Nanoparticle-Based Drug Delivery for Cancer Therapy

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***Abstract*—Nanoparticle-based drug delivery systems have emerged as a transformative strategy in cancer therapy by improving drug solubility, enhancing targeted delivery, reducing systemic toxicity, and overcoming multidrug resistance. Conventional chemotherapy often lacks specificity, leading to adverse side effects and limited therapeutic efficacy. Nanotechnology offers innovative approaches for precise drug delivery through engineered nanoparticles such as liposomes, polymeric nanoparticles, dendrimers, metallic nanoparticles, and lipid-based carriers. These systems can exploit passive targeting through the enhanced permeability and retention (EPR) effect and active targeting using ligands directed toward tumor-specific receptors. This review discusses the principles, types, mechanisms, applications, advantages, limitations, and future prospects of nanoparticle-based drug delivery systems in cancer treatment. Cancer remains one of the leading causes of morbidity and mortality worldwide and continues to pose a major challenge to global healthcare systems despite remarkable progress in diagnostic and therapeutic approaches. Conventional cancer treatment strategies such as chemotherapy, radiotherapy, surgery, hormone therapy, and immunotherapy have significantly improved patient survival rates; however, these approaches are frequently associated with several serious limitations including poor drug selectivity, severe systemic toxicity, nonspecific biodistribution, multidrug resistance, rapid drug degradation, limited therapeutic index, and damage to healthy tissues. Among these, conventional chemotherapy remains one of the most widely used modalities for cancer treatment, but its lack of specificity often results in harmful side effects such as cardiotoxicity, nephrotoxicity, neurotoxicity, immunosuppression, and gastrointestinal complications. Consequently, there is an urgent need for advanced therapeutic systems capable of delivering anticancer agents more safely and effectively while minimizing adverse effects on normal tissues.**

***Index Terms*—Nanoparticles; Cancer therapy; Drug delivery systems; Targeted drug delivery; Nanomedicine; Liposomes; Polymeric nanoparticles.**

I. INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide. Traditional treatment modalities such as chemotherapy, radiotherapy, and surgery have improved patient survival rates; however, chemotherapy still faces significant challenges including non-specific distribution, severe toxicity, low bioavailability, and development of drug resistance (1,2).

Nanotechnology has introduced advanced drug delivery platforms capable of transporting therapeutic agents directly to tumor tissues while minimizing damage to healthy cells. Nanoparticles are typically materials with dimensions ranging from 1 to 100 nanometers. Due to their small size and modifiable surface properties, nanoparticles can efficiently penetrate biological barriers and selectively accumulate within tumor tissues (3,4).

Cancer is one of the most serious and life-threatening diseases worldwide and remains a major public health challenge despite continuous progress in medical science and healthcare technologies. It is characterized by the uncontrolled growth and proliferation of abnormal cells that invade surrounding tissues and may spread to distant organs through metastasis. According to global health statistics, cancer is among the leading causes of mortality and is responsible for millions of deaths each year. The increasing incidence of cancer is associated with multiple factors including aging populations, environmental pollution, unhealthy lifestyles, genetic mutations, viral infections, smoking, alcohol consumption, radiation exposure, and dietary habits. Common forms of cancer such as breast cancer, lung cancer, colorectal cancer, prostate cancer, liver cancer, and leukemia continue to contribute significantly to global morbidity and mortality (5-7).

Conventional approaches for cancer treatment include surgery, chemotherapy, radiotherapy, hormone

therapy, targeted therapy, and immunotherapy. Among these methods, chemotherapy remains one of the most commonly used therapeutic strategies for both localized and metastatic cancers. Chemotherapeutic agents function by inhibiting the growth and division of rapidly proliferating cancer cells. However, conventional chemotherapy is often associated with severe drawbacks due to its nonspecific distribution throughout the body. Since anticancer drugs cannot effectively distinguish between cancerous and healthy rapidly dividing cells, they frequently damage normal tissues such as bone marrow, hair follicles, gastrointestinal epithelium, and immune cells. As a result, patients commonly experience severe side effects including nausea, vomiting, hair loss, anemia, fatigue, nephrotoxicity, cardiotoxicity, neurotoxicity, immunosuppression, and reduced quality of life (8,9).

Another major limitation of conventional chemotherapy is poor bioavailability and rapid degradation of therapeutic agents before reaching the target site. Many anticancer drugs exhibit low water solubility, short circulation half-life, instability in physiological conditions, and inadequate penetration into tumor tissues. Furthermore, repeated exposure to chemotherapeutic agents often leads to multidrug resistance (MDR), where cancer cells develop mechanisms to evade the cytotoxic effects of drugs through drug efflux pumps, genetic mutations, enhanced DNA repair mechanisms, and altered cellular signaling pathways. These challenges significantly reduce therapeutic efficacy and limit successful treatment outcomes (10,11).

In recent decades, nanotechnology has emerged as a revolutionary and interdisciplinary field with tremendous potential to improve cancer diagnosis and therapy. Nanotechnology involves the design, synthesis, characterization, and application of materials and devices at the nanoscale level, generally ranging from 1 to 100 nanometers. At this scale, materials exhibit unique physical, chemical, optical, magnetic, and biological properties that differ significantly from their bulk counterparts. These distinctive properties make nanoparticles highly suitable for biomedical and pharmaceutical applications, particularly in targeted drug delivery systems (12,13).

Nanoparticle-based drug delivery systems have attracted substantial interest in oncology because they offer innovative solutions to many limitations associated with conventional cancer therapies. Nanoparticles can serve as carriers for therapeutic agents, enabling efficient transport of drugs directly to tumor tissues while minimizing exposure to healthy organs. Their nanoscale dimensions allow them to penetrate biological barriers and accumulate within tumors more effectively than traditional drug formulations. In addition, nanoparticles possess a large surface-area-to-volume ratio, which enhances drug loading capacity and enables surface modification with targeting ligands, polymers, antibodies, peptides, or imaging molecules (14).

One of the key advantages of nanoparticle-mediated drug delivery is the ability to achieve targeted therapy. Tumor targeting may occur through passive targeting or active targeting mechanisms. Passive targeting is primarily based on the enhanced permeability and retention (EPR) effect, a phenomenon resulting from the abnormal and leaky vasculature of tumor tissues combined with impaired lymphatic drainage. Due to the EPR effect, nanoparticles can preferentially accumulate in tumor tissues, increasing local drug concentration and reducing systemic toxicity. Active targeting further improves specificity by conjugating nanoparticles with ligands that bind selectively to receptors overexpressed on cancer cells, such as folate receptors, transferrin receptors, epidermal growth factor receptors (EGFR), and HER2 receptors. This targeted approach improves cellular uptake and enhances therapeutic efficacy (15-17).

1.1 Principles of Nanoparticle-Based Drug Delivery

Enhanced Permeability and Retention (EPR) Effect

Tumor tissues possess abnormal vasculature with leaky blood vessels and poor lymphatic drainage. Nanoparticles can passively accumulate in tumor tissues through the EPR effect, allowing higher drug concentrations at the tumor site (22).

1.2 Active Targeting

Active targeting involves surface modification of nanoparticles with ligands such as antibodies, peptides, folic acid, aptamers, or transferrin. These ligands bind specifically to receptors overexpressed on cancer cells, thereby improving cellular uptake and therapeutic efficacy (23).

1.3 Controlled Drug Release

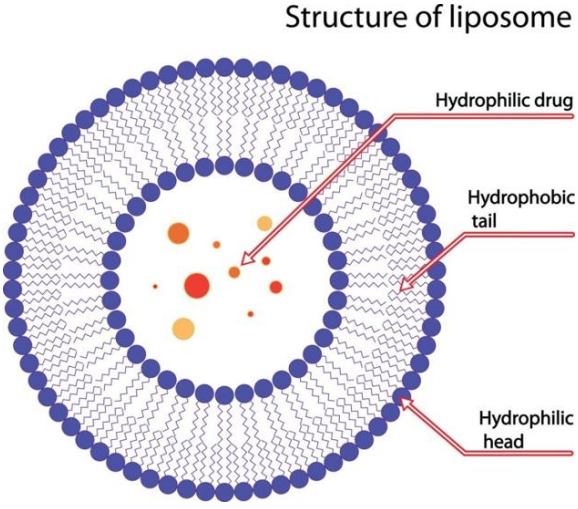
Stimuli-responsive nanoparticles represent a groundbreaking frontier in precision medicine by

acting as smart delivery vehicles that release their therapeutic payload only when triggered by specific cues. These engineered nanoparticles can be designed to respond to internal biological triggers, such as pH changes commonly found in acidic tumor microenvironments or specific enzymes overexpressed at disease sites. Alternatively, they can be activated by external, user-controlled physical stimuli, including temperature shifts, magnetic fields, light wavelengths, or ultrasound waves. By shielding the drug during circulation and deploying it exclusively at the target site, these adaptable nanocarriers dramatically improve localized treatment precision while minimizing toxic off-target effects on healthy tissues.

II. TYPES OF NANOPARTICLES USED IN CANCER THERAPY

A. Liposomes

Liposomes are microscopic, spherical vesicles composed of one or more phospholipid bilayers that closely mimic natural cell membranes. This unique structural architecture grants them the remarkable ability to encapsulate both hydrophilic (water-loving) drugs within their aqueous core and hydrophobic (fat-loving) drugs within the lipid bilayer itself.

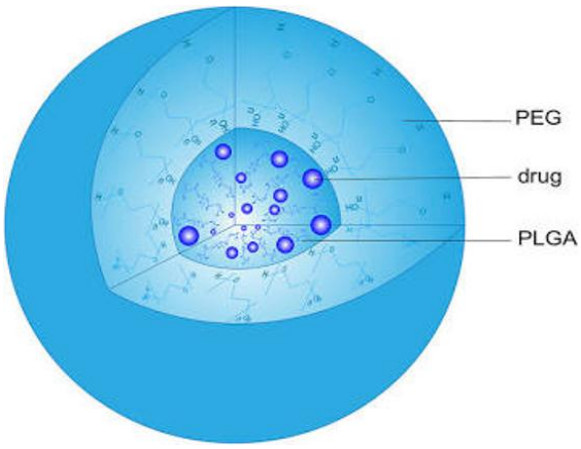


As a drug delivery platform, liposomes offer several clinical advantages. Because they are constructed from natural lipids, they exhibit excellent biocompatibility and low systemic toxicity. They can carry highly diverse therapeutic agents, protect them from premature degradation, and provide a prolonged circulation time in the bloodstream. These properties have translated into significant real-world clinical applications; most notably, liposomal formulations of the chemotherapy drug doxorubicin have achieved great success in targeted treatments for breast cancer, ovarian cancer, and Kaposi's sarcoma by concentrating the medication within tumor tissues while shielding healthy organs like the heart.

B. Polymeric Nanoparticles

Polymeric nanoparticles are highly versatile drug delivery systems formulated from biodegradable polymers, which can be either synthetic-such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polylactic acid (PLA)-or natural, like chitosan. The primary advantage of these nanoparticles lies in their exceptional structural stability and their capacity for highly controlled, sustained drug release, which ensures that therapeutics are slowly liberated at the target site over an extended period. Furthermore, they offer enhanced protection for sensitive payloads against premature enzymatic or chemical degradation. Because their polymer outer shell can be readily modified, these systems possess excellent surface functionalization capability, allowing scientists to attach specific targeting ligands (like antibodies) directly to the surface to recognize diseased cells. In clinical oncology, polymeric nanoparticles are heavily utilized for the targeted delivery of potent, poorly water-soluble anticancer drugs including paclitaxel and cisplatin, safely ferrying them through the bloodstream directly into solid tumors. However, their development is bound by notable limitations, including highly complex manufacturing processes required to ensure uniform particle size and precise drug entrapment. Additionally, while the base materials are biodegradable, researchers must continuously monitor potential polymer toxicity, as the accumulation of degraded polymer byproducts or synthetic residues can sometimes trigger localized inflammatory responses or adverse cellular reactions in the body.

Dendrimers: Dendrimers are a unique class of highly branched, three-dimensional macromolecules characterized by a perfectly symmetrical, well-defined molecular architecture that resembles the limbs of a tree.



Unlike traditional linear polymers, their precise, step-by-step synthetic construction provides an outer shell radiating with numerous reactive endpoints, offering unparalleled surface modification flexibility for attaching targeting ligands or imaging agents. Additionally, their hollow, cavernous interior voids combined with these dense surface groups yield an exceptionally high drug loading capacity, allowing both hydrophilic and hydrophobic molecules to be structurally encapsulated or chemically conjugated. Because of this structural adaptability, dendrimers are being aggressively explored across multiple biomedical frontiers, including gene delivery-where they safely package and transport fragile nucleic acids-as well as diagnostic imaging and targeted cancer chemotherapy. However, their clinical transition is restricted by two major limitations: their complex, multi-step synthesis is highly labor-intensive and expensive to scale up, and certain formulations, particularly those with positively charged surfaces, present significant cytotoxicity concerns due to their tendency to interact with and disrupt cell membranes.

C. Metallic Nanoparticles:

In cancer nanomedicine, inorganic nanoparticles-specifically gold, silver, iron oxide, and silica nanoparticles-are widely studied due to their unique physical, optical, and magnetic properties. A major advantage of these materials is their built-in imaging capability, allowing them to act as highly sensitive contrast agents for techniques like MRI and CT scans. Furthermore, they enable advanced photothermal therapy applications and magnetic targeting, where an external magnetic field can guide iron oxide nanoparticles directly to a tumor site. A prime clinical application of this technology is found in gold nanoparticles used for photothermal therapy; when exposed to a specific wavelength of laser light, these nanoparticles absorb the light energy and convert it into localized, intense heat, effectively destroying nearby tumor cells while leaving healthy surrounding tissue unharmed. Despite these advanced therapeutic capabilities, inorganic nanoparticles face significant hurdles regarding their long-term safety profile. Unlike biodegradable polymer or lipid-based carriers, these inorganic cores do not readily break down or dissolve in the body, which leads to major bioaccumulation risks as they get trapped in organs like the liver and spleen. This inability to be easily excreted raises serious long-term toxicity concerns, as the persistent presence of metallic or mineral particles within healthy tissues could potentially trigger chronic inflammation, oxidative stress, or cellular damage over time.

D. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) represent an innovative hybrid drug delivery system engineered to combine the most desirable traits of both liposomes and polymeric nanoparticles. Structurally, SLNs replace the liquid lipid core found in traditional emulsions with a solid lipid matrix at room and body temperature, stabilized by an outer surfactant layer. This solid core grants them high structural stability and offers improved drug stability, shielding sensitive therapeutic payloads from chemical degradation. Like liposomes, they boast good biocompatibility and low toxicity because they are made from physiological, well-tolerated lipids. Additionally, because the matrix is solid, it slows down the diffusion of the encapsulated molecules, providing a highly predictable and controlled release profile over an extended period. Because of their affinity for lipophilic substances, SLNs are widely utilized in oncology applications to deliver poorly soluble anticancer drugs, enhancing their bioavailability and allowing them to circulate more effectively in the bloodstream. However, these delivery systems are constrained by two interconnected limitations. First, because the solid lipid matrix forms a highly ordered, perfect crystalline lattice, it offers limited drug incorporation, meaning there are relatively few spaces or "defects" within the crystal structure to trap the drug molecules. Second, during storage, these lipids naturally undergo a slow transition into a more stable,

tightly packed crystalline state; this structural compaction squishes the internal spaces, frequently leading to drug expulsion where the medication is pushed completely out of the nanoparticle matrix before it ever reaches the patient.

III. MECHANISMS OF TARGETED DRUG DELIVERY

In cancer nanomedicine, maximizing therapeutic impact while minimizing systemic side effects relies on two distinct strategies: passive and active targeting. Passive targeting: is a foundational mechanism that relies completely on the unique physical characteristics of tumor biology. Rapidly growing tumors develop disorganized, leaky blood vessels with large gaps in their endothelial walls, combined with poor lymphatic drainage. This physiological anomaly is known as the Enhanced Permeability and Retention (EPR) effect. Because of the EPR effect, circulating nanoparticles naturally escape through these leaky vessel walls and preferentially accumulate within the tumor tissue rather than healthy organs. While passive targeting helps accumulate nanocarriers inside the tumor mass,

Active targeting: takes precision a step further by ensuring the nanoparticles actively bind to and enter the individual cancer cells. This method enhances cellular selectivity by engineering the surface of the nanoparticle with specific ligands (such as antibodies, peptides, or small molecules) designed to attach to highly overexpressed receptors on the tumor cell surface. Common biological landmarks targeted in oncology include HER2 receptors (frequently overexpressed in aggressive breast cancers), folate receptors (highly sought after in ovarian and lung malignancies due to the cell's high demand for folic acid), EGFR (Epidermal Growth Factor Receptor), and transferrin receptors (which malignant cells utilize to hijack iron uptake for rapid growth). By combining the anatomical accumulation of passive targeting with the lock-and-key precision of active receptor-ligand interactions, these systems ensure the drug payload is internalized directly by the cancer cells, radically lowering off-target toxicity.

IV. STIMULI-RESPONSIVE DELIVERY

Beyond passive and active targeting, the precision of nanomedicine can be further heightened through the use of stimuli-responsive nanoparticles, which are engineered to act as smart, gated containers that release their therapeutic agents only when they encounter specific physical or biochemical triggers. These triggers are broadly categorized into internal and external stimuli. Internal stimuli rely on the distinct, localized microenvironment created by the tumor itself. For instance, because malignant tissues exhibit accelerated metabolism, they create an acidic tumor pH that can trigger nanoparticles to dissolve or swell. Similarly, the intracellular redox environment characterized by high concentrations of reducing agents like glutathione or specific elevated enzyme activity at the disease site can be exploited to cleave chemical bonds on the nanoparticle shell, safely unleashing the medication exactly where it is needed. Conversely, external stimuli grant clinicians direct, spatial-temporal control over when and where a drug is deployed by applying energy from outside the patient's body. Magnetic fields can be used to vibrate or heat magnetic nanoparticles, disrupting their structure to free the payload, while precise light irradiation (such as near-infrared laser light) can trigger photochemical reactions. Additionally, ultrasound waves can generate mechanical or thermal disruptions to push drugs out of carriers, and focused heat application can alter polymer permeability. By leveraging these internal pathological differences and external physical inputs, stimuli-responsive systems offer an elegant way to prevent premature drug leakage in healthy circulation, drastically reducing systemic side effects.

V. APPLICATIONS IN CANCER THERAPY

A. Chemotherapy

In modern oncology, nanotechnology has fundamentally revolutionized the deployment of traditional chemotherapy by reshaping how these potent cytotoxic drugs move through the human body. Conventional chemotherapy routinely floods the entire system, leading to severe side effects because it cannot differentiate between a malignant tumor and healthy, rapidly dividing cells in the bone marrow, gut, and hair follicles. By encapsulating these hazardous agents

within engineered nanocarriers, scientists can significantly improve the delivery of chemotherapeutic drugs, utilizing anatomical anomalies like the leaky blood vessels of tumors to increase localized drug accumulation while shielding healthy tissues from direct exposure. This sophisticated shielding mechanism maximizes the therapeutic punch delivered to the cancer site while drastically minimizing systemic toxicity, translating to fewer severe side effects for patients undergoing treatment. Several clinical blockbusters and cutting-edge formulations perfectly illustrate this approach. For instance, doxorubicin-loaded liposomes package a highly cardiotoxic drug within a protective lipid bubble, preventing it from damaging the heart muscle while allowing it to gather inside tumors to treat breast and ovarian cancers. Similarly, paclitaxel nanoparticles (such as albumin-bound formulations) eliminate the need for toxic chemical solvents previously required to dissolve the drug, heavily reducing severe allergic reactions and allowing safer, higher doses to be administered. Finally, cisplatin polymeric carriers wrap this highly effective but kidney-damaging platinum drug inside a biodegradable polymer matrix, ensuring the drug is released at a slow, calculated pace that maintains steady tumor destruction while keeping blood concentrations safely below the threshold that causes renal failure.

B. Gene Therapy

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C. Immunotherapy

Immunotherapy represents a paradigm shift in oncology that seeks to treat cancer not by directly killing tumor cells with toxic chemicals, but by training and amplifying the patient's own immune system to recognize and destroy them. While highly promising, traditional immunotherapy agents like checkpoint inhibitors often struggle with systemic immune-related adverse effects or poor infiltration into "cold" tumors that actively suppress immune responses. Nanotechnology tackles these hurdles by acting as a powerful orchestrator of the immune microenvironment. Engineered nanoparticles can simultaneously deliver tumor antigens and immune-stimulating adjuvants directly to antigen-presenting cells (such as dendritic cells) in the lymph nodes. This targeted delivery effectively acts as a cancer vaccine, training T-cells to specifically hunt down and eliminate cancer cells throughout the body while avoiding healthy tissue. Furthermore, nanotechnology can be designed to reprogram the highly suppressive environment immediately surrounding a tumor. For instance, nanoparticles can carry targeted small molecules or genetic payloads that switch tumor-promoting "M2" macrophages into tumor-killing "M1" macrophages, effectively stripping away the shield that cancer cells use to hide. They can also be packed with multiple synergistic therapies—such as

combining a chemotherapeutic drug that causes immunogenic cell death with an immunotherapy molecule that prevents immune exhaustion. By improving the stability, circulation time, and cellular targeting of these complex biological agents, nanomedicine enhances the durability and success rate of cancer immunotherapies, turning once-unresponsive tumors into prime targets for immune elimination (36).

VI. ADVANTAGES OF NANOPARTICLE-BASED DRUG DELIVERY

Nanoparticle-mediated cancer therapy provides a comprehensive suite of clinical advantages that fundamentally reshape the effectiveness and tolerability of oncological treatments. At its core, this technology solves a major pharmacological hurdle by providing enhanced drug solubility and improved bioavailability for highly potent anticancer agents that are naturally hydrophobic and difficult to dissolve in the bloodstream. By encapsulating these compounds, nanocarriers ensure target-specific delivery directly to tumor sites via active or passive targeting mechanisms, which simultaneously leads to reduced systemic toxicity by keeping the hazardous chemicals away from healthy organs. Furthermore, the specialized composition of the nanoparticle matrix allows for a highly controlled drug release, keeping therapeutic levels steady over an extended period while ensuring the protection of drugs from degradation by circulating blood enzymes. Beyond these pharmacokinetic benefits, nanotechnology plays a critical role in overcoming multidrug resistance (MDR); because nanoparticles enter cancer cells through endocytosis rather than passive diffusion, they bypass the cell membrane's efflux pumps that normally kick out free chemotherapy drugs. Ultimately, by eliminating the need for aggressive solvent mixtures, minimizing grueling side effects, and lowering the required frequency of treatments, this approach leads to significantly enhanced patient compliance and a better overall quality of life during therapy.

VII. CONCLUSION

Nanoparticle-based drug delivery systems represent a promising advancement in cancer therapy by addressing many limitations associated with conventional chemotherapy. Their ability to selectively target tumors, improve drug bioavailability, reduce toxicity, and enable controlled drug release has significantly advanced oncology research.

Although challenges related to toxicity, manufacturing, and regulatory approval remain, continuous technological innovations are accelerating clinical translation. Future developments in smart nanoparticles, personalized nanomedicine, and multifunctional therapeutic platforms are expected to further enhance the effectiveness of cancer treatment.

Nanotechnology has the potential to transform cancer management and contribute substantially to precision medicine in the coming decades.

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