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Nanohybrid-Based Drug Delivery Systems in Cancer Therapy: Advances in Targeted Delivery, Controlled Release, and Translational Challenges

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ABSTRACT

Nanohybrid-based drug delivery systems have emerged as a promising strategy to overcome the limitations of conventional cancer therapies, including poor solubility, off-target toxicity, and rapid drug clearance. By integrating multiple materials such as polymers, lipids, metals, and inorganic nanostructures, nanohybrids combine the unique advantages of each component, enabling enhanced drug loading, controlled and stimuli-responsive release, and precise tumour targeting. This review provides a comprehensive overview of the current advances in nanohybrid platforms for cancer therapy, highlighting their design principles, preparation methods, mechanisms of action, and therapeutic applications, including chemotherapy, gene delivery, immunotherapy, and theranostics. Key advantages, such as improved pharmacokinetics, reduced systemic toxicity, and multifunctionality, are discussed alongside challenges related to biocompatibility, stability, scale-up, and clinical translation. Furthermore, preclinical and clinical progress are examined, emphasizing the translational potential and regulatory considerations. Finally, future perspectives, including smart, personalized, and AI-assisted nanohybrid systems, are presented, underscoring their potential to revolutionize precision oncology. This review aims to serve as a consolidated resource for researchers and clinicians seeking to advance nanohybrid-based cancer therapeutics toward safe and effective clinical applications.

Keywords: Nanohybrid drug delivery; cancer therapy; targeted delivery; controlled release; stimuli-responsive nanocarriers; polymer–lipid hybrids

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INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, with millions of new cases and cancer related deaths reported annually [1]. Conventional treatment modalities such as surgery, chemotherapy, and radiotherapy play a foundational role in cancer management, but they often suffer from limitations including poor specificity, systemic toxicity, limited drug solubility, and the development of multidrug resistance [1,2]. These challenges have driven substantial research into alternative therapeutic strategies that can improve drug delivery to tumour tissues while reducing off target effects.

Nanotechnology has emerged as a promising approach to address these limitations by enabling the development of nanoscale drug delivery systems capable of enhancing drug solubility, stability, and pharmacokinetic profiles, and by facilitating targeted delivery to tumour sites [3,4]. Nanocarrier based systems exploit both passive targeting through the enhanced permeability and retention (EPR) effect in tumour vasculature and active targeting using surface ligands to improve tumour accumulation and uptake by cancer cells [5,6]. Despite progress with various nanocarriers such as liposomes, polymeric nanoparticles, and inorganic nanoparticles, individual systems often face trade offs between stability, controlled drug release, targeting efficacy, and biological interactions [3,7].

To overcome these limitations, nanohybrid drug delivery systems have been developed. These systems integrate multiple material components, combining the beneficial properties of different nanoscale materials such as polymers, lipids, metals, and inorganic nanostructures into a single platform with improved functional capabilities [8,9]. Nanohybrids can be engineered for controlled and stimuli responsive drug release, enhanced tumour targeting and penetration, and the co delivery of therapeutic and diagnostic agents (theranostics), addressing critical challenges in cancer therapy [8,10]. Moreover, the multifunctionality of nanohybrid platforms supports combination therapies and precise modulation of drug release kinetics, which are essential for maximising therapeutic outcomes while minimising adverse effects [9].

In this review, we provide a comprehensive overview of recent advances in nanohybrid based drug delivery systems for cancer therapy, focusing on their design principles, mechanisms of action,

therapeutic applications, advantages, limitations, and translational challenges.

Nanohybrid Drug Delivery Systems: Concept and Classification

Nanohybrid drug delivery systems (NDDS) are advanced multifunctional platforms created by combining two or more nanomaterials, typically organic and inorganic components, to leverage their complementary properties for cancer therapy [6,7]. Unlike conventional nanoparticles, nanohybrids offer enhanced drug loading, improved stability, controlled release, targeted delivery, and the ability to integrate therapeutic and diagnostic (theranostic) functions [8,9]. By tailoring the composition and structure, these systems can be stimuli-responsive, releasing drugs in response to tumour-specific conditions such as acidic pH, redox gradients, enzymes, or external triggers (light, temperature, magnetic field) [7,9] [Table 1].

These classifications allow researchers to customise nanohybrids for specific therapeutic goals, such as co-delivery of drugs and genes, combination therapy, or theranostic applications. The versatility of NDDS has made them a promising strategy in next-generation cancer nanomedicine, bridging the gap between laboratory development and clinical application [6,8].

MATERIALS AND PREPARATION METHODS

The choice of materials and preparation methods is crucial for designing effective nanohybrid drug delivery systems. The materials determine biocompatibility, drug loading capacity, stability, and targeting ability, while preparation techniques influence particle size, morphology, surface properties, and controlled-release profiles [12,13].

Materials Used in Nanohybrid Systems

1. Polymers: Natural (chitosan, alginate) and synthetic (PLGA, PEG) polymers provide structural stability, biodegradability, and drug encapsulation efficiency [12,14].

2. Lipids: Phospholipids and solid lipids contribute biocompatibility, membrane-mimetic properties, and sustained release when combined with polymers [13].

3. Inorganic Materials: Metals (gold, silver), metal oxides (iron oxide, zinc oxide), and silica nanoparticles enhance imaging, photothermal therapy, and magnetic responsiveness [15,16].

4. Carbon-Based Nanomaterials: Graphene oxide, carbon nanotubes, and nanodiamonds provide high surface area for drug loading and facilitate targeted delivery [15].

5. Biomolecules and Targeting Ligands: Peptides, antibodies, aptamers, and cell membranes enable active targeting, immune evasion, and enhanced tumour accumulation [16,17].

Preparation Methods

Various methods are employed to fabricate nanohybrids depending on the materials and intended application [Table 2]:

These materials and methods allow precise engineering of nanohybrids for desired size, stability, drug loading, release kinetics, and tumour-targeting capabilities, which are critical for maximizing therapeutic efficacy and minimizing off-target toxicity [12,17].

Table 1: Classification of Nanohybrids.

Type of Nanohybrid	Composition	Key Features & Applications
Organic–Inorganic	Polymers/lipids + metals, silica, carbon	Biocompatibility, imaging, photothermal therapy, drug protection and release [7,9]
Organic–Organic	Polymer + lipid	Improved stability, enhanced circulation, controlled drug release [8]
Inorganic–Inorganic	Metal + metal oxide, metal + silica	Multifunctional: imaging, photothermal, chemo/phototherapy combination [10]
Biohybrid Systems	Cell membranes, proteins, exosomes + synthetic nanoparticles	Immune evasion, tumor targeting, enhanced biodistribution [11]
Stimuli-Responsive Nanohybrids	Any hybrid with pH, redox, enzyme, light, or magnetic triggers	Site-specific and controlled release, combination therapy, theranostics [7,9]

Table 2: Preparation Methods for Nanohybrids.

Method	Principle	Advantages
Nanoprecipitation	Polymer and drug precipitate in a non-solvent	Simple, reproducible, suitable for hydrophobic drugs
Emulsification–Solvent Evaporation	Drug dissolved in organic solvent, emulsified in aqueous phase, solvent removed	High encapsulation efficiency, scalable
Self-Assembly	Amphiphilic molecules spontaneously form micelles or vesicles	Mild conditions, controlled size
Sol–Gel Method	Hydrolysis and condensation of metal alkoxides	Suitable for inorganic-organic hybrids, tunable porosity
Layer-by-Layer Assembly	Alternating deposition of oppositely charged materials	Surface functionalization, multifunctionality
Microfluidics	Controlled flow in microchannels to assemble nanoparticles	Precise control over size, monodispersity
Surface Functionalization & Ligand Conjugation	Chemical or physical attachment of ligands	Enables active targeting, stimuli-responsive release

Mechanisms of Action of Nanohybrid Drug Delivery Systems

Nanohybrid drug delivery systems (NDDS) enhance cancer therapy by improving drug accumulation at tumour sites, promoting cellular uptake, and enabling controlled and stimuli-responsive release. Their multifunctionality allows precise targeting and minimizes systemic toxicity [18,19]. The mechanisms of action can be broadly categorized as follows:

Passive Targeting

NDDS exploit the Enhanced Permeability and Retention (EPR) effect, where leaky tumour vasculature and impaired lymphatic drainage allow preferential accumulation of nanoparticles in tumour tissues. Nanohybrids' size and surface properties are optimized to enhance circulation time and retention at the tumour site [18,20].

Active Targeting

Surface functionalization with ligands, antibodies, peptides, or aptamers enables active targeting of tumor-specific receptors, such as folate, transferrin, integrins, or HER2. This receptor-mediated uptake increases internalization by cancer cells while reducing uptake in healthy tissues [19,21].

Stimuli-Responsive and Controlled Drug Release

Nanohybrids can be strategically engineered to achieve controlled and site-specific drug release in response to distinct endogenous and exogenous stimuli [19,22]. Among endogenous triggers, pH-sensitive nanohybrids are designed to remain relatively stable under physiological conditions but release their therapeutic payload in the acidic tumour microenvironment or within acidic intracellular compartments such as endosomes and lysosomes. Redox-responsive nanohybrids exploit the markedly elevated intracellular glutathione concentration in tumour cells, enabling cleavage of redox-sensitive bonds and subsequent drug release. Similarly, enzyme-responsive nanohybrid systems are developed to undergo selective degradation or structural transformation in the presence of tumour-associated enzymes, thereby enhancing localized drug availability while minimizing premature release in healthy tissues.

Cellular Uptake and Intracellular Trafficking

Once at the tumour site, nanohybrids are internalized via endocytosis pathways (clathrin-mediated, caveolae-mediated, macropinocytosis). After uptake, some nanohybrids can escape endosomes to release their cargo directly into the cytoplasm, enhancing therapeutic efficacy [20,22].

Multifunctional Mechanisms

Advanced nanohybrids can combine multiple therapeutic actions, such as chemotherapy, photothermal therapy, photodynamic therapy, and immunomodulation in a single platform. Some designs also allow theranostic imaging, enabling simultaneous diagnosis and treatment [18,23].

Therapeutic Applications of Nanohybrid Drug Delivery Systems

Nanohybrid drug delivery systems (NDDS) offer multifunctional platforms that improve cancer therapy by enhancing drug solubility, stability, tumour targeting, and controlled release. By integrating organic and inorganic components, nanohybrids enable delivery of chemotherapeutics, natural compounds, nucleic acids, immunotherapeutics, and facilitate theranostic imaging, allowing for personalized and combination cancer therapies [24,25].

Chemotherapy Delivery

Nanohybrids efficiently deliver chemotherapeutic drugs like doxorubicin, paclitaxel, and cisplatin by protecting them from degradation and improving their accumulation at tumour sites via passive (EPR effect) and active targeting strategies. Controlled release reduces systemic toxicity and enhances antitumor efficacy [24,26].

Natural Anticancer Compound Delivery

Phytochemicals such as curcumin and resveratrol have limited solubility and stability. Encapsulation in nanohybrids improves their bioavailability and intracellular delivery, resulting in higher antiproliferative activity in tumour cells compared to free compounds [25,27].

Gene and siRNA Delivery

NDDS can deliver siRNA, miRNA, and plasmid DNA, protecting them from enzymatic degradation and enhancing cellular uptake. Ligand-functionalized nanohybrids achieve targeted gene silencing in tumour cells, suppressing oncogene expression and inducing apoptosis [26,28].

Photothermal and Photodynamic Therapy

Nanohybrids containing gold, graphene, or iron oxide enable light- or heat-triggered therapies. Photothermal therapy (PTT) produces localized heat, while photodynamic therapy (PDT) generates reactive oxygen species (ROS) for selective tumour cell death. Combined chemo-PTT or chemo-PDT can further improve therapeutic outcomes [27,29].

Immunotherapy Delivery

Nanohybrids can deliver immune modulators like cytokines and checkpoint inhibitors directly to tumours, enhancing antitumor immune responses while minimising systemic side effects. This targeted delivery can synergise with chemotherapy or gene therapy for improved outcomes [28,30].

Combination Therapy

NDDS can co-deliver multiple agents such as chemotherapy drugs

with siRNA or photosensitizers, achieving synergistic effects, overcoming drug resistance, and allowing personalised therapy by tuning drug ratios and release kinetics [25,29] [Table 3].

ADVANTAGES AND CHALLENGES OF NANOHYBRID DRUG DELIVERY SYSTEMS

Nanohybrid drug delivery systems (NDDS) offer several distinct advantages over conventional chemotherapy and single-component nanoparticles. These systems enhance drug solubility and stability by encapsulating therapeutic agents within hybrid architectures, thereby protecting them from premature degradation and improving pharmacokinetic profiles [31]. The combination of organic and inorganic components allows for controlled and stimuli-responsive drug release, ensuring that drugs are delivered specifically to the tumour microenvironment, which minimizes systemic toxicity and enhances therapeutic efficacy [31,32]. Furthermore, surface functionalization with targeting ligands or antibodies enables active targeting, while the nanoscale size and prolonged circulation facilitate passive accumulation at tumour sites through the EPR effect [32,33]. NDDS also support multifunctional applications, combining chemotherapy, gene therapy, phototherapy, and immunotherapy in a single platform, which is particularly valuable for theranostic applications that allow simultaneous imaging and treatment [32,35]. By enabling co-delivery of multiple agents, nanohybrids can achieve synergistic effects, overcome drug resistance, and facilitate personalized therapy tailored to individual patient needs [33].

Despite these advantages, several challenges remain for the clinical translation of nanohybrids. Some inorganic components, such as metal nanoparticles or carbon-based nanomaterials, can induce cytotoxicity or unwanted immune responses, highlighting the need for thorough biocompatibility testing [34]. Stability during storage and circulation is another concern, as nanohybrids may aggregate or degrade, affecting particle size, drug release profiles, and targeting efficiency [31]. The complex design and multi-step fabrication processes, including surface functionalization and ligand conjugation, often result in high production costs and scalability issues [33]. Additionally, regulatory challenges and the lack of standardized protocols for characterization, safety assessment, and large-scale manufacturing hinder clinical translation, despite promising preclinical results [35]. Addressing these limitations is critical for the successful application of nanohybrid drug delivery systems in precision oncology [Table 4].

Preclinical and Clinical Progress of Nanohybrid Drug Delivery Systems

Nanohybrid drug delivery systems (NDDS) have demonstrated remarkable preclinical success in various cancer models, bridging the gap between laboratory research and clinical application. In in vitro studies, NDDS have shown enhanced cellular uptake, controlled drug release, and superior cytotoxicity against multiple cancer cell lines compared to free drugs or single-component nanoparticles [36,37]. These studies also confirm that hybrid systems can co-deliver multiple agents, such as chemotherapeutics and siRNA, achieving synergistic effects and overcoming multidrug resistance [36].

In animal models, NDDS exhibit improved pharmacokinetics and biodistribution, with enhanced tumor accumulation via both passive and active targeting mechanisms. Preclinical studies in murine and xenograft models have demonstrated significant tumor growth inhibition, reduced systemic toxicity, and minimal off-target effects [37,38]. Additionally, certain NDDS formulations incorporating photothermal or photodynamic therapy components have shown combined therapeutic and imaging (theranostic) capabilities, enabling real-time monitoring of treatment efficacy [39].

Despite these promising results, clinical translation remains limited. Only a few nanohybrid platforms have reached early-phase clinical trials, mainly lipid-polymer hybrids or biohybrid nanoparticles, highlighting challenges such as large-scale reproducibility,

Table 3: Therapeutic Applications of Nanohybrid Drug Delivery Systems.

Application	Examples / Agents	Mechanism / Advantage
Chemotherapy	Doxorubicin, Paclitaxel	Targeted delivery, reduced systemic toxicity
Natural Anticancer Compounds	Curcumin, Resveratrol	Enhanced solubility, stability, intracellular delivery
Gene/siRNA Delivery	siRNA, miRNA, Plasmid DNA	Gene silencing, protection from degradation, targeted
Photothermal / Photodynamic Therapy	Gold nanoparticles, Graphene oxide	Light/heat-triggered selective tumor killing, synergistic with chemo
Immunotherapy	Cytokines, Checkpoint inhibitors	Enhanced immune response, targeted delivery, reduced side effects
Combination Therapy	Drug + siRNA, Drug + PTT	Synergistic effects, overcome drug resistance, personalized therapy

Table 4: Advantages and Challenges of Nanohybrid Drug Delivery Systems.

Category	Advantages	Challenges
Solubility & Stability	Protects therapeutic agents, enhances pharmacokinetics, improves drug half-life	Aggregation, long-term stability issues
Targeting & Toxicity	Active and passive targeting, reduced systemic toxicity	Potential cytotoxicity or immune response from inorganic components
Drug Release	Controlled and stimuli-responsive release (pH, redox, enzymes, light)	Trigger reliability may vary in vivo, affecting release kinetics
Multifunctionality	Combines chemo/gene/phototherapy, theranostics	Complex design increases cost and fabrication difficulty
Combination Therapy	Co-delivery enables synergistic effects, personalized therapy	Reproducibility and standardization challenges hinder clinical translation

Table 5: Preclinical and Clinical Progress of Nanohybrid Drug Delivery Systems.

Study Type	Model / Cancer Type	Nanohybrid System	Key Findings
In vitro	Breast, lung, liver cancer cell lines	Polymer-lipid hybrids	Enhanced drug uptake, controlled release, cytotoxicity
In vivo (animal)	Xenograft, murine tumor models	Biohybrid nanoparticles, gold-polymer hybrids	Improved tumor accumulation, reduced systemic toxicity
Combination therapy	Murine breast cancer	Chemotherapy + siRNA-loaded NDDS	Synergistic effect, overcoming multidrug resistance
Theranostic studies	Murine tumor imaging models	Gold-graphene or silica-based hybrids	Combined therapy and imaging (PTT/PDT + chemotherapy)
Early-phase clinical	Various solid tumors	Lipid-polymer hybrid NDDS	Ongoing trials, safety and pharmacokinetics under evaluation

Table 6: Future Directions and Opportunities for Nanohybrid Drug Delivery Systems.

Future Perspective	Potential Advantages	Challenges	References
Smart, stimuli-responsive NDDS	Dynamic, tumor-specific drug release, combination therapy	Complexity in design and synthesis	[42,44]
Biomimetic NDDS	Immune evasion, enhanced tumor targeting	Stability, scalability, and reproducibility	[45,47]
AI-assisted design	Optimized size, surface properties, and release kinetics, personalized therapy	Need for large datasets, integration with preclinical/ clinical data	[46]
Combination therapy platforms	Synergistic anticancer effects, overcome drug resistance	Multi-drug loading, regulatory hurdles	[43,44]
Theranostic nanohybrids	Simultaneous imaging and therapy, real-time monitoring	Cost, regulatory approval, translational barriers	[42,44,45]

regulatory approvals, and long-term safety evaluation [40,41]. Nonetheless, NDDS represent a promising strategy for precision oncology, and ongoing clinical investigations are expected to expand their applicability for various cancer types [Table 5].

FUTURE PERSPECTIVES

Nanohybrid drug delivery systems (NDDS) represent a next-generation strategy in cancer therapy, integrating multifunctional capabilities that allow precise, controlled, and targeted treatment. Looking forward, the field is expected to benefit from advances in smart nanohybrids, including stimuli-responsive, biomimetic, and personalized platforms that can adapt dynamically to tumor microenvironments [42,43].

Smart and multifunctional nanohybrids are being developed to respond to multiple internal and external stimuli, enabling real-time control of drug release, imaging, and combination therapy. For example, hybrid systems combining chemotherapy with photothermal or photodynamic therapy, guided by tumor-specific imaging, can maximize therapeutic efficacy while minimizing systemic toxicity [44]. Biomimetic approaches, such as cell membrane-coated nanoparticles, allow NDDS to evade immune clearance and increase tumor targeting, which may significantly improve clinical translation success [45].

The integration of artificial intelligence (AI) and machine learning in nanohybrid design is another promising avenue. AI can optimize particle size, surface properties, drug loading, and release kinetics, leading to highly personalized cancer therapeutics tailored to individual patient profiles and tumor characteristics [46]. Additionally, combination therapies using NDDS are anticipated to overcome drug resistance, a major limitation of conventional chemotherapy, by simultaneously delivering multiple synergistic agents [43,44].

Despite these exciting prospects, challenges remain. Large-scale manufacturing, reproducibility, long-term safety, and regulatory approvals continue to hinder the widespread clinical use of NDDS [47]. Preclinical studies have demonstrated promising outcomes, but rigorous clinical trials are essential to validate efficacy and safety. Addressing these challenges will be critical for translating the full potential of NDDS into precision oncology applications.

In conclusion, nanohybrid drug delivery systems offer transformative potential for cancer therapy by combining targeted delivery, controlled release, multifunctionality, and theranostics in a single platform. With continued research and technological innovations, including AI-guided design, biomimetic coatings, and combination therapy strategies, NDDS are poised to become a cornerstone of personalized cancer treatment, improving patient outcomes and reducing systemic toxicity [Table 6].

CONCLUSIONS

In conclusion, nanohybrid drug delivery systems offer transformative potential for cancer therapy by combining targeted delivery, controlled release, multifunctionality, and theranostics in a single platform. With continued research and technological innovations, including AI-guided design, biomimetic coatings, and combination therapy strategies, NDDS are poised to become a cornerstone of personalized cancer treatment, improving patient outcomes and reducing systemic toxicity.

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