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Nano-Drug Delivery Systems for Tumor Therapy: A Review of Design Strategies, Evaluation, and Mechanisms

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Abstract. Traditional cancer chemotherapy remains limited by serious systemic toxicity, poor tumor targeting, and multidrug resistance, resulting in unsatisfactory clinical therapeutic outcomes. Nano-drug delivery systems, featuring tunable physicochemical properties, EPR-mediated tumor accumulation and tumor microenvironment responsiveness, have emerged as a promising strategy to overcome these limitations. However, existing studies focus on individual material optimization, lacking a systematic synthesis of the complete research paradigm. This paper adopts literature induction and comparative analysis to examine the complete research paradigm of tumor-targeted nano-delivery systems. It compares four mainstream nanocarrier platforms, including lipid-based, polymer-based, inorganic, and hybrid systems. It then evaluates their design strategies, physicochemical properties, in vitro cellular uptake and cytotoxicity assays, and in vivo therapeutic efficacy and biosafety verification. Furthermore, this paper clarifies the core mechanisms underlying targeted delivery, pH/redox-responsive drug release, multidrug resistance reversal and synergistic multi-modal therapy. The reviewed studies indicate that rationally designed nano-drug delivery systems can enhance drug accumulation in tumors, reduce off-target systemic toxicity, and improve therapeutic outcomes. The systematic synthesis offers valuable references and identifies key directions for the rational design, performance optimization and clinical translation of high-efficiency, low-toxicity anti-tumor nanoformulations.

Keywords: Nano-drug delivery systems, tumor therapy, targeted delivery, stimuli-responsive release, tumor microenvironment

1. Introduction

Malignant tumors remain one of the leading causes of global death because of their high proliferation, metastasis and recurrence rates. Chemotherapy is the main systemic treatment for advanced tumors, but conventional chemotherapeutic agents suffer from non-specific distribution, low tumor accumulation, severe systemic toxicity and multidrug resistance, which seriously limit clinical therapeutic outcomes. As an emerging advanced strategy, nano-drug delivery systems are defined as functional nanocarriers with particle sizes of 1 to 1000 nm that encapsulate, protect and deliver therapeutic drugs. By exploiting the enhanced permeability and retention (EPR) effect and

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responsiveness to the tumor microenvironment, nanocarriers may facilitate preferential accumulation in tumor tissues and controlled drug release, which may help address some limitations of conventional chemotherapy.

Current anti-tumor nanocarriers mainly include polymer, lipid, inorganic and biomimetic nanoparticles, which have been investigated for drug resistance reversal and synergistic multi-modal therapy. Most of this work, however, stays at the level of one material or one mechanism. Attempts to assemble the fragments into a coherent paradigm are rare. This review takes the wider view: how nano-delivery systems for tumor therapy are designed, tested and, finally, argued for [1].

Three questions run through what follows. Which design and surface-modification strategies are actually in use across the main carrier families? What procedures (characterization, in vitro and in vivo verification, biosafety testing) have become the de facto benchmark, and where do they differ between groups? And what is known, precisely, about how targeting, responsive release and synergy arise, as opposed to merely being asserted?

No review can close these gaps. It can, however, give designers, evaluators and clinicians a common reference point. For formulation groups that means a clearer rationale for choosing one carrier over another; for translational teams, a more realistic sense of which claims survive preclinical testing. Where the evidence is thin, the gap is marked rather than smoothed over, and the closing section sets out what still blocks translation of high-efficiency, low-toxicity anti-tumor nanoformulations.

2. Design and physicochemical characterization of nano-drug delivery systems

Nanodelivery systems are functional nanocarriers with sizes ranging from 1 to 1000 nm. Benefiting from their unique dimensional effects, tunable surface properties and excellent biological barrier permeability, they can protect drugs, genes and biomacromolecules from in vivo degradation, achieve targeted lesion accumulation and controlled drug release. These advantages effectively improve therapeutic outcomes and reduce systemic side effects. Based on material composition and structural features, mainstream nanodelivery platforms are classified into lipid-based, polymer-based, inorganic and hybrid systems with distinct properties and application prospects.

2.1. Classification and characteristics of nanodelivery systems

Lipid-based nanocarriers are the most technically mature and clinically translational delivery systems, mainly including liposomes, solid lipid nanoparticles and lipid nanoparticles (LNPs) [2]. Their amphipathic structure enables efficient encapsulation of both hydrophobic drugs and hydrophilic biomolecules, while their lipid composition generally provides good biocompatibility and cargo compatibility. Traditional liposomes suffer from poor colloidal stability and premature drug leakage, while solid lipid nanoparticles with rigid lipid cores achieve better structural stability and sustained drug release. As cutting-edge nucleic acid delivery vectors, LNPs can effectively protect genetic drugs and promote intracellular delivery, greatly facilitating the development of mRNA vaccines and gene therapy [3].

Polymeric nanocarriers are fabricated from biodegradable natural or synthetic polymers such as PLGA, PLA, chitosan and hyaluronic acid [4], featuring highly tunable nanostructures and release kinetics. Adjusting polymer molecular weight, copolymer ratio and crosslinking degree can precisely regulate particle degradation, drug loading and in vivo retention. Polymeric micelles significantly enhance the solubility of insoluble drugs with uniform particle size and low critical micelle concentration. Natural polymer-based nanosystems also exhibit favorable bioadhesion for

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improved mucosal and targeted delivery [5]. However, partial polymeric degradation products may trigger mild inflammation, limiting their further clinical translation.

Inorganic nanoplatforms, including mesoporous silica [6], gold, magnetic iron oxide and carbon-based nanoparticles, possess outstanding physicochemical stability and rigid structures. Their high specific surface area and porous architecture enable high drug loading and controllable release. Some inorganic nanocarriers possess unique optical and magnetic properties, supporting multifunctional therapeutic and diagnostic applications [7]. Specifically, magnetic nanoparticles realize precise targeting via external magnetic guidance, while gold nanoparticles integrate drug delivery with photothermal therapy [8]. Nevertheless, low in vivo biodegradability and potential long-term biosafety risks restrict their large-scale clinical application.

Hybrid nanosystems integrate organic and inorganic components to compensate for the defects of single-material carriers. They combine the strengths of multiple materials to achieve enhanced stability, better biocompatibility and intelligent stimulus-responsive release. For example, lipid-coated polymeric nanoparticles integrate the biocompatibility of lipids and the sustained-release performance of polymers. Rational surface modification can effectively avoid immune clearance, prolong blood circulation and improve targeting efficiency [9]. Despite their comprehensive performance advantages, complex preparation processes and strict batch consistency requirements hinder their industrial production.

2.2. Physicochemical characterization methods

A high-performance nanodelivery system requires systematic evaluation of physicochemical properties, delivery performance, release behavior, biocompatibility, in vivo efficacy and industrial feasibility. Particle size and polydispersity index (PDI) are key indicators of colloidal uniformity, a PDI below 0.3 is generally considered indicative of relatively good particle-size uniformity and colloidal stability. Zeta potential determines particle dispersion stability and cellular uptake efficiency, with appropriate surface potential effectively preventing particle aggregation.

Encapsulation efficiency and drug loading capacity are core functional parameters of nanocarriers. High encapsulation efficiency reduces free drug leakage and systemic toxicity, while satisfactory drug loading decreases carrier dosage and improves delivery efficacy. Ideal nanosystems should maintain stable drug retention under physiological conditions while enabling controlled drug release in response to tumor microenvironment stimuli, such as acidic pH or reducing conditions. This design can minimize premature drug release and improve therapeutic efficacy.

2.3. Biocompatibility and safety evaluation

Superior biocompatibility and biosafety are essential prerequisites for clinical transformation. Qualified nanocarriers exhibit negligible cytotoxicity, low hemolytic activity and minimal inflammatory responses, and can be gradually degraded and metabolized in vivo without long-term accumulation. In vivo evaluation can further assess circulation time, tumor accumulation through passive or active targeting, and tissue or biological barrier penetration. In addition, scalable preparation, low cost and reliable batch reproducibility are indispensable for clinical popularization and industrialization.

In summary, the four types of nanodelivery systems have unique advantages to meet diverse delivery demands. Excellent nanocarriers should integrate stable physicochemical properties, efficient drug loading, controllable responsive release, favorable biosafety, outstanding in vivo

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targeting capability and scalable production potential, laying a solid foundation for precision drug delivery and advanced disease treatment.

3. Evaluating nano-drug delivery systems in tumor therapy

3.1. Cellular evaluation in vitro

Most nanoformulations are judged for the first time in culture. The setting is convenient and, in one respect, misleading. A free drug crosses the membrane slowly and is often pumped straight back out, whereas a carrier is taken up by endocytosis or adsorbs to the surface and is internalized. Intracellular dose can therefore be far higher than the extracellular concentration would suggest. Once inside, the particle meets endosomal pH falling toward 5.5 and glutathione rising into the millimolar range, conditions that responsive systems are designed to exploit.

The panel of assays is narrow and well established. Viability is read with CCK-8 or MTT, uptake is quantified by flow cytometry or confocal microscopy, the payload is localized subcellularly, apoptosis is scored with Annexin V and propidium iodide, and, where oxidative stress is part of the mechanism, reactive oxygen species are detected with DCFH-DA. Passing all five proves little on its own. Selectivity is the harder test: growth arrest in tumor cells at concentrations that leave fibroblasts or hepatocytes largely intact. Potency without selectivity has no clinical future.

Trafficking decides the outcome, not uptake alone. A particle that enters efficiently but never leaves the endosome has simply delivered its cargo to the lysosome, where acid and enzymes dispose of it. This failure is common, and it is easy to miss when only total cell-associated fluorescence is measured. Escape by proton-sponge effect, membrane fusion or osmotic rupture releases the drug into the cytosol, where it can act. Four readouts carry most of the weight: how much enters, where it goes, how fast it is released, and whether the cells actually change phenotype.

3.2. Therapeutic efficacy and biosafety in vivo

Preclinical work moves between two settings that are opposite in character. Culture is controllable and unrealistic; animals are realistic and noisy. Free drug is cleared within minutes to hours and distributes widely, so tumor exposure is brief and the dose is capped by toxicity elsewhere. Longer circulation, achieved by PEGylation or by a biomimetic surface, shifts the balance: more of the dose reaches the lesion, passively through leaky tumor vasculature or through ligand- and antibody-mediated targeting, and less reaches healthy tissue [10].

Between the two sits a layer of tissue-mimetic models that is often skipped. Transwell inserts with 8 μm pores answer a blunt question: does the particle cross a barrier at all? Spheroids and 3D bioprinted constructs answer a sharper one: does it penetrate beyond the outer two or three cell layers, roughly where passive diffusion stalls? Both models are crude. Both, however, catch a failure early, namely carriers that look excellent in monolayer culture and never reach the tumor core in a mouse.

Animal work supplies what culture cannot: an organism in which pharmacokinetics, efficacy and toxicity interact. Efficacy is usually reported as tumor growth inhibition or inhibition rate, backed by body weight, survival and, increasingly, imaging of tumor burden rather than caliper measurement alone. Toxicity is read in parallel from serum biochemistry (ALT, AST, BUN, creatinine), hematology, and hematoxylin and eosin sections of heart, liver, spleen, lung and kidney. The pairing is the point. A formulation must be effective at a dose the animal tolerates, and a growth-inhibition figure divorced from that constraint means very little.

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4. Anti-tumor mechanisms of nano-drug delivery systems

Why should a carrier outperform the free drug at all? The molecule does not change. What changes is its distribution, its exposure profile and its route into the cell. Three levers are available: particle size, surface chemistry and responsiveness to the tumor microenvironment. Nearly every mechanism discussed below traces back to one of them.

Targeting is usually divided into a passive and an active half, although in practice the two overlap. Tumor vessels are fenestrated and poorly drained, so particles of roughly 50 to 200 nm extravasate and are retained. This is the EPR effect, and it explains why carrier size is specified so carefully in most reports. Active targeting adds a ligand (folate, transferrin, an RGD peptide, an antibody fragment) that binds a receptor overexpressed on tumor cells. Such ligands do not necessarily extend circulation, and in some reports they shorten it, but they raise the chance of internalization on arrival. Both routes lower exposure of normal tissue and raise intratumoral concentration [9].

Releasing the drug only where it is needed is the second lever, and it depends on a difference the body already provides. Solid tumors are mildly acidic (pH 6.5 to 6.9 extracellularly, lower in endosomes and lysosomes), rich in glutathione and in proteases such as matrix metalloproteinases, and hypoxic. Responsive carriers are built to read one of these signals: acid-labile bonds, disulfide crosslinks, enzyme-cleavable peptide linkers, hypoxia-activated prodrugs. The intent never varies. Keep the payload inside the carrier while it circulates, then release it quickly once the carrier reaches the tumor [9].

Multidrug resistance is the third obstacle, and the most stubborn. In resistant tumors the ATP-binding cassette transporters, above all P-glycoprotein (ABCB1), are overexpressed on the cell surface and pump cytotoxics back out at the expense of ATP. Intracellular concentrations fall below the effective threshold, and the tumor survives what should have been a lethal dose. A carrier can sidestep this in part by entering through endocytosis rather than diffusion, since the drug never meets the transporter as a free molecule in the membrane. Responsive systems go further. Releasing a bolus inside the acidic lysosome or the cytoplasm creates a local gradient steep enough to saturate the pump. Some functionalized carriers attack the machinery directly, silencing ABCB1 with siRNA, inhibiting transporter ATPase activity, or blocking the survival signaling on which resistance depends. Autophagy-related resistance and enhanced repair of chemotherapy-induced DNA damage are further routes that have been targeted. It is worth recalling why the earlier approach failed. Small-molecule inhibitors such as verapamil, elacridar and tariquidar performed poorly in patients, partly because the same transporters protect healthy tissue, so doses high enough to block them in tumors were not tolerated. Delivering such an inhibitor through a carrier, rather than systemically, restores sensitivity at a tolerable dose [11].

Beyond delivery, carriers interfere with the tumor's own programs. Sustained release holds the intracellular concentration above threshold long enough to keep cells in cycle arrest. The same exposure suppresses angiogenesis and shifts glycolytic metabolism, two dependencies a growing tumor cannot easily abandon. Once the payload reaches the cytosol or the nucleus, apoptosis follows the familiar route: caspase-9 and caspase-3 activation, a fall in the Bcl-2 to Bax ratio and, depending on the agent, down-regulation of oncogenes such as MYC. Proliferation, invasion and metastatic seeding all decline [12].

The fourth mechanism is immunological, and it has attracted most of the recent interest. Tumors defend themselves with a microenvironment rich in regulatory T cells, M2-polarized macrophages and myeloid-derived suppressor cells, and poor in infiltrating CD8+ T cells. Carriers can deliver

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immunomodulators such as STING agonists, TLR agonists, checkpoint inhibitors or mRNA into the tumor itself or into draining lymph nodes. The balance then shifts. CD8+ infiltration rises, Foxp3+ regulatory T cells and CD206+ macrophages fall, and immunological memory against the tumor is established. The consequence is not only slower growth of the treated lesion but resistance to rechallenge and to distant metastasis [13].

None of these mechanisms works alone, and this is where much of the literature converges. Accumulation without release leaves the drug trapped. Release without accumulation exposes healthy tissue. MDR reversal without immune engagement buys a temporary response at best. Where carriers have performed best in preclinical models, two or three mechanisms were engaged at once. It is that combination, not any single design feature, which separates them from free chemotherapy [8].

5. Conclusion

This review targets the core research gap identified in the introduction—namely, existing studies focus on individual material optimization and single therapeutic mechanisms, while lacking systematic sorting and holistic induction of the complete research paradigm of tumor-targeted nano-drug delivery systems. Based on comprehensive literature collation and comparative analysis, this paper concludes that multi-dimensional design, evaluation and mechanistic integration may offer advantages over conventional chemotherapy, particularly in improving tumor targeting, reducing systemic toxicity, and addressing multidrug resistance.

Specifically, this paper confirms that the four mainstream nanocarrier platforms have differentiated performance advantages and applicable scenarios, and the unified physicochemical characterization and hierarchical in vitro/in vivo evaluation system can effectively verify the delivery efficiency and biosafety of nanoformulations.

The combined effects of targeted accumulation, stimulus-responsive drug release, MDR reversal, and tumor microenvironment remodeling may contribute to the antitumor efficacy of nanodelivery systems. This review provides an integrated framework for understanding the mechanisms underlying these effects.

Nevertheless, this study has several limitations consistent with the inherent defects of current research in this field. As a literature-based review, it lacks original experimental verification of the summarized design and evaluation strategies, and the research conclusions are susceptible to publication bias. Critically, the EPR effect, as the core passive targeting mechanism of nanodrugs, has prominent inter-species heterogeneity between mouse models and human tumors, and its clinical application value remains controversial, which greatly limits the clinical transformation of preclinical research results. In addition, most existing studies are confined to conceptual verification, with insufficient research data on large-scale industrial production, batch stability and long-term human biosafety.

Based on the above research conclusions and limitations, future research should focus on solving the bottlenecks restricting clinical translation. Three bottlenecks stand out. The first is methodological. Without agreed protocols for particle sizing, serum-containing release media or standardized dosing schedules, results from different laboratories cannot be compared, and regulators have little on which to base an assessment. The second is design. Carriers still need deeper tumor penetration and more reliable active targeting if they are to cope with heterogeneity and with metastatic lesions that the EPR effect never reaches. The third is evidence. Pharmacokinetics and toxicology in large animals remain scarce, yet they separate a promising preclinical formulation from one that can enter first-in-human studies.

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