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Targeted and Controlled Drug Delivery Using Lipid Vesicular Systems for Cancer Therapy

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ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide, and its effective treatment continues to be limited by poor drug selectivity, systemic toxicity, multidrug resistance, rapid drug clearance, and inadequate accumulation of therapeutic agents at the tumour site. Conventional chemotherapy often affects both malignant and healthy cells, resulting in severe adverse effects and reduced patient compliance. In this context, targeted and controlled drug delivery systems have gained significant attention as promising approaches to improve the therapeutic outcome of anticancer agents. Lipid vesicular systems, including liposomes, niosomes, transferosomes, ethosomes, phytosomes, and cubosomes, offer several advantages such as biocompatibility, improved drug solubility, enhanced cellular uptake, protection of drugs from degradation, prolonged circulation time, and controlled release behaviour. These vesicular carriers can encapsulate both hydrophilic and lipophilic drugs and can be modified with specific ligands to achieve active targeting toward tumour cells. In addition, lipid vesicular systems can respond to tumour microenvironmental conditions such as acidic pH, enzymatic activity, redox potential, and temperature changes, allowing site-specific and controlled drug release. This review discusses the fundamental concepts, major types, formulation approaches, characterisation parameters, targeting mechanisms, and therapeutic applications of lipid vesicular systems in cancer therapy. It also highlights their role in improving the delivery of chemotherapeutic drugs, natural anticancer compounds, gene-based therapeutics, and immunotherapeutic agents. Despite their potential, challenges related to stability, large-scale production, sterilisation, regulatory approval, and clinical translation remain important concerns. Overall, lipid vesicular drug delivery systems represent a promising platform for targeted and controlled cancer therapy, with strong potential to improve treatment efficacy, reduce toxicity, and support the future development of precision oncology.

Keywords: Cancer therapy; Lipid vesicular systems; Targeted drug delivery; Controlled release; Liposomes; Niosomes; Nanocarriers.

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INTRODUCTION

Cancer remains a major global health burden and one of the leading causes of morbidity and mortality worldwide. According to GLOBOCAN 2022, nearly 20 million new cancer cases and 9.7 million cancer-related deaths were reported globally, showing the urgent need for more effective and safer treatment strategies [1]. Although chemotherapy, radiotherapy, surgery, immunotherapy, and targeted therapy have improved cancer management, conventional chemotherapy is still limited by poor drug selectivity, systemic toxicity, rapid clearance, low tumour accumulation, and development of multidrug resistance [2,3].

Most anticancer drugs act on rapidly dividing cells, but they cannot completely differentiate between cancer cells and normal proliferating cells. This non-specific action often leads to serious adverse effects such as myelosuppression, gastrointestinal toxicity, mucositis, alopecia, nephrotoxicity, and cardiotoxicity. In addition, poor aqueous solubility, short half-life, low bioavailability, and instability of many anticancer agents further reduce their therapeutic effectiveness [2]. These limitations have increased the interest in advanced drug delivery systems that can improve drug targeting, regulate drug release, and reduce toxicity to healthy tissues.

Targeted and controlled drug delivery systems are promising approaches for improving cancer therapy. Targeted delivery enhances drug accumulation at the tumour site, while controlled delivery regulates the release of the drug over time or in response to specific tumour conditions. Nanocarrier-based systems can protect drugs from premature degradation, improve pharmacokinetics, enhance cellular uptake, and reduce systemic exposure [3]. Among these systems, lipid vesicular drug delivery systems have gained significant attention because of their biocompatibility, structural similarity to biological membranes, ability to encapsulate both hydrophilic and lipophilic drugs, and potential for surface modification [4,5].

Lipid vesicular systems are microscopic or nanosized carriers usually composed of lipid bilayers or surfactant-based vesicular structures enclosing an aqueous core. Liposomes are the most widely studied lipid vesicular carriers and have shown strong potential in cancer therapy due to their ability to improve drug solubility, prolong circulation time, and reduce drug-associated

toxicity [4,6]. The clinical success of pegylated liposomal doxorubicin, Doxil®, the first FDA-approved nanodrug, confirmed the therapeutic value of lipid-based nanocarriers in oncology [8]. Apart from liposomes, other vesicular systems such as niosomes, transfersomes, ethosomes, phytosomes, and cubosomes have also been investigated for anticancer drug delivery because of their stability, flexibility, penetration-enhancing ability, and controlled release properties [11].

Tumour targeting by lipid vesicular systems may occur through passive or active mechanisms. Passive targeting is mainly associated with the enhanced permeability and retention effect, where nanosized carriers accumulate in tumour tissues due to leaky tumour vasculature and poor lymphatic drainage [7]. However, this effect varies across tumour types and may not always confer sufficient selectivity. Therefore, active targeting strategies have been developed by attaching ligands such as folic acid, transferrin, antibodies, peptides, aptamers, or hyaluronic acid to the vesicle surface, allowing receptor-mediated uptake by cancer cells [9]. Furthermore, stimuli-responsive lipid vesicles can release drugs in response to tumour-specific conditions such as acidic pH, enzyme activity, redox potential, temperature, light, ultrasound, or magnetic field [10].

Despite their advantages, lipid vesicular systems face challenges related to physical and chemical stability, drug leakage, sterilization, scale-up production, batch-to-batch variation, cost, and regulatory approval [12]. Therefore, careful formulation design, proper characterization, reproducible manufacturing, and strong preclinical and clinical evaluation are essential for successful translation. Overall, lipid vesicular systems provide a promising platform for targeted and controlled cancer drug delivery by improving therapeutic efficacy, reducing toxicity, and supporting the development of precision oncology.

Lipid Vesicular Drug Delivery Systems: Overview

Lipid vesicular drug delivery systems are colloidal carrier systems composed mainly of lipids, phospholipids, cholesterol, surfactants, or related amphiphilic molecules arranged in vesicular structures. These systems are designed to improve the delivery of therapeutic agents by protecting drugs from degradation, enhancing solubility, modifying biodistribution, and promoting drug accumulation at the desired site of action. In cancer therapy, lipid vesicular systems have gained considerable importance because they can reduce non-specific toxicity and improve the therapeutic performance of anticancer drugs [13].

Structurally, lipid vesicles generally consist of one or more bilayer membranes enclosing an aqueous compartment. This arrangement allows the encapsulation of hydrophilic drugs in the aqueous core and lipophilic drugs within the lipid bilayer. The vesicle size, surface charge, lipid composition, membrane rigidity, and surface modification strongly influence drug loading, circulation time, cellular uptake, release behavior, and biological stability. Liposomes are the most widely investigated vesicular carriers, while other systems such as niosomes, transfersomes, ethosomes, phytosomes, and cubosomes have expanded the scope of lipid-based nanocarriers in oncology [14,15].

The composition of lipid vesicular systems plays a key role in determining their stability and drug delivery efficiency. Phospholipids provide the basic bilayer structure, cholesterol improves membrane rigidity and reduces premature drug leakage, and surfactants or edge activators may enhance flexibility and penetration. In niosomes, non-ionic surfactants form the vesicular bilayer and are often combined with cholesterol to improve stability. These formulation components can be adjusted to obtain desirable particle size, entrapment efficiency, controlled release, and tumor-targeting capacity [16].

In cancer treatment, lipid vesicular systems offer several advantages over conventional drug administration. They can improve the aqueous solubility of poorly soluble anticancer drugs, prolong systemic circulation, protect unstable drugs from enzymatic or chemical degradation, and reduce exposure of healthy tissues to cytotoxic agents. Their nanoscale size supports passive tumor accumulation, while surface functionalization with targeting ligands can enhance receptor-mediated uptake by cancer cells. Moreover, lipid vesicular systems can be engineered for sustained or stimuli-responsive drug release, allowing better control over drug availability at the tumor site [13,14].

Another important advantage of lipid vesicular systems is their versatility. They can deliver small-molecule chemotherapeutic agents, natural anticancer compounds, peptides, proteins, genes, siRNA, mRNA, and immunotherapeutic molecules. This flexibility makes them suitable for single-drug therapy as well as combination therapy. Recent advances in lipid-based nanocarriers have also supported their use in tumor microenvironment-responsive delivery, cancer vaccines, and precision oncology approaches. Therefore, lipid vesicular systems represent an important platform for targeted and controlled drug delivery in modern cancer therapy [13,15].

Major Types of Lipid Vesicular Systems

Lipid vesicular systems include several carrier platforms with different compositions, structures, and drug delivery properties. In cancer therapy, the most important vesicular carriers include liposomes, niosomes, transfersomes, ethosomes, phytosomes, and cubosomes. These systems are useful because they can improve drug solubility, enhance tumor targeting, reduce systemic toxicity, and support controlled drug release.

Liposomes are the most widely studied lipid vesicular systems in cancer drug delivery. They are spherical vesicles composed mainly of phospholipid bilayers enclosing an aqueous core. This structure allows liposomes to carry both hydrophilic and lipophilic anticancer drugs. Liposomal formulations can improve drug stability, prolong systemic circulation, enhance tumour accumulation, and reduce adverse effects compared with free drugs. Surface modification with polyethylene glycol or targeting ligands can further improve circulation time and tumour selectivity [17].

Niosomes are vesicular carriers formed from non-ionic surfactants, usually stabilized with cholesterol. They are structurally similar to liposomes but are often considered more chemically stable and cost-effective. Niosomes can encapsulate hydrophilic, lipophilic,

and amphiphilic drugs and have been investigated for the targeted delivery of chemotherapeutic agents in cancers such as breast cancer. Their advantages include improved drug penetration, controlled release, enhanced bioavailability, and reduced off-target toxicity [18].

Transfersomes are ultra-deformable vesicles composed of phospholipids and edge activators such as surfactants. Their high flexibility allows them to pass through narrow biological barriers, especially the skin, without losing vesicular integrity. Transfersomes are mainly useful for transdermal drug delivery and may be beneficial for localised cancer treatment, especially skin-related malignancies. They can enhance drug permeation, improve patient compliance, and provide sustained drug release [19].

Ethosomes are soft, flexible lipid vesicles containing phospholipids, water, and a high concentration of ethanol. Ethanol increases vesicle flexibility and improves penetration through biological membranes, particularly the stratum corneum. In cancer therapy, ethosomes are mainly explored for topical and transdermal delivery of anticancer drugs and natural bioactive compounds. Their ability to improve drug permeation and local drug retention makes them useful for skin cancer and other localized therapeutic applications [20].

Phytosomes are lipid-compatible complexes formed between phospholipids and plant-derived bioactive compounds. They are especially useful for improving the solubility, absorption, and bioavailability of phytoconstituents such as curcumin, quercetin, resveratrol, and other natural anticancer agents. In cancer therapy, phytosomes may enhance the therapeutic potential of herbal compounds by improving membrane permeability, cellular uptake, and systemic availability [21].

Cubosomes are lipid-based nanostructured carriers with a bicontinuous cubic phase arrangement. Their internal structure provides a large surface area and enables the loading of hydrophilic, lipophilic, and amphiphilic drugs. Cubosomes are promising for cancer therapy because they can provide controlled release, improved drug stability, and potential tumour-targeted delivery. Their unique architecture also supports their use in advanced nanomedicine and combination drug delivery approaches [22] [Table 1].

Overall, each lipid vesicular system offers distinct advantages in cancer drug delivery. Liposomes and niosomes are widely used for systemic delivery, transfersomes and ethosomes are valuable for transdermal and localized delivery, phytosomes enhance the delivery of natural anticancer compounds, and cubosomes provide advanced structural features for controlled and targeted release [Figure 1].

FORMULATION AND CHARACTERIZATION

Formulation of lipid vesicular drug delivery systems requires careful selection of lipids, phospholipids, cholesterol, surfactants, stabilizers, solvents, and aqueous phases to obtain vesicles with suitable size, stability, drug-loading capacity, and release behavior. Common preparation methods include thin-film hydration, ethanol injection, solvent injection, reverse-phase evaporation, sonication, extrusion, high-pressure homogenization, and microfluidic-based techniques. Among these, conventional methods such as thin-film hydration and solvent injection are widely used at laboratory scale, whereas microfluidic approaches are gaining attention because they allow better control over particle size, size distribution, reproducibility, and scale-up potential [23].

Quality-by-design approaches are increasingly used in lipid-based formulation development to identify critical material attributes and critical process parameters that influence final product quality. Factors such as lipid concentration, drug-to-lipid ratio, cholesterol content, surfactant concentration, hydration temperature, sonication time, homogenization speed, and flow rate can significantly affect vesicle size, entrapment efficiency, stability, and drug release profile. Therefore, systematic optimization is important to develop stable, reproducible, and clinically acceptable lipid vesicular formulations [24].

Characterization is essential to confirm the quality, safety, and performance of lipid vesicular systems. Particle size and polydispersity index are commonly measured by dynamic light scattering and indicate vesicle uniformity and distribution. Zeta potential reflects surface charge and helps predict colloidal stability, aggregation tendency, and interaction with biological membranes. Morphological evaluation using transmission electron microscopy, scanning electron microscopy, or atomic force microscopy provides

Table 1: Types of Lipid Vesicular Systems Used in Cancer Therapy.

Type of lipid vesicular system	Basic composition/structure	Key features	Relevance in cancer therapy
Liposomes	Phospholipid bilayer vesicles enclosing an aqueous core	Can carry both hydrophilic and lipophilic drugs; biocompatible; surface can be modified	Used for delivery of anticancer drugs such as doxorubicin, daunorubicin, irinotecan, and paclitaxel; helps reduce toxicity and improve tumor accumulation
Niosomes	Vesicles made from non-ionic surfactants and cholesterol	More chemically stable and cost-effective than some phospholipid vesicles	Useful for targeted and controlled delivery of chemotherapeutic agents and natural anticancer compounds
Transfersomes	Ultra-flexible vesicles containing phospholipids and edge activators	Highly deformable; can pass through narrow biological barriers	Useful for transdermal and localized anticancer drug delivery, especially in skin-related tumors
Ethosomes	Phospholipid vesicles containing a high concentration of ethanol	Soft, flexible, and penetration-enhancing	Useful for topical and transdermal delivery of anticancer drugs and phytoconstituents
Phytosomes	Complexes of phospholipids with plant-derived bioactive compounds	Improve solubility, absorption, and bioavailability of natural compounds	Used for natural anticancer agents such as curcumin, quercetin, resveratrol, and silybin
Cubosomes	Nanostructured lipid carriers with bicontinuous cubic phase	High internal surface area; suitable for controlled release	Useful for sustained and controlled delivery of anticancer drugs and combination therapy

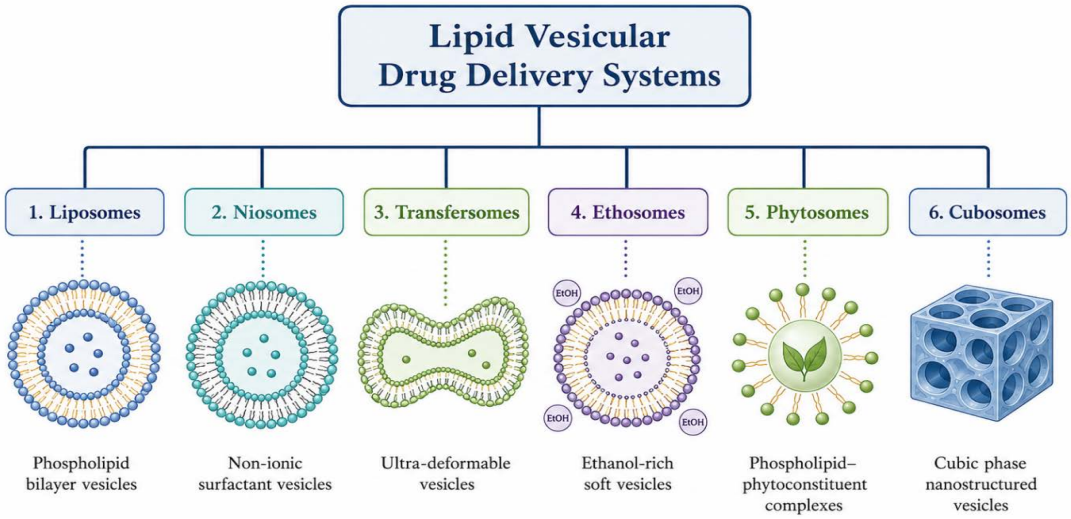


Figure 1. Classification of Lipid Vesicular Drug Delivery Systems.

information about vesicle shape, surface structure, and lamellarity [25].

Entrapment efficiency and drug-loading capacity are important parameters that determine how much drug is incorporated into the vesicular system. These parameters are usually evaluated after separating the free drug from the encapsulated drug by centrifugation, ultrafiltration, dialysis, or chromatography-based methods. In vitro drug release studies are performed to evaluate whether the formulation provides immediate, sustained, controlled, or stimuli-responsive release. However, release testing of colloidal carriers remains challenging because standardized protocols are still limited, and the selected method should be suitable for the carrier type, drug properties, and intended route of administration [26].

Stability studies are also necessary to assess changes in particle size, zeta potential, drug leakage, aggregation, appearance, and drug content during storage. In cancer drug delivery research, biological evaluation generally includes in vitro cytotoxicity studies using cancer cell lines, cellular uptake studies, hemocompatibility tests, apoptosis assays, and, where required, in vivo biodistribution and antitumor efficacy studies. Together, these characterization parameters help determine whether a lipid vesicular formulation is suitable for further preclinical or clinical development [25].

Targeted and Controlled Drug Delivery Mechanisms

Lipid vesicular systems improve cancer therapy through targeted drug delivery and controlled drug release mechanisms. Targeting may occur through passive targeting, active targeting, or tumour microenvironment-responsive delivery. Passive targeting is mainly associated with the enhanced permeability and retention effect, where nanosized vesicles accumulate in tumour tissues due to leaky tumour vasculature and poor lymphatic drainage. However, this effect is not uniform in all tumours and may vary according to tumour type, vascularisation, stromal density, and interstitial fluid pressure [28].

Active targeting involves surface modification of lipid vesicles with specific ligands that can recognise receptors overexpressed on cancer cells or tumour-associated cells. Common targeting ligands include folic acid, transferrin, peptides, antibodies, aptamers, and hyaluronic acid. After ligand-receptor binding, the vesicular carrier may enter cancer cells through receptor-mediated endocytosis, resulting in higher intracellular drug concentration and improved therapeutic selectivity. This strategy is useful for reducing non-specific toxicity and improving drug accumulation at the cellular level [27,28] [Figure 1].

Tumour microenvironment-responsive delivery is another important mechanism for controlled cancer therapy. Tumour tissues commonly show acidic pH, high glutathione concentration, increased reactive oxygen species, enzyme overexpression, hypoxia, and abnormal temperature gradients. Lipid vesicular systems can be engineered to respond to these internal signals and release the drug preferentially at the tumour site. pH-sensitive vesicles release drugs in acidic tumour or endosomal environments, redox-sensitive systems respond to intracellular glutathione, and enzyme-responsive systems release drugs in the presence of tumour-associated enzymes [28,29].

Controlled drug release can also be achieved through external triggers such as temperature, ultrasound, light, and a magnetic field. Thermosensitive lipid vesicles release drugs when exposed to mild hyperthermia, while ultrasound-responsive and light-responsive systems can enhance local drug release and tissue penetration. These externally triggered systems provide spatial and temporal control over drug release, which may improve antitumor activity while minimising systemic exposure [27,29].

Overall, targeted and controlled drug delivery mechanisms allow lipid vesicular systems to improve the pharmacokinetic profile, tumour accumulation, intracellular uptake, and therapeutic index of anticancer agents. By combining passive targeting, ligand-mediated active targeting, and stimuli-responsive release, lipid vesicular systems can support more selective, effective, and safer cancer therapy.

Applications in Cancer Therapy

Lipid vesicular systems have wide applications in cancer therapy because they can deliver different categories of therapeutic agents, including chemotherapeutic drugs, natural anticancer compounds, genes, RNA-based therapeutics, and immunotherapeutic agents. These systems improve drug solubility, protect unstable molecules, enhance tumor accumulation, reduce systemic toxicity, and support controlled release at the tumor site [30].

Chemotherapeutic drugs are the most common agents delivered through lipid vesicular systems. Drugs such as doxorubicin, paclitaxel, cisplatin, irinotecan, cytarabine, daunorubicin, and 5-fluorouracil have been incorporated into lipid-based carriers to improve their pharmacokinetic behavior and reduce dose-related toxicity. Liposomal encapsulation can decrease exposure of healthy tissues to cytotoxic drugs while increasing drug retention in tumor tissues. This approach is especially useful for drugs with poor solubility, short half-life, severe systemic toxicity, or narrow therapeutic index [30].

Lipid vesicular systems are also useful for delivering natural anticancer compounds such as curcumin, quercetin, resveratrol, silybin, berberine, and other phytoconstituents. Many natural compounds show promising anticancer activity but have limited clinical utility due to poor aqueous solubility, low bioavailability, rapid metabolism, and instability. Phytosomes and other lipid-based vesicles can improve the absorption, membrane permeability, and therapeutic availability of these compounds, thereby enhancing their anticancer potential [31] [Table 2].

Gene and RNA-based therapeutics represent another important application of lipid vesicular systems in oncology. Lipid nanoparticles and related vesicular carriers can protect nucleic acids from enzymatic degradation and promote intracellular delivery. These systems have been studied for the delivery of siRNA, miRNA, mRNA, plasmid DNA, and gene-editing components. In cancer therapy, RNA-based delivery may be used to silence oncogenes, restore tumor suppressor activity, encode tumor antigens, or stimulate antitumor immune responses [32,33].

Lipid vesicular systems are increasingly investigated for cancer immunotherapy. They can deliver tumor antigens, immune adjuvants, cytokine-encoding mRNA, checkpoint-modulating molecules, and cancer vaccine components. Lipid nanoparticle-based mRNA platforms are particularly promising because they can encode tumor-associated antigens, neoantigens, cytokines, antibodies, or immune-cell receptors. These approaches may improve antigen presentation, activate cytotoxic T cells, and support personalized cancer immunotherapy [32,34].

Overall, lipid vesicular systems provide a flexible platform for both conventional and advanced cancer therapeutics. Their ability to co-deliver multiple agents also makes them suitable for combination therapy, where chemotherapeutic drugs, genetic material, natural compounds, or immunotherapeutic agents can be delivered together to improve therapeutic response and overcome drug resistance.

Clinical Relevance and Recent Advances

The clinical relevance of lipid vesicular systems is supported by the successful development of several liposomal anticancer formulations and by increasing preclinical and clinical research on advanced lipid-based nanomedicines. Clinically used liposomal products have demonstrated that encapsulation can improve drug distribution, reduce toxicity, and enhance the therapeutic index of anticancer agents. Examples include liposomal doxorubicin, liposomal daunorubicin, liposomal irinotecan, liposomal vincristine, and liposomal daunorubicin-cytarabine combinations [30].

Recent clinical studies have also highlighted the growing importance of lipid-based systems in personalized oncology. In a randomized phase 2b trial, the individualized neoantigen mRNA therapy mRNA-4157/V940 combined with pembrolizumab showed improved recurrence-free survival compared with pembrolizumab alone in patients with resected high-risk melanoma, supporting the clinical potential of mRNA-based cancer immunotherapy [35]. In 2024, the U.S. FDA approved irinotecan liposome with oxaliplatin, fluorouracil, and leucovorin for first-line treatment

Table 2: Applications of Lipid Vesicular Systems in Anticancer Drug Delivery.

Category of therapeutic agent	Examples	Role of lipid vesicular systems	Cancer therapy relevance
Chemotherapeutic drugs	Doxorubicin, paclitaxel, cisplatin, irinotecan, daunorubicin, 5-fluorouracil	Improve solubility, reduce systemic toxicity, prolong circulation, and enhance tumour accumulation	Useful in breast cancer, ovarian cancer, lung cancer, pancreatic cancer, leukaemia, and other malignancies
Natural anticancer compounds	Curcumin, quercetin, resveratrol, berberine, silybin	Improve bioavailability, membrane permeability, stability, and cellular uptake	Supports safer adjunct or alternative anticancer strategies using bioactive phytoconstituents
Gene-based therapeutics	Plasmid DNA, gene-editing components	Protect genetic material from degradation and support intracellular delivery	Useful for correcting cancer-related genetic pathways or enhancing tumour suppressor activity
RNA-based therapeutics	siRNA, miRNA, mRNA	Protect RNA from enzymatic degradation and improve cytoplasmic delivery	Useful for oncogene silencing, tumour antigen expression, and personalized cancer vaccines
Immunotherapeutic agents	Tumour antigens, immune adjuvants, cytokine-encoding mRNA, checkpoint-related molecules	Improve antigen delivery, immune activation, and targeted immune response	Supports cancer vaccines, immune modulation, and combination with checkpoint inhibitors
Combination therapy agents	Chemotherapy + siRNA, chemotherapy + immunotherapy, drug + imaging agent	Allows co-delivery of multiple agents in controlled ratios	Helps improve synergistic anticancer activity and overcome multidrug resistance

of metastatic pancreatic adenocarcinoma, further confirming the clinical value of liposomal chemotherapy in oncology [36].

Preclinical studies continue to expand the role of lipid vesicular systems beyond conventional chemotherapy. Recent work has shown that lipid nanoparticle-formulated mRNA encoding immune-stimulatory molecules can induce systemic antitumor immunity after intratumoral administration. Such findings suggest that lipid vesicles may act not only as passive drug carriers but also as active immunomodulatory platforms capable of reshaping the tumor immune microenvironment [34].

Combination therapy is another important recent direction. Lipid vesicular systems can co-deliver two or more therapeutic agents with different mechanisms of action, such as chemotherapy with immunotherapy, chemotherapy with gene silencing agents, or mRNA vaccines with immune checkpoint inhibitors. This approach may improve synergistic anticancer effects, reduce multidrug resistance, and enable more precise control of drug ratio and release kinetics [37].

Recent advances in lipid vesicular cancer nanomedicine include ligand-targeted vesicles, PEGylated long-circulating liposomes, stimuli-responsive liposomes, theranostic vesicles, RNA-loaded lipid nanoparticles, and microfluidic-based manufacturing methods. Despite these advances, clinical translation still requires better control over large-scale production, long-term stability, sterility, reproducibility, regulatory evaluation, and patient-specific tumor variability [37,38].

Overall, lipid vesicular systems have moved from experimental drug carriers to clinically relevant cancer nanomedicines. Their established use in approved liposomal drugs and their growing role in mRNA vaccines, immunotherapy, combination therapy, and precision oncology indicate that they will remain important platforms for future cancer treatment.

Advantages, Limitations, and Challenges

Lipid vesicular systems offer several important advantages in cancer therapy. They can improve the solubility and bioavailability of poorly water-soluble anticancer drugs by incorporating lipophilic drugs within the lipid bilayer and hydrophilic drugs within the aqueous core. This improves drug stability, enhances circulation time, and supports better drug accumulation at the tumor site [39]. Lipid vesicles can also reduce systemic toxicity by limiting the direct exposure of healthy tissues to cytotoxic agents. Clinically successful liposomal formulations have shown that lipid-based encapsulation can improve the therapeutic index of anticancer drugs by modifying their pharmacokinetics and biodistribution [30,38] [Table 3].

Another major advantage is enhanced tumor targeting. Lipid vesicular systems can accumulate in tumor tissues through passive targeting and can also be surface-modified with ligands, antibodies, peptides, or polymers to improve active targeting. These modifications may increase receptor-mediated uptake by cancer cells and reduce off-target toxicity. In addition, vesicular carriers can provide controlled and sustained drug release, which helps maintain therapeutic drug concentration for a longer duration and may reduce dosing frequency [39,40]. Their ability to co-deliver multiple drugs also makes them useful for combination cancer therapy, especially in cases involving multidrug resistance.

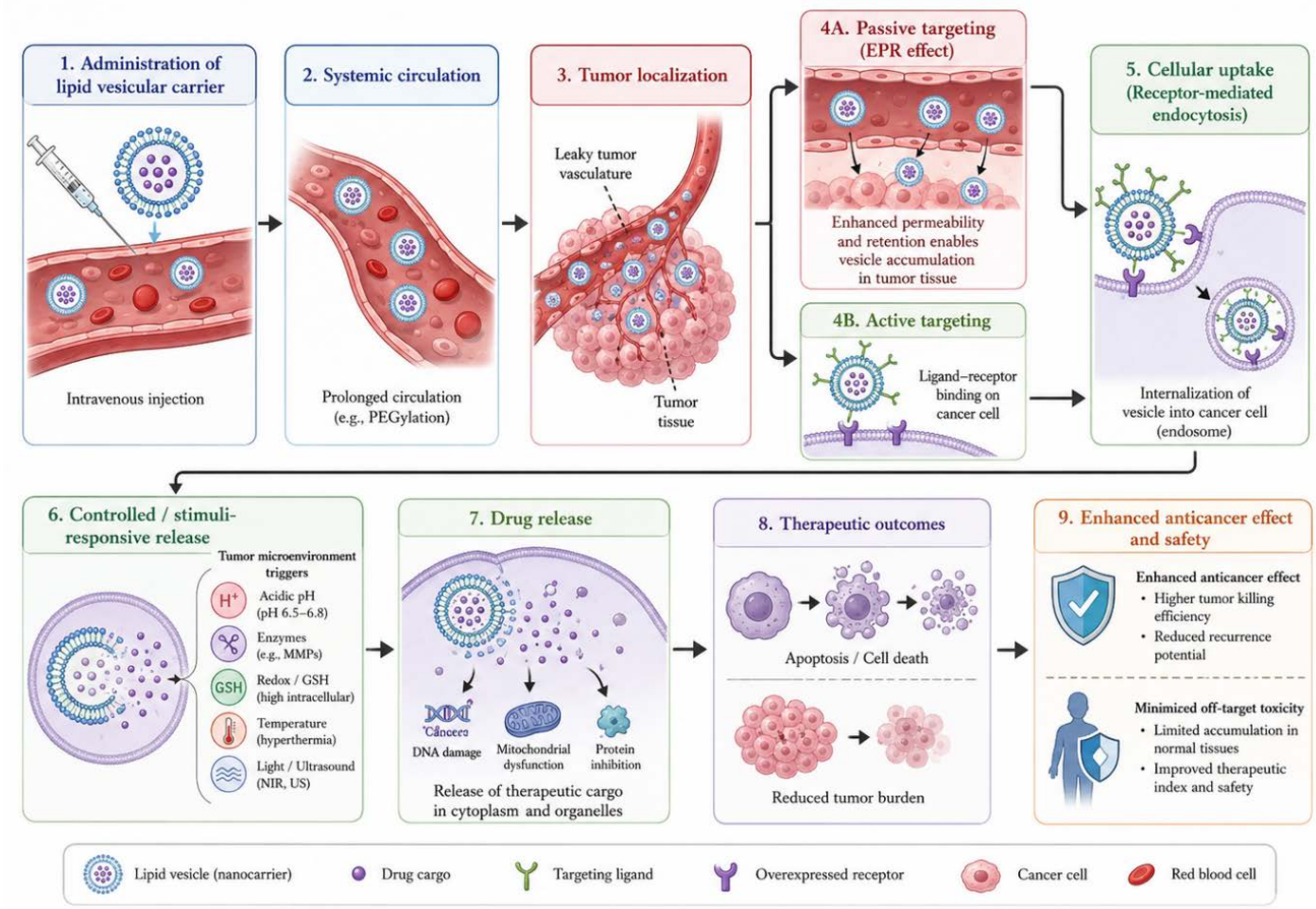
Despite these benefits, lipid vesicular systems face several limitations. Physical and chemical instability remain major challenges, as vesicles may undergo aggregation, fusion, phospholipid oxidation, hydrolysis, or drug leakage during storage. Changes in particle size, zeta potential, membrane rigidity, and drug entrapment can affect formulation performance and safety [39]. Sterilization is another concern because heat-based sterilization may damage lipid vesicles, while filtration may be difficult for larger vesicles or highly concentrated formulations. Therefore, aseptic processing, suitable sterilization strategies, and stability-enhancing approaches such as lyophilization are often required.

Scale-up and manufacturing reproducibility are also critical challenges. Laboratory-scale methods such as thin-film hydration, solvent injection, and sonication may not always translate easily

Table 3: Advantages and Limitations of Lipid Vesicular Systems.

Advantages	Explanation	Limitations/challenges	Explanation
Improved drug solubility	Lipid vesicles can encapsulate poorly water-soluble anticancer drugs and improve their dispersibility	Physical instability	Vesicles may aggregate, fuse, or change size during storage
Reduced systemic toxicity	Encapsulation limits direct exposure of healthy tissues to cytotoxic drugs	Drug leakage	Encapsulated drug may leak from vesicles during storage or circulation
Enhanced tumor targeting	Vesicles can accumulate in tumors through passive targeting and can be modified for active targeting	Scale-up difficulty	Laboratory preparation methods may be difficult to reproduce at industrial scale
Controlled drug release	Vesicles can provide sustained, delayed, or stimuli-responsive release	Sterilization problems	Heat or filtration methods may damage vesicle structure or affect drug loading
Improved pharmacokinetics	Lipid vesicles can prolong circulation time and modify biodistribution	Batch-to-batch variation	Small changes in lipid composition or process parameters may affect final product quality
Protection of unstable drugs	Vesicles protect drugs, genes, and RNA molecules from degradation	High production cost	Specialized materials, equipment, and quality testing increase development cost
Possibility of combination therapy	Multiple drugs or therapeutic agents can be co-loaded in one system	Regulatory complexity	Lipid vesicular systems are complex products requiring detailed safety, quality, and stability evaluation
Versatile drug-loading capacity	Can carry hydrophilic, lipophilic, and amphiphilic molecules	Limited clinical translation	Many promising formulations remain at preclinical stage due to manufacturing and regulatory barriers

Figure 2. Mechanism of Targeted and Controlled Drug Delivery in Cancer Therapy.



into industrial-scale production. Large-scale manufacturing requires strict control of particle size, polydispersity, drug loading, residual solvents, sterility, and batch-to-batch consistency [39]. Although microfluidic and continuous manufacturing technologies are improving reproducibility, cost, technical complexity, and equipment requirements remain important barriers [23,42].

Regulatory issues further limit clinical translation. Lipid vesicular systems are considered complex drug products because their therapeutic performance depends not only on the active drug but also on lipid composition, vesicle structure, particle size, surface properties, drug-release profile, and manufacturing process. Therefore, detailed chemistry, manufacturing, and control data, validated analytical methods, pharmacokinetic studies, toxicity evaluation, and long-term stability data are required [12,39]. These requirements increase development time and cost. Overall, although lipid vesicular systems are highly promising in cancer therapy, their successful clinical use depends on improving stability, reproducibility, scalable manufacturing, cost-effectiveness, and regulatory acceptance.

FUTURE PERSPECTIVES

The future of lipid vesicular systems in cancer therapy is moving toward smart, personalized, and multifunctional nanomedicine. Smart vesicles can be designed to respond to tumor-specific signals such as acidic pH, enzyme overexpression, redox imbalance, hypoxia, or external stimuli such as heat, ultrasound, magnetic field, and light. These stimuli-responsive systems may improve site-specific drug release, reduce premature leakage, and enhance anticancer efficacy with lower systemic toxicity [27,40].

Personalized cancer therapy is another important future direction. Since tumors differ in receptor expression, genetic mutations, vascularity, immune profile, and microenvironmental conditions, lipid vesicular systems can be customized according to patient-specific tumor characteristics. Ligand-functionalized vesicles, RNA-loaded lipid nanoparticles, and neoantigen-based cancer vaccines may support more precise and individualized treatment strategies [35,37]. Such approaches may be especially useful in resistant, recurrent, or metastatic cancers where conventional therapies show limited response.

Theranostic lipid vesicular systems are also gaining attention. These systems combine therapeutic and diagnostic functions in a single platform by incorporating anticancer drugs along with imaging agents, fluorescent probes, magnetic materials, or radioisotopes. Theranostic vesicles may allow real-time tracking of biodistribution, tumour accumulation, drug release, and therapeutic response. This can support image-guided therapy, early response monitoring, and better treatment planning in oncology [41].

Artificial intelligence-assisted formulation development is expected to play a growing role in the future of lipid vesicular drug delivery. Machine learning models can help predict particle size, entrapment efficiency, drug loading, surface charge, release behaviour, stability, and biological performance. AI-assisted tools may reduce trial-and-error experimentation, accelerate formulation optimisation, and improve the design of lipid nanoparticles with specific tissue-targeting properties [42–44]. When combined with quality-by-design principles and high-throughput screening, AI may improve reproducibility and support faster clinical translation.

For successful clinical translation, future research should focus on robust manufacturing methods, standardised characterisation protocols, long-term stability, scalable production, cost reduction, and clear regulatory pathways. Stronger collaboration between formulation scientists, oncologists, pharmacologists, regulatory agencies, and industry will be necessary to move lipid vesicular systems from laboratory research to clinical practice. Overall, smart vesicles, personalised delivery, theranostic platforms, and AI-guided formulation design may significantly strengthen the future role of lipid vesicular systems in targeted and controlled cancer therapy.

CONCLUSIONS

Lipid vesicular drug delivery systems represent a promising and versatile approach for improving cancer therapy. Conventional anticancer treatment is often limited by poor drug solubility, non-specific distribution, rapid clearance, systemic toxicity, and the development of drug resistance. Lipid vesicular systems help address these limitations by improving drug encapsulation, protecting therapeutic agents from degradation, enhancing tumour accumulation, and enabling controlled drug release.

Different lipid vesicular carriers, including liposomes, niosomes, transfersomes, ethosomes, phytosomes, and cubosomes, offer unique advantages for the delivery of chemotherapeutic drugs, natural anticancer compounds, genes, RNA-based therapeutics, and immunotherapeutic agents. Their ability to carry both hydrophilic and lipophilic molecules makes them highly suitable for diverse anticancer applications. In addition, surface modification with targeting ligands and the development of stimuli-responsive vesicles have further improved their potential for selective tumour delivery.

Despite these advantages, several challenges still limit the wider clinical translation of lipid vesicular systems. Issues such as physical and chemical instability, drug leakage, sterilisation difficulties, scale-up limitations, high production cost, batch-to-batch variation, and complex regulatory requirements must be carefully addressed. Future progress will depend on improved formulation design, standardised characterisation, reproducible manufacturing, and stronger clinical validation.

Overall, lipid vesicular systems provide an important platform for targeted and controlled drug delivery in cancer therapy. With continued advances in smart vesicles, personalised medicine, theranostic systems, and AI-assisted formulation development, these carriers have strong potential to improve therapeutic efficacy, reduce adverse effects, and support the future development of precision oncology.

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