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Advancements in Drug Delivery Systems for Cancer Therapy: Mechanisms, Clinical Translation, and Future Directions

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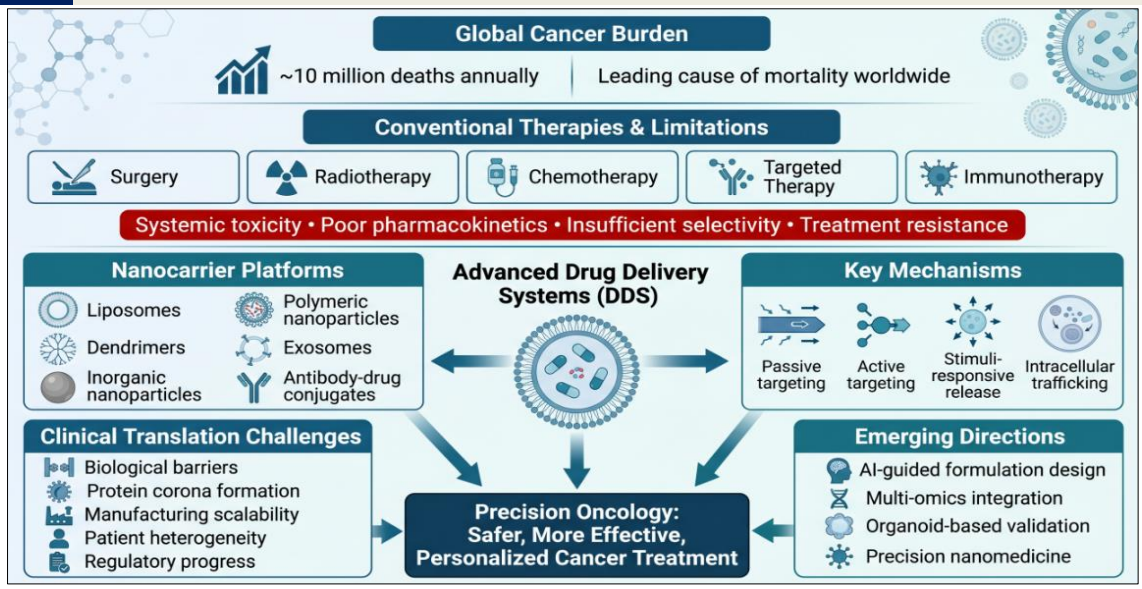
Abstract



Cancer continues to be a leading cause of death globally, with almost 10 million people dying from the disease annually, presenting a significant global health challenge. While traditional therapies - surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy - have extended survival rates, they are often compromised due to systemic toxicity, inadequate pharmacokinetics, lack of selectivity, and drug resistance. Innovative drug delivery systems (DDS), especially nanotechnology-based DDS, have recently gained attention as potential methods to improve therapeutic outcomes and outcomes. This review critically examines the advances in drug delivery for cancer treatment, with particular emphasis on nanotechnology-based systems such as liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles, exosomes, and antibody–drug conjugates. Various features such as passive and active targeting strategies, drug release in response to stimuli, internalization and intracellular trafficking, administration routes, and in vivo considerations are thoroughly reviewed. Further, the review outlines the current clinical translation, regulatory advances, and key challenges, such as biological barriers, protein corona, scalability and tumor heterogeneity. The review also outlines future perspectives - such as artificial intelligence-driven formulation development, multi-omics integration, organoid-based systems for drug validation and precision nanomedicine - are also discussed as key factors for next-generation cancer treatment. In general, advanced DDS are helping to transform non-specific, conventional chemotherapy into targeted, efficient and individualized cancer therapies.

Keywords: Cancer therapy, drug delivery systems, nanomedicine, nanoparticles, targeted delivery, EPR effect, antibody–drug conjugates, precision oncology.

1. INTRODUCTION

Cancer is one of the most difficult and challenging medical problems. It's estimated that 20 million new cases are diagnosed globally every year, and this figure is likely to increase dramatically in the next few decades as a result of an ageing population, urbanization and environmental and lifestyle changes. It is important to note that cancer is not a single entity, but rather a collection of over one hundred different cancers, each with its own molecular profile, behaviour and response to treatment [1].

Although tremendous progress has been made in cancer research, therapeutic outcomes are restricted by multiple factors, such as intratumoral heterogeneity, multidrug resistance, metastatic disease and poor drug delivery [3]. Traditional systemic chemotherapy is non-selective, which leads to systemic distribution and dose-limiting side effects in rapidly proliferating normal cells (such as bone marrow, gut and hair follicles). So, selectivity of drug action is a key goal of cancer treatment without compromising efficacy [2].

Drug delivery systems (DDS) have shown potential to overcome these limitations by facilitating controlled, targeted and responsive delivery of drugs specifically to the site of the tumor, thus overcoming unwanted side effects and enhancing therapeutic efficacy [3].

2. Evolution in Drug Delivery Systems in Cancer

The treatment of cancer with drugs has progressed from the use of non-specific toxic agents to more complex drug delivery approaches [4]. The first chemotherapeutic agents showed systemic administration could lead to tumor regression; but their therapeutic index was poor. As a result, drug carriers were developed to alter drug pharmacokinetics without changing their inherent activity [5].

This journey culminated in the FDA approval of PEGylated liposomal doxorubicin, displaying reduced cardiotoxicity without compromising efficacy [6]. More recently, the application of nanotechnology, biomaterials and molecular oncology has allowed the design of next-generation DDS for targeted drug delivery, overcoming biological barriers and responding to tumor microenvironmental cues [7].

Today, drug delivery systems include targeting ligands, imaging agents, controlled drug release and the potential to deliver multiple drugs [9]. As such, they are no longer passive carriers, but have become multifunctional therapeutic agents that are key to next-generation cancer therapies [8].

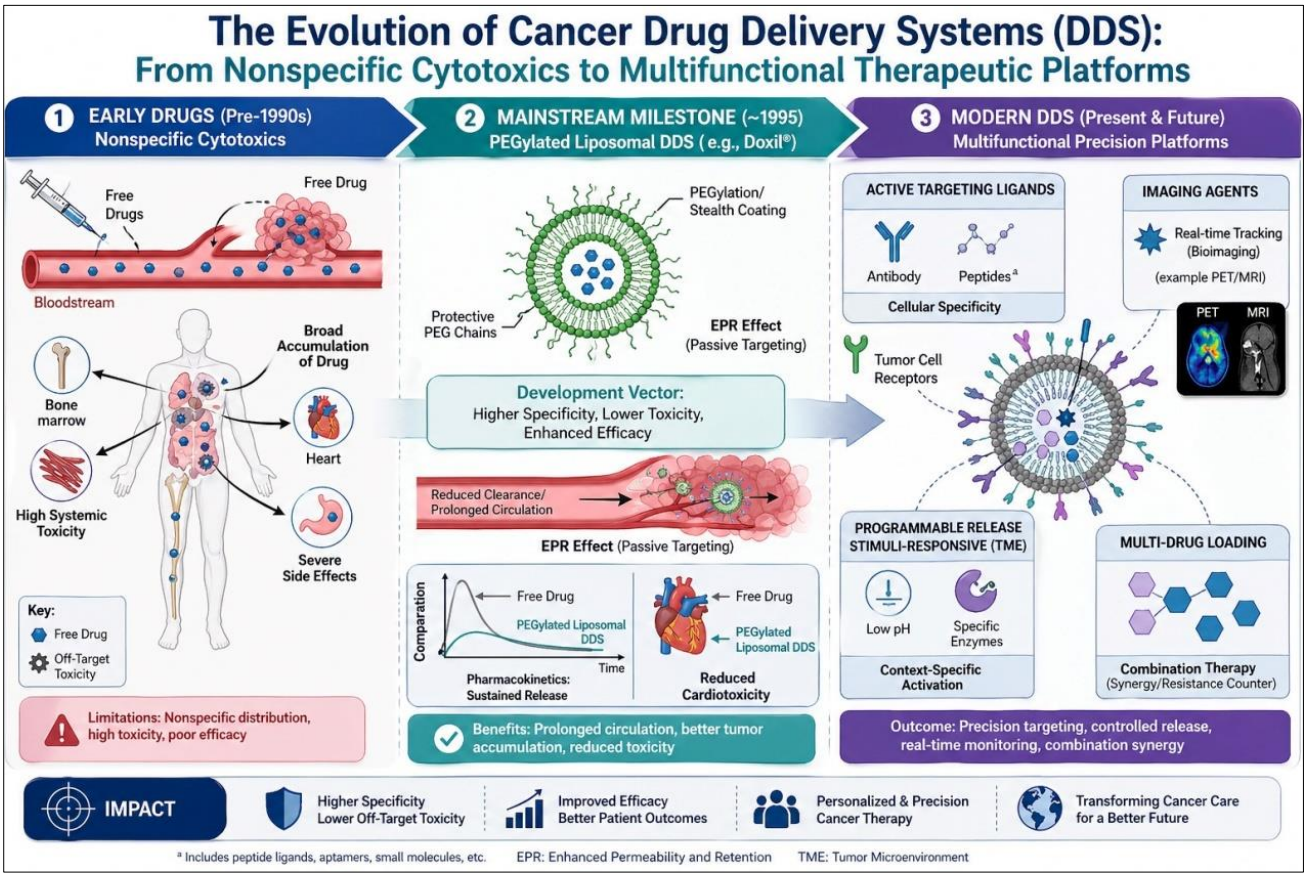


Figure 1: Evolution of Cancer Drug Delivery System

3. Limitations of Conventional Cancer Treatment Modalities

While traditional methods of cancer treatment remain vital in the management of cancer patients, each therapeutic approach has limitations and advanced drug delivery systems need to be developed [9].

3.1 Surgery

Surgical intervention is still the mainstay of treatment for primary tumors. But it has no impact on metastatic disease, and it can lead to inflammatory responses that can further spread the tumor. Moreover, complications and recovery issues restrict its use, especially in the elderly and frail [10].

3.2 Radiotherapy

Radiotherapy is a powerful local treatment, which kills cancer cells by damaging their DNA. But it is ineffective in treating micrometastatic disease. It also has delayed side effects such as fibrosis and induces a secondary cancer risk [11].

3.3 Conventional Chemotherapy

Traditional chemotherapy has a cytotoxic effect on rapidly proliferating cells, but is non-specific for cancer cells, resulting in high toxicity. This results in side effects such as blood toxicity, gastrointestinal toxicity and neurotoxicity. Additionally, the effect of the treatment is confounded by resistance to chemotherapy through mechanisms such as drug transporters and survival pathways [12].

3.4 Targeted Therapy

Targeted therapies enhance selectivity by targeting specific pathways of action; but are only effective in patients with certain genetic mutations. Acquiring resistance through secondary mutations and redundancy often limits their effectiveness over time [13].

3.5 Immunotherapy

Immunotherapy, such as immune checkpoint inhibitors and cellular therapies, has revolutionized the field of cancer therapy. However, this approach shows limited efficacy in many solid tumors, and can induce serious immune-related side effects, especially with cellular therapies [14].

Overall, these challenges underline the need for novel drug delivery systems to increase therapeutic index, tumor selectivity and reduce off-target effects [15].

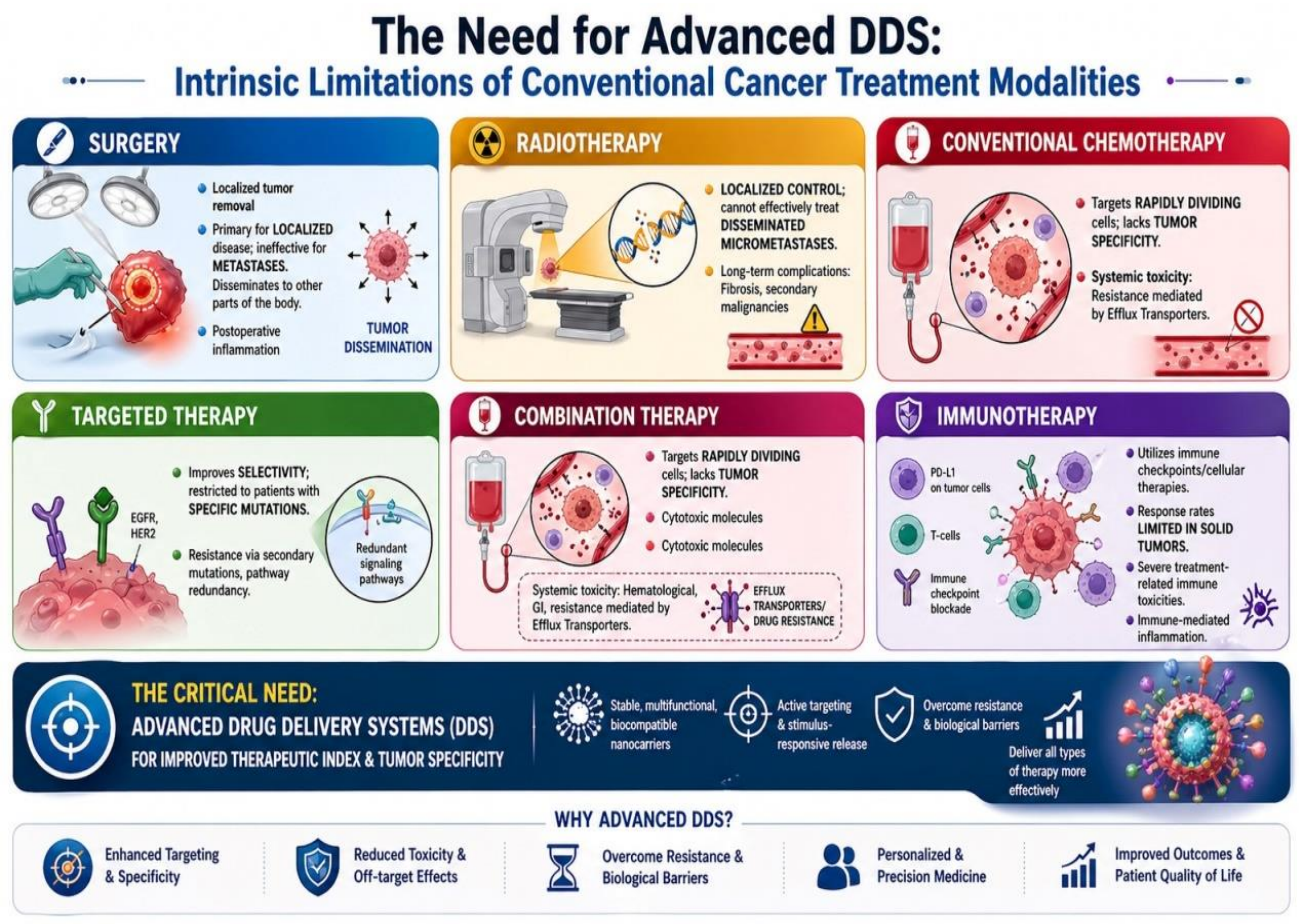


Figure 2: Need for Advanced DDS

4. Routes of Administration in Cancer Drug Delivery

Pharmacokinetics, biodistribution, and target site drug concentration are all affected by the route of administration, which has a profound effect on the efficacy of nanomedicine [16].

The most common route of administration for nanomedicines is intravenous injection because of its high bioavailability and the feasibility of delivering nanomedicines with certain properties. Intramuscular administration can be used to create a depot effect for sustained drug release for some formulations [17].

New modes of administration, such as intratumoral injection, oral nanomedicine formulations, intrathecal transport, intranasal transport and transdermal microneedles are being investigated to enhance compliance and allow innovative approaches. Some of these methods hold great promise for crossing biological barriers, such as the blood–brain barrier [18].

5. Nanotechnology-Based Drug Delivery Systems

Nanotechnology-based drug delivery platforms are an important enabling technology for next-generation therapies in cancer. Their wide range of physical and chemical properties - size, shape, charge, hydrophobicity, ligand density and release profiles- enable tight control of biodistribution and intratumoral fate of the drug [19].

5.1 Nanocarrier Engineering Manufacturing Processes

Robust and scalable fabrication methods are crucial for the clinical development and commercialization of nanocarriers. Typical engineering techniques include:

Nanoprecipitation: Allows for the preparation of polymeric nanoparticles with excellent batch-to-batch consistency, narrow particle size distribution and precise drug loading.

Emulsion - solvent evaporation: This is a commonly used method for entrapment of hydrophobic drugs into biodegradable polymers like PLGA.

Microfluidic-based synthesis: Offers high reproducibility and tight particle size control, and is suitable for clinical manufacture.

Self-assembly methods: Often used for the preparation of micelles and lipid nanoparticles, especially for delivery of nucleic acids.

Layer-by-layer surface modification: Enables tailored modification of the particle surface, for example, with ligand conjugation and triggered-release coating [20].

Fine-tuning of these manufacturing processes has a profound impact on nanoparticle blood circulation, tumor targeting and therapeutic outcome [21].

5.2 Liposomes

Liposomes are phospholipid vesicles that can carry drugs in both the aqueous and the non-aqueous phases. They can be surface-modified by PEGylation to increase their blood circulation time due to their reduced opsonization and macrophage uptake [22]. Liposomal drugs that are currently in clinical use have shown better pharmacokinetics and reduced cardiotoxicity compared to traditional drug formulations [23].

5.3 Polymeric Nanoparticles and Micelles

Polymeric nanoparticles, usually made of biodegradable polymers, such as PLGA, provide sustained drug release. Polymeric micelles enhance the solubility of poorly soluble drugs, and avoid the use of organic solvents [24].

5.4 Dendrimers

Dendrimers are highly branched structures with defined structures and surface-chemistry. This allows the conjugation of drugs, labels and ligands. Any potential toxicity due to their positively charged surface can be reduced by surface modification [25].

5.5 Inorganic Nanoparticles

Inorganic nanoparticles, such as gold, silica and iron oxide nanoparticles, have unique optical, magnetic and radiosensitizing properties. They can be used for theranostic (diagnosis and therapy) purposes [26].

5.6 Exosomes

Exosomes are naturally occurring nanovectors that are biocompatible and have targeting abilities. Their ability to overcome barriers makes them attractive for delivering RNA and gene therapies [27].

5.7 Antibody–Drug Conjugates

Antibody–drug conjugates (ADCs) take advantage of the selectivity of monoclonal antibodies to deliver potent drugs to target cells. ADCs specifically target cancer cells by binding to tumour-associated antigens, and are taken up into cancer cells through receptor-mediated endocytosis. ADCs are one of the most successful targeted drug delivery systems to have reached the clinic [28].

5.8 Comparative Engineering Performance of Major Nanocarriers

Table 1: Comparative Performance of Nanocarriers.

Nanocarrier Type	Typical Size Range	Key Advantages	Limitations	Clinical Translation Status
Liposomes	50–200 nm	Biocompatible, dual drug loading	Leakage risk	Multiple FDA-approved systems
Polymeric nanoparticles	80–250 nm	Controlled release capability	Complex fabrication	Several clinical-stage candidates
Dendrimers	5–20 nm	Precise surface functionality	Cytotoxicity concerns	Early clinical investigation
Gold nanoparticles	10–150 nm	Imaging + therapy compatibility	Long-term retention issues	Translational research stage
Exosomes	30–150 nm	Natural targeting ability	Isolation scalability	Emerging clinical trials
Antibody–drug conjugates	Variable	High molecular specificity	High manufacturing cost	Multiple approved therapeutics

6. Targeting Mechanisms in Nanomedicine

6.1 Passive Targeting

Passive targeting is mainly dependent on the enhanced permeability and retention (EPR) effect, which is caused by a leaky tumor vasculature and dysfunctional lymphatics. This facilitates the accumulation of nanoparticles in the tumor. Physical characteristics of nanoparticles, such as size, charge and shape, are crucial for the accumulation and retention in tumors [29].

6.2 Active Targeting

Active targeting is based on the binding of ligands to cancer-related receptors like HER2, EGFR, transferrin receptors and folate receptors. This strategy involves modifying the surface of nanoparticles with ligands to increase binding affinity with cancer cells, and cellular uptake via receptor-mediated endocytosis, which increases therapeutic efficacy and decreases side effects [30].

6.3 Stimuli-Responsive Drug Release

Stimuli-responsive drug delivery systems allow the release of drugs in response to the tumor environment. These could be low pH, high glutathione, over-expressed enzymes and reactive oxygen species (ROS). Furthermore, external stimuli such as ultrasound, radiation, magnetic fields, and near-infrared (NIR) light can be used to further enhance temporal and spatial control over drug release to enable more precise treatment [31].

7. Biological Challenges for Clinical Translation

Although major progress has been made, there are still important biological barriers to the clinical success of drug delivery systems (DDS). The protein corona, which modifies the surface characteristics of nanoparticles, is a key problem, impairs targeting. Another issue is the rapid clearance by the mononuclear phagocytic system (MPS) that shortens their circulation and reduces their accumulation in the tumor [32].

Heterogeneity in tumors also causes variability in the EPR effect among patients and tumor types, making it difficult to predict therapeutic outcomes. Beyond biological considerations, complexity of manufacturing, regulatory uncertainties and low yield with high production costs also contribute to challenges in the successful translation of nanomedicine from research to clinical practice [33].

8. Regulatory and Clinical Advances

In the last 20 years, more than a hundred nanomedicine formulations have been approved by regulatory agencies globally while several hundred are undergoing clinical testing. These have shown better safety, target specificity and lower side effects than traditional chemotherapy [34].

But the rate of clinical success has been low. This can be attributed to the absence of reliable predictive markers, patient-specific responses and lack of guidelines for nanoparticle characterisation. Overcoming these barriers is crucial to enhance the efficacy of next-generation drug delivery systems.

9. Future of Personalised Drug Delivery

The future of drug delivery for cancer treatment is likely to involve a combination of nanotechnologies, artificial intelligence and translational engineering strategies to enable more targeted and personalized treatment strategies [35].

9.1 Nanocarrier Design with Artificial Intelligence

Artificial intelligence (AI) and machine learning are being employed to fine-tune design properties of nanoparticles, such as size, ligand density, drug loading and release. These AI techniques greatly streamline experimentation and lead to more efficient design of high-efficiency systems [36].

9.2 Microfluidics-Enabled Precision Manufacturing

Nanoparticle synthesis in microfluidic devices provides high control over fabrication, ensuring

consistent and uniform preparation of nanoparticles. Such platforms are especially useful for scaling up production using Good Manufacturing Practice (GMP) protocols for clinical translation [37].

9.3 Organoid Screening Platforms

Organoid models derived from patients can be used to predict the penetration and therapeutic efficacy of nanoparticles prior to clinical application [38].

9.4 Multifunctional Theranostic Platforms

The future of nanocarriers is that they are designed to be theranostic systems capable of integrating diagnosis and therapy in one system. This combination enables real-time tracking of drug delivery, disease response and progression, thus better informing clinical practice [39].

10. CONCLUSION

Drug delivery systems are revolutionising cancer treatment by enhancing pharmacokinetics, selectivity for the tumor, and reduced toxicity. Nanotechnology-based drug carriers, such as liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles, exosomes and antibody–drug conjugates, are among the driving forces behind this advancement.

While there are many challenges in this field including biological, regulatory and manufacturing issues, the use of artificial intelligence, precision diagnostics and patient-specific approaches to treatment will help to expedite clinical translation.

In the end, advanced drug delivery systems will be a key element to facilitate safer, more effective and personalised cancer treatment, representing a paradigm shift from traditional chemotherapy to precision nanomedicine.

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