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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 7: Polymeric and Lipid Based Nanocarriers

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Abstract

Cancer continues to be a huge global health problem, and the shortcomings of conventional treatment methods, including the non-specific distribution of drugs in the body, toxicity, and inefficiency, have resulted in an innovative way of drug delivery. Nanoparticles based delivery of drugs has been identified as one of the efficient ways to target cancer because it helps enhance the solubility, pharmacodynamics, and bioavailability of drugs. Among the several available systems for cancer therapy, polymer and lipid-based carriers have received much interest due to their biocompatibility and biodegradability. This chapter focuses on different nanocarriers, including polymer and lipid-based carriers, and discusses their designs and physicochemical properties. Some of the carriers discussed include polymer nanoparticles, polymer micelles, Dendrimers, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and hybrid nanoparticles. Passive and active targeting of tumors, drug release, and ways of overcoming multidrug resistance are described in the chapter as well. Recent achievements in stimuli-responsive, multifunctional, and theranostic nanocarriers, preclinical and clinical successes, regulatory issues, manufacturing problems, and safety aspects are considered. The last section of the chapter deals with recent trends in research and possibilities of future clinical application of polymeric and lipidic nanocarriers for cancer treatment.





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Keywords: Cancer Therapy; Nanoparticle-Mediated Drug Delivery; Polymeric Nanoparticles; Lipid-Based Nanocarriers; Liposomes; Solid Lipid Nanoparticles; Nanostructured Lipid Carriers; Polymeric Micelles; Dendrimers; Targeted Drug Delivery; Stimuli-Responsive Nanocarriers; Theranostic; Tumor Targeting; Drug Resistance; Nanomedicine.

1. Introduction

1.1 Global Burden of Cancer

Cancer continues to pose a significant public health problem globally, with an estimated 20 million new cases and 9.7 million deaths in 2022. Cancers of the lungs, breasts, colon and rectum, prostate, and stomachs are among the leading types of cancers. The increasing trend of cancer cases is associated with the population increase, aging, urbanization, environmental factors, and unhealthy lifestyle. However, despite improvements in the diagnostic tools and treatment modalities, most cancers are diagnosed when it is too late, making their treatment less effective (1).

1.2 Limitations of Conventional Cancer Therapies

While surgical treatments, chemotherapy, radiotherapy, targeted treatments, and immunotherapy have been successful in terms of survival and managing cancer diseases, they come with certain limitations. For instance, surgical treatment is most ideal in the case of local cancers, while radiotherapy may lead to toxicities on healthy cells. On the other hand, chemotherapy plays a pivotal role in managing advanced cases of cancer, although the lack of tumor specificity, poor pharmacokinetics, and low bioavailability makes it difficult for it to be successful in cancer treatment and leads to dose-limiting toxicity. Furthermore, multidrug resistance due to drug efflux, target modifications, increased DNA repair, and apoptosis inhibition makes the drugs ineffective. In the case of targeted treatment and immunotherapy, their long-term benefits are compromised by tumor heterogeneity, immune escape, and acquired resistance (2,3).

1.3 Role of Nanotechnology in Cancer Treatment

Nanotechnology is considered a promising solution to tackle the drawbacks associated with existing cancer treatment modalities. Nano carriers have been developed to improve the physicochemical characteristics of drugs like solubility, stability, bioavailability, and pharmacokinetics along with control over the delivery process. The small size and adjustable nature of the nano carriers help penetrate biological barriers, reach tumors and provide better





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therapeutic effects. Ligand, antibody or peptide based surface functionalization can increase the specificity of the nano carriers, drug uptake by tumor cells and decrease toxicity to non-tumor tissues. Polymeric and lipid-based nano carriers like polymeric nanoparticles, micelles, dendrimers, liposomes, SLNs, NLCs, and LNPs have gained great importance due to their biocompatible, biodegradable and versatile nature (4,5).

1.4 Scope of the Chapter

This chapter examines the polymeric and liposomal drug delivery carriers for cancer therapy in terms of their design, applications in medicine, recent developments, and clinical potential. It explores the concepts of drug delivery via nanoparticles, tumor targeting, as well as the various types of polymeric, liposomal, and hybrid nanoparticles. In addition, the concepts of active/passive targeting, responsive/theranostic nanocarriers, and recent preclinical/clinical progress are also discussed. Moreover, the challenges related to regulation, manufacture, and safety of the nanoparticles are assessed and the future directions in the field are indicated.

2. Fundamentals of Nanoparticle-Mediated Drug Delivery

2.1 Principles of Nanocarrier-Based Drug Delivery

Drug delivery using nanoparticles provides various benefits in cancer treatment, including drug stability, increased drug solubility, increased circulation time, and drug release control. Overcoming biological barriers results in higher tumor uptake and efficacy. Properties of nanocarriers are determined by physicochemical parameters including size, shape, charge, composition, and surface characteristics that impact bio distribution, circulation, and uptake by cells. The size of nanoparticles in the range of 20-200 nm is especially advantageous in cancer drug delivery as it allows tumor uptake and prevents renal elimination. Surface modification of nanoparticles with hydrophilic polymers such as PEG can increase the circulation time by preventing immunogenicity. Drugs can be loaded into nanoparticles either inside, bound to the surface, or covalently attached with release via diffusion, degradation, cleavage by enzymes, and stimulation (4).

2.2 Tumor Microenvironment and Enhanced Permeability and Retention (EPR) Effect

The tumor microenvironment (TME) plays a significant role in the drug delivery mechanism using nanoparticles. The TME includes cancer cells, stroma cells, immune cells, extracellular matrix, signaling molecules, and abnormal vasculature which play a role in tumor development and therapy response. Some characteristics of the TME such as hypoxia, acidic pH levels, increased interstitial pressure, and increased extracellular matrix could play an important role





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in determining the distribution of nanoparticles into the tumor tissues. The enhanced permeability and retention effect makes it possible for nanoparticles to accumulate selectively in tumors owing to leaky vasculature and inadequate lymphatic drainage. However, the EPR effect differs in different tumors and in different patients as a result of vascularization, stroma content, increased interstitial pressure, and tumor position (4,5).

2.3 Passive and Active Targeting Strategies

The approaches for targeted drug delivery are used to increase the selective delivery of antitumor agents and can be divided into two broad categories – passive and active targeting. Passive targeting uses the phenomenon of enhanced permeation and retention (EPR), which is based on the characteristics of nanoparticles including their size, surface charge, hydrophilicity, and blood circulation time. The process of active targeting entails the use of ligand-functionalized nanoparticles that interact with overexpressed receptors on the surface of cancer cells and tumor microenvironment. Ligands for receptor-mediated active targeting include antibodies, peptides, aptamers, carbohydrates, and folic acid and contribute to endocytosis through receptor recognition. Some receptors often targeted include folate receptors, transferrin receptors, EGFR, HER2, and CD44 (4,5).

3. Polymeric Nanocarriers for Cancer Drug Delivery

There is extensive research conducted on the use of polymeric nanoparticles in cancer treatment because of their ability to be biocompatible, biodegradable, highly flexible and effective at delivering drugs into the body. The nature of their composition allows for the improvement in the properties of drugs that treat cancer while avoiding toxicity. These nanoparticles are able to carry various therapeutic entities such as small molecules, proteins and nucleic acids among others (4).

3.1 Overview and Classification

Polymeric nanocarriers are drug delivery carriers that are made from natural or synthetic polymers and consist of polymeric nanoparticles, micelles, dendrimers, hydrogels, and nanogels. Such nanocarriers increase the stability, distribution, circulation time, and specificity of drug delivery. Polymers such as PLA, PLGA, PEG, PCL, chitosan, alginate, gelatin, and hyaluronic acid, among others, are usually used as nanocarriers. They have tuneable physiochemical properties that allow for controlled drug release and targeted delivery (4,6).

3.2 Polymeric Nanoparticles





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These polymeric nanoparticles comprise solid colloids (10-500 nm), which are categorized as either Nano spheres where the drugs are distributed throughout the polymeric matrix, or Nanocapsules where the drugs are entrapped inside a polymeric membrane. They ensure drug protection against degradation and control drug release. PLGA is highly valued for being bio-compatible, bio-degradable, and safe. The nanoparticles increase the tumor-specific delivery of the drugs, enable efficient cellular uptake, and minimize toxicity to healthy tissues (4).

3.3 Polymeric Micelles

Polymeric micelles are nano-aggregates obtained from the self-assembly of block copolymers which are amphiphilic in nature within an aqueous environment. They consist of a hydrophobic core for incorporation of insoluble drugs along with a hydrophilic shell which increases stability. Usually measuring 10-100 nm, these micelles have enhanced circulation as well as penetration into tumors. Polymeric micelles have special utility for the delivery of hydrophobic anti-cancer drugs like paclitaxel, docetaxel, and doxorubicin (7).

3.4 Dendrimers

Dendrimers are macromolecules that have many branches with surface groups which make them very useful in delivering drug molecules. The surface of dendrimers can be attached with various drugs, imaging molecules, or targeting molecules. Amongst all the dendrimers studied to date, PAMAM dendrimers have been studied the most for cancer applications. But clinical applications are restricted due to complicated preparation process and high cost of synthesis (6).

3.5 Hydrogels and Nanogels

Nanogels are nano-sized hydrogels that exhibit excellent bioavailability properties. Due to their sensitivity to various stimuli including pH, temperature, enzyme, and oxidative-reductive stimuli, nanogels offer great potential for localized delivery of drugs to tumor sites. Nanogels have the capability of delivering more than one type of medication at the same time (8).

3.6 Biodegradable and Biocompatible Polymers

The selection of the polymer is very important for successful design of the nanocarrier. Biodegradable polymers break down to harmless substances that can be easily excreted from the body. The common synthetic polymers like PLA, PLGA, PEG, and PCL are used for their safety and biomedical applications. Natural polymers include chitosan, alginate, gelatin,





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dextran, and hyaluronic acid which have biocompatibility and biological activities. Hyaluronic acid targets CD44 receptors that are highly expressed in various cancers (4,6).

3.7 Advantages and Limitations of Polymeric Nanocarriers

Polymeric Nano vehicles improve the stability of drugs, sustained release, increased circulation time, and tumor-specific targeting of drugs, and hence have immense potential in Nano therapy for cancer. But their application in the clinical setting has been hampered by various limitations like complex manufacture process, batch-to-batch variations, scale-up problems, regulatory issues, and safety testing (4,9).

Table 1: Comparison of Polymeric Nanocarriers Used in Cancer Drug.

Nanocarrier	Major Components	Advantages	Limitations	References
Polymeric nanoparticles	PLGA, PLA, chitosan	Controlled release, stability	Complex preparation	(6,10)
Polymeric micelles	Amphiphilic copolymers	Solubilize hydrophobic drugs	Limited stability	(11,12)
Dendrimers	PAMAM, PPI	High drug loading	Potential toxicity	(7,13)
Hydrogels	Natural/synthetic polymers	Localized delivery	Limited penetration	(8)
Nanogels	Cross-linked polymers	Stimuli responsiveness	Scale-up challenges	(9,14)

4. Lipid-Based Nanocarriers for Cancer Drug Delivery

Lipid-based nanocarriers are considered one of the best nanomedicine approaches that have been used for the treatment of cancer because of their biological compatibility, less toxicity, and formulation flexibility. They increase the solubility of the drugs, improve circulation time, increase tumor targeting, and decrease side effects (10).





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4.1 Liposomes

Liposomes are vesicular structures composed of phospholipids that can load both hydrophilic and hydrophobic drug molecules, thus serving as a delivery system for cancer treatment. Liposomes improve the pharmacokinetics of the drug molecules and decrease their toxicity; PEGylation and ligand attachment increase the circulation time and tumor specificity. Theranostics based on liposomes can be achieved by loading the liposome with imaging agent(s). Nonetheless, issues such as drug leakage and low stability still exist (10,12)

4.2 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are sub-micron-sized carriers that consist of solid lipids stabilized with the help of surfactants. SLNs provide good biocompatibility, increased stability, and drug release control, providing protection against degradation of the loaded drugs. SLNs have been extensively studied for the delivery of various therapeutics, including chemotherapy drugs, nucleic acids, and other biologicals. Due to their biodegradability, low toxicity, and drug availability, SLNs can be effectively used in cancer treatment. Nevertheless, the crystallinity of the lipid matrix reduces drug loading and causes drug leakage (13).

4.3 Nanostructured Lipid Carriers (NLCs)

Nanocarriers of lipid origin or nanolipid carriers (NLCs) were discovered as an answer to the drawbacks of SLNs. The composition of NLCs involves solid as well as liquid lipids. It allows the formation of a less ordered matrix and increases the capacity of the drug within NLCs and decreases the probability of drug leakage during the storage period. NLCs possess a great potential in anticancer drug delivery (14,15).

4.4 Lipid Nanoparticles (LNPs)

Lipid nanoparticles (LNPs) are effective transport vehicles for nucleic acid-based therapeutics like mRNA, siRNA, and other gene-editing technologies. The LNPs are made up of ionizable lipids, phospholipids, cholesterol, and PEGylated lipids. They offer protection to nucleic acids against any kind of degradation, and help in delivering them into cells. LNPs have been used extensively for treatment of cancers due to their capabilities of regulating oncogenic signaling pathways (16,17).





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4.5 Advantages and Challenges of Lipid-Based Nanocarriers

The nanocarriers made from lipids provide good biocompatibility, increased solubility, pharmacodynamics, controlled delivery, and decreased toxicity. Although lipid-based nanocarriers have achieved great success in the treatment of cancers, the problems associated with these nanocarriers include stability, scale up manufacturing, variability, regulations, and knowledge of nanoparticles that hamper their application in clinics. The future nanocarriers will be designed for better targeting, easy manufacture, safety, and effectiveness (14,16).

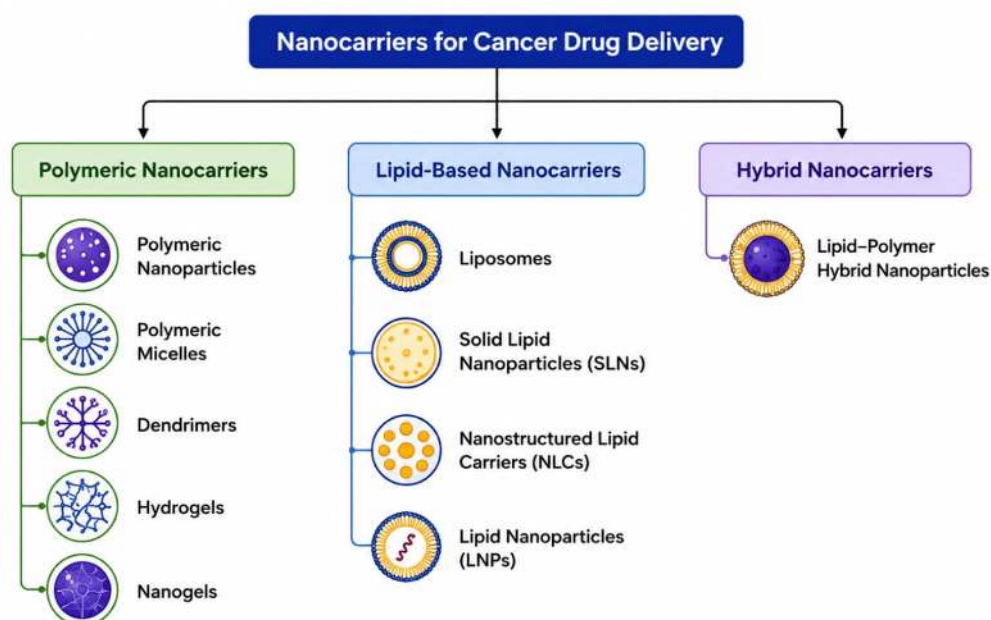


Fig. 1 Classification of Polymeric and Lipid-Based Nanocarriers

5. Lipid-Polymer Hybrid Nanocarriers

The lipid-polymer hybrid nanocarriers (LPHNs) represent a combination of polymeric nanoparticles and liposomes with high stability and biocompatibility. LPHNs are considered good candidates for anticancer treatment owing to their improved stability, high loading efficiency, and sustained release of the loaded drugs (18).





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5.1 Design and Structural Features

LPHN is normally made up of a polymeric core which is surrounded by a lipid shell and may have PEG shell coating. The polymeric core is responsible for stabilization and containment of the drug; on the other hand, the lipid shell ensures biocompatibility, reduces leakage of drugs, and makes the membrane more interactive. They can exist in different forms and can be coated to target the tumor cells and improve cellular uptake (18,19).

5.2 Drug Loading and Release Characteristics

LPHNs can be effective in loading a variety of drugs where hydrophobic drugs are loaded within the polymeric matrix or lipid core while hydrophilic drugs are conjugated with the outer shell. The drug release pattern can be regulated by diffusion, degradation of polymer or lipids, or any other stimuli, which will enable controlled drug release with minimal side effects. In addition, stimuli-responsive LPHNs can take advantage of the tumor microenvironment that is characterized by low pH, high enzyme concentration, hypoxia, and redox imbalance (18–20).

5.3 Applications in Cancer Therapy

LPHN nanoparticles have proven to be effective in delivering anticancer drugs, nucleic acids, proteins, peptides, and imaging agents. The improvement of the circulation time, tumor targeting, and drug stability increases their efficacy. LPHNs combined with other nanocarriers have been able to deliver different drugs including doxorubicin, paclitaxel, docetaxel, and cisplatin. It is also possible to combine therapy because of the delivery of several substances at once. LPHN particles are theranostic in nature, meaning that they can both diagnose and treat using imaging and therapy agents. LPHN nanoparticles are effective in gene therapy, cancer immunotherapy, and delivery of mRNAs and siRNAs (18,20,21).

Table 2 Comparison of Lipid-Based Nanocarriers

Nanocarrier	Structure	Advantages	Challenges	References
Liposomes	Phospholipid bilayer vesicles	Clinically established	Stability issues	(15)





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SLNs	Solid lipid matrix	Good biocompatibility	Drug expulsion	(16)
NLCs	Mixed solid-liquid lipids	Higher drug loading	Formulation complexity	(17)
LNPs	Ionizable lipid systems	Nucleic acid delivery	Storage requirements	(15,17)
Lipid-polymer hybrids	Polymer core + lipid shell	Combined advantages	Manufacturing complexity	(18–21)

5.4 Advantages and Limitations

The lipid-polymer hybrid nanocarrier system shows great promise for cancer drug delivery due to its high loading capacity, increased stability, enhanced circulation time, and controlled release. These systems also have the capability to encapsulate targeting agents as well as imaging agents. The clinical development of these systems faces several challenges including difficulty in manufacturing, standardization and quality control, optimization, storage stability, and safety assessment (18–20).

6. Targeting Strategies Using Polymeric and Lipid-Based Nanocarriers

In order to increase the efficacy of cancer treatment using nanocarriers, targeted methods of delivery are needed. As opposed to existing cancer treatments, which are characterized by their high systemic toxicity, both polymeric and liposomal nanocarriers may be designed for increased tumor-specific drug delivery and cellular uptake. Passive and active targeting may be used as such delivery mechanisms (5).

6.1 Ligand-Mediated Targeting

Ligand-targeting has been widely recognized as one of the active targeting approaches in cancer nanomedicine. This method refers to the functionalization of the nanoparticles with the ligands that interact with the receptors which are overexpressed in the cancer cells to facilitate the internalization via the receptor-mediated endocytosis. Ligands such as folic acid, transferrin, hyaluronic acid, peptides, aptamers, and carbohydrates are some of the examples. Cell membrane-based nanoparticles have been reported recently (5,22).





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6.2 Antibody-Based Targeting

The antibody-directed delivery is a successful nanomedicine treatment option for cancers based on antibody-coated nanoparticles, which specifically transport drugs to the targeted cancerous cells. Antibodies like trastuzumab, cetuximab, rituximab, and bevacizumab recognize the markers HER2, EGFR, CD20, and VEGF, respectively. This technique increases tumor specificity, receptor-mediated endocytosis, and intracellular delivery of the drug molecules. Contemporary studies aim at the development of antibody-based nanocarriers loaded with chemotherapeutic agents, nucleic acid drugs, and immunotherapies (23,24).

6.3 Receptor-Specific Targeting

Receptor-specific targeting involves targeting receptors that are over-expressed on the surface of cancer cells or in the tumor microenvironment such as Folate receptors, transferrin receptors, EGFR, HER2, integrin's, and CD44. The modification of nanocarriers with receptor-specific ligands is designed to increase tumor uptake and increase drug localization in the tumors by limiting the toxicity of drugs to other normal tissues. This mode of drug delivery may also assist in crossing the biological barriers and cellular drug delivery (5,23,24).

6.4 Cell-Penetrating Systems

In order to overcome the limitation of intracellular delivery, there is a need for functionalizing these nanocarriers with the help of cell-penetrating peptides (CPPs). Some of the cell penetrating peptides are TAT, Penetratin, Transportan, and arginine-rich peptides. This makes these nanocarriers useful for gene therapy, nucleic acid delivery, intracellular drug targeting, and theranostic (25).

Pros: The nanocarriers modified with CPPs show improvement in cell entry, intracellular trafficking, nucleic acid delivery, and organelle targeting therapies.

Cons: The nanocarriers modified with CPPs may have limitations such as tumor selectivity issues, nontargeted uptake, enzymatic degradation, and other safety aspects (25).





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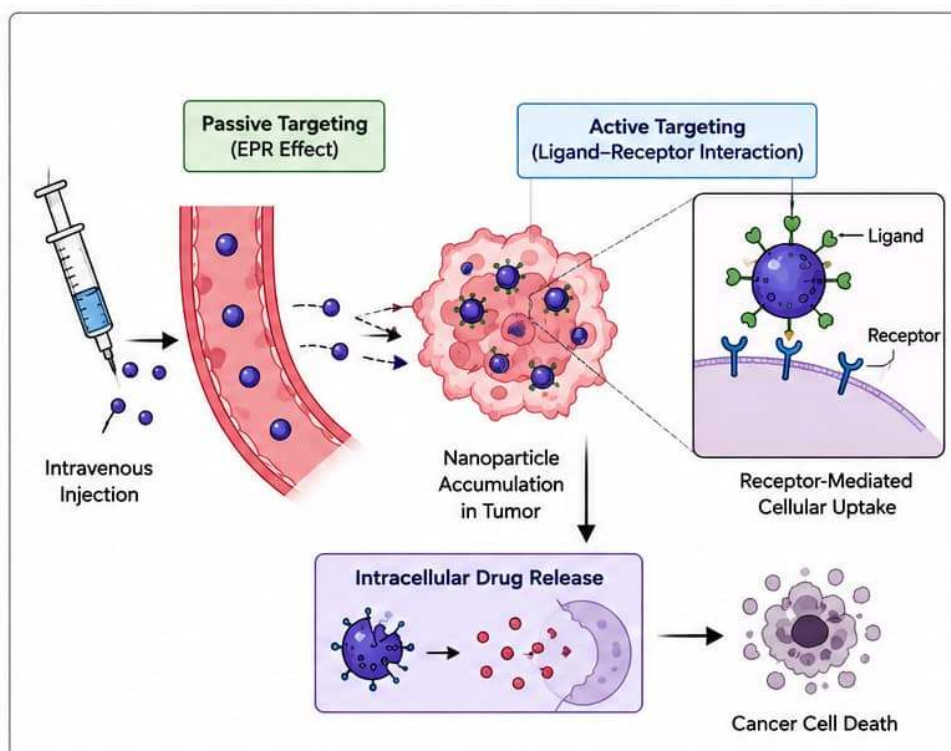


Fig. 2: Tumor Targeting Strategies of Nanocarriers.

7. Stimuli-Responsive and Smart Nanocarriers

Smart or stimulus-responsive drug delivery systems allow for the targeted release of the drug upon stimuli. Using properties of tumors such as low pH, presence of higher ROS concentration, abnormal enzyme activity, and redox conditions, these drug delivery systems are able to control the release of drugs in time and space (8).

7.1 PH-Responsive Systems

PH responsive nanocarriers are designed to take advantage of the low pH tumor microenvironment for targeted drug delivery. These nanocarriers are composed of acid-labile polymer, coating, or linkages that retain stability at physiological conditions, while becoming destabilized under acidic conditions. Typical materials include poly(histidine), poly(β -amino esters), and hydrazone/acetal-containing linkages. The use of such systems improves tumor accumulation of drugs and intracellular drug delivery in acidic endo-/lysosomes (8,26).





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7.2 Temperatures-Responsive Systems

Temperature-sensitive nanocarriers have the ability to deliver drugs under hyperthermia, which is between 40°C and 42°C. Usually, temperature-sensitive nanocarriers contain thermo sensitive polymers like PNIPAM, which have the ability to change their structure due to heating and thus release drugs in a controlled manner. Temperature-sensitive nanocarriers have been extensively researched in conjunction with hyperthermia, photo thermal therapy, and ultrasound-heating (27).

7.3 Redox-Responsive Systems

Nanocarriers with redox responsiveness take advantage of increased levels of intracellular GSH found in cancer cells. Such nanocarriers have linkages that are sensitive to redox reactions. While stable outside of the cells, such linkages can be cleaved inside the cell because of the reduced nature of the intracellular environment. Redox-responsive carriers have potential for drug delivery, including combination therapy.

Redox-sensitive nanocarriers have been shown to deliver drugs with high intracellular specificity, efficient cytoplasmic drug release, appropriate nucleic acid and gene delivery, and minimal exposure (28).

7.4 Enzyme-Responsive Systems

The enzyme-sensitive Nanocarrier system involves enzyme-degradable linkers or substrates which cause drug release under the catalytic action of enzymes that are found in tumors like MMPs, cathepsins, phospholipases, and hyaluronidases. This helps in site-specific drug delivery.

Enzyme-responsive nanocarriers offer specific targeting to tumors, localized drug delivery, enhanced therapeutic ratio, and can be used as combinations.

Potential disadvantages of enzyme-responsive nanocarriers include variability of enzyme expression in tumors, possibility of non-intended activation, and complex formulations (26).

7.5 Multifunctional Smart Nano platforms

In recent years, nanomedicine developments have resulted in nanoplatforms that have combined features like stimulus-induced drug release, targeting molecules, imaging modalities, and drugs. They have provided an opportunity for targeted drug delivery, drug release control, imaging diagnostics, and monitoring in real-time. This makes them suitable for precision oncology through the integration of functionalities such as pH-controlled drug release,





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receptor-targeting, and imaging. Nanoplatfroms that have multiple functions provide targeting and release control function, incorporate both diagnostic and therapeutic features, enhance treatment accuracy, and offer personalized cancer treatment.

Their drawbacks are their complex formulation, higher cost, regulatory issues, and the need for thorough safety evaluation (4).

8. Theranostic Applications

Theranostic is the use of cancer nanomedicine which involves integration of both therapeutic and diagnostic roles into one platform. Polymer and lipid-based nanoparticles have the capability to load both imaging and therapeutic drugs at the same time to allow targeted delivery and drug release as well as monitoring the therapeutic response (4,29,30).

8.1 Imaging-Guided Drug Delivery

Imaging guided drug delivery forms an important part of theranostic nanomedicine in which imaging probes are introduced into nanocarriers for tracking biodistribution, targeting tumors, and assessing therapeutic efficacy. Different types of imaging techniques, including MRI, CT, PET, fluorescence, photo acoustic, and multimodal imaging have been incorporated into nanocarriers through magnetic nanoparticles, fluorescent dyes, radionuclides, or contrast agents. Stimuli-responsive theranostic have taken this concept one step further through development of systems that remain dormant while circulating in blood but activate in presence of the tumor microenvironment .

Theranostic Nanoplatfroms offer the capability to monitor real-time drug delivery, nanoparticle distribution, better treatment planning, and early assessment of drug efficacy (4,29,30).

Disadvantages associated with them include their complicated formulations, high cost of development and manufacture, regulations, and lack of clinical applications (4,12,30).

8.2 Diagnostic and Therapeutic Integration

One of the important characteristics of theranostic nanomedicine is the merging of the diagnostic and therapeutic activities into one nanosystem that allows for the diagnosis of the tumor, the monitoring of the disease, and delivery of the therapeutic action. The polymeric nanovehicles can carry both imaging and therapeutic components like fluorescent labels and magnetic nanoparticles together with the anticancer medications for the purposes of imaging and treatment at once. The lipid nanovehicles, in particular, the liposomes, can carry both therapeutic and imaging agents at once (6,12,29).





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8.3 Personalized Cancer Treatment

Personalized medicine relies on the molecular differences between individuals and the tumors for treatment purposes. Nanocarriers in the field of theranostics facilitate personalization through their ability to provide individualized diagnosis, selection of treatment, and management of treatments. It is possible to customize these carriers to identify specific markers, receptors, or molecular malfunctions for provision of targeted treatment based on customized protocols. Imaging-based monitoring facilitates the assessment of the effects of the treatment and subsequent adjustments. The use of precision nanomedicine technology has improved the capabilities of personalization in theranostics in the past years, with future advancements involving artificial intelligence and molecular diagnostics among others (4,30).

8.4 Future Outlook of Cancer Theranostics

Despite many developments that have been witnessed in the field of theranostic nanomedicine, a number of difficulties still exist in the translational aspect of the same including formulation complications, manufacturing scalability, approval from regulatory agencies, safety concerns, and costs involved. In addition to these, there is need for better knowledge about the biological activity of multifunctional nanocarriers in tumor microenvironments. Nevertheless, development in the fields of nanotechnology, imaging, molecular biology, and precision medicine allows the development of advanced theranostic systems (4,29,30).

9. Preclinical and Clinical Advances

Translation of Nanocarrier systems for drug delivery from the laboratory into clinics marks a major milestone for cancer nanomedicine. In the last two decades, progress in polymeric and lipid nanocarriers has resulted in the approval of various nanomedicines and a number of clinical studies. It has improved the pharmacokinetics of drugs, decreased their toxicity, and improved cancer treatment. Nevertheless, while promising preclinical data exists, very few nanocarrier systems have been clinically translated due to limitations associated with tumor biology, heterogeneous tumor microenvironment, large-scale production, regulations, and long-term safety issues (4,31–33).





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9.1 Approved Nanoformulations

The transition of nanocarriers systems used for drug delivery from laboratories to clinics is one of the most significant landmarks in cancer nanomedicine. Over the past two decades, research related to polymeric and lipid-based nanocarriers has made tremendous improvements, leading to the development of a variety of nanomedicine and numerous clinical trials. It has helped enhance the pharmacokinetic profile of medicines, reduce their toxicity, and improve cancer therapy. However, despite positive preclinical results, few Nanocarrier systems have made it to the clinical phase owing to various limitations related to tumor biology, heterogeneous tumor microenvironment, large-scale manufacturing, regulation, and safety (4,33).

Table 3 Clinically Approved Nano medicines for Cancer Therapy.

Product	Nanocarrier Type	Drug	Clinical Indication	Reference
Doxil®/Caelyx®	PEGylated liposome	Doxorubicin	Ovarian cancer, Kaposi's sarcoma	(33)
Abraxane®	Albumin nanoparticle	Paclitaxel	Breast, lung, pancreatic cancers	(4,33)
Onivyde®	Liposomal formulation	Irinotecan	Pancreatic cancer	(33)
Vyxeos®	Liposomal combination	Daunorubicin + Cytarabine	Acute myeloid leukemia	(33)

9.2 Clinical Trials of Polymeric and Lipid-Based Systems

The success of the nanomedicine that was already approved clinically has led to a lot of research on the use of polymeric and lipid-based nanovectors in cancer treatment. Clinical trials have involved using different nanoparticle formulations to improve drug delivery, tumor selectivity, and lower the toxicity of chemotherapy drugs. The polymeric nanocarriers, which





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include polymer-drug conjugates, micelles, dendrimers, and biodegradable nanoparticles, allow for adjustable physicochemical properties, controlled drug release, increased stability, prolongation of circulation time, and tumor targeting. The lipid-based nanocarriers like liposomes, lipid nanoparticles (LNPs), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have remained the most clinically advanced because of their safety, biocompatibility, and large-scale production. These nanocarriers have been researched for drug and nucleic acid delivery with the progress in the LNPs technology pushing the field of cancer vaccines and gene therapies forward (34,35).

9.3 Translational Success Stories

Some Nanocarrier-based nanomedicines have already managed to move from basic research into clinical application. For example, drugs like Doxil®, Abraxane®, Onivyde® and Vyxeos® have increased the efficiency of drug delivery and decreased side effects of treatment. Doxil® helped in solving problems with the toxicity of standard doxorubicin treatment, while Abraxane® improved the delivery of paclitaxel without its solvent formulations. Apart from the above-listed products, there are numerous nanomedicine undergoing investigation which demonstrate excellent clinical results. New discoveries related to active targeting, responsive drug delivery, and multifunctional nanoplateforms increase the target specificity and efficiency of treatment. Moreover, innovations in the field of delivery of nucleic acids expand the scope of application of nanocarriers for the treatment of various diseases (4,31,32,35).

9.4 Remaining Challenges in Clinical Translation

Even with all the progress that has been made, translating cancer nanomedicine to the clinic is still difficult. There are many nanoparticle formulations with preclinical successes that have failed to make it through clinical development due to poor efficacy, safety considerations, manufacturing issues, and regulatory problems. A problem that stands out is the heterogeneity of the EPR effect since differences in the vascular system of the tumor, the stroma of the tumor, and the immune response affect how nanoparticles interact and deliver their payload. Large-scale production and quality control of multifunctional nanoparticles is also difficult. Better understanding of nanoparticle-biological interaction and better preclinical assessment models are needed to translate nanomedicine into the clinic (31–33).

10. Challenges and Regulatory Considerations

Despite the advancements that have been made so far, the process of translating cancer nanomedicine to the clinic is not an easy one. This is because there exist several nanoparticle





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formulations that despite showing success in preclinical studies, have been unable to pass through clinical translation due to their poor efficacy, safety concerns, manufacturing difficulties, and regulation complications. One issue that comes up frequently is the heterogeneous nature of the EPR effect due to the fact that variations in the tumor vasculature, tumor stromal tissue, and immune responses influence how nanoparticles work and deliver their cargo. It is hard to produce and maintain quality control of multifunctional nanoparticles on a large scale (36–38).

10.1 Toxicity and Safety Assessment

Safety evaluation is crucial for nanomedicines since nanoparticles' physicochemical characteristics play an important role in determining their biological behavior. Such features as size, surface charge, nanoparticle composition, morphology, and functionalization impact biodistribution, cellular internalization, interaction with immune system, and elimination. Unlike conventional drugs, nanoparticles can demonstrate unique interactions, such as protein corona formation, peculiar pharmacokinetics, and distribution among tissues. After intravenous injection, nanoparticles might accumulate in liver, spleen, and lungs, leading to potential chronic toxicity, inflammation, and other adverse effects. Another significant issue that should be addressed during nanoparticle safety evaluation is immunotoxicity, which refers to nanoparticle capability to induce complement activation, inflammation, and alter immune cells. Some nanomedicines might be linked to complement activation-related pseudoallergy (CARPA) development; hence, complement interaction evaluation is an integral part of safety evaluation process. Toxicological evaluations usually include cytotoxicity, hemocompatibility, immunotoxicity, genotoxicity, biodistribution, pharmacokinetic, and long-term organ toxicity evaluations. Advanced in vitro and in vivo models are increasingly applied to enhance safety prediction for clinical trials (36,39).

Primary Safety Hazards: Organ deposition and toxicity, immunogenicity and complement activation, oxidative stress and inflammation, altered biodistribution with side effects, and batch variability impacting safety results.

10.2 Scaling Up and Manufacturing Challenges

While nanoparticle formulations can be successfully produced in the lab scale, their manufacture in an industrial setting is difficult. During the scale up process, uniform control of particle size, drug loading, stability, and release profile must be achieved according to regulations. Manufacture is especially difficult in the case of multifunctional nanocarriers, as small changes during manufacturing may impact safety and efficacy. For polymeric





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nanoparticles, reproducibility, purification and degradation control are problematic, and for lipids, there are problems concerning formulation stability and large-scale manufacturing. Despite the use of advanced technologies like microfluidic and continuous-flow manufacturing, consistent manufacturing is still a major challenge (37).

Challenges in Manufacturing: Reproducibility of properties of nanoparticles, process variability during scale-up, stability during storage and transport, manufacturing cost, and effective transition from research to commercial manufacturing.

10.3 Quality Control and Regulatory Guidelines

Quality control is vital to assure the safety, effectiveness and reproducibility of nanomedicine products. The complexity of nanoparticle systems makes traditional approaches to characterization insufficient. Important quality attributes include particle size, polydispersity, zeta potential, morphology, drug loading, encapsulation efficiency, release kinetics and stability. Biological characterization includes cell uptake, biodistribution, immunological effects and toxicity. The absence of standardized approaches to characterization was one of the reasons behind poor reproducibility in the past, hence the need to develop an integrated approach to characterization and reporting. Regulatory organizations, such as the FDA, EMA, and ICH, realize the need for special evaluation schemes, but due to variety of nanomedicine formulations, it may be necessary to consider each case separately. Harmonized international standards would facilitate the development and commercialization of nanomedicine products (38,40).

Key Quality Control Parameters

Particle size and distribution, surface charge and morphology, drug-loading capacity and encapsulation efficiency, stability and shelf life, sterility and endotoxin content, and in vitro/in vivo drug-release profiles (37,40–42).

11. Future Perspectives

The future of cancer drug delivery technologies will be driven by innovations in fields such as nanotechnology, biomaterials, computational science, and precision oncology. Though nanocarriers based on polymers and lipids have demonstrated substantial success, new innovations are allowing for more intelligent, patient-specific, and multi-functional drug carriers. Future research efforts will concentrate on surmounting translational hurdles using artificial intelligence, precision nanomedicine, biomaterials, and hybrid nanosystems (4,31,43).





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11.1 Artificial Intelligence in Nanocarrier Design

Nanomedicine is an emerging field which is becoming more dependent on artificial intelligence (AI) and machine learning (ML). Unlike the traditional ways of working, ML uses big datasets for analyzing the relationship between the characteristics of nanoparticles and their efficiency in providing therapeutic benefits. It helps in creating advanced nanocarriers that target effectively, have regulated drug delivery and ensure safety. AI will also be useful in personalizing treatments and patient selection. With the development of computational methods, the significance of AI in nanomedicine development will rise even further (43).

Potential Applications of AI in Nanomedicine: Predictive nanoparticle design, formulation optimization, drug-carrier compatibility analysis, toxicity prediction, safety assessment, personalized therapy planning, and clinical decision support (43).

11.2 Precision Nanomedicine

In the context of precision medicine, treatment is targeted according to the biology of the individual. As a result of heterogeneity in terms of genetics, receptors, metabolism, and drug response, precision nanomedicine relies on the use of nanocarriers tailored to specific patients or types of tumors. Precision nanotherapy has been made possible by developments in genomics, proteomics, and biomarker discovery such that there exist specific biomarkers, antigens, and mutations in the genetic material that can be treated (4).

11.3 Emerging Biomaterials and Smart Delivery Systems

The future trends in nanocarrier science will be toward the development of stimuli-sensitive biomaterials for the purpose of providing controlled drug delivery. pH sensitive drug delivery systems hold much promise since they do not dissociate during circulation and release their payload in the acidic environment of the tumor. The other materials include temperature sensitive, redox sensitive, enzymatically sensitive, hypoxically sensitive, ultrasensitive, magnetically sensitive, and light sensitive materials. These provide better drug specificity and increase efficacy and decrease toxicity. Bio-degradable polymers, bio-inspired materials, and natural products will be incorporated into nanocarriers (44).





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11.4 Hybrid and Multifunctional Nanoplatforms

The future of nanomedicine in cancer therapy will consist of increasing use of hybrid nanostructured systems, which take the best from different carriers of medications and diagnostic reagents. The examples are hybrid lipid-polymer nanoparticles, theranostic vehicles for delivering multiple types of therapeutic agents, and integrated delivery systems performing multiple functions. They combine the chemical stability of polymer particles and biological properties of lipid carriers and may be equipped with ligands for cell targeting, imaging elements, and elements responding to environmental changes (31).

11.5 Future Clinical Translation

However, despite considerable developments in cancer nanotherapy, the clinical translation of nanocarrier-based approaches is one of the main research challenges. Improvements in nanofabrication, quality control, regulatory science, and nanocarrier analysis can increase scalability and reproducibility. Combining nanotechnology with artificial intelligence, molecular diagnostics, precision medicine, and biomaterials will contribute to developing novel generation nanomedical devices. Next generation systems will possess diagnostic, treatment, and monitoring capabilities. Meeting the above challenges will necessitate the efforts of scientists, clinicians, engineers, industry and regulatory organizations to overcome the existing obstacles and translate the clinical utility of nanocarriers into oncology applications (4,31,43).

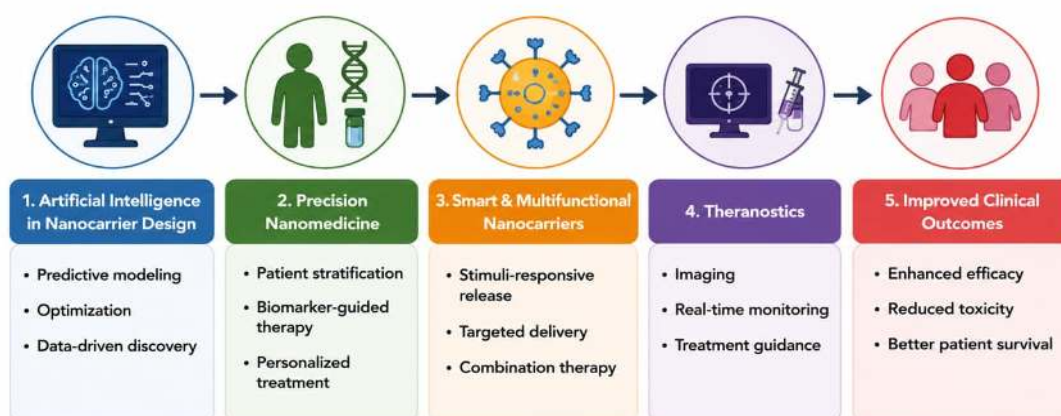


Fig. 3:

Future Perspectives in Cancer Nanomedicine.





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12. Conclusion

Cancer is one of the largest health problems on earth and continues to necessitate safer and more efficient methods of treatment. The application of nanotechnology for the delivery of antitumor drugs involves several beneficial aspects such as increased solubility, extended circulation time, controlled drug release and targeted delivery. Nanocontainers made from polymers such as nanoparticles, micelles, dendrimers, hydrogels and nanogels offer the advantage of modularity and controlled drug delivery while liposomal systems (liposomes, SLNs, NLCs, and LNPs) allow to achieve better therapeutic results and minimize toxic effects on the organism. Nowadays, many novel approaches like targeting and active delivery, stimulus-responsive systems, theranostic systems, personalized nanomedicine, and AI-assisted drug design help to improve the potential of nanocarriers in cancer therapy but there are still some obstacles connected with safety concerns, production processes, quality control issues, regulatory and translational barriers. Examples of successful nanoformulations of anticancer drugs include Doxil®, Abraxane®, Onivyde®, and Vyxeos®. Future advancements in the fields of nanotechnology, biomaterials, artificial intelligence, and precision medicine will help to design advanced nanomedicines for cancer treatment.

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