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ADVANCES AND CHALLENGES IN NANOPARTICLE DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT: A SYSTEMATIC REVIEW

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Abstract
Nanoparticle drug delivery systems have emerged as a transformative approach in cancer therapy, offering targeted delivery, reduced systemic toxicity, and improved therapeutic efficacy. Despite significant advancements, challenges such as biocompatibility, scalability, and clinical translation remain unresolved. This systematic literature review aims to synthesize recent developments and identify critical gaps in nanoparticle-based drug delivery systems for cancer treatment, focusing on their design, functionality, and application across diverse cancer types. We conducted a comprehensive analysis of peer-reviewed studies, evaluating the progress in general nanoparticle systems, specific nanoparticle types, and their mechanisms of action in targeted cancer therapy. The review highlights the versatility of nanoparticles, including liposomes, polymeric nanoparticles, and inorganic carriers, which exhibit unique advantages in drug encapsulation, stability, and controlled release. Furthermore, we examine how these systems address the heterogeneity of cancers, enabling precise delivery to tumours while minimizing off-target effects. Key findings reveal that surface modifications and stimuli-responsive designs significantly enhance targeting efficiency and therapeutic outcomes. However, translational challenges such as immune responses, manufacturing consistency, and regulatory hurdles persist. By consolidating current knowledge, this review provides a critical assessment of the field's state, emphasizing the need for interdisciplinary collaboration to bridge the gap between preclinical research and clinical implementation. The insights gained underscore the potential of nanoparticle drug delivery systems to revolutionize cancer treatment while outlining future directions for overcoming existing limitations.

Keywords: *Nanoparticle drug delivery, Targeted cancer,Nanomedicine,Liposomes,Polymeric nanoparticles,Inorganic nanoparticles,Stimuli-responsive delivery,Tumourtargeting, Clinicaltranslation.*

INTRODUCTION

Cancer remains one of the most formidable challenges in modern medicine, with conventional therapies such as chemotherapy, radiation, and surgery often limited by systemic toxicity, poor drug bioavailability, and resistance mechanisms [1]. The advent of nanotechnology has revolutionized drug delivery by enabling precise targeting of tumour tissues while minimizing damage to healthy cells [2]. Nanoparticle-based drug delivery systems (NDDS) have emerged as a promising strategy to overcome these limitations, offering controlled release, enhanced permeability, and improved pharmacokinetics [3]. These systems exploit the unique physicochemical properties of nanoparticles, such as their high surface-area-to-volume ratio and tuneable surface chemistry, to optimize therapeutic outcomes [4].

The background of NDDS in cancer therapy is rooted in the concept of the enhanced permeability and retention (EPR) effect, which allows nanoparticles to accumulate preferentially in tumour tissues due to their leaky vasculature and impaired lymphatic drainage [5]. This passive targeting mechanism, combined with active targeting strategies such as ligand-receptor interactions, has significantly improved the specificity of drug delivery [6]. Moreover, nanoparticles can encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids, thereby expanding their applicability across diverse cancer types [7]. Recent advances in material science have further enabled the design of stimuli-responsive nanoparticles that release their payload in response to tumour-specific triggers such as pH, redox potential, or enzymatic activity [8].

Despite these advancements, several research gaps persist. For instance, the heterogeneity of tumour microenvironments often leads to variable nanoparticle accumulation and efficacy, necessitating more robust targeting strategies [9]. Additionally, the long-term biocompatibility and potential immunogenicity of

nanoparticles remain poorly understood, posing challenges for clinical translation [10]. The scalability and reproducibility of nanoparticle manufacturing also present hurdles, as slight variations in synthesis protocols can significantly alter their therapeutic performance [11]. Furthermore, while preclinical studies have demonstrated remarkable success, the translation of NDDS into clinical practice has been slower than anticipated, highlighting the need for more comprehensive safety and efficacy evaluations [12].

CORE PRINCIPLES AND FUNCTIONAL DIVERSITY OF NANOPARTICLE DRUG DELIVERY SYSTEMS

Nanoparticle-based drug delivery systems have emerged as a transformative platform in oncology, offering solutions to longstanding challenges in cancer therapy. The foundational studies analysed in this section collectively demonstrate how nanoparticles transcend their role as passive carriers to become dynamic therapeutic agents. These systems capitalize on the enhanced permeability and retention (EPR) effect while incorporating sophisticated targeting mechanisms to improve tumour accumulation and reduce off-target effects [13, 14].

The taxonomy presented in Table 01 captures the multidimensional nature of general nanoparticle systems, revealing four critical functional aspects. First, their capacity as drug carriers has been extensively documented, with studies showing improved pharmacokinetics and biodistribution profiles compared to conventional chemotherapy [15]. Second, technological advancements in nanocarrier design have enabled precise control over particle size, surface charge, and drug release kinetics, addressing previous limitations in formulation reproducibility [16]. Third, stability considerations have gained prominence, particularly regarding storage conditions and long-term colloidal stability in physiological environments [17]. Fourth, historical analyses provide valuable insights into the evolution of nanoparticle systems, tracing their development from simple drug carriers to multifunctional therapeutic platforms [16].

Table 01. Taxonomy of general nanoparticle-based drug delivery systems for cancer therapy

Nanoparticle Type	Key Functionality	Sources
General Nanoparticle Systems	Drug carriers for enhanced cancer therapy	[14, 16]
	Development of nanocarrier technologies	[15, 16]
	Stability and formulation considerations	[17]
	Review of historical developments	[16]

The interplay between these functional aspects reveals an important paradigm shift in the field. Where early systems primarily focused on passive accumulation through the EPR effect, contemporary designs increasingly incorporate active targeting ligands and stimuli-responsive elements. This evolution reflects growing recognition of tumour heterogeneity and the need for precision medicine approaches. However, the studies also highlight persistent challenges in clinical translation, particularly regarding scale-up production and batch-to-batch consistency. The stability data from [17] suggest that nanoparticle formulations may require specialized storage conditions, potentially complicating their clinical deployment. These findings collectively underscore the need for continued innovation in nanoparticle engineering to balance therapeutic performance with practical considerations for real-world application.

CLASSIFICATION AND FUNCTIONAL ATTRIBUTES OF NANOPARTICLE SYSTEMS IN CANCER THERAPY

The landscape of nanoparticle-based drug delivery systems for cancer therapy encompasses diverse materials and architectures, each offering distinct advantages for tumour targeting and therapeutic delivery. As shown in Table 02, three primary categories emerge from the analysed studies: polymeric nanoparticles, metallic nanoparticles, and hybrid/multifunctional systems. These classifications reflect both the material composition and the functional capabilities that define their therapeutic potential.

Table 02: Taxonomy of specific nanoparticle types for cancer therapy

Nanoparticle Type	Material/ Composition	Key Features	Sources
Polymeric Nanoparticles	PHAs, PLGA, CDs	Biodegradable, controlled drug release, tumour-targeting capabilities	[18,19]
Metallic Nanoparticles	Gold	High biocompatibility, surface functionalization, photothermal therapy potential	[21]
Other Nanoparticle Systems	Magnetic nanoparticles, nano emulsions, liposomes	Multifunctional platforms for combination therapy, imaging contrast agents	[19]

Polymeric nanoparticles represent one of the most extensively studied categories, with polyhydroxyalkanoates (PHAs), poly(lactic-co-glycolic acid) (PLGA), and cyclodextrins (CDs) serving as prominent examples. These systems exhibit exceptional biodegradability and tuneable drug release kinetics, making them particularly suitable for sustained therapeutic delivery [18]. The versatility of polymeric nanoparticles is further enhanced by their capacity for

surface modification, enabling active tumour targeting through ligand-receptor interactions. For instance, PLGA-based systems have demonstrated improved tumour accumulation when conjugated with targeting moieties such as antibodies or peptides [19].

Metallic nanoparticles, particularly gold nanoparticles, occupy a unique niche due to their plasmonic properties and ease of surface functionalization. Their high biocompatibility and ability to convert light into heat have positioned them as promising agents for photothermal therapy, where localized hyperthermia can induce tumour cell death [20]. Moreover, the surface of gold nanoparticles can be engineered with precision, allowing for the simultaneous attachment of therapeutic payloads and targeting ligands. This dual functionality enables synergistic approaches that combine drug delivery with physical ablation techniques.

The category of other nanoparticle systems encompasses a broader range of materials, including magnetic nanoparticles, nano emulsions, and liposomes. These systems often serve as multifunctional platforms capable of integrating therapeutic delivery with diagnostic imaging. Magnetic nanoparticles, for example, can be guided to tumour sites using external magnetic fields while simultaneously serving as contrast agents for magnetic resonance imaging. Liposomes, on the other hand, excel in encapsulating hydrophobic drugs and have been widely adopted in clinical settings due to their favourable safety profile. The diversity within this category underscores the adaptability of nanoparticle systems to address specific therapeutic challenges, from overcoming biological barriers to enabling real-time treatment monitoring [21].

The comparative analysis of these nanoparticle types reveals a trade-off between material-specific advantages and broader applicability. While polymeric and metallic nanoparticles offer specialized functionalities, hybrid systems bridge multiple therapeutic modalities, reflecting the field's progression toward combinatorial approaches. This taxonomy not only organizes existing knowledge but also highlights opportunities for future innovation, particularly in the design of next-generation nanoparticles that integrate the strengths of these distinct categories.

NANOPARTICLE-MEDIATED DELIVERY STRATEGIES FOR OVARIAN CANCER

Ovarian cancer presents unique challenges for drug delivery due to its complex tumour microenvironment and frequent late-stage diagnosis. The study by [22] provides critical insights into how nanoparticle systems address these challenges through both passive and active targeting mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect, which allows nanoparticles to accumulate preferentially in tumour tissues due to their leaky vasculature and impaired lymphatic drainage. Active targeting, in contrast, involves surface modifications with ligands that bind specifically to receptors overexpressed on ovarian cancer cells, thereby enhancing cellular uptake and therapeutic efficacy.

The taxonomy in Table 03 systematically categorizes the nanoparticle delivery approaches for ovarian cancer based on the study findings. Passive targeting strategies rely on the inherent physicochemical properties of nanoparticles, such as size and surface charge, to facilitate tumour accumulation. These systems often employ polyethylene glycol (PEG) coatings to prolong circulation time and avoid immune clearance. Active targeting strategies, however, incorporate ligands such as folate, antibodies, or peptides that recognize biomarkers like HER2 or CA-125, which are frequently overexpressed in ovarian cancer. This dual classification underscores the adaptability of nanoparticle systems to the biological heterogeneity of ovarian tumours.

Table 03: Taxonomy of nanoparticle delivery systems for ovarian cancer therapy

Cancer Type	Targeting Strategy	Delivery System	Sources
Ovarian Cancer	Passive targeting	Nano drug delivery systems	[22]
	Active targeting	Nano drug delivery systems	[22]

The study by [22] highlights the advantages of active targeting in overcoming the dense stromal barriers characteristic of ovarian tumours. Ligand-conjugated nanoparticles demonstrate superior penetration into tumour spheroids compared to their non-targeted counterparts, suggesting their potential for treating metastatic lesions. However, the research also notes limitations in passive targeting efficiency due to variability in the EPR effect among patients, emphasizing the need for personalized approaches. These findings align with broader trends in precision oncology, where nanoparticle systems are increasingly tailored to individual tumour profiles.

Comparative analysis of the two strategies reveals complementary strengths. While passive targeting benefits from simplicity and scalability, active targeting offers higher specificity, particularly for residual disease after surgery. The integration of both approaches in multi-functional nanoparticles could potentially optimize therapeutic outcomes by combining broad tumour accumulation with precise cellular uptake. Nevertheless, clinical translation faces hurdles such as ligand stability and manufacturing consistency, which require further investigation. The insights from [22] thus provide a foundation for advancing nanoparticle-based therapies for ovarian cancer while highlighting critical areas for future research.

TARGETED DELIVERY MECHANISMS AND FUNCTIONAL INNOVATIONS IN NANOPARTICLE SYSTEMS

Nanoparticle drug delivery systems have evolved beyond simple carriers to incorporate sophisticated targeting mechanisms and specialized functions that

address critical challenges in cancer therapy. The study by [23] demonstrates how nanoparticles achieve cancer-specific drug delivery through both inherent physicochemical properties and engineered surface modifications. These systems leverage the enhanced permeability and retention (EPR) effect while incorporating active targeting ligands to enhance tumour accumulation and cellular uptake. The integration of these passive and active targeting strategies represents a significant advancement in precision oncology, enabling higher therapeutic doses at tumour sites with reduced systemic toxicity.

Table 04: Functional mechanisms of nanoparticle drug delivery systems in cancer therapy

Mechanism Type	Key Characteristics	Biological Impact	Sources
Passive Targeting	Relies on EPR effect and nanoparticle size/surface properties	Enhanced tumour accumulation, reduced off-target effects	[23]
Active Targeting	Utilizes ligands (antibodies, peptides, aptamers) for receptor binding	Improved cellular internalization, biomarker-specific delivery	[23]
Stimuli-Responsive Release	Responds to tumour microenvironment (pH, enzymes, redox)	Spatiotemporal control of drug release, minimized premature leakage	[23]

The functional taxonomy in Table 04 reveals three dominant mechanisms that define modern nanoparticle systems. Passive targeting capitalizes on the pathophysiological differences between tumour and healthy tissues, particularly the leaky vasculature and impaired lymphatic drainage characteristic of many cancers. Nanoparticles within the 10-200 nm size range preferentially extravasate through these defective blood vessels, achieving higher local concentrations than free drugs. Active targeting builds upon this foundation by conjugating nanoparticles with ligands that bind to receptors overexpressed on cancer cells, such as folate receptors or epidermal growth factor receptors. This dual-targeting approach addresses the heterogeneity of the EPR effect across tumour types and individual patients, as noted in [23].

Stimuli-responsive nanoparticles represent a further refinement, incorporating materials that release their payload only upon encountering tumour-specific triggers. pH-sensitive polymers, for example, remain stable in the bloodstream (pH 7.4) but degrade in the acidic tumour microenvironment (pH 6.5-6.8), ensuring precise drug release. Similarly, redox-responsive systems exploit the elevated glutathione levels in cancer cells to trigger intracellular drug release. These mechanisms collectively enhance therapeutic specificity while mitigating side effects associated with conventional chemotherapy. The study by [23] particularly emphasizes how such innovations have expanded the applicability of nanoparticle systems across diverse cancer types, including those with challenging biological barriers like pancreatic and brain tumours.

Emerging research directions highlighted in these studies point toward multifunctional "theranostic" nanoparticles that combine therapy and diagnostic imaging. These systems often integrate contrast agents (e.g., quantum dots or iron oxide nanoparticles) with therapeutic payloads, enabling real-time monitoring of drug delivery and treatment response.[24] While clinical translation of these advanced systems faces challenges-including scalability, regulatory approval, and long-term safety assessments-their potential to revolutionize cancer management remains unparalleled. The mechanisms outlined here not only reflect the current state of nanoparticle drug delivery but also provide a roadmap for future innovations in targeted cancer therapy [25].

DISCUSSION

The synthesis of findings across the reviewed studies reveals several critical patterns that shape our understanding of nanoparticle drug delivery systems in cancer therapy. Taken together, the evidence consistently demonstrates that nanoparticle-based approaches offer substantial advantages over conventional drug delivery methods, particularly in terms of targeted accumulation and reduced systemic toxicity. The enhanced permeability and retention (EPR) effect emerges as a fundamental mechanism enabling passive tumour targeting, though its efficacy varies significantly depending on tumour type and vascularization. Active targeting strategies, such as ligand-receptor binding, further improve specificity but introduce complexities related to ligand stability and immunogenicity. These observations collectively suggest that while nanoparticles have transformed drug delivery paradigms, their clinical success hinges on balancing passive and active mechanisms to accommodate heterogeneous tumour microenvironments.

From a theoretical perspective, the reviewed studies contribute to a growing conceptual framework that positions nanoparticles as dynamic therapeutic platforms rather than inert carriers. The integration of stimuli-responsive functionalities, for example, challenges traditional drug delivery models by introducing spatiotemporal control over drug release. This shift aligns with broader trends in precision medicine, where treatments are increasingly tailored to individual tumour biology. Practically, these advancements imply that clinicians may soon have access to nanoparticle formulations capable of selectively targeting resistant cancer subpopulations or overcoming biological barriers such as the blood-brain barrier. However, the translation of these innovations

into clinical practice requires addressing manufacturing inconsistencies and establishing standardized characterization protocols

Several limitations in the current literature warrant careful consideration. The predominance of preclinical studies in our review sample raises concerns about publication bias, as positive results are more likely to be reported than negative or inconclusive findings. Moreover, the variability in experimental models-ranging from 2D cell cultures to murine xenografts-complicates cross-study comparisons of nanoparticle efficacy. The scarcity of long-term toxicity data represents another critical gap, particularly for metallic and hybrid nanoparticles whose biological fate remains incompletely understood. These methodological constraints suggest that our synthesis may overestimate the readiness of some nanoparticle systems for clinical deployment while underestimating potential safety concerns.

Future research should prioritize several understudied areas to address these limitations. There is a pressing need for standardized in vitro and in vivo models that better recapitulate human tumour heterogeneity and microenvironmental conditions. Comparative studies evaluating different nanoparticle types within uniform experimental frameworks would help clarify their relative advantages for specific cancer indications. Additionally, the field would benefit from increased investigation into immune-nanoparticle interactions, as these determine both therapeutic efficacy and potential adverse effects. Finally, translational research must bridge the gap between small-scale academic studies and industrial-scale production, with particular attention to quality control and regulatory requirements. By addressing these gaps, future work can accelerate the development of nanoparticle therapies that fulfil their promise in clinical oncology.

The implications of this review extend beyond academic discourse to inform real-world therapeutic development. The consistent finding that nanoparticle design must be tailored to specific cancer types underscores the importance of interdisciplinary collaboration between material scientists, oncologists, and bioengineers. For example, the success of pH-responsive nanoparticles in preclinical models of acidic solid tumours suggests immediate opportunities for clinical adaptation. Similarly, the demonstrated ability of gold nanoparticles to synergize photothermal therapy with chemotherapy could revolutionize treatment protocols for superficial or accessible malignancies. These examples illustrate how insights from nanoparticle research can directly influence clinical trial design and therapeutic decision-making.

Emerging challenges also merit attention in light of the reviewed evidence. The variability of the EPR effect across patients poses a significant hurdle for passive targeting strategies, potentially necessitating companion diagnostics to identify likely responders. Similarly, the immune system's role in clearing nanoparticles-while beneficial for reducing off-target effects-may limit therapeutic payload delivery to tumours, suggesting a need for stealth coatings or immune-modulating approaches . These challenges highlight the complexity of translating nanoparticle systems from bench to bedside, requiring solutions that integrate biological understanding with engineering innovation.

CONCLUSION

This systematic review has synthesized current knowledge on nanoparticle drug delivery systems for cancer treatment, addressing their design principles, functional mechanisms, and therapeutic applications. The findings confirm that nanoparticles offer distinct advantages over conventional therapies, particularly in targeted drug delivery and reduced systemic toxicity. The integration of passive and active targeting strategies, along with stimuli-responsive functionalities, has significantly advanced the field toward precision oncology. However, the review also highlights persistent challenges in clinical translation, including manufacturing scalability, long-term biocompatibility, and patient-specific variability in tumour targeting efficiency.

The theoretical implications of this work extend to the broader framework of drug delivery, where nanoparticles are increasingly recognized as dynamic therapeutic platforms rather than passive carriers. Practically, these insights can guide the development of next-generation nanomedicines by emphasizing the need for interdisciplinary approaches that combine material science with tumour biology. Future research should prioritize standardized evaluation models, immune-nanoparticle interactions, and scalable manufacturing processes to bridge existing gaps between preclinical promise and clinical reality. By addressing these challenges, nanoparticle drug delivery systems can fulfil their potential to revolutionize cancer therapy.

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