes of administration. There are considerable interests in exploiting the advantages of DDS for in vivo delivery of new drugs and for their use in targeted therapeutics. Drug targeting can improve the efficacy of therapy and reduce side effects associated with drugs and therapeutic agents [10–12]. Various carriers can be used to deliver a drug in a stable and protective form for conventional or targeted shape (Figure 1); however, it is nanotechnology that offers the most unique and intriguing approach in the field of nanomedicine.
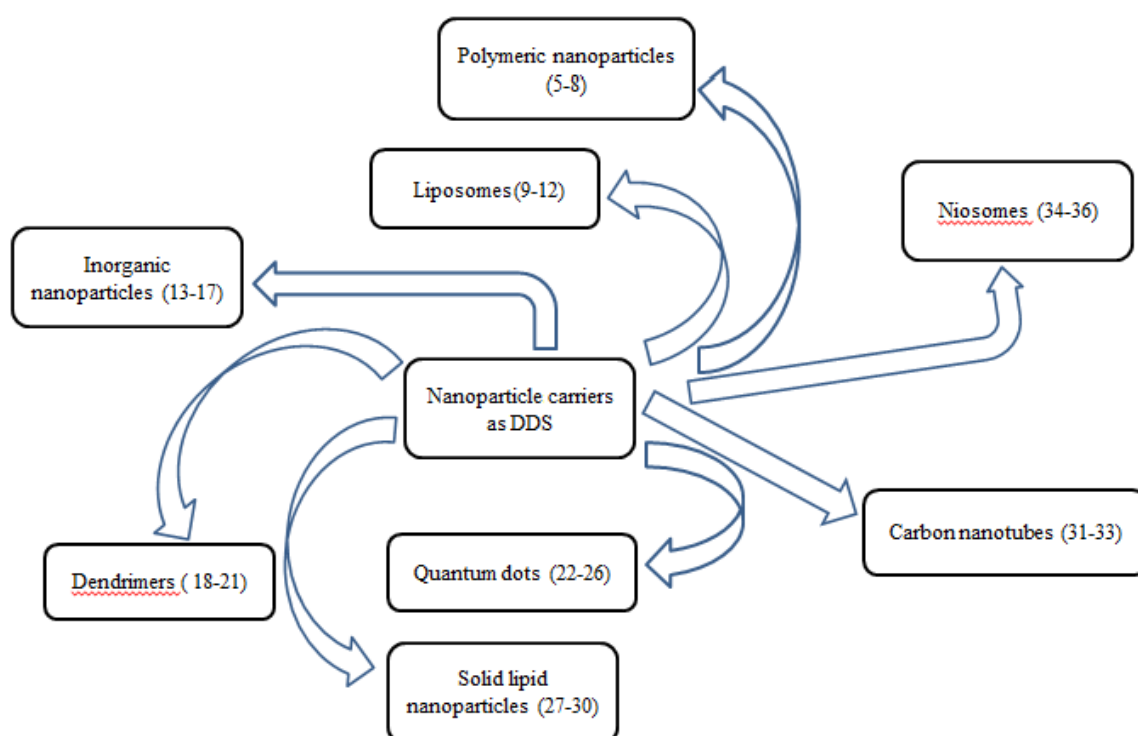
Figure 1. The different types of nanocarriers

Nanobiotechnology, defined as biomedical applications of nano-sized biomacromolecular systems or nano-sized materials with biomaterials, is a rapidly developing area within nanoscience. We define nanomedicines as delivery systems in the nanometer size range (preferably 1–100 nm) containing encapsulated, dispersed, adsorbed, or conjugated drugs and imaging agents. They can also facilitate the important advances in detection, diagnosis, and treatment of diseases, human cancers, vaccine delivery, etc., and have led to a new discipline of nanobiotechnology [13–16]. Nanoparticles are being actively developed for in vivo tumor imaging, biomolecular profiling of cancer biomarkers, and targeted drug delivery. These nanotechnology-based techniques can be applied widely in the management of different malignant diseases [17, 18].

Nanocarriers have numerous points of interest contrasted with free drugs. They protect the labile drugs from degradation in biological environments, increase uptake of the drugs into a chosen tissue such as solid tumors, facilitate modification of the pharmacokinetics and body distribution, and enhance intracellular infiltration.

Nanotechnology applications in medicine, termed as nanomedicine, have introduced a number of nanoparticles of variable chemistry and architecture in the targeted drug delivery system. Nanotechnology involves engineering multifunctional devices with dimensions on the nanoscale with similar dimensions of large biological molecules in the body, viruses, and other synthesized macromolecules. These devices can carry one or two detection signals and/ or therapeutic agents for drug delivery targeting [19, 20].

Nanotechnology is well introduced in drug delivery technology for several advantages such as first passive drug delivery, increasing of drug solubility, increasing of drug half-life in the body, modification of the drug distribution pattern, and improvement of pharmacokinetics, which will result in improved efficacy. With these advantages, the future of drug delivery cannot be predicted and some problems exist such as site cytotoxicity [21–26].

Currently, the fundamental issue with cancer treatment is that they include an exercise in careful control between the destruction of malignant tissue and healthy tissues, such as damage to the immune system and profoundly replicating cells (gastrointestinal epithelia and hair follicles).

It is important to detect the revelation of malignant cells sufficiently early and in a stage that is sensible for convenient treatment. Recently, created nanotechnology drug delivery systems are promising approaches for oncologists.

The use of nanoparticles in medical treatment has increased in recent years. For example, micro- and nanoparticles, such as polymeric nanoparticles (synthetic or natural polymers), polymeric micelles, dendrimer, and solid lipid nanoparticles (SLN) have long been used as drug delivery systems to encapsulate drugs and protect them from extracellular enzymatic degradation, providing vehicles for delivering drugs to the target area, and are now being investigated as powerful platforms for vaccine delivery [27–33]. Figure 2 represents some kind of nanocarrier in drug delivery.

Being inspired by physiologically existing nanomachines, nanoparticles are designed to safely reach their target and specifically release their therapeutic agent at the site of the disease, thus increasing the drug's tissue bioavailability. Nanoparticles used in this manner for enhanced permeation and retention effect of cancerous cells that are caused by leaky angiogenetic vessels and poor lymphatic drainage has been, in turn, used to explain why macromolecules and nanoparticles are found at higher ratios in tumors compared with normal tissues [29]. Carriers are associated with the drug in a covalent or noncovalent attached mode of targeting materials, and they have been used for the delivery of drug exactly on the target tissue.

In this study, we focus on important nanoparticles such as polymeric nanoparticles and liposomes and their recent results on targeting drug delivery systems for the purpose of biomaterial.
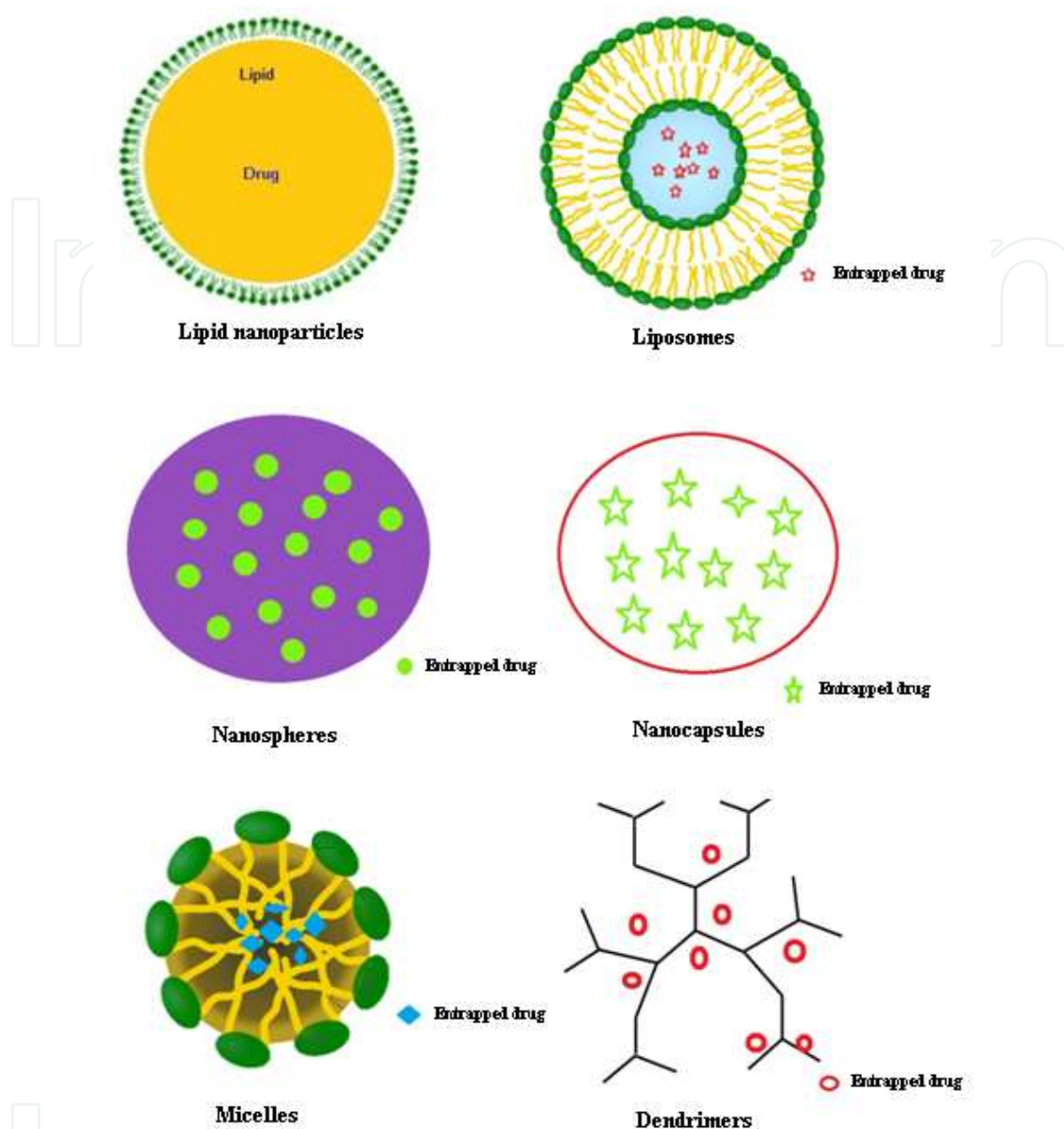
Figure 2. Basic structure of nanoparticles

3. Bioconjugation of nanocarriers for target therapy

The conjugation of bioagents to nanocarriers is one of the most important functions of the targeted drug delivery system. For this purpose, several methods and works have been performed until now [34–36].

One of the usual methods for attaching biomolecular ligands to nanoparticle's surface is diimide-activated amidation by direct coupling of carboxylic acid to legends using N-ethyl-N-(3-dimethyl aminopropyl) carbodiimide hydrochloride (EDAC) or N,N-dicyclohexyl

carbodiimide (DCC) as a coupling agent. The schematic perspective of the connection of proteins to carbon nanotubes (CNTs) by means of diimide-activated amidation is presented in Figure 3. Functionalization of carbon nanotubes was likewise completed using 1-pyrene-butanoic acid, succinimidyl ester for the immobilization of biomolecules, anti-fullerene IgG monoclonal antibody bound to single-wall carbon nanotubes. Proteins and DNA have also been used to modify multiwall carbon nanotubes (MWCNT) [36].
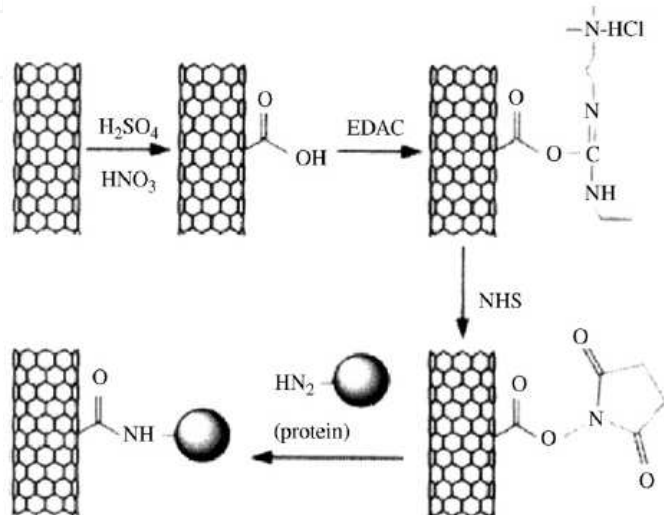
Figure 3. Schematic view of the attachment of proteins to CNTs via diimide activated amidation [51]

Recently, the ubiquitous alkyne–azide Huisgen "click" reaction has been used to attach proteins to NPs (Figure 4). A variety of proteins have been attached in functional form using this method, including lipase, horseradish peroxidase, and luciferase [34]. Hapuarachchige et al. [37] investigated the click reaction for specific internalization of nanotherapeutics. In this study, the pretargeting component, anti-HER2 humanized monoclonal antibody, functionalized with azide groups, labels cancer cells. This group demonstrated high efficacy for targeted nanotherapeutics using the click reaction.
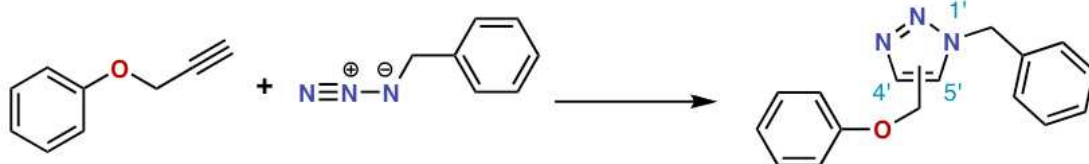
Figure 4. Azide–alkyne Huisgen cycloaddition "click" reaction

The biotin–streptavidin interaction (Figure 5) is widely used for the conjugation of NP systems. The formation of avidin (or streptavidin)–biotin complexes is useful in a wide variety of applications. This specific binding is largely used to immobilize enzymes, antibodies, or DNA. Biotin is a small molecule, which could bind to avidin or streptavidin binding sites with very high affinity ($K_a = 10^{15}$ M^{-1}).

In addition, avidin and streptavidin are tetrameric proteins that have four known binding sites for biotin (Figure 5). Streptavidin with an isoelectric point equivalent to 5 is accordingly ideally utilized over avidin, which has a PI of 10.5, to maintain a strategic distance from nonspecific interactions [35, 38].

(a)   (b)
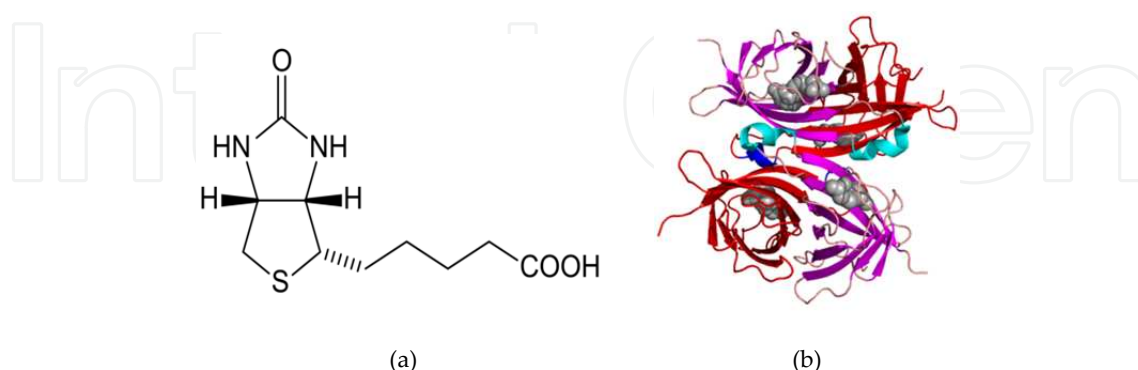
Figure 5. Biotin structure (a) and the simple graph for biotin–avidine binding (b)

4. Active targeting using polymeric nanocarrier

Polymeric nanoparticles with specific recognition ligands bound to the surface have a good potential for site-selective delivery, and offer higher drug carrier capacity than bioconjugates, as well as improved specificity for drug targeting [1, 39–41]. The attached ligands to the surface of nanocarriers can include any molecule that specifically binds to target cells such as peptides, glycoproteins, carbohydrates and polymers, and monoclonal antibodies, which have been the most broadly studied [20, 24].

Kocbek and coworkers developed new active-targeted poly (D,L-lactic-co-glycolic acid) (PLGA) nanoparticles by attaching mAb, which have the ability to target specific antigens on breast epithelial cancer cell lines. Attempts to attach mAb to nanoparticles by covalent bonding were less successful, since the natural action of the bound mAb was inactivated. The specificity of the immunonanoparticles was shown from their selective distribution in a co-culture of MCF-10A neoT and Caco-2 cells, resulting in their final internalization by the former cells [42].

A novel, nonviral, polyethylenimine (PEI)-based, HER2-targeted gene transfer vector has been investigated. The anti-HER2 humanized antibody, trastuzumab (HerceptinR), was used as the targeting moiety to the HER2 overexpressing cancer cells. Subsequently, trastuzumab conjugation of PEI may render PEI a much more selective gene delivery carrier for anticancer gene therapy. The opinion of attaching a targeting ligand, with intrinsic antitumor activity, to a gene transfer vector may be beneficial for further investigations [43].

Recently, poly (butyl cyanoacrylate) (PBCA) NPs coated with polysorbate-80 have been proposed as suitable drug carriers for brain drug delivery. Nerve growth factor (NGF) is important for the survival of peripheral ganglion cells and central cholinergic neurons of the

basal forebrain. In spite of its inability to cross the blood–brain barrier (BBB), the NGF activity on these neuronal populaces and its adequacy in avoiding neurodegeneration recommended its potential utilization in the treatment of neurological pathologies, for example, diabetic neuropathies and Huntington's disease. Systemic administration of NGF loaded in P80-coated PBCA NPs successfully reversed scopolamine-induced amnesia and improved recognition and memory in acute amnesia rat model [44].

Yang and coworkers synthesized doxorubicin magnetic PLGA nanoparticles conjugated with well-tailored antibodies for the detection and therapy of breast cancer. They suggested that magnetic nanocrystals embedded in polymeric nanoparticles did not inhibit the nanoparticle formulation or drug release kinetics. The multimodal nanoparticles demonstrated remarkable cancer cell affinity and ultrasensitivity via magnetic resonance imaging. However, the in vivo effects of the NPs were not evaluated [45].

Due to the overexpression of the folate receptor on tumor surface, the folate has been popularly used as a targeting moiety for various anticancer agents to avoid their nonspecific attacks on normal tissues and also to increase their cellular uptake within target cells [46–48]. Derakh-shandeh et al. prepared the folate-decorated biodegradable PLGA nanoparticles for tumor targeting. In this study, folate-conjugated PLGA was synthesized and then PLGA-Fol nano-particles were prepared by nanoprecipitation method, adopting PLGA as a drug carrier, folic acid (FA) as a targeting ligand, and 9-nitrocampthotecin (9-NC) as an anticancer drug model. The in vitro intracellular uptake of nanoparticles showed that the PLGA-Fol nanoparticles have been more efficiently taken up by MCF-7 cells compared with nonfolate-mediated carriers, and also showed greater cytotoxicity than other treated groups [49].

Active-targeted nanocarriers to the special sites and cellular uptake are especially important to therapeutics that is not taken up easily by cells, and they require facilitation by fusion, endocytosis, or other processes to access their cellular active sites. They can also enhance the penetration and distribution of nanomedicine within the tumor interstitium and resistant cancer cells. Active targeting nanocarriers have various points of interest over targeting ligand–drug conjugates [47].

Recently, Wu et al. [50] investigated polymeric nanoparticles for the treatment of metastases. This group studied the ability of micellar nanocarriers incorporating (1,2-diaminocyclohexane) platinum(II) for liver metastases of bioluminescent murine colon adenocarcinoma C-26 treatment, during overt and preangiogenic metastatic stages and thus obtained a novel approach for early diagnosis and treatment of metastases.

5. Inorganic nanoparticles for targeted drug delivery

Porous inorganic nanoparticles with high specific surface area have recently emerged as attractive material for the development of delivery systems, where various guest molecules could be absorbed into the pores and later released into various solutions [51, 52].

Inorganic nanoparticles, for example, gold and iron oxide, are usually conjugated with the drug, polyethylene glycol (PEG), and the targeting ligands. It gives the idea that the PEG coating and ligand design are common constituents in most types of nanoparticles for anticancer delivery. These carriers have several applications in cancer diagnosis and treatment, and large portions of them have quickly moved into clinical trials. Overall, there is still a space for optimization in the field of nanoparticle pharmacokinetics such as enhanced plasma retention time and tumor bioavailability and understanding the effectiveness of targeting ligands in the cancer treatment. The need to add to a novel and productive legand has never been more noteworthy, and the use of proper conjugation chemistry is essential [20].

Recently, Zhou et al. prepared a surface engineered of NaGd F4:Ce/Tb hybrid nanoparticles with DNA for new type of pH-responsive therapeutic platform to enhance the therapeutic efficiency while minimizing side effects. The introduction of the layer of aptamer molecule on the surface facilitated the cellular uptake of the resulting nanocomposite into specific target cells via receptor-mediated endocytosis. This group proved that the hybrid nanocarrier may serve as a practical and multifunctional probe for cancer therapy [53].

6. Liposomes in targeting drug delivery

Dispersion of neutral phospholipids or amphiphilic lipids (i.e., cholesterol, glycolipids) in the aqueous solution leads to the formation of closed vesicular structures, which morphologically resemble cells. These closed vesicles have been called "Liposomes" [54] (fat bodies) and consist of hydrated bilayers. Liposomes not only have the ability to mimic structures of cell membranes but also have the potential either to encapsulate hydrophilic materials in the inner liposome water phase or to associate the lipophilic materials within the lipid bilayer region. Initial studies on the fate of liposomes and entrapped agents started in 1970 [55].

Liposomes were recommended as drug carriers in cancer chemotherapy by Gregoriadis in 1974 and later the interest in liposomes has increased and is currently being widely concentrated on as drug carriers. Three fundamental requirements need to be met if liposomes are to be fruitful in drug delivery, specifically to cancerous tissues: (i) prolonged blood circulation, (ii) adequate tumor accumulation, and (iii) controlled drug release and uptake by tumor cells with a release profile coordinating the pharmacodynamics of the drug [56–60].

Stealth liposomes are suggested to carry the drug in the aqueous core, and they are usually decorated by recognition molecules, being widely studied and applied [61]. The poor outcome of current therapies continuously stimulates the search for new treatment strategies. This includes the activation of the normal vasculature to form tumor blood vessels and the involvement of immune response elements in tumor development proliferation. The hindrance of these procedures introduces an attractive therapeutic strategy and a new class of anticancer therapeutics such as angiogenesis inhibitors and anti-inflammatory drugs [62].

Tumor-associated inflammation has been perceived as an important tumor growth propagator and, therefore, represents an attractive target for anticancer therapy. Glucocorticoids (GCs), a

potent class of anti-inflammatory drugs, showed antitumor effects at high daily doses. Unfortunately, this dose leads to severe side effects, including morbidity and mortality, attributable to severe immunosuppression. Recently, researchers have improved this unfavorable therapeutic index using long circulating liposomes as the glucocorticoid delivery nanocarrier. This vehicle could strongly inhibit tumor growth, after administration of a single weekly dose [63].

The effectiveness of the liposomal formulation was attributed to modification in drug pharmacokinetics such as increased blood circulation and glucocorticoid accumulation in the tumor, and the so-called enhanced permeability and retention effect.

Inspired by recent findings, in the tumor microenvironment, a main mechanism of the antitumor activity of GC is the inhibition of macrophage activity and downregulation of pro-angiogenic factors, which are produced by functional tumor-associated macrophages. In addition, in vitro information proposed a direct cytotoxic and antiproliferative activity to both endothelial and tumor cells [64].

Kluza et al. developed paramagnetic and fluorescent liposomes, encapsulating prednisolone phosphate, to evaluate its antitumor activity and therapeutic response. In this study, cytotoxicity of the new multifunctional liposomes (120 nm diameter) was tested in B16F10 melanoma subcutaneously (20 mg/kg/week) inoculated in C57BL/6 mice and compared with the free drug formulation. It was significantly found to inhibit tumor growth compared with nontreated mice and similarly to free form [63].

PEGylated liposomal doxorubicin (DOX) is approved for the treatment of refractory ovarian cancer and Kaposi sarcoma in the United States. In this carrier, the efficacy of the drug was preserved and a cardiac toxic effect was significantly decreased [18].

Albumin nanoparticle-bound paclitaxel, is also approved in the United States for the treatment of metastatic breast cancer, has greater efficacy compared with the conventional castor oil-based formulation and has lesser side effects [18].

Liposomes can also be used as a nonviral vector to deliver siRNA to target cells for gene therapy. Mokhtarieh and his coworkers developed a novel method of producing asymmetric liposome particles (ALPs) with highly efficient siRNA encapsulation. In their work, liposomes were prepared by the solvent evaporation and dialysis method, composed of ionizable cationic 1,2- dioleoyl-3- dimethyl ammonium-propane and 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), which entrap siRNA, and the outer one is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine, DOPE, polyethylene glycol- 1,2-distearoyl-sn-glycero-3-phosphatidyl ethanolamine (PEG–PE), and cholesterol. Ninety percent of siRNA was entrapped in negatively charged surface liposomes. The surface-modified ALPs with a polyarginine peptide (R12) induced nonspecific cell penetration, while naked liposome has almost no uptake into cells. The modification of ALP's surface by the antihuman epidermal growth factor receptor antibody (anti-EGFR) induces an EGFR-mediated uptake into the nonsmall cell lung cancer cell lines and did not take up NIH-3T3 cell line without the receptor [65].

The triggered release of pH-sensitive liposomes is probably the most biocompatible method for releasing drugs directly in the cytoplasm of cells. When liposomes are internalized to endosomes, they enter an acidic environment. Reddy and Low prepared the pH-sensitive lipid formulation from DOPE and citraconic anhydride and used them to prepare liposomes. They observed that the resulting liposomes were stable at neutral pH but fusogenic at pH 5 [66]. Figure 6 shows the schematic diagram of the liposome in targeted drug delivery.
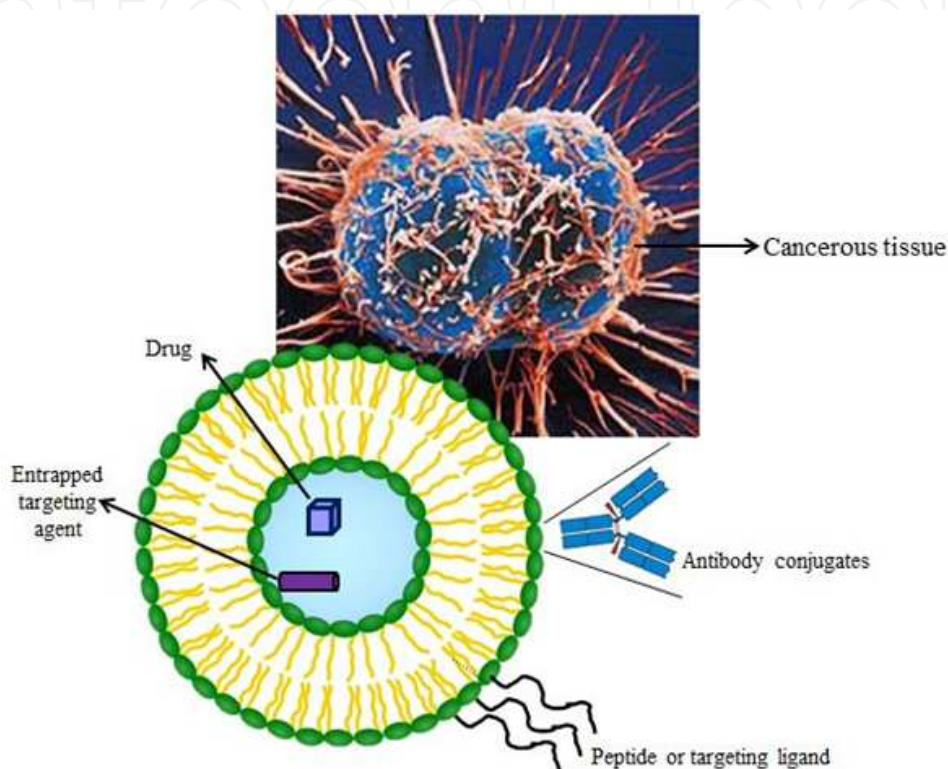
Figure 6. Liposome in target drug delivery

Choi and coworkers synthesized an amphiphilic DNA hybrid duplex by using Watson–Crick base pairing and DNA bioconjugation with cholesterol or tLyp-1 tumor-homing peptide. The resultant amphiphilic DNA hybrid duplexes can self-assemble in an aqueous solution into nanoliposome with the outer ligand of tLyp-1 peptides. This nanocarrier can efficiently entrap doxorubicin and also has the pH-dependent structure, which can release the drug in the acidic environment of cytosol of tumor cells [67]. These results provide an alternative approach to specifically deliver doxorubicin into targeted cells for cancer therapy as well as controlling drug release under acidic conditions such as endosomes or lysosomes.

Chiang et al. investigated the combination of polymer and liposome in carrier preparation. This group prepared pH-responsive polymer–liposome for intracellular drug transfer and targeted cancer therapy. From this work, it was obvious that the combination of carrier should be a promising for targeted drug delivery in the future, exactly when this new carrier combines with biotechnology.

7. Solid lipid nanoparticles as a targeted drug delivery system

In the late 1990s, SLNs were proposed for brain drug targeting application independently by two research groups, although the first proof of lipid particle transport across the BBB had already been provided. SLNs are colloidal carrier systems, which provide controlled–release profiles for many substances [68–72]. Kashanian et al. prepared aqueous dispersions of lipid nanoparticles using a modified, pH-sensitive derivative of phosphatidyl ethanolamine loaded with triamcinolone acetonide as a drug. The SLNs prepared in this study were able to control the release of drug under acidic conditions. This group showed that with increasing pH, the amount of releasing drug is increased due to the burst effect in this condition as well [30].

Studying the pharmacokinetics of two anticancer agents, namely camptothecin and doxorubicin, drug accumulation in the brain was observed after both oral and i.v. administration when loaded into SLN. As previously shown in PACA NPs, better results in brain targeting were achieved when SLN surface characteristics were modified by means of PEG derivatives or PEG-containing surfactants [73].

8. Gold nanoparticles in target drug delivery

Bactericidal efficacy of gold nanoparticles (GNPs) conjugated with ampicillin, streptomycin, and kanamycin was evaluated. Gold nanoparticles were conjugated with the antibiotics and drugs during the synthesis of nanoparticle utilization [74-76], by functionalizing gold particles, where amino acids, glutathione, polyethylene glycol, etc. were used as linkers [77-79]. The conjugated gold nanoparticles showed greater antibacterial effects and lower MIC compared with the free drug in three bacterial strains, Escherichia coli DH5a, Micrococcus luteus, and Staphylococcus aureus. In addition, nanoconjugate could increase their heat stability [80,81].

Bergen and coworkers prepared nanoparticle formulations of GNPs with varying particle size, surface charge, and surface hydrophilicity. In this study, the galactose attached to the surface of NPs by conjugation of PEG-thiol and galactose-PEG-thiol to gold colloids. This platform was applied to screen for NP formulations that demonstrate hepatocyte-targeted delivery in vivo. This group investigated that the presence of galactose ligands was found to significantly affect the targeting efficiency [82].

9. Niosomes

Nonionic surfactant vesicles (niosomes), are biodegradable, relatively nontoxic, more stable, and inexpensive, and therefore could be an alternative to liposomes [83]. Due to the encapsulation of a wide range of toxic drugs such as antiviral, anticancer, and anti-AIDS drugs in niosomes, this carrier is so valuable in the delivery of proteins and biological medications. Niosome is a promising carrier system in comparison with ionic drug carriers, which are relatively toxic and moderately harmful [84].

Bragagni and coworkers developed a stable and safe niosomal formulation to effectively encapsulate DOX. The developed formulation, in virtue of its relatively high efficiency of drug encapsulation and good stability, could find useful applications as an effective tool for achieving DOX brain delivery, exploiting the brain uptake properties of the glucose-targeted vesicles [85].

Preliminary in vivo studies involved the i.v. administration of a single dose of the developed niosome formulation with respect to the target tissue. This formulation gave rise to stable and nano-sized vesicles, which are able to improve doxorubicin brain delivery. Positive results of preliminary in vivo studies require future pharmacokinetic studies to gain more insight into the mechanism of drug transport of functionalized niosomes [86].

10. Quantum dots

Quantum dots (QDs), semiconductor fluorescent nanoparticles, ranging from 2 to 10 nm in size has a core of hundreds to thousands of atoms of group II and VI elements (e.g., cadmium, technetium, zinc, and selenide) or group III (e.g., tantalum) and V elements (e.g., indium). This carrier with a cadmium selenide core and a zinc sulfide shell, by a coating of an amphiphilic polymer, is ordinarily utilized for drug delivery systems [87]. QDs greatly expand the possibilities for fluorescence imaging of cells and living animals [88].

QDs have been conjugated to antibodies, allowing for simultaneous labeling and accurate quantification of these target proteins in one target section. Direct conjugation of targeted antibodies to the surface of QDs in a molar ration of four to ten, without the use of secondary antibodies, might be the best approach to achieve multiplex detection of molecular targets.

QDs can be bioconjugated to either the 3′ or 5′ end of an oligo sequence. Xiao and Barker have discussed the ability to control the number of attached oligonucleotides by the use of a streptavidin–biotin quantum dot system [89].

This bioconjugate has a high affinity to target cells and causes minimum nonspecific binding to normal cells. The quantum dot-based assay was developed that could quantitatively detect the estrogen receptor, progesterone receptor, and ERBB2 (e.g., MCF-7, BT474, and MDA-231 cells) in paraffin-embedded human breast cancer cells [90]. These cell lines were overexpressed by these receptors and were stained simultaneously with multiple quantum dots, which were directly bioconjugated to targeting antibodies for these three proteins [91].

Biotinylated DNA probes for labeled cells by streptavidin-coated quantum dots could identify of ERBB2, even at low levels of expression. This information recommends that the use of quantum dot-labeled oligonucleotides for detecting gene amplification especially at low levels of expression may offer points of interest over the standard fluorescence in situ hybridization (FISH) method [91].

11. Targeting drug delivery with magnetic nanoparticles

Magnetic nanoparticles (MNPs) offer several advantages when used as a drug carrier, including the large surface area, which can be properly modified to attach to drug molecules. Magnetic NPs can also be used with other carriers for drug delivery. Ensuring biocompatibility and nontoxicity, iron oxide-based particles (magnetite) with superparamagnetic characteristics are commonly used as magnetically responsive components, which can be manipulated by an external magnetic field gradient. Based on these properties, the superparamagnetic nanoparticles could be transported through the vascular system, concentrated in a specific part of the body with the aid of a magnetic field, and used as a carrier [92–94].

Iron oxide nanoparticles have found applications in the so-called magnetic drug targeting. Iron oxide nanoparticles in an external magnetic field are able to deliver particles to the desired target area [95, 96] and fix them there while the drug is released to exert a local effect [97]. Although magnetic targeting has been evaluated for a number of tumor-targeting studies, the most recent work is related to brain cancer.

It has been demonstrated that the release of drugs from magnetoliposomes could be controlled by an alternative current magnetic heating [98]. Although magnetoliposomes could be specifically heated to 42°C, the heating was mostly limited inside the thin lipid bi-layers [99].

Hsu and Su developed magnetic lipid nanoparticles with sizes ranging from 5 to 25 mm, composed of multiple drugs controlling their release in a desired pattern. The lipid matrices are solid at body temperature and melt around 45–55°C. In this study, the dissipated magnetic heat liquefied the encompassing lipid networks and resulted in an accelerated release of the encapsulated drugs.

Three accomplishments resulted: (1) Preparation of magnetic lipid nanoparticles with co-encapsulated drugs and heating components; (2) conjugation of surface-modified g-Fe_2O_3 particles that can be remotely energized to activate the heating and rapid drug release; and (3) designing a new nanocarrier, which can accomplish localized heating and pulsative release [99].

Zhu et al. prepared the chitosan-coated magnetic nanoparticles (CS MNPs) as carriers of 5-fluorouracil (CS–5-FuMNPs) through a reverse microemulsion method. It was found that the synthesized CS–5-Fu MNPs were spherical in shape with an average size of 100 ± 20 nm, low aggregation, and good magnetic responsivity. The result of CS–5-Fu MNPs cytotoxicity on K562 cancer cells showed that the nanoparticles have significant antitumor activities, and FITC-labeled nanoparticles could effectively enter into the cancer cells and induce cell apoptosis [74].

Gollavelli and Ling [75] investigated a novel magnetic and fluorescent graphene nanoparticles with a simple noncovalent approach. In this work, a hydrophobic silicon napthalocyanine bis (trihexylsilyloxide) (SiNc4) photosensitizer was adopted to immobilizing onto water-dispersible magnetic and fluorescent graphene (MFG) via pep stacking to yield MFGeSiNc4 functioned as a theranostic nanocarrier. The developed MFGeSiNc4 may thus be utilized as a potential theranostic nanocarrier for phototherapy of cancer cells with a single light source for less time-consuming and cost-effective treatments with a minimal therapy dose.

12. Targeted delivery for vaccine

The unique properties of nanoparticles, which can be altered by planned application, make excellent approaches for immunization and treatment of different diseases. The use of nanoparticles as vaccine adjuvants and carriers has opened up an entire new field of research. Different materials in the viral (20–200 nm) or bacterial (200–5000 nm) size ranges introduced in vaccine formulations with a stable half-life prevent enzymatic degradation of antigen and increase antigen uptake by specifically targeting specialist antigen-presenting cells (APCs) [76,100]. Some nanoparticle-based vaccines are designed to include ligands that can target APC and hence help trigger immune responses. Some possess internal adjuvants, triggering toll-like receptor (TLR) ligation and local danger signals to potentiate the effective antigen presentation to T cells.

Different designs and compositions of nanoparticle-based vaccines allow for specific tailoring of antigen delivery to the target cell type or specific tissue. In addition, the size of the particles plays a major role in the mechanism of particle uptake by APCs, influencing the type of the resulting immune response [100].

More recently a synthetic nanoparticle vaccine platform that targets lymph node-resident dendritic cells (DCs) has been developed, capable of mounting an immune response to conjugated antigen. The cross-presentation by DCs was demonstrated by direct antibody staining and in vitro stimulation of CD8+ T cells from OT-I mice and was indeed the most efficient with the reduction-sensitive conjugation.

Similarly, interferon (IFN) production by CD4+ T cells from OT-II mice has been observed. Finally, immunization with OVA peptide-bearing nanoparticles resulted in in vivo proliferation and IFN production by adoptively transferred CD8+ OT-I T cells and was also the most efficient with reduction-sensitive linking of the peptide antigen. These results demonstrate the relevance of the poly (propylene sulfide) nanoparticle vaccine platform and antigen conjugation scheme for activating both cytotoxic and helper T-cell responses [101].

13. Noncovalent protein–nanoparticle conjugation used for targeted drug delivery

Some of the studies have investigated the thermodynamics of binding between proteins and nanomaterials, demonstrating that properly functionalized NPs interact with proteins in an analogous fashion to protein–protein interactions. The biophysical characteristics of these interactions, such as binding affinity, residence time, binding cooperatively of NP, and the common serum proteins such as albumin, have been quantitatively described in the buffer medium to determine the behavior of proteins on NP surfaces [34,102].

Carbon nanotubes have a high surface area for chemical interactions and conjugations. The nonspecific protein–nanotube conjugates contain electrostatic interactions and hydrogen

bonding, especially when carbon nanotubes are pretreated with oxidative acids (Figure 7) [103,104].
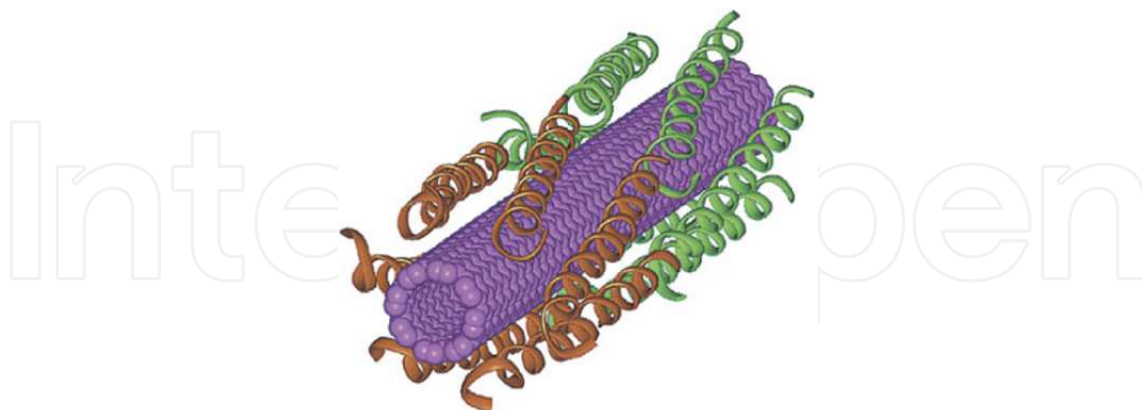
Figure 7. Immobilization of biomacromolecules on carbon nanotube surfaces

In this conjugation reaction, selected chemical reagents are utilized with known chemistry to link proteins to nanotubes in a more controllable manner. Protein surface amino groups of residues, such as lysine and nanotube-bound carboxylic acids, which are exposed by oxidative acid treatments, are widely involved in some of these specific conjugations and form amide linkages [35].

In another report, PEG was co-adsorbed onto single-wall nanotube (SWNT) devices with polyethylenimine. The pendant primary amine groups on PEI were available for subsequent biotin derivatization, and thus streptavidin recognition (Figure 8) [105].
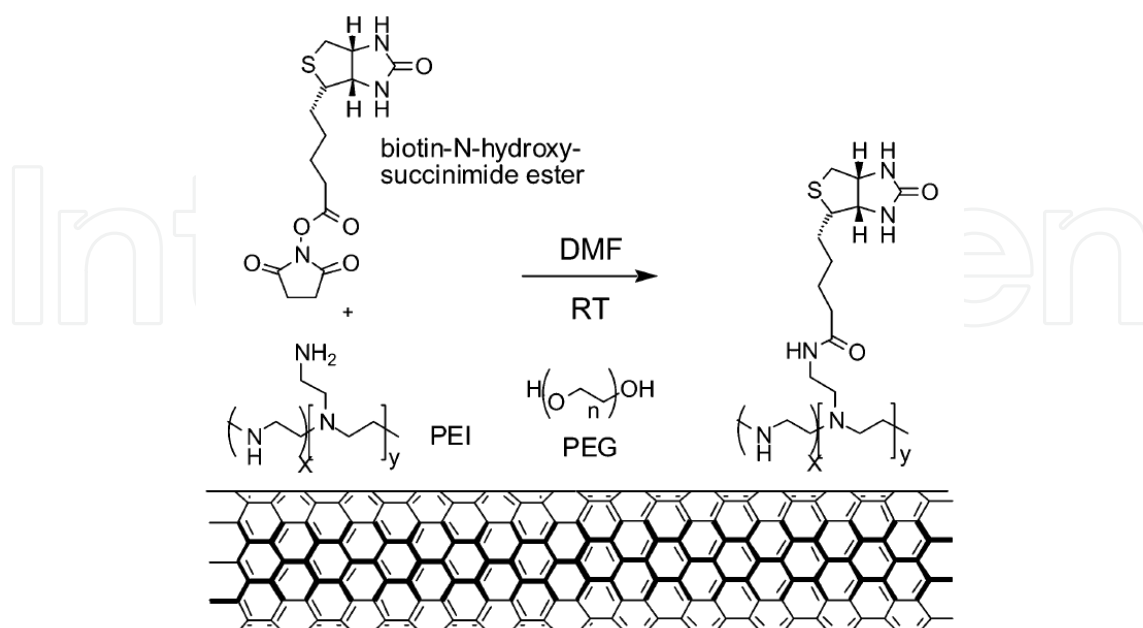
Figure 8. Absorption of polymer on the nanotube surface with the aid of PEG and PEI

14. Conclusions

Targeted drug delivery, sometimes called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in infective organs or cells, relative to others. The objective of a targeted drug delivery system is to prolong, localize, and concentrate the drug in the target diseased tissue. The advantages of the targeted release system are the reduction in the frequency of the dose administration by the patient, more uniform effect of the drug, reduction of drug side effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost, which makes profitability more troublesome and productivity difficult.

Nanotechnology plays an important role in therapies of the future as "nanomedicines" by enabling this situation to happen, thus lowering doses required for efficacy as well as expanding the therapeutic windows and safety profiles of new medicines.

Conventional chemotherapeutic agents are distributed nonspecifically in the body where they influence both cancerous and normal cells, thereby limiting the dose achievable within the tumor and also resulting in suboptimal treatment due to excessive toxicities. Molecularly targeted therapy has developed as one way to overcome the problem of nonspecifity of routine anticancer drugs. However, the development of resistance in cancer cells can avoid the cytotoxicity of ordinary chemotherapeutics as well as the more up-to-date targeted therapeutics [105].

Both passive- and active-targeted nanoparticles can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells. Furthermore, when nanoparticles bind to specific receptors and then enter the cell, they are usually enveloped by endosomes via receptor-mediated endocytosis, thereby bypassing the recognition of P-glycoprotein, one of the main drug resistance mechanisms. However, although nanoparticles offer many advantages as drug carrier systems, there are still many limitations to be solved such as poor oral bioavailability, instability in circulation, inadequate tissue distribution, and toxicity.

15. Nomenclature

Phrase	Abbreviation
Blood brain barrier	(BBB)
1,2-dioleoyl-sn-glycero-3-phosphoethanolamine	DOPE
Antigen-presenting cell	APC
Carbon nanotubes	CNT
Dendritic cells	DC
N,N-dicyclohexyl carbodiimide	DCC
Doxorubicin	DOX

Phrase	Abbreviation
Drug delivery systems	DDS
N-ethyl-N-(3-dimethylaminopropyl) carbodiimide hydrochloride	(EDAC)
Epidermal growth factor receptor	EGFR
Enhanced permeation and retention	EPR
Fluorescein isothiocyanate	FITC
Folic acid	FA
Glucocorticoid	GC
Gold nanoparticles	GNP
Murine canin fibroblast	MCF-7
Minimum inhibition concentration	MIC
Magnetic nanoparticles	MNP
Monoclonal antibodies	mAb
Multiwall carbon nanotubes	MWCNT
Poly (D, L-lactic-co-glycolic acid)	PLGA
Quantum dots	QD
Single-wall carbon nanotubes	SWCNT
Solid lipid nanoparticles	SLN
Triggering toll-like receptor	TLR

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