



(REVIEW ARTICLE)



## Review on nanoparticles used in drug delivery for cancer

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GSC Biological and Pharmaceutical Sciences, 2021, 16(01), 062–069

Publication history: Received on 03 June 2021; revised on 10 July 2021; accepted on 13 July 2021

Article DOI: <https://doi.org/10.30574/gscbps.2021.16.1.0194>

### Abstract

Current cancer treatments include surgical intervention, radiation, and chemotherapy medications. Nanoparticles have a variety of advantages as medication delivery systems. Nanoparticles (NPs) are newly discovered methods for delivering medicines to tumour cells with little drug leakage into healthy cells. To enhance biodistribution and increase circulation duration in the bloodstream, nanoparticles have been developed with optimum size and surface properties. Here, I look at the many types and features of nanoparticles. Examples of commercially available nanocarrier-based medicines include: Therapeutic nanoparticles, the function of metal nanoparticles in cancer diagnosis and therapy, are important ideas in nanoparticle medication delivery for cancer.

**Keywords:** Nanoparticles; Nanocarriers; Drug delivery; Cancer

### 1. Introduction

With more than 10 million new cases diagnosed each year, cancer remains one of the world's most deadly diseases [1]. However, due to a greater understanding of tumor biology and improved diagnostic technologies and treatments, mortality has dropped in the last two years [2]. Surgical intervention, radiation, and chemotherapy medications are currently used to treat cancer, but these treatments typically damage healthy cells and create toxicity in the patient. Conventional chemotherapeutic drugs also lack focused action and are dispersed non-specifically throughout the body, affecting both cancerous and non-cancerous cells, limiting the amount delivered to tumor cells and resulting in unsatisfactory treatment due to high toxicity. Molecular targeted therapy has emerged as one solution to the lack of specificity in traditional chemotherapeutic drugs [3]. Resistance development in cancer cells, on the other hand, can avoid the cytotoxicity of both traditional chemotherapeutics and novel molecular targeted treatments [4]. Nanoparticles can boost intracellular drug concentration in cancer cells while minimizing toxicity in normal cells by using both passive and active targeting techniques [5, 6]. Passive targeting exploits tumor biology's distinctive traits, such as increased permeability and retention (EPR), which permits nanocarriers to concentrate in a tumor [2]. Active techniques do this by combining chemotherapeutic-loaded nanocarriers with compounds that attach to overexpressed antigens or receptors on target cells. However, while nanoparticles have numerous advantages as drug carrier systems, they still have a number of drawbacks to overcome, such as low oral bioavailability, circulation instability, insufficient tissue distribution, and toxicity. In this review, I look at how nanotechnology can be used as a fundamental tool in cancer research and nanomedicine [7, 8]. The types and features of nanoparticles, examples of nanocarrier-based medications on the market, therapeutic nanoparticles, important concepts in nanoparticle drug delivery for cancer, and the significance of metal nanoparticles in cancer diagnosis and treatment are all discussed in this section [9].

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## 2. Nanoparticle size and surface properties

For successful drug delivery to the targeted tumor tissue, nanoparticles must be able to stay in the bloodstream for an extended period of time without being removed. Depending on their size and surface properties, conventional surface particles and non-modified nanoparticles are frequently caught in the circulation by the reticuloendothelial system, such as the liver and spleen [10]. Adjusting the size and surface properties of injected nanoparticles can regulate their fate.

### 2.1. Features of the surface

The surface properties of nanoparticles play a key role in defining their longevity and fate during circulation in relation to macrophage uptake. Nanoparticles should ideally have a hydrophilic surface to avoid being captured by macrophages [11]. This can be accomplished in two ways: first, coating the surface of nanoparticles with a hydrophilic polymer, such as PEG, and then repelling plasma proteins to protect them from opsonization; or, alternatively, nanoparticles can be formed from block copolymers with hydrophilic and hydrophobic domains [12].

### 2.2. Size

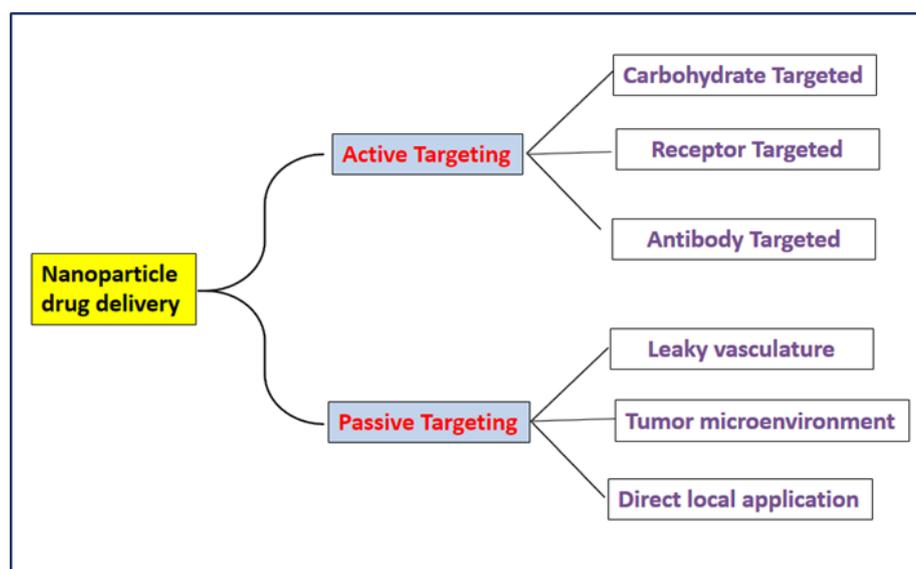
**Table 1** Examples of nanocarrier-based drugs on the market

System/type	Characteristics	Examples of compounds	Reference
<b>Polymeric nanoparticles (polymer drug conjugates)</b>	(a)Water-soluble, nontoxic, (b)Biodegradable Surface modification (pegylation) (c)Selective accumulation and retention in tumour tissue(EPR effect) (d)Specific targeting of cancer cells while sparing normal cells–receptor-mediated targeting with a ligand	Albumin-Taxol(Abraxane) PGA-Taxol(Xyotax) PGA-Camptothecin(CT-2106) HPMA-DOX(PK1) HPMA-DOX-galactosamine(PK2)	[15-18]
<b>Liposome</b>	(a)Amphiphilic, biocompatible (b)Ease of modification (c)Targeting potential	Pegylated liposomal DOX(Doxil) Non-pegylated liposomal DOX(Myocet) Liposomal daunorubicin (DaunoXome)	[19-21]
<b>Polymeric micelles</b>	(a)Suitable carrier for water-insoluble drug (b)Biocompatible, self-assembling, biodegradable (c)Ease of functional modification (d)Targeting potential	PEG-pluronic-DOX PEG-PAA-DOX(NK911) PEG-PLA-Taxol(Genexol-PM)	[22-24]
<b>Viral nanoparticles</b>	(a)Surface modification by mutagenesis or bioconjugation – multivalency (b)Specific tumour targeting, multi functionality (c)Defined geometry and remarkable uniformity (d)Biological compatibility and inert nature	HSP-DOX CPMV-DOX	[9]
<b>Carbon nanotubes</b>	a)Water-soluble and biocompatible through chemical modification (organic functionalization) (b)Multifunctionality	CNT-MTX CNT-amphotericin B	[9]
<b>Dendrimers</b>	(a)Biodistribution and PK can be tuned (b)High structural and chemical homogeneity (c)Ease of functionalization, high ligand density (d)Controlled degradation (e)Multifunctionality	PAMAM-MTX PAMAM-platinate	[25]

Nanoparticles also have the advantage of being able to change their size, in addition to their surface properties. Nanoparticles employed in drug delivery systems should be tiny enough to avoid capture by fixed macrophages stuck in the reticuloendothelial system, such as those found in the liver and spleen, yet large enough to prevent rapid leaking into blood capillaries. The size of the sinusoid in the spleen and the fenestra of Kuffer cells in the liver ranges from 150 to 200nm [13], and the gap junction between endothelial cells of the leaky tumor vasculature can range from 100 to 600nm [14]. Nanoparticles should have a size of up to 100nm to pass through these two circulatory systems and reach tumor tissues [9].

### 3. Therapeutic NPs

Several therapeutic nanoparticles have been used in a wide range of pathologic situations over the last two decades [26]. Bangham [27] discovered liposomes with a lipid scaffold structure 40 years ago. Liposomes are made up of spherical bilayers of self-assembled phospholipids [28]. These nanoparticles range in size from 30 nm to microns [29]. Within the vesicles and lipid bilayer, liposomes can incorporate both hydrophilic and hydrophobic therapeutic agents. These nanocarriers are biocompatible and may be easily modified to demonstrate improved features such as longer circulation times and active targeting [30]. Several liposome-based anti-cancer therapeutics are currently in clinical trials, including DaunoXome Myocet®, VincaXome® DepoCyt Doxil®, and Caelyx® [31]. NLCs (nanostructured lipid carriers) were first discovered in the late 1990s and are made up of a blend of solid and liquid lipids [32]. These nanocarriers have a high drug loading capacity, regulated drug release, increased drug stability, and are easy to manufacture in large quantities [33, 34]. SLNs (solid lipid nanoparticles) are non-toxic nanocarriers made from natural or synthesized lipids [35]. The use of harmful organic solvents is not required in the production of SLNs, which aids in the preservation of the drug's composition. Both lipophilic and hydrophilic medicines can be carried by these nanoparticles. SLNs are adaptable nanocarriers because they can manage the release and protection of pharmaceuticals, allowing them to be administered by both parenteral and non-parenteral routes [36]. The Food and Drug Administration (FDA) has approved poly lactic-co-glycolic acid (PLGA) for drug administration [37]. It is a biodegradable polymeric NP consisting of co-polymerization of glycolic acid and lactic acid. PLGA is a particularly helpful nanovector since it is hydrolyzed in the body to its original components. Lupron Depot®, a commercial nanocarrier based on PLGA, is used to treat advanced prostate cancer. Dendrimers are polymeric star-like molecules having a 3D geometric structure that is repeatedly strongly branched. Dendrimers are made up of three distinct components: a central core, branches, and an external surface with diverse surface functional groups [38]. Divergent (outward from the core) and convergent (inward towards the core) techniques are the two basic strategies for producing these dendrimers [39].



**Figure 1** Mechanism of Nanoparticle drug delivery via two main mechanism –Passive and Active targeting [53]

The presence of tertiary amines in dendrimer structures allows for the addition of a variety of molecules for active targeting [40]. The production of monomers (G) added to a primary core characterizes dendrimers. Dendrimers are the smallest nanocarriers produced, with sizes of 1.9 nm for G1 and 4.4 nm for G4, allowing them to be used in a variety of situations [41]. They're used for diagnostic (imaging) as well as therapeutic (treatment) applications [42]. The FDA has given Vivagel® Fast Track Status [43], making it the first dendrimer-based chemical to get this designation.

Iron oxide NPs, which have a diameter of 1–100 nm, are one of the most common forms of inorganic NPs. These particles have been exploited for imaging purposes in various malignancies because they may be viewed by Magnetic Resonance Imaging (MRI) [44]. With regard to the magnetic properties of these nanomaterials, they can be employed for therapeutic purposes via hyperthermia via external magnetic field conduction into the tumor location [45]. Because these NPs are biodegradable, and degraded iron may be absorbed by hemoglobin in the body, they can also be employed for in vivo studies [46]. SPIONs (superparamagnetic iron oxide nanoparticles) are valuable nanomaterials that can be used for imaging and therapeutic purposes [47]. Ferridex I.V., Ferumoxytol and Combidex® are examples of iron oxide-based NPs that can be employed for medicinal or imaging applications [47]. Michael Faraday was the first to discover gold nanoparticles [48]. For tumor-specific targeting, amine and thiol groups can simply be added to the surface of gold NPs. Gold NPs also exhibit surface plasmon resonance [49]. Because of their small size, these nanocarriers can infiltrate tumor cells via the EPR effect. Gold NPs-based therapies have also undergone early-phase clinical trials, which have yielded promising results [50]. Gold NPs can also be utilized as imaging vectors for tumor-selective photothermal treatment due to their high atomic number [51, 52].

#### **4. Important principles in cancer nanoparticle drug delivery**

In nanoparticle medication delivery, there are a few key concepts to remember. The EPR effect, nanoparticle clearance by the mononuclear phagocyte system (MPS), and desired nanoparticle properties for cancer applications are among them. [9].

##### **4.1. Increased permeability and retention**

The vasculature of tumors is typically atypical, with asymmetric branching and porous walls [54]. The lack of pericytes and the fast multiplication of endothelial cells cause this leakiness. Large pores in the tumor vasculature, ranging from 100nm to several hundred nanometers in diameter, are the result of these characteristics, as opposed to typical vascular junctions of 5–10nm [55]. Large holes in tumors allow for greater vascular permeability and hydraulic conductivity, allowing macromolecules like nanoparticles to flow through [54, 56]. The lymphatic system removes macromolecules from healthy tissue. Solid tumors, on the other hand, are frequently characterized by compromised lymphatics [57]. Lymphatic arteries are compressed and collapsed by proliferating tumor cells, especially in the center of tumors. The EPR effect is caused by a compromised lymphatic system combined with enhanced permeability of tumor vasculature. Nanoparticles, like other macromolecules, have longer retention durations in tumors than in plasma or other organs, resulting in larger concentrations. As a result of the EPR effect, nanoparticles can perform passive tumor targeting.

##### **4.2. The mononuclear phagocyte system clears nanoparticles.**

Nanoparticles must be in circulation long enough for tumor accumulation to completely benefit from the EPR effect. Nanoparticles, on the other hand, are susceptible to clearance by the mononuclear phagocyte system, also known as the reticuloendothelial system. The MPS is an immune system component that is in charge of removing macromolecules from circulation. Cancer immunotoxin treatment [58]. Bone marrow progenitors, blood monocytes, and tissue macrophages make up the MPS. It also comprises the liver's Kupffer cells and the spleen's macrophages, which are in charge of clearing macromolecules from the circulation. Nanoparticles can opsonize MPS cells when they engage with them. Because premature removal from circulation prevents nanoparticles from accumulating in tumors, a great deal of work has gone into developing "stealth" nanoparticles. Grafting PEG or other macromolecules such as polysaccharides onto the nanoparticle surface is the most prevalent technique [59]. The inclusion of PEG or other compounds allows for steric stability, which prevents protein adsorption, particle interactions, and immune cell contacts.

#### **5. Metal nanoparticles' role in cancer detection and treatment**

Because of their extraordinarily strong absorption and light scattering in plasmon resonance, metal nanoparticles (silver and gold) are frequently used in cell imaging, DNA hybridization detection, protein interaction, and photothermal therapy [60]. The unique optical features, simple surface chemistry, and appropriate size scale all contribute to the great appeal of utilizing gold and silver nanoparticles in cancer diagnosis and therapy. Controlling the size and form of these nanoparticles, or conjugating them with certain ligands/biomarkers, can improve tumor detection and treatment [61]. For in vivo imaging and/or therapy, the selective administration of metal nanoparticles is critical. Topical therapy for skin tumors, direct injection or surgical application for accessible deep tumors, and intravascular injection for inaccessible tumors are all options for delivering these nanoparticles into the tumor. Because the poor dispersion of body fluids does not ensure the requisite flow through these tissues and, as a result, through the tumoral tissue in the case of tumors located in hard tissues, direct intraoperative application is required. Anticancer chemotherapeutics can

also be carried via PEGylated gold or silver nanoparticles. PEG coating ensures great biocompatibility, reduced aggregation, and immune system masking. It has a long retention duration when given intravenously into the body, especially in solid tumors. NIR irradiation can then be used to selectively ablate the nanoparticle-enhanced tumor once it has been retained in the tumor [62-64]. The synthetic attachment of nanoparticles with antibodies targeting to receptors overexpressed on cancer cells makes molecular specific imaging and therapy of cancer a breeze. Guo et al. demonstrated that silver-based nanostructured materials may be employed as bioimaging labels for human lung cancer H1299 cells. The production of silver and gold spherical metal nanoparticles of various sizes for IR-sensitive antitumoral activity was reported by Xu et al. [65]. Fetal Bovine Serum was used to generate and modify silver nanoparticles (AgNPs) of 10, 20, and 40nm, as well as gold nanoparticles (AuNPs) of 20, 50, and 100nm. AgNPs with a diameter of 12nm were also produced and functionalized using meso-2,3-dimercaptosuccinic acid and silanes containing various functional groups such as amino, short chain PEG, and carboxylic groups. Three lines of C6 glioma cells (derived from mice), U251, and SHG-44 cells were used to test the nanoparticles (originated from human GBM). The antitumoral ability of these nanoparticles is dependent on concentration, IR dose, and nanoparticle size, according to the researchers. In summary, smaller nanoparticles are more efficient; higher irradiation doses result in more killing capabilities; and higher concentrations result in fewer survivors. Even if the mathematical quantification is more challenging, the capping agent utilized is also important. The studies revealed that nanoparticles treated with meso-2, 3-dimercaptosuccinic acid, and PEGylated silane have no effect on cell sensitivity to radiation, while carboxy- and amino-silane carrying nanoparticles dramatically reduce cell viability. Galvanic replacement reaction between Ag template and HAuCl<sub>4</sub> was used to make gold nanocages. In a nutshell, 30–200nm silver nanocubes are changed into Au nanoboxes and nanocages (nanoboxes with porous walls) with tunable optical characteristics ranging from blue (400nm) to near-infrared (1200nm). Near-infrared light is required to achieve deeper penetration. Forming agglomerates from spherical Au nanoparticles; elongating the nanoparticles from spherical gold nanoparticles to nanorods/whiskers; and emptying the interiors of spherical nanoparticles to form hollow gold nanostructures are the three strategies currently known for shifting the surface plasmon resonance from visible to near-infrared. The majority of these structures can be designed by modifying the synthesis pathway or utilizing appropriate capping agents [66].

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## 6. Conclusion

Bangham discovered liposomes with a lipid scaffold structure 40 years ago. Within the vesicles and lipid bilayer, liposomes can incorporate both hydrophilic and hydrophobic therapeutic agents. Nanocarriers are biocompatible and can be easily modified to exhibit better features, including longer circulation times and active targeting. These nanomaterials have the ability to effectively internalize into tumor cells and offer a number of benefits, including high drug loading potential, controlled drug release, improved drug stability, and ease of large-scale production. Iron oxide NPs, which have a diameter of 1–100 nm, are one of the most common forms of inorganic NPs. Magnetic Resonance Imaging (MRI) can visualize these particles, and they've been utilized to image cancers in the past. Ferridex I.V., Ferumoxytol, and Combidex are examples of iron oxide-based NPs that can be employed for medicinal or imaging applications.

Cell imaging, DNA hybridization detection, protein interaction, and photothermal therapy all involve gold and silver nanoparticles (silver and gold). Controlling the size and form of these nanoparticles, or conjugating them with certain ligands/biomarkers, can improve tumor diagnosis and treatment. ...

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## Compliance with ethical standards

### *Acknowledgments*

I am thankful to those people who contributed generously their time to preparing this review paper. I would also like to thank and express my gratitude to my colleagues.

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