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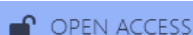
Advances in Lipid-Based Drug Delivery Systems for Cancer Therapy

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ABSTRACT

Background: Cancer remains one of the leading causes of morbidity and mortality worldwide despite substantial progress in diagnostic and therapeutic strategies. Conventional anticancer therapies are often associated with poor selectivity, systemic toxicity, multidrug resistance, limited bioavailability, and inadequate tumour penetration, which collectively reduce therapeutic efficacy and compromise patient outcomes. In recent years, lipid-based drug delivery systems have emerged as promising platforms for targeted and controlled delivery of anticancer agents. These systems improve drug solubility, enhance pharmacokinetic properties, reduce systemic adverse effects, and facilitate site-specific drug accumulation within tumour tissues.

Aim: To review recent advances in lipid-based drug delivery systems and their applications in cancer therapy.

Methods: The present narrative review was conducted using published scientific literature retrieved from electronic databases including PubMed, Scopus, Google Scholar, and ScienceDirect. Relevant articles focusing on lipid-based nanocarriers, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, lipid-polymer hybrid nanoparticles, and lipid-based targeted delivery systems in cancer therapy were included. Studies discussing mechanisms of drug delivery, therapeutic applications, advantages, limitations, and recent innovations were critically analyzed.

Results: Lipid-based drug delivery systems have demonstrated significant potential in improving therapeutic outcomes in various malignancies. Liposomes have shown enhanced drug encapsulation and reduced toxicity of chemotherapeutic agents such as doxorubicin and paclitaxel. Solid lipid nanoparticles and nanostructured lipid carriers provide improved drug stability, controlled release, and enhanced tumor targeting. Lipid-polymer hybrid nanoparticles combine the advantages of polymeric and lipid systems, resulting in better structural integrity and drug loading efficiency. Surface modification with ligands, antibodies, and polyethylene glycol has further enhanced selective targeting and prolonged systemic circulation. Recent advances in stimuli-responsive and multifunctional lipid nanocarriers have contributed to improved intracellular drug delivery and overcoming multidrug resistance.

Conclusion: Lipid-based drug delivery systems represent an important advancement in modern cancer therapeutics due to their ability to enhance drug bioavailability, reduce toxicity, and improve targeted delivery. Continuous innovations in nanotechnology and molecular targeting have expanded the clinical applicability of lipid-based carriers in oncology. Further large-scale clinical studies and translational research are necessary to optimize safety, efficacy, and large-scale commercialization of these advanced delivery platforms.

Keywords: Cancer Therapy; Lipid-Based Drug Delivery Systems; Liposomes; Solid Lipid Nanoparticles; Nanostructured Lipid Carriers; Targeted Drug Delivery; Nanotechnology; Oncology.

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INTRODUCTION

Cancer represents one of the most pressing challenges in contemporary medicine. Its hallmark features—genomic instability, phenotypic heterogeneity, and the capacity to evade immune surveillance—make durable disease control elusive [1]. Chemotherapeutic agents, while often cytotoxic to rapidly dividing cells, are indiscriminate in their distribution, exposing healthy tissues to significant harm. Poor aqueous solubility, rapid systemic clearance, inadequate penetration of the tumor microenvironment, and the progressive development of resistance further diminish the therapeutic window of many established anticancer drugs [2].

Nanoparticulate drug delivery platforms arose as a direct response to these pharmacological limitations. Among these, lipid-based carriers stand out for their inherent biocompatibility, structural versatility, and capacity to accommodate both hydrophilic and hydrophobic payloads within a single formulation. Physiologically derived lipids constitute the building blocks of cellular membranes, lending these systems an intrinsic compatibility with biological interfaces that synthetic polymer counterparts often lack [3,4].

The lipid nanocarrier landscape encompasses a broad spectrum of architecture. Liposomes—closed bilayer vesicles with an aqueous interior—were among the first to demonstrate clinical utility, and several liposomal formulations have since received regulatory approval. Solid lipid nanoparticles exploit the physical properties of solid-phase lipids to achieve controlled release, while their successor, nanostructured lipid carriers, incorporates a fraction of liquid lipid to overcome drug-loading limitations. Lipid-polymer hybrids integrate the structural rigidity of polymeric cores with the surface characteristics of lipid coatings. More recently, stimuli-responsive systems have been engineered to exploit physicochemical abnormalities within the tumor microenvironment—including acidic pH, elevated temperatures, and aberrant enzymatic activity—to trigger on-demand drug release [5–10].

Beyond cytotoxic payload delivery, lipid nanoparticles have emerged as foundational technologies in nucleic acid therapeutics. Their role in encapsulating and intracellularly delivering siRNA, mRNA, plasmid DNA, and CRISPR-associated components has been validated through both preclinical experimentation and the successful clinical translation of mRNA vaccines [11]. These developments underscore the versatility of lipid-based platforms across the evolving therapeutic landscape of oncology.

The present review aims to provide a structured appraisal of recent advances in LBDDS for cancer therapy, examining their design principles, mechanisms of drug delivery, targeting strategies, therapeutic applications, limitations, and future directions.

AIM AND OBJECTIVES

Aim

To review recent advances in lipid-based drug delivery systems and their applications in cancer therapy.

Objectives

1. To describe the various types of lipid-based drug delivery systems used in cancer therapy.
2. To discuss the mechanisms involved in lipid-mediated targeted drug delivery to tumor tissues.
3. To evaluate the advantages of lipid-based nanocarriers over conventional anticancer drug delivery systems.
4. To review recent advances in liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and lipid-polymer hybrid nanoparticles in oncology.
5. To assess the role of surface modification and targeted ligand conjugation in enhancing therapeutic efficacy.
6. To analyze the applications of lipid-based drug delivery systems in overcoming multidrug resistance in cancer therapy.
7. To discuss the limitations, safety concerns, and challenges associated with lipid-based nanocarriers.
8. To explore future perspectives and emerging innovations in lipid-based drug delivery systems for cancer management.

MATERIALS AND METHODS

Study Design and Duration

This study employed a narrative review methodology, with literature curation and analysis conducted over a six-month period.

Data Sources

Relevant scientific literature was retrieved from electronic databases including PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science.

Search Strategy

Searches were constructed using controlled vocabulary (MeSH terms) and free-text keywords, combined with Boolean operators (AND, OR) to optimize retrieval specificity.

Core search words included:

- “Lipid-based drug delivery systems”
- “Cancer therapy”
- “Liposomes”
- “Solid lipid nanoparticles”

- “Nanostructured lipid carriers”
- “Lipid-polymer hybrid nanoparticles”
- “Targeted drug delivery”
- “Nanotechnology in oncology”
- “Anticancer drug delivery”
- “Lipid nanocarriers”

Inclusion Criteria

1. Original research and review articles on Lipid based drug delivery systems in cancer
2. Articles published in English language in peer-reviewed journals.
3. Experimental, preclinical, and clinical studies evaluating efficacy and safety of lipid-based drug delivery systems.
4. Studies addressing mechanisms, targeting, and drug resistance

Exclusion Criteria

1. Articles not related to cancer therapy.
2. Non-English publications.
3. Duplicate studies and conference abstracts lacking sufficient data.
4. Studies with incomplete methodology or insufficient scientific evidence.
5. Publications unrelated to lipid-based nanocarriers.

Data Collection and Analysis

Eligible articles were screened by title, abstract, and full text. Relevant data on carrier types, formulation characteristics, targeting strategies, therapeutic outcomes, limitations, and technological innovations were extracted and grouped into thematic categories for comparative synthesis.

Ethical Consideration

As the present study was based on previously published scientific literature and did not involve human participants or experimental animals directly, institutional ethical approval was not required. Proper citation and acknowledgment of all referenced scientific sources were ensured throughout the review process.

CURRENT ADVANCES IN LIPID-BASED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY

Lipid-based drug delivery systems have emerged as an important area of research in oncology due to their potential to improve therapeutic efficacy and minimize systemic toxicity associated with conventional anticancer therapies. Advances in nanotechnology, molecular targeting, and pharmaceutical sciences have significantly expanded the applications of lipid nanocarriers in cancer treatment. Various lipid-based formulations including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nano emulsions, and lipid-polymer hybrid nanoparticles have demonstrated promising outcomes in both experimental and clinical settings [13].

1. Liposomes in Cancer Therapy

Liposomes are spherical vesicular structures composed of phospholipid bilayers surrounding an aqueous core. They are among the most extensively studied lipid-based carriers for anticancer drug delivery due to their improved drug stability, prolonged systemic circulation relative to free drug, reduced non-specific tissue distribution, facilitated intracellular delivery via endocytic pathways, and ability to encapsulate both hydrophilic and lipophilic drugs. Liposomal formulations improve drug pharmacokinetics and reduce systemic toxicity [14].

Several clinically approved liposomal formulations have demonstrated significant therapeutic benefits in oncology. Liposomal doxorubicin formulations have shown reduced cardiotoxicity and improved tolerability compared to conventional doxorubicin therapy. Pegylation—the covalent attachment of polyethylene glycol (PEG) chains to the liposomal surface, confers a hydrophilic steric barrier that limits recognition by the mononuclear phagocyte system, thereby extending circulation half-life and allowing greater accumulation at tumor sites through the enhanced permeability and retention (EPR) effect. Active targeting strategies, achieved by conjugating tumor-specific antibodies or receptor-binding ligands to the liposome surface, have further refined delivery precision, directing drug accumulation toward cells expressing particular surface antigens

2. Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles are submicron colloidal carriers composed of physiological lipids that remain solid at body temperature. These systems provide controlled drug release, improved stability, enhanced drug protection, and reduced toxicity. Solid lipid nanoparticles have gained considerable attention for delivery of poorly water-soluble anticancer drugs such as docetaxel and curcumin, for which conventional aqueous formulations are pharmacologically suboptimal [15].

Studies have demonstrated that solid lipid nanoparticles enhance cellular uptake and intracellular retention of chemotherapeutic agents. Their nanoscale size facilitates enhanced permeability and retention effect within tumor tissues. Surface modification of solid lipid nanoparticles with targeting ligands including folic acid, transferrin, and monoclonal antibodies has further improved selective tumor delivery and reduced off-target toxicity.

3. Nanostructured Lipid Carriers (NLC)

NLC were developed specifically to address a key limitation of SLN: the tendency of highly ordered solid lipid matrices to expel encapsulated drug molecules during storage—a phenomenon termed drug expulsion. By incorporating a spatially incompatible liquid lipid component into the solid lipid matrix, NLC introduce structural imperfections that create

additional accommodation space for drug molecules, yielding higher encapsulation efficiencies and greater formulation stability over time [16].

Nanostructured lipid carriers have demonstrated improved stability, higher encapsulation efficiency, and controlled drug release characteristics. Research studies have shown enhanced antitumor efficacy and improved bioavailability of various chemotherapeutic drugs using nanostructured lipid carriers. Multifunctional nanostructured lipid carriers capable of co-delivering chemotherapeutic agents and gene therapy molecules are also being actively investigated.

4. Lipid-Polymer Hybrid Nanoparticles (LPHN)

LPHN represent a convergent design philosophy: a polymeric core provides structural rigidity and high drug loading efficiency, while a surrounding lipid shell imparts biocompatibility, controls surface interactions, and facilitates cellular membrane fusion. This hybrid architecture achieves a pharmacokinetic profile that generally surpasses that of either purely polymeric or purely lipidic carriers, combining the prolonged drug release of polymer matrices with the favorable in vivo behavior of lipid coatings [17].

Recent studies have highlighted the potential of lipid-polymer hybrid nanoparticles in targeted cancer therapy and multidrug resistance modulation. Surface engineering with polyethylene glycol, antibodies, peptides, and aptamers has enabled improved tumor specificity and reduced immune clearance. Hybrid nanoparticles have also shown promise in combination therapy approaches involving simultaneous delivery of anticancer drugs and nucleic acids.

5. Targeted Lipid-Based Drug Delivery

Targeted drug delivery represents one of the most significant advances in modern cancer therapeutics. Lipid-based carriers can be engineered for passive or active targeting. Passive targeting relies primarily on the EPR effect: tumor vasculature is characteristically fenestrated and poorly organized, allowing extravasation and retention of nanoparticles in the range of 50–400 nm. Active targeting augments this by decorating the carrier surface with ligands that bind to receptors or antigens overexpressed on tumor cell surfaces [18].

Surface-modified lipid nanocarriers containing folate receptors, transferrin receptors, antibodies, peptides, and aptamers have demonstrated improved tumor localization and cellular internalization. Active targeting minimizes systemic exposure and enhances therapeutic efficacy by increasing selective uptake by malignant cells.

6. Stimuli-Responsive Lipid Nanocarriers

Stimuli-responsive or smart lipid nanocarriers are designed to release therapeutic agents in response to internal or external stimuli such as pH, temperature, enzymes, ultrasound, magnetic field, or light. Tumor microenvironment-responsive systems exploit acidic pH and abnormal enzymatic activity within tumors for site-specific drug release [19].

Thermosensitive liposomes and pH-sensitive lipid nanoparticles have demonstrated enhanced intracellular drug delivery and improved antitumor activity. These advanced systems provide controlled and selective release of drugs while minimizing systemic adverse effects.

7. Lipid Nanocarriers in Gene and Immunotherapy

Lipid-based delivery systems have gained increasing importance in gene therapy and cancer immunotherapy. Lipid nanoparticles facilitate delivery of nucleic acids including siRNA, mRNA, plasmid DNA, and CRISPR-associated genetic materials. Their ability to protect nucleic acids from enzymatic degradation significantly improves intracellular gene transfer [20].

Recent advances in mRNA-based therapeutics and cancer vaccines have highlighted the importance of lipid nanoparticles as efficient delivery platforms. Lipid-based carriers also support delivery of immunomodulatory agents and tumor antigens, thereby enhancing antitumor immune responses.

Comparative Overview of LBDDS Platforms

Platform	Key Advantage	Primary Limitation	Clinical Examples
Liposomes	Dual payload, reduced cardiotoxicity, PEGylation extends circulation	Bilayer instability, drug leakage	Liposomal doxorubicin, liposomal daunorubicin
SLN	Controlled release, drug stability, EPR accumulation	Drug expulsion on storage, low loading capacity	Paclitaxel SLN (investigational)
NLC	High encapsulation efficiency, improved stability over SLN	Complex manufacturing, scale-up challenges	Multiple preclinical oncology studies
LPHN	Superior structural integrity, combined polymer-lipid properties	Synthesis complexity, cost	Co-delivery of chemotherapy + siRNA (preclinical)
Stimuli-Responsive	Site-specific triggered release, reduced systemic toxicity	Precise external trigger required	ThermoDox (clinical trials for liver cancer)

Lipid NP (Nucleic Acid)	Efficient intracellular RNA/DNA delivery, immunotherapy potential	Off-target immune activation	mRNA cancer vaccines (clinical trials)
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Limitations and Challenges

- Physical instability: lipid matrices are susceptible to oxidation, hydrolysis, polymorphic crystallization, and particle aggregation, all of which can compromise drug retention and therapeutic consistency during storage and administration.
- Drug leakage: premature release of encapsulated cargo—particularly for hydrophilic drugs—can reduce bioavailability at the target site while increasing exposure to non-tumor tissues.
- Manufacturing scalability: reproducible fabrication of nanocarriers at industrial scale, while maintaining tight particle size distributions and encapsulation efficiencies, remains technically and economically demanding.
- Clearance by the mononuclear phagocyte system: despite PEGylation strategies, prolonged circulation is not guaranteed, and accelerated blood clearance upon repeated dosing has been documented for PEGylated formulations.
- Regulatory and safety considerations: the long-term toxicological profiles of novel lipid excipients, surface ligands, and polymer components require extensive evaluation before regulatory authorities can approve them for routine clinical use.
- Cost and accessibility: the complexity of lipid nanocarrier synthesis translates into higher production costs relative to conventional dosage forms, potentially limiting accessibility in resource-constrained healthcare settings.

FUTURE PERSPECTIVES

The field of lipid-based drug delivery systems has witnessed remarkable growth in recent years and continues to evolve rapidly with advances in nanotechnology, molecular biology, pharmaceutical sciences, and precision medicine. Future developments are expected to focus on improving specificity, therapeutic efficacy, safety, and clinical translation of lipid nanocarriers for cancer therapy.

1. Theranostic Platforms

A particularly exciting frontier is the engineering of theranostic lipid nanocarriers—formulations that integrate diagnostic imaging agents and therapeutic molecules within a single particulate system. By enabling real-time tracking of carrier biodistribution and monitoring of tumor response, theranostics offer the potential for highly individualized treatment adaptation, accelerating dose optimization and early identification of non-responders.

2. Precision Oncology and Personalized Nanomedicine

Surface-engineered and ligand-targeted lipid nanocarriers are expected to play a major role in precision oncology. Advances in receptor biology and tumor biomarker identification may facilitate development of highly selective delivery systems directed against tumor-specific antigens and molecular pathways. Personalized nanomedicine approaches based on genetic and molecular profiling of tumors could improve treatment outcomes while minimizing systemic toxicity.

3. Artificial Intelligence in Formulation Design

Machine learning and computational modeling are beginning to reshape the drug delivery development pipeline. AI-driven platforms can process multidimensional datasets—encompassing lipid composition, particle geometry, surface chemistry, and in vitro release profiles—to predict in vivo pharmacokinetic behavior, identify optimal targeting ligands, and streamline quality-by-design formulation development, significantly reducing the experimental burden of iterative optimization.

4. Combination and Multi-Modal Delivery

Combination therapy using lipid nanocarriers is gaining increasing importance in oncology. Future delivery platforms are likely to support simultaneous transport of chemotherapeutic agents, nucleic acids, immunotherapeutic molecules, and gene-editing tools such as CRISPR-Cas systems. Such multidimensional approaches may help overcome multidrug resistance and improve therapeutic efficacy in aggressive and refractory malignancies.

Advances in messenger RNA therapeutics and cancer vaccines have further highlighted the importance of lipid nanoparticles as efficient nucleic acid delivery platforms. Future research may expand the application of lipid nanocarriers in personalized cancer vaccines, immune modulation, and targeted gene therapy. Integration of immunotherapy with lipid-based drug delivery systems may significantly improve antitumor immune responses and long-term disease control.

CONCLUSION

Lipid-based drug delivery systems have matured from a conceptual framework into a clinically validated and rapidly expanding technology platform in oncology. Their capacity to enhance drug solubility, modulate pharmacokinetics, reduce systemic toxicity, and deliver therapeutic payloads with spatial and temporal precision has been substantiated across a broad spectrum of preclinical models and, in select cases, in clinical practice. From the approved liposomal chemotherapy formulations that have reduced cardiotoxicity in breast cancer patients to the next-generation lipid nanoparticle platforms

now entering clinical trials for personalized cancer vaccines, the trajectory of this field reflects both its scientific maturity and its continuing innovation.

Various lipid-based systems including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and lipid-polymer hybrid nanoparticles have demonstrated substantial therapeutic potential in preclinical and clinical studies. These carriers facilitate improved pharmacokinetic properties, prolonged systemic circulation, enhanced intracellular drug uptake, and better accumulation within tumor tissues through passive and active targeting mechanisms.

Surface modification with polyethylene glycol, antibodies, peptides, aptamers, and receptor-specific ligands has further enhanced the selectivity and efficacy of lipid nanocarriers in oncology. In addition, stimuli-responsive and multifunctional lipid delivery systems have shown encouraging results in achieving controlled drug release and overcoming multidrug resistance in cancer cells.

Lipid-based nanocarriers have also expanded their applications beyond conventional chemotherapy to include gene therapy, immunotherapy, messenger RNA therapeutics, and combination therapy approaches. Their role in delivery of nucleic acids and immunomodulatory agents has opened new possibilities for personalized and precision-based cancer treatment strategies.

Despite remarkable progress, challenges related to formulation stability, scalability, manufacturing cost, regulatory approval, and long-term safety continue to limit broader clinical translation. Further research focusing on optimization of carrier design, standardization of manufacturing processes, and large-scale clinical trials is necessary to establish safety and therapeutic effectiveness.

Overall, lipid-based drug delivery systems represent a rapidly evolving and transformative area in oncology with substantial potential to improve cancer diagnosis, targeted therapy, and patient outcomes. Continued interdisciplinary research and technological innovation are expected to further strengthen the role of lipid nanotechnology in future cancer therapeutics.

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