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Review Article

Advances in Targeted Drug Delivery Systems for Cancer Therapy: Nanotechnology to Clinical Translation

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ARTICLEINFO ABSTRACT

The treatment of cancer remains a significant challenge due to the limitations of conventional chemotherapeutics, including systemic toxicity, poor tumor specificity, and multidrug resistance. Targeted drug delivery systems have emerged as a transformative approach to improve the efficacy and safety of cancer therapy by selectively delivering therapeutic agents to tumor sites. Among these, nanotechnology-based carriers such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and micelles have demonstrated promising results in both preclinical and clinical settings. These nanocarriers enhance drug solubility, stability, and circulation time, and can be engineered for passive or active tumor targeting through surface modifications with ligands such as antibodies, peptides, and aptamers. Furthermore, stimuli-responsive systems that release drugs in response to tumor-specific triggers offer an added layer of precision. Several nanoformulations have been approved for clinical use, including Doxil and Abraxane, while others are progressing through clinical trials. Despite significant advancements, challenges such as large-scale manufacturing, regulatory hurdles, and long-term safety concerns continue to limit widespread clinical adoption. This review provides a comprehensive overview of the latest developments in targeted drug delivery systems for cancer, focusing on nanotechnology-enabled strategies and their journey toward clinical translation.

Keywords: Targeted Drug Delivery, Cancer Therapy, Nanotechnology, Nanocarriers, Clinical Translation

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with millions of new cases and deaths reported annually. Despite significant advances in oncology, the effectiveness of conventional chemotherapy continues to be hindered by major limitations such as nonspecific biodistribution, poor solubility of anticancer agents, rapid systemic clearance, dose-limiting toxicity, and the development of multidrug resistance. These drawbacks often lead to suboptimal therapeutic outcomes and severe side effects, significantly impacting patient quality of life [1].

To address these challenges, targeted drug delivery systems have gained considerable attention in recent years. These systems are designed to transport therapeutic agents directly to tumor tissues, thereby enhancing drug accumulation at the disease site while minimizing off-target effects. The concept of targeting in cancer therapy can be broadly classified into passive and active mechanisms. Passive targeting relies on the enhanced permeability and retention (EPR) effect characteristic of tumor vasculature, while active targeting utilizes specific ligands—such as antibodies, peptides, or aptamers—to bind selectively to overexpressed receptors on cancer cells [2].

Nanotechnology has revolutionized the field of targeted cancer therapy by enabling the development of sophisticated nanocarriers with controlled release profiles, high loading capacities, and customizable surface properties. Various nanoscale platforms—including liposomes, polymeric nanoparticles, dendrimers, micelles, and solid lipid nanoparticles—have been extensively explored for the encapsulation and targeted delivery of chemotherapeutic drugs. Some of these nanomedicines have already been approved for clinical use, while many others are advancing through different stages of clinical trials [3].

This review provides an in-depth overview of recent advancements in targeted drug delivery systems for cancer therapy, emphasizing nanotechnology-enabled platforms and their progress from laboratory research to clinical application. The article also discusses the challenges associated with the clinical translation of nanomedicine and highlights future directions in the field [4].

2. 2. Principles of Targeted Drug Delivery

The fundamental goal of targeted drug delivery in cancer therapy is to enhance the therapeutic index of anticancer agents by maximizing their concentration at the tumor site while minimizing systemic toxicity. Unlike conventional drug delivery methods, targeted systems are engineered to deliver drugs selectively to cancer cells through specific biological or physicochemical mechanisms. The two primary approaches to targeting are passive targeting and active targeting, along with emerging strategies like stimuli-responsive delivery systems [5].

2.1 Passive Targeting

Passive targeting primarily exploits the Enhanced Permeability and Retention (EPR) effect, a phenomenon in which nanoparticles preferentially accumulate in tumor tissues due to the leaky vasculature and poor lymphatic drainage associated with solid tumors. Nanocarriers sized between 10–200 nm can passively accumulate in tumors through this mechanism. However, the efficiency of the EPR effect varies significantly across tumor types and between patients, limiting its universal application [6].

2.2 Active Targeting

Active targeting involves the functionalization of nanocarriers with specific ligands that bind to receptors overexpressed on the surface of cancer cells. These ligands include monoclonal antibodies, peptides, folic acid, transferrin, and aptamers. Upon receptor-ligand interaction, the nanocarrier is internalized via receptor-mediated endocytosis, leading to higher intracellular drug concentrations. This approach enhances selectivity and therapeutic efficacy while minimizing effects on healthy tissues [7].

2.3 Stimuli-Responsive Drug Delivery

Stimuli-responsive or "smart" delivery systems are designed to release their drug payload in response to specific internal (e.g., pH, redox potential, enzymes) or external (e.g., temperature, light, magnetic field) stimuli present in the tumor microenvironment. These systems provide spatiotemporal control over drug release, improving treatment precision and reducing systemic exposure. For instance, pH-sensitive nanoparticles can exploit the acidic tumor milieu to trigger drug release selectively within cancerous tissues [8].

3. Types of Nanocarriers Used in Cancer Therapy

Nanocarriers are at the forefront of advanced drug delivery systems due to their ability to improve drug solubility, stability, bioavailability, and targeted delivery to tumor sites. Several types of nanocarriers have been developed and investigated for cancer therapy, each with unique characteristics, advantages, and limitations [9].

3.1 Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. Their biocompatibility and ability to be surface-modified with targeting ligands make them ideal for cancer therapy. Approved formulations like Doxil® exemplify their clinical potential [10].

3.2 Polymeric Nanoparticles

Made from biodegradable polymers such as PLGA or PEG-PLA, polymeric nanoparticles offer controlled and sustained drug release. They can be engineered for active targeting and stimuli responsiveness.

3.3 Dendrimers

Dendrimers are highly branched, tree-like nanostructures with a defined molecular architecture. They provide multivalent surfaces for drug loading and targeting ligands but require careful control of toxicity and synthesis [11].

3.4 Solid Lipid Nanoparticles (SLNs)

SLNs are composed of solid lipids and are known for good biocompatibility, physical stability, and controlled release. They offer an alternative to polymeric carriers for lipophilic drugs [12-15].

3.5 Polymeric Micelles

Micelles are formed from amphiphilic block copolymers that self-assemble in aqueous environments. They are particularly useful for solubilizing poorly water-soluble anticancer drugs [16].

3.6 Exosomes

Exosomes are naturally derived extracellular vesicles with inherent targeting ability and low immunogenicity. They represent a biomimetic approach to drug delivery, although standardization and scalability remain challenges [17-19].

Table 1: Comparative Overview of Nanocarriers Used in Cancer Drug Delivery [20]

Nanocarrier Type	Structure	Drug Type Carried	Advantages	Limitations	Clinical Status
Liposomes	Phospholipid bilayer vesicles	Hydrophilic & hydrophobic	Biocompatible, modifiable, FDA-approved (e.g., Doxil®)	Stability, short circulation time (unmodified)	Approved, in clinical use
Polymeric Nanoparticles	Biodegradable polymer spheres	Hydrophobic mainly	Controlled release, scalable, customizable	Possible cytotoxicity from polymers	Clinical trials, some approved
Dendrimers	Branched, tree-like structures	Hydrophilic & hydrophobic	Precise structure, multivalency for targeting	Complex synthesis, potential toxicity	Preclinical and early clinical
SLNs	Solid lipid core	Lipophilic	High stability, biocompatible	Limited drug loading	In clinical research
Micelles	Amphiphilic block copolymers	Poorly soluble drugs	High drug solubilization, easy to formulate	Dilution instability, rapid clearance	Clinical trials
Exosomes	Natural extracellular vesicles	Proteins, RNA, small molecules	Natural origin, low immunogenicity	Scalability, isolation complexity	Preclinical and clinical research

4. Targeting Ligands and Surface Modifications

To enhance specificity and therapeutic efficacy, nanocarriers are often surface-modified with targeting ligands that recognize and bind to overexpressed receptors on cancer cells. This approach facilitates active targeting and increases intracellular drug accumulation through receptor-mediated endocytosis.

4.1 Common Targeting Ligands

Monoclonal antibodies: High specificity; used to target HER2, EGFR, and other tumor markers.

Peptides: Small size and ease of synthesis; examples include RGD peptides targeting integrins.

Folic acid: Binds to folate receptors, commonly overexpressed in many cancers (e.g., ovarian, breast).

Transferrin: Targets transferrin receptors found on rapidly dividing cancer cells.

Aptamers: Short DNA/RNA sequences that bind to specific proteins or receptors with high affinity.

4.2 Surface Modification Strategies

Surface modifications improve nanocarrier stability, circulation time, and targeting efficiency. The most common strategies include:

PEGylation: Attachment of polyethylene glycol (PEG) chains to prevent recognition by the reticuloendothelial system (RES), thus prolonging circulation time and enhancing accumulation at tumor sites.

Charge modulation: Adjusting surface charge to improve cell membrane interaction or reduce nonspecific uptake.

Dual-targeting or multi-functionalization: Combining more than one ligand or incorporating imaging agents for theranostic applications.

These modifications enable nanoparticles to overcome biological barriers, increase tumor selectivity, and reduce systemic side effects, thus contributing significantly to the success of nanomedicine-based cancer therapy.

7. Conclusion

Targeted drug delivery systems represent a paradigm shift in cancer therapy by offering improved drug specificity, reduced toxicity, and enhanced therapeutic outcomes. Nanotechnology has enabled the design of sophisticated carriers that exploit passive, active, and stimuli-responsive mechanisms to deliver anticancer agents more effectively. Among the various nanocarriers, liposomes, polymeric nanoparticles, dendrimers, and micelles have shown substantial preclinical and clinical success, with several formulations already approved for clinical use.

Surface modifications with targeting ligands and PEGylation further improve the pharmacokinetics and selectivity of these nanocarriers. However, challenges such as large-scale manufacturing, regulatory standardization, long-term safety assessment, and tumor heterogeneity continue to limit their widespread adoption.Looking ahead, the integration of personalized medicine, biomarker-based targeting, and artificial intelligence in drug delivery design holds great promise. With ongoing innovations and clinical trials, nanotechnology-based targeted drug delivery systems are poised to become a cornerstone of precision oncology in the coming decades.

Conflict of Interest

The authors declare no conflict of interest.

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