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A Comprehensive Review on Etoposide – Loaded Liposomal Drug Delivery Systems for Effective Management of Lung Cancer

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Abstract: *Lung cancer remains one of the leading causes of cancer-related mortality worldwide, demanding therapeutic strategies that offer improved efficacy, reduced systemic toxicity, and enhanced patient outcomes. Etoposide, a topoisomerase II inhibitor widely used in lung cancer chemotherapy, is limited by poor aqueous solubility, low bioavailability, rapid clearance, and dose-dependent adverse effects. In recent years, liposomal drug delivery systems have emerged as a promising platform to overcome these challenges. Liposomes offer multiple advantages, including targeted delivery, enhanced permeability and retention (EPR) effects, reduced off-target toxicity, and controlled drug release. This review provides a comprehensive analysis of etoposide-loaded liposomal formulations, focusing on their physicochemical characteristics, preparation techniques, optimization strategies, pharmacokinetics, and therapeutic potential in lung cancer management.*

Recent advancements in PEGylated, ligand-targeted, and inhalable liposomal systems are discussed to highlight their enhanced tumour localization and improved therapeutic index. Additionally, current preclinical and clinical findings are summarized, along with key challenges such as scalability, stability, regulatory considerations, and future research directions. Overall, etoposide-loaded liposomes represent a significant advancement in nanomedicine, offering a safer and more effective approach for the treatment of lung cancer.

Keywords: Etoposide; Liposomes; Lung cancer; Nanocarriers; Targeted delivery; Chemotherapy

I. INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide and contributes significantly to the global health burden. According to global cancer statistics, the incidence of cancer continues to rise due to population growth, aging, and increased exposure to environmental risk factors. Lung cancer is one of the most aggressive cancers and ranks among the top causes of cancer-related deaths globally [1].

Lung cancer accounts for a large proportion of new cancer cases annually and shows very high mortality rates because symptoms typically appear after the disease has reached an advanced stage. Cigarette smoking—including active and passive exposure—remains the major risk factor. Other contributing factors include occupational exposure to asbestos, radon, air pollution, genetic factors, and chronic respiratory diseases [2].

Lung cancer develops due to uncontrolled proliferation of abnormal cells in lung tissue. It is classified mainly into: Non-Small Cell Lung Cancer (NSCLC): Constituting almost 80–85% of cases, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Small Cell Lung Cancer (SCLC): Highly aggressive, fast-growing, and strongly linked to tobacco smok [3].

Present therapeutic strategies include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Chemotherapy remains the primary choice for advanced stages of both NSCLC and SCLC. Agents like etoposide, cisplatin, carboplatin, and paclitaxel are commonly used, but they often cause severe systemic toxicity and limited tumor selectivity

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Conventional chemotherapy suffers from several drawbacks, including: Non-specific biodistribution ,Toxicity to healthy tissues, Low tumor accumulation ,Poor solubility and short plasma half-life. Development of multi-drug resistance These limitations necessitate advanced drug-delivery systems to enhance cancer therapeutic outcomes [4].

Novel drug-delivery systems such as nanoparticles, polymeric carriers, and liposomes improve drug solubility, stability, circulation time, and tumor-specific accumulation. Liposomes, due to their biocompatibility and ability to reduce toxicity while enhancing therapeutic response, have become one of the most promising carriers for anticancer drugs [5].

Etoposide is a widely used chemotherapeutic agent, especially for SCLC, but its clinical utility is limited by poor solubility, rapid clearance, systemic toxicity, and resistance. Encapsulating etoposide in liposomes helps improve stability, enhance tumor targeting, prolong circulation, and reduce toxicity, leading to better antitumor efficacy compared to the free drug [6].

Literature Review

1. Islami F. (2021).

Islami (2021) discusses the global burden, incidence, and mortality trends of lung cancer across different countries. The review shows that lung cancer continues to be one of the leading causes of cancer-related deaths worldwide, mainly due to high tobacco use, delayed diagnosis, and limited access to treatment in many regions. The paper highlights that incidence rates are decreasing in many high-income countries because of reduced smoking rates, but increasing in low- and middle- income countries where smoking prevalence is still high. The author also explains that air pollution, occupational exposures, and genetic factors contribute significantly to lung cancer cases. Overall, the review stresses the need for strong tobacco-control policies, early detection programs, and improved healthcare access to reduce the global impact of lung cancer.

2. Siegel , RL.,Miller, K.D.& Fuchs, H.E.(2023).

Siegel, Miller, and Fuchs (2023) present updated cancer statistics for the United States, covering incidence, mortality, survival trends, and major changes in cancer patterns. The report shows that overall cancer death rates continue to decline, mainly because of reduced smoking, early detection, and better treatments. The authors highlight that lung, colorectal, and breast cancers remain major causes of mortality, but lung cancer deaths have dropped significantly due to screening and improved therapies. The report also notes rising cases of breast cancer in women, prostate cancer in men, and early-onset cancers (cancers occurring in younger adults). Overall, the paper emphasizes the importance of prevention, screening programs, lifestyle changes, and access to modern treatments to further reduce the cancer burden.

3. Patel, K. & Patel, D.(2023).

Patel & Patel (2023) discuss how liposomal drug delivery systems can improve the treatment of lung cancer. The review explains that conventional chemotherapy often causes high toxicity and poor targeting, which limits its effectiveness. Liposomes—small, biodegradable lipid vesicles— can encapsulate anticancer drugs and deliver them directly to tumor tissues. This enhances drug stability, increases circulation time in the blood, reduces side effects, and improves therapeutic outcomes.The paper also covers different types of liposomes, their formulation methods, mechanisms of targeting lung cancer cells, and advantages such as controlled drug release and better drug solubility. Overall, the authors conclude that liposomal drug delivery is a promising, more effective, and safer approach for lung cancer therapy compared to traditional chemotherapy.

4. Carvallo, J.W.P.(2024).

Carvalho (2024) reviews the latest progress in lipid-based nanoformulations—such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs)—for cancer therapy. The paper explains how these systems improve drug solubility, protect drugs from degradation, and enhance targeted delivery to tumor tissues while reducing side effects. Recent advances discussed include surface-functionalized nanoparticles, stimuli-responsive lipid systems, and combination-therapy carriers. Overall, the paper concludes that lipid-based nanocarriers offer significant potential for more effective and safer cancer treatments, with strong possibilities for future clinical translation.

5. Giesen,J.(2023).

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Giesen (2023) discusses how PEGylated liposomes—liposomes coated with polyethylene glycol (PEG)—help achieve long circulation time in the bloodstream, allowing better drug delivery to target tissues. The review explains that PEGylation reduces immune system recognition, prevents rapid clearance, and improves stability. The paper also highlights their role in targeted cancer therapy, enhanced drug accumulation at tumor sites, and reduced toxicity. Challenges such as immune reactions to PEG and manufacturing limitations are also discussed. Overall, the review concludes that PEGylated liposomes are an effective and promising platform for targeted drug delivery.

6. Li, X., Zhou, L.(2022).

Li, Zhou & Wang (2022) provide a systematic review of different nanocarrier-based drug delivery systems used for lung cancer treatment, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles. The paper explains how these nanocarriers improve drug targeting, enhance penetration into tumor tissue, increase drug stability, and reduce side effects compared to conventional chemotherapy.The authors also discuss current clinical progress, challenges such as toxicity and manufacturing complexity, and the need for more standardized studies. Overall, the review concludes that nanocarriers offer significant potential to improve lung cancer therapy, but further clinical validation is required.

7. Patel, S. & Singh, D (2023).

Patel & Singh (2023) systematically review the use of liposomal formulations for lung cancer therapy. They describe how liposomes enhance drug delivery by improving drug stability, increasing circulation time, and enabling targeted delivery to tumor cells. The review highlights various liposomal drugs, their mechanisms, and recent advancements such as surface modification and ligand-targeted liposomes.The authors also discuss limitations like production challenges and variability in clinical outcomes. Overall, they conclude that liposomal formulations are a promising and effective strategy for improving lung cancer treatment, with strong potential for clinical application.

Etoposide: A Chemotherapeutic Agent

Etoposide is a semisynthetic derivative of podophyllotoxin and is one of the most widely used chemotherapeutic agents in the management of various solid tumors. It belongs to the class of topoisomerase II inhibitors and plays a crucial role in inhibiting DNA replication in rapidly dividing cancer cells. Because of its strong cytotoxic properties, etoposide has been incorporated in standard treatment regimens for lung cancer, testicular cancer, Hodgkin's disease, nonHodgkin lymphoma, and certain leukemias [7].

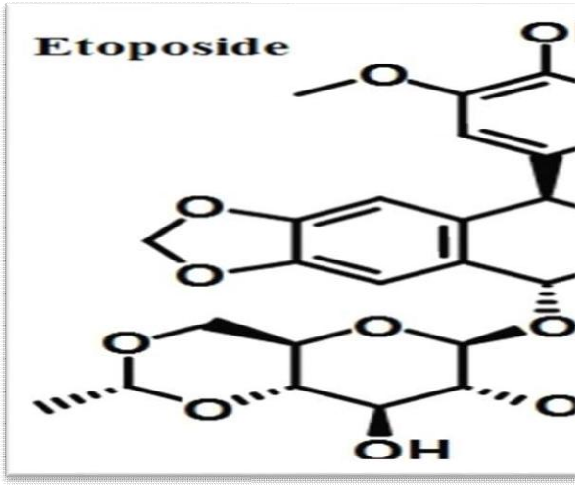

Fig. Etoposide structure

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1. Chemical Structure and Classification

Chemically, etoposide is a glycosidic derivative of podophyllotoxin, classified under semisynthetic epipodophyllotoxins. Its IUPAC name is (5R,5aR,8aR,9R)-5-(4,5-dimethoxy-2methylphenyl)-9- (4-hydroxy-3,5-dimethoxyphenyl)-5a,6,8,8atetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6- one.

Structurally, it contains:

A polycyclic ring system A glycosidic linkage

Aromatic methoxy groups

A lactone ring essential for cytotoxic activity

It is classified pharmacologically as:

Topoisomerase II inhibitor

Cell cycle–specific cytotoxic drug (acts mainly in S and G2 phases) [8].

2. Mechanism of Action (MOA)

Etoposide acts primarily by inhibiting DNA topoisomerase II, an enzyme required for DNA unwinding during replication and transcription. Its mechanism involves:

1. Etoposide binds to the topoisomerase II–DNA complex.
2. It stabilizes the "DNA double-strand break complex," preventing re-ligation.
3. Accumulated DNA breaks trigger apoptosis in cancer cells.
4. The drug is most active in the late S and G2 phases of the cell cycle.

Because lung cancer cells are rapidly proliferating, they are particularly sensitive to this mechanism of cytotoxicity [9].

3. Pharmacokinetic and Pharmacodynamic Profile Absorption & Distribution:

Etoposide shows variable oral absorption (bioavailability ~50%). It is highly protein-bound (about 97%) and distributes extensively into tissues but poorly into the CNS.

Metabolism:

Primarily metabolized in the liver by CYP3A4 to catechol and quinone metabolites.

Elimination:

Approximately 40–60% of the drug is excreted unchanged in urine.

Half-life ranges from 4–11 hours depending on liver and kidney function.

Pharmacodynamics:

Activity depends on:

Drug concentration in plasma Duration of exposure

Cell cycle timing

High systemic exposure often increases toxicity without proportionally improving therapeutic effects [10].

4. Clinical Uses in Lung Cancer

Etoposide is a key component in the therapy of small-cell lung cancer (SCLC). It is commonly used in combination with:

Cisplatin (EP regimen)

Carboplatin (EC regimen)

It enhances survival, reduces tumor mass, and is standard first-line therapy in both limited-stage and extensive-stage SCLC. In NSCLC, its use is more limited but may be included in certain combination regimens [11].

5. Limitations of Free Etoposide

Despite its therapeutic importance, free (unformulated) etoposide faces several critical limitations: Low aqueous solubility, requiring solvents that cause hypersensitivity reactions

Poor stability and susceptibility to degradation

Rapid renal clearance, resulting in short circulation time

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Dose-limiting systemic toxicities, such as myelosuppression and GI toxicity Development of multidrug resistance (MDR) due to P-glycoprotein efflux Non-specific tissue distribution, damaging healthy cells
These drawbacks significantly reduce therapeutic efficacy and limit dose escalation [12].
6. Need for Improved Drug-Delivery Approaches
The limitations of conventional etoposide therapy have highlighted the need for advanced drugdelivery technologies.
An improved delivery system is needed to:
1. Enhance solubility and stability of etoposide
2. Increase tumor site accumulation (via EPR effect or active targeting)
3. Reduce systemic toxicity by avoiding exposure to healthy tissues
4. Prolong circulation time to improve therapeutic index
5. Overcome multidrug resistance (MDR) by bypassing efflux pumps
6. Enable controlled and sustained release
7. Improve bioavailability, especially in oral formulations
Liposomal encapsulation is considered one of the most effective approaches because liposomes: Protect the drug from degradation
Improve solubility
Modify biodistribution
Achieve higher tumor accumulation Reduce toxicity [13].
This makes etoposide-loaded liposomes a promising strategy for lung cancer treatment.

Liposomal Drug Delivery System
1. Liposome / Basic Structure & Composition
Liposomes are spherical vesicular structures formed by one or more phospholipid bilayers that enclose an aqueous core. Their phospholipid bilayer mimics the cell membrane — a hydrophilic "head" and hydrophobic "tail" — which enables them to encapsulate both hydrophilic (in the aqueous core) and hydrophobic (within the lipid bilayer) drugs [15].
Typically, liposome diameters range from tens of nanometres to several micrometres (often 0.01–5.0 µm, though for nanomedicine applications, nanoscale ~100–200 nm is common) [16].
The basic components include phospholipids (e.g. phosphatidylcholine, phosphatidylethanolamine), cholesterol (to modulate membrane fluidity and stability), and sometimes charged lipids or PEGylated lipids to achieve desired properties [15].
Thus, liposomes act as versatile carriers — the amphiphilic bilayer + aqueous core arrangement allows for loading a wide variety of drugs, irrespective of their solubility nature (hydrophilic or hydrophobic).

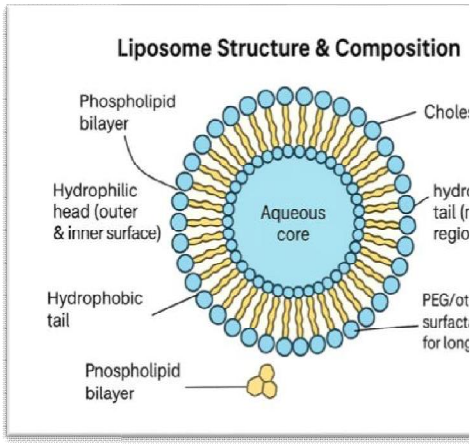

Fig . Liposome structure & composition

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2. Types / Variants of Liposomes

Over time, researchers have developed various modifications/ types of liposomes for improved performance. Some major types:

Conventional liposomes — basic phospholipid bilayer vesicles.

Long-circulating / "Stealth" liposomes — liposomes whose surface is modified (often via PEGylation) to evade rapid clearance by the reticuloendothelial system (RES), thereby prolonging their circulation time in the bloodstream.

Targeted liposomes / Immunoliposomes — liposomes conjugated with ligands, antibodies or other targeting moieties on their surface to enhance binding to specific cell types (e.g. tumor cells), enabling active targeting rather than passive distribution.

Stimuli-responsive liposomes — liposomes designed to release their payload in response to specific internal (e.g. pH, enzyme) or external (e.g. temperature, light) stimuli. This allows controlled or triggered release at the target site (e.g. tumor microenvironment).

Thus, through modifications in lipid composition, surface chemistry, and addition of targeting/stimuli-responsive elements — liposomes are adaptable to varied therapeutic needs [16].

3. Advantages of Liposomal Drug Delivery for Cancer (and specifically for agents like Etoposide)

Liposomal drug delivery offers many advantages over conventional (free-drug) chemotherapy or unencapsulated drug formulations — which is why they are intensely studied and considered promising for cancer therapy. Major advantages:

Enhanced drug solubility & stability: Many anticancer drugs are poorly water-soluble; liposomes can solubilize hydrophobic drugs within their bilayer, improving bioavailability and administration feasibility. Also, encapsulation protects drugs from premature degradation or inactivation in the bloodstream.

Improved pharmacokinetics & prolonged circulation: Especially with PEGylated (stealth) liposomes, circulation time increases, reducing clearance and enabling better accumulation at target sites.

Targeted delivery to tumor tissue: Via passive targeting (exploiting enhanced permeability and retention — EPR effect in tumors) and/or active targeting (ligand- or antibody-mediated), liposomes can preferentially deliver drugs to cancer cells, sparing healthy tissues.

Reduced systemic toxicity / side effects: Since the drug is more selectively delivered to tumor sites, exposure of healthy tissues to toxic chemotherapeutic agents is minimized. This reduces adverse side-effects associated with traditional chemotherapy.

Controlled or stimuli-triggered drug release: Stimuli-responsive liposomes (pH-sensitive, thermosensitive, etc.) can release drug preferentially in tumor microenvironment (e.g. acidic pH) or upon external trigger, enhancing efficacy and minimizing off-target effects.

Versatility: They can carry a wide range of therapeutic agents — small molecule drugs, hydrophobic/hydrophilic drugs, nucleic acids (DNA/RNA), proteins, imaging agents — making them suitable for chemotherapy, gene therapy, immunotherapy, and theranostics.

In summary, liposomal delivery can substantially improve therapeutic index (efficacy vs toxicity), improve patient outcomes, and enable use of drugs which otherwise are limited by poor solubility/toxicity [17].

4. Challenges / Limitations & Critical Issues with Liposomal Systems

Although liposomes are very promising, there are several significant challenges and limitations that must be addressed — especially when translating from bench to clinic:

Stability issues: Liposomes (especially conventional ones) are prone to physical and chemical instability — including drug leakage, fusion/aggregation, lipid peroxidation or hydrolysis, size change — which can compromise encapsulation efficiency and controlled release.

Short circulation half-life (for non-stealth liposomes): Without modifications (like PEGylation), liposomes are rapidly cleared by RES (macrophages), reducing their chance to accumulate at tumor sites.

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Complex manufacturing / high production cost: Producing liposomes — especially in reproducible, scalable, sterile, clinical-grade form — requires advanced equipment, precise control of parameters, and quality assurance. This increases cost compared to conventional formulations.

Limited drug loading and encapsulation efficiency: Not all drugs — especially certain hydrophobic or very large molecules — can be efficiently loaded into liposomes; sometimes loading capacity is insufficient for therapeutic doses.

Premature drug release / leakage: Over time or under certain physiological conditions, liposomes might leak or fuse, releasing drug before reaching target — reducing targeting efficacy and increasing off-target effects.

Immunogenicity / Recognition by immune system: Liposomes may be recognized as foreign entities by the immune system (RES), leading to rapid clearance or potential immune responses.

Difficulty in sterilization & regulatory hurdles: For clinical use (especially parenteral), liposomal formulations must be sterile, pyrogen-free, and meet strict regulatory standards — sterilization is challenging because liposomes are sensitive to heat, radiation; filtration methods have limitations.

Batch-to-batch reproducibility and scale-up challenges: Translating lab-scale formulation to large-scale manufacturing often leads to variability in key parameters (size, lamellarity, encapsulation, stability), which can affect consistency and clinical performance.

Because of these challenges, not all promising liposomal formulations from research have successfully transitioned to clinical use, and extensive formulation optimization is often required [18].

5. Liposomal Delivery is Especially Needed for Drugs like Etoposide — The Rationale

Integrating the properties of liposomes with the known limitations of free chemotherapeutic drugs (like Etoposide) clarifies why liposomal delivery is highly desirable:

Etoposide often suffers from poor solubility, rapid clearance, systemic toxicity, non-specific tissue distribution, and dose-limiting side effects. Encapsulating it in liposomes can enhance solubility and stability, ensuring adequate drug remains intact until it reaches tumor tissue.

Long-circulating (stealth) liposomes can prolong circulation time, increasing probability of accumulating at the tumour site via enhanced permeability and retention (EPR) effect.

Targeted or ligand-conjugated liposomes can further improve selectivity — delivering etoposide preferentially to lung tumor cells, reducing exposure (and toxicity) to normal tissues (e.g. bone marrow, GI tract).

Controlled or stimuli-responsive release from liposomes (e.g. pH-sensitive, triggered by tumor microenvironment) can maximize drug concentration at tumor, and minimize off-target effects.

Overall, such liposomal etoposide formulations can improve therapeutic index, potentially allowing lower dosage, reducing side-effects, and improving patient compliance.

Thus, for agents like etoposide with known limitations, liposomal encapsulation offers a compelling solution — justifying the inclusion of a full section on liposomal drug-delivery systems in the review [19].

6. Summary — The Promise and the Challenges

Liposomal drug delivery systems represent a powerful and flexible platform to improve anticancer therapy. Their ability to encapsulate diverse drugs, modulate pharmacokinetics, target tumors, reduce toxicity, and allow controlled release makes them ideal candidates for modern cancer treatment — especially in context of agents that have poor solubility or high systemic toxicity (like etoposide).

However, liposomes are not a panacea: formulation stability, encapsulation efficiency, drug leakage, immune clearance, manufacturing complexity, cost, and regulatory hurdles remain major obstacles. Overcoming these will require careful optimization, surface engineering (e.g. PEGylation, ligand conjugation), advanced manufacturing, and thorough in vivo testing.

Given these advantages + challenges, it's clear why liposomal delivery merits intensive research, and indeed, a dedicated section in any comprehensive review on etoposide-based therapy for lung cancer.

Etoposide-Loaded Liposomes

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1. Formulation Aspects of Etoposide-Loaded Liposomes

Formulating liposomes for etoposide delivery requires careful optimization of lipid composition, charge, size, and bilayer rigidity. The selection of phospholipids with high transition temperatures can enhance stability, whereas incorporating cholesterol improves membrane integrity and reduces drug leakage during storage. Buffer composition also plays a crucial role because the pH of the hydration medium affects drug solubility and bilayer interactions [20]. Etoposide, being poorly water-soluble, requires strategies such as pH modification, co-solvent use, or passive/active loading systems to achieve desirable encapsulation levels. Overall, rational formulation improves both drug retention and systemic circulation time [21].

2. Selection of Lipids and Cholesterol, Buffers, Surfactants

Selecting appropriate lipids is vital for controlling vesicle stability and drug interaction. Phosphatidylcholine is frequently used due to its biocompatibility, while negatively charged lipids (e.g., DPPG) help stabilize vesicles electrostatically. Cholesterol is typically added to modulate membrane fluidity, decrease permeability, and improve resistance to oxidative degradation. Surfactants such as Tween-80 or PEGylated lipids can enhance membrane flexibility and circulation longevity. Even the type of hydration buffer—such as ammonium sulfate, citrate buffer, or PBS—determines drug loading efficiency and pH-driven active loading potential [22].

3. Methods of Liposome Preparation

Several techniques have been employed for preparing etoposide-loaded liposomes, including thin- film hydration, ethanol injection, reverse-phase evaporation, and microfluidics-based synthesis. Thin-film hydration is the most widely used laboratory method due to its simplicity, whereas ethanol injection offers better control over particle size [23]. Reverse-phase evaporation produces high-encapsulation vesicles but may expose the drug to organic solvents. Modern microfluidic systems can generate highly uniform liposomes with narrow size distribution, which are suitable for scale-up and clinical translation [24].

4. Factors Affecting Encapsulation Efficiency

Encapsulation efficiency (EE%) of etoposide in liposomes depends on lipid composition, vesicle size, drug–lipid ratio, preparation method, and pH gradient strength. Higher cholesterol concentrations can reduce EE% by tightening the membrane, whereas incorporating charged lipids enhances drug–lipid interaction. Smaller vesicles often exhibit lower EE% due to limited internal volume, while larger multilamellar vesicles can entrap more drug. Active loading using pH gradients significantly improves efficiency by driving etoposide into the vesicle core [25].

5. Drug Loading Techniques

Etoposide can be incorporated into liposomes using passive or active loading techniques. Passive loading includes hydration, solvent dispersion, and mechanical agitation, but it often results in low drug entrapment because etoposide is highly hydrophobic [26]. Active loading techniques, such as pH gradient loading or ammonium sulfate gradient methods, allow higher drug retention by promoting drug diffusion into vesicles based on ion trapping. Such methods produce more stable formulations with improved pharmacokinetic behavior [27].

6. Surface Modification of Liposomes

Surface engineering of liposomes significantly enhances their therapeutic performance. PEGylation (attachment of polyethylene glycol chains) prolongs systemic circulation by reducing recognition by the mononuclear phagocyte system. Targeting ligands such as folic acid, antibodies, or peptides can be conjugated to the liposome surface to facilitate selective delivery to cancer cells overexpressing specific receptors. Additionally, cationic surface modification enhances interaction with negatively charged tumor membranes, improving drug uptake [28].

Characterization of Etoposide-Loaded Liposomes

1. Particle Size Analysis

Particle size is one of the most critical parameters determining the biological performance of liposomes. Nanosized vesicles (typically 50–200 nm) enhance circulation time, promote tumour penetration, and reduce uptake by the reticuloendothelial system [29]. Dynamic Light Scattering (DLS) is widely used to measure average diameter and

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polydispersity index (PDI). A low PDI (<0.3) indicates uniform particle distribution, which is essential for reproducible therapeutic response [30].

2. PDI and Zeta Potential

The polydispersity index (PDI) reflects the uniformity of liposomal populations, while zeta potential indicates surface charge and colloidal stability. Higher absolute zeta potential values (±30 mV) promote electrostatic repulsion between vesicles, preventing aggregation during storage [31]. For etoposide liposomes, slightly negative or neutral charges are preferred to minimize rapid protein adsorption and extend circulation time [32].

3. Encapsulation Efficiency

Encapsulation efficiency (EE%) indicates the proportion of etoposide successfully entrapped within liposomal vesicles. It is influenced by lipid composition, preparation technique, and drug– lipid affinity. High EE% ensures improved therapeutic delivery and reduced drug wastage. Ultracentrifugation or dialysis methods are typically employed to separate free drug from encapsulated drug before quantification via UV or HPLC [33].

4. Morphology Analysis (TEM/SEM)

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are essential for observing liposomal shape, lamellarity, and surface texture [34]. TEM provides high-resolution images of lipid bilayers and vesicle geometry, whereas SEM reveals surface topology. Spherical, smooth-surfaced vesicles indicate successful formulation and structural stability, which are desirable for drug delivery efficiency [35].

5. In-Vitro Drug Release Studies

In-vitro release studies evaluate the rate and extent of etoposide diffusion from liposomes. Dialysis membrane techniques or Franz diffusion cells are commonly used [36]. Release kinetics are influenced by bilayer rigidity, cholesterol content, and vesicle size. Sustained release behaviour is desirable because it prolongs systemic drug availability and minimizes burst toxicity [37].

6. Thermal Analysis (DSC, TGA)

Differential Scanning Calorimetry (DSC) assesses lipid transition temperature and drug–lipid interactions, revealing whether etoposide is incorporated within bilayers or merely adsorbed on the surface [38].Thermogravimetric Analysis (TGA) determines thermal stability by measuring weight loss at different temperatures. These analyses help ensure liposomal stability under storage and processing conditions [39].

7. FTIR & XRD for Compatibility

Fourier Transform Infrared Spectroscopy (FTIR) is used to detect potential chemical interactions between etoposide and lipids by evaluating shifts in characteristic peaks. X-Ray Diffraction (XRD) helps determine crystalline vs. amorphous nature of the drug inside the liposomes. Loss of crystallinity often indicates successful molecular dispersion within lipid bilayers [40].

8. Stability and Accelerated Stability Studies

Stability studies evaluate liposome integrity over time under different storage conditions such as refrigeration, room temperature, and stress environments. Key parameters monitored include particle size, PDI, zeta potential, leakage of encapsulated drug, and visual appearance. Accelerated stability testing predicts long-term behaviour by exposing formulations to elevated temperatures and humidity [41].

9. In-Vitro Hemocompatibility Studies

Hemocompatibility testing determines whether the liposomal formulation is safe for intravenous administration. Tests include hemolysis percentage, plasma protein binding, and erythrocyte morphology [42]. Low hemolysis (<5%) indicates good biocompatibility. Since liposomes directly interact with blood components, ensuring compatibility is essential to avoid immune reactions or coagulation issues [43].

In-Vitro Evaluation of Etoposide-Loaded Liposomes

1. Cytotoxicity Studies (MTT, SRB, or XTT assays)

In-vitro cytotoxicity tests determine whether liposomal etoposide enhances anticancer activity compared to free drug [44]. Liposomes often show improved uptake and sustained cytotoxicity due to better internalization by tumour cells.

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Cell viability assays such as MTT or SRB measure metabolic activity after exposure to formulations. A lower IC50 value indicates stronger anticancer potential [45].

2. Cellular Uptake Studies

Cellular uptake analysis evaluates how efficiently cancer cells internalize liposomal etoposide. Fluorescently labelled liposomes or HPLC drug quantification are used to measure drug accumulation inside cells [46]. Nanoliposomes enhance uptake through endocytosis, improving intracellular drug availability and apoptosis [47].

3. In-Vitro Drug Release Studies

In-vitro release testing is performed to examine the drug diffusion profile from liposomes under physiological conditions (pH 7.4) [48]. Sustained release indicates strong lipid–drug interaction and long-term therapeutic activity. Data are typically fitted to kinetic models (Higuchi, Korsmeyer- Peppas) to understand the release mechanism [49].

4. Hemocompatibility Testing

Hemolysis assays ensure that etoposide-loaded liposomes do not damage red blood cells during intravenous administration. Low hemolysis (<5%) indicates acceptable blood compatibility and safety [50].

In-Vivo Evaluation of Etoposide-Loaded Liposomes

1. Pharmacokinetic Studies (PK Studies)

In-vivo pharmacokinetics evaluate plasma concentration, half-life, area under curve (AUC), and clearance of liposomal etoposide. Liposomes significantly prolong circulation time and reduce rapid elimination. This results in improved drug exposure at tumour sites and reduced systemic toxicity [51].

2. Biodistribution Studies

Biodistribution assesses localization of liposomal etoposide in organs such as liver, spleen, lungs, and tumour tissues. Nanoliposomes enhance drug accumulation in tumour tissues via the Enhanced Permeability and Retention (EPR) effect while reducing deposition in healthy organs [52].

3. In-Vivo Antitumor Efficacy

Animal studies (usually mice bearing lung cancer or solid tumour xenografts) are performed to measure tumour volume reduction, survival rate, and apoptosis. Liposomal etoposide generally demonstrates significantly greater tumour suppression compared to conventional etoposide due to improved delivery and reduced systemic toxicity [53].

4. Toxicity Studies (Acute and Sub-chronic)

Toxicity evaluations involve monitoring changes in body weight, behavior, blood chemistry, liver and kidney markers, and histopathology [54]. Liposomal formulations usually show reduced toxicity due to controlled release and lower exposure of normal tissues [55].

Therapeutic Potential of Liposomal Drug Delivery for Lung Cancer

1. Why Liposomes Hold Promise for Lung Cancer Therapy

Liposomes — phospholipid-bilayer vesicles — can encapsulate both hydrophilic and hydrophobic chemotherapeutic agents, protecting them from premature degradation, improving solubility, and enabling controlled release.

For lung cancer, lipid-based nanocarriers (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, etc.) offer a flexible platform to deliver anticancer drugs locally (in lungs) or systemically

— with improved bioavailability and reduced systemic toxicity.

Liposomes are biocompatible, biodegradable, and relatively non-immunogenic — making them suitable for repeated administration required in cancer chemotherapy.

These inherent advantages make liposomal delivery a promising strategy to overcome key limitations of conventional chemotherapy: poor solubility, non-specific distribution, doselimiting toxicity, and suboptimal drug accumulation at tumour sites [56].

2. Evidence from Lung Cancer Studies & Clinical Trials

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A systematic review of liposomal formulations used in lung cancer over the past two decades reported that liposomal chemotherapy (e.g. liposomal cisplatin + paclitaxel) significantly improved therapeutic outcomes compared to conventional therapy, with better efficacy and lower toxicity.

Also in that review, a liposome-based immunotherapy candidate (tecemotide) demonstrated a lower toxicity profile compared to control groups.

Liposomal formulations can increase drug accumulation in the tumour (due to enhanced permeability and retention — EPR effect), thereby enhancing anticancer efficacy while reducing side effects in healthy tissue.

Use of lipid-based nanocarriers for pulmonary (inhalation) delivery has potential for lungtargeted therapy — delivering high local drug concentrations directly to lung tissues, which is especially relevant for lung cancer.

Thus, both preclinical and clinical evidence suggests that liposomal (and lipid-based) drug delivery enhances the therapeutic index — combining higher efficacy with reduced systemic toxicity — for lung cancer treatment [57].

3. How Liposomal Delivery Improves Key Therapeutic Parameters

Therapeutic Problem with Conventional Chemotherapy How Liposomal / Lipid – based Delivery Addresses It

Poor aqueous solubility or instability of drugs Enacapsulation in liposome bilayer or core improves solubility and stabilizes drug against degradation.

Rapid clearance / short circulation half – life Long – circulating liposomes (eg.PEGylated) evades RES clearance , extending half- life and increasing AUC in plasma / tumour.

Low tumor specificity & high systemic toxicity EPR effect + possibility of ligand – targeting improves tumor accumulation ; readuce off- target exposure and side –effect

Need for high / dose- intensive therapy with toxicity risk Controlled and sustained release from liposomes allows effective cocentrations locally while minimizing peak systemic concentarions

Multidrug resistance (MDR) of tumor cells Liposomal delivery may bypass some drug – efflux mechanisms and improves intacellular drug retention.

Need for local / lung – speacific delivery (to minimize systemic toxicity) Pulmonary (inhalable) liposome formulations permit direct delivery to lung tissue , maximizing local drug concentration while readucing systemic exposure [58].

4. Additional Therapeutic Modalities Enabled by Liposomes

Beyond classic chemotherapy, liposomes enable immunotherapy, targeted therapy, and combination therapy approaches: immunoliposomes (antibody or ligand-targeted), liposomebased immunotherapeutic agents, and combination of chemotherapy + immunotherapy/allied modalities.

Liposomal carriers also make it feasible to deliver poorly soluble or unstable newer anticancer agents, including small-molecules, nucleic acids (siRNA, mRNA), peptides — broadening treatment possibilities.

For lung cancer specifically, pulmonary delivery (inhalation) of liposomal formulations allows localized therapy — potentially improved tumour penetration, reduced systemic toxicity, and better patient compliance [59].

5. Challenges / What Needs to Be Optimized — But Potential Remains High

While liposomal delivery holds great promise, successful translation to effective lung-cancer treatment requires overcoming certain challenges (as highlighted in recent reviews):

Optimization of liposome size, surface, and formulation for efficient targeting to lung tumours or metastatic sites.

Ensuring stable aerosolization and lung deposition when liposomes are used for inhalation therapy

— to deliver therapeutic doses effectively to all affected lung regions.

Demonstrating long-term safety and immunocompatibility, especially for repeated administration, since chemotherapy often requires multiple cycles.

Conducting large-scale, randomized, controlled clinical trials to confirm improved survival outcomes, reduced toxicity, and real-world efficacy compared to standard therapy.

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Nevertheless, the accumulating preclinical and early clinical evidence strongly supports liposomal (lipid-based) drug delivery as a viable and promising therapeutic approach in lung cancer management [60].

Conclusion: Therapeutic Potential Summarised

Liposomal drug delivery systems represent a major advancement in lung cancer therapy — they combine high drug-loading capacity, improved pharmacokinetics, reduced systemic toxicity, enhanced tumour targeting, and versatility (chemotherapy, immunotherapy, inhalation), making them ideally suited to overcome many limitations of conventional chemotherapy [61]. As research and clinical data accumulate, liposomal formulations are increasingly emerging as leading candidates to improve treatment outcomes and quality of life for lung cancer patients [62].

Recent Advances and Clinical Studies

Recent advancements in liposomal technology have improved drug stability and tumor-targeting efficiency, allowing etoposide to reach deep lung tumor tissues more effectively .

PEGylated liposomes ("stealth liposomes") help the formulation escape rapid immune clearance, resulting in prolonged circulation time [63].

Ligand-targeted liposomes such as EGFR-targeted and transferrin-targeted liposomes enhance cellular uptake in lung cancer cells compared to non-targeted carriers.

Clinical research also shows that nanoformulations improve therapeutic efficacy and reduce systemic toxicity of conventional chemotherapy.

Some recent clinical trials have demonstrated better tolerability and tumor response when liposomal drugs are used instead of free etoposide [64].

Challenges and Future Perspectives

Despite progress, liposomal formulations face issues such as instability during long-term storage, which may cause leakage of etoposide .

Another challenge is rapid clearance by mononuclear phagocyte system (MPS) when PEG is not used or surface modification is insufficient [65].

High manufacturing costs and batch-to-batch variability limit large-scale production .

Tumor heterogeneity and dense extracellular matrix in lung cancer restrict deep penetration of nanoparticles .

Future trends include stimuli-responsive liposomes, AI-guided formulation design, and theranostic liposomes that can perform imaging and therapy simultaneously [66].

II. CONCLUSION

Liposomal drug delivery systems provide enhanced bioavailability, controlled release, and improved tumor targeting for lung cancer treatment. They also reduce systemic toxicity compared to the free drug, making them suitable for long-term therapy. Although challenges exist in stability and large-scale manufacturing, continued nanotechnology innovations promise improved clinical outcomes in lung cancer management. Clinical evidence supports the therapeutic advantage of nanoparticle-based etoposide delivery for better patient response.

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