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REVIEW ARTICLE

A Review on Liposomal Nanocarriers for Improving Bioavailability of Poorly Soluble Drugs

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Abstract: Inadequate aqueous solubility severely hampers the therapeutic efficacy and clinical use of a substantial proportion of newly discovered chemical moieties and established active pharmaceutical ingredients. Encapsulation of hydrophobic molecules within liposomal nanocarriers provides a structurally flexible methodology to overcome dissolution-rate limited absorption, chemical degradation, and systemic toxicity. Phospholipid bilayers host lipophilic molecules within their acyl chains while aqueous cores accommodate hydrophilic moieties, forming biocompatible vesicular assemblies that mimic biological membranes. Enhanced oral and parenteral bioavailability stems from increased apparent solubility, augmented intestinal mucosal permeability, protection against enzymatic hydrolysis, and preferential uptake through the lymphatic vasculature. Selection of fabrication technology like thin-film hydration, reverse-phase evaporation, ethanol injection, and high-pressure microfluidization directly governs critical quality attributes such as hydrodynamic diameter, polydispersity index, surface charge, and entrapment efficiency. Physicochemical characterization utilizing dynamic light scattering, electron microscopy, and in vitro release kinetics establishes the structural integrity and stability profiles necessary for therapeutic performance. Advanced surface functionalization, including polyethylene glycol coating and target-specific ligand conjugation, extends circulation half-life and achieves preferential accumulation in diseased tissues. Clinical applications in oncology, infectious disease management, vaccine adjuvantation, and nucleic acid transport validate the capacity of liposomes to widen therapeutic windows and minimize systemic adverse effects.

Keywords: Liposomal Drug Delivery; Poorly Soluble Drugs; Bioavailability; Phospholipid Vesicles; Nanotechnology.

1. Introduction

The development of small-molecule drug molecules from discovery phase into therapeutic agents requires appropriate aqueous solubility and systemic membrane permeability. A primary barrier in contemporary drug development involves the high frequency of hydrophobic molecules emerging from modern drug discovery techniques [1]. High-throughput screening and combinatorial chemical synthesis routinely yield lipophilic hits optimized for target binding affinity, often at the expense of physicochemical properties essential for oral absorption [2].

According to the Biopharmaceutics Classification System (BCS), therapeutic molecules are categorized based on aqueous solubility and intestinal permeability parameters. Compounds assigned to BCS Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability) suffer from incomplete oral absorption, highly erratic pharmacokinetic profiles, and elevated inter-patient variability [3]. When dissolution within the gastrointestinal fluid operates as the rate-limiting step, escalating the administered dose fails to achieve proportional systemic exposure. Instead, unabsorbed active pharmaceutical ingredients pass through the gastrointestinal tract or generate localized mucosal irritation, raising the risk of off-target toxicities without therapeutic gain [4]. Conventional approaches such as salt selection, particle size reduction via micronization, solid dispersion matrices, cyclodextrin complexation, and co-crystallization offer localized solubilization benefits but frequently face physical instability, limited drug loading, or recrystallization risks during storage or transit [5].

Liposomal systems originated as primary artificial membrane models following their initial characterization in the mid-1960s [6]. Phospholipid assemblies were recognized for their intrinsic self-assembling capability, forming enclosed lipid bilayers that capture aqueous volumes. Over subsequent decades, these structures evolved from basic biological membrane models into sophisticated clinical nanocarriers [7]. The structural homology between liposomal lipid bilayers and mammalian cellular membranes provides high biocompatibility, biodegradability, and minimal intrinsic immunogenicity.

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Initial clinical iterations of liposomes were limited by rapid clearance from blood circulation through uptake by the mononuclear phagocyte system (MPS), primarily located in the liver and spleen [8]. This limitation sparked the development of second-generation liposomes, characterized by surface polymer grafting most notably with polyethylene glycol (PEG). Steric stabilization shielded the vesicular surface from opsonin protein adsorption, prolonging systemic circulation times and establishing the groundwork for target-selective delivery platforms [9].

Nanocarrier-mediated delivery addresses biopharmaceutical constraints by altering the spatio-temporal distribution of active substances rather than modifying their core chemical structures. Liposomes accommodate drugs with diverse polarities simultaneously or independently, preserving molecular integrity while improving effective solubility in biological fluids [10]. Through systemic encapsulation, liposomal vehicles mask unfavorable physicochemical characteristics, facilitate movement across physiological barriers, and modify tissue disposition profiles [11]. The primary goal of implementing liposomal systems for poorly soluble compounds is to transform dissolution-limited drug absorption into predictable permeation kinetics, thereby enhancing therapeutic indices across oral, parenteral, pulmonary, and ocular administration routes [12].

2. Fundamental Structure and Composition of Liposomes

2.1. Lipid Bilayer Architecture and Vesicular Dynamics

Liposomes consist of spherical lipid bilayers enclosing an internal aqueous cavity. The driving force behind bilayer assembly is the amphiphilic nature of phospholipids, which contain polar headgroups paired with nonpolar aliphatic chains [13]. When exposed to an aqueous medium, hydrophobic interactions force the hydrocarbon tails to cluster inward, minimizing thermodynamically unfavorable contact with water molecules. The hydrophilic headgroups align outward to engage in hydrogen bonding and electrostatic interactions with the surrounding aqueous phase [14].

These self-assembly yields closed, energetically stable structures (Figure 1). Hydrophobic drugs integrate into the fatty acid tail domain within the core of the membrane, while hydrophilic entities reside in the central aqueous chamber [15]. Molecules showing amphiphilic characteristics position themselves at the interface between the hydrophilic headgroups and hydrophobic acyl chains.

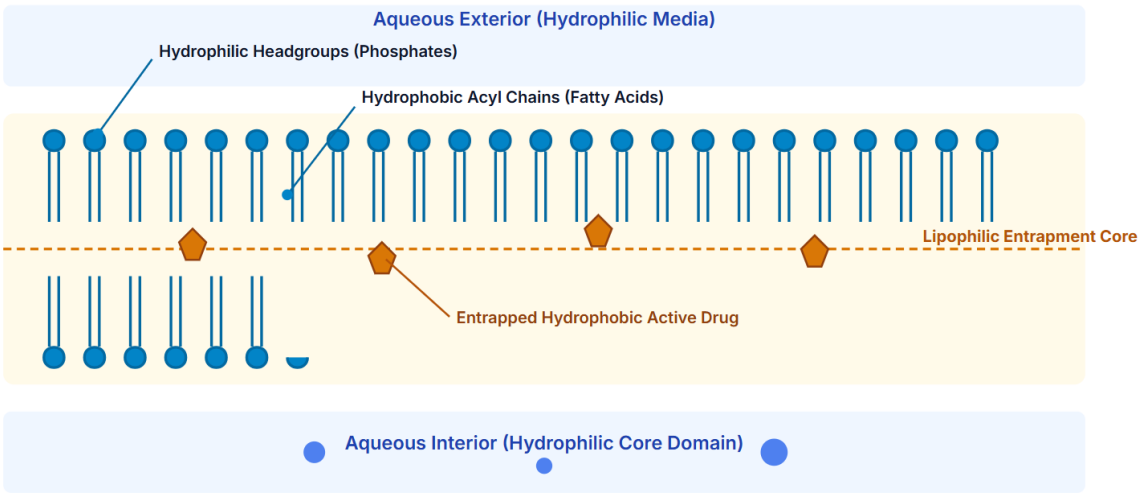

Figure 1. Bilayer Lipid Structure

2.2. Phospholipid Selection and Membrane Fluidity

The chemical composition of phospholipids determines the physical rigidity, phase behavior, and permeability of liposomal membranes [16]. Phospholipids consist of a glycerol backbone esterified to two fatty acid chains and a phosphate group modified with alcohol moieties such as choline, ethanolamine, serine, or glycerol. Naturally derived phospholipids, including phosphatidylcholine extracted from soybean or egg yolk, contain unsaturated fatty acid chains that impart fluidity to the membrane at physiological temperatures [17].

Synthetic phospholipids such as dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), and dimyristoylphosphatidylcholine (DMPC) offer defined chain lengths and saturated fatty acid structures. The main phase transition temperature (Tm), at which the lipid bilayer converts from a rigid gel state to a fluid liquid-crystalline state, depends directly on

chain length and saturation level. Lipids with higher Tm values form structurally ordered bilayers at 37°C, restricting premature drug leakage during systemic circulation [18].

2.3. Role of Cholesterol and Charge-Imparting Lipids

Cholesterol functions as a primary regulatory component within liposomal formulations. Although cholesterol does not form bilayer structures independently, its intercalation between phospholipid molecules alters packing geometry and membrane dynamics [19]. The hydroxyl group of cholesterol aligns near the hydrophilic headgroup region, while its rigid steroid ring system interacts with the aliphatic hydrocarbon chains.

In fluid-state membranes (above Tm), cholesterol restricts the conformational mobility of fatty acid chains, increasing packing density and reducing membrane permeability to small water-soluble molecules [20]. Conversely, in gel-state membranes (below Tm), cholesterol interrupts the uniform packing of saturated chains, preventing phase separation and crystallization. Incorporating 30-50 mol% cholesterol maximizes mechanical stability, decreases serum protein insertion, and minimizes drug loss during storage and circulation [21].

Charged lipids are integrated into formulations to impart electrostatic repulsion, preventing particle aggregation through colloidal stabilization [22]. Anionic lipids such as dipalmitoylphosphatidylglycerol (DPPG) and phosphatidic acid (PA) introduce negative surface charges that lower aggregation rates. Cationic lipids including 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) are used to complex negatively charged genetic material via electrostatic interactions [23].

2.4. Classification Based on Lamellarity and Vesicle Size

Liposomes are classified based on size dimensions and the number of concentric lipid bilayers:

2.4.1. Small Unilamellar Vesicles (SUVs)

Ranging from 20 to 100 nm in diameter, SUVs feature a single bilayer membrane. Their small hydrodynamic radius yields prolonged circulation times and enhanced tissue penetration, though their aqueous encapsulation volume remains restricted [24].

2.4.2. Large Unilamellar Vesicles (LUVs)

Spanning 100 to 1000 nm, LUVs consist of a single lipid bilayer surrounding a substantial internal aqueous core. They offer high entrapment efficiencies for hydrophilic moieties while maintaining structural stability [25].

2.4.3. Multilamellar Vesicles (MLVs)

Measuring above 500 nm up to several micrometers, MLVs display an onion-like morphology composed of multiple concentric lipid bilayers separated by aqueous layers. MLVs provide high lipid-to-aqueous volume ratios, favoring the entrapment of hydrophobic drug molecules [26].

2.4.4. Multivesicular Vesicles (MVVs)

Comprising non-concentric aqueous compartments enclosed within a single outer lipid membrane, MVVs allow high volume encapsulation and sustained release kinetics [27].

3. Mechanisms involved for Enhancement of Bioavailability

3.1. Solubilization and Dissolution

For hydrophobic molecules, inadequate dissolution in gastrointestinal fluids limits intestinal absorption. Liposomal encapsulation alters these solubilization kinetics [28]. Entrapping hydrophobic molecules within the aliphatic core of phospholipid bilayers maintains the active drug in an amorphous or molecularly dispersed state, preventing crystal lattice formation.

Upon contact with biological fluids, liposomal dispersions bypass the high activation energy barrier required for crystalline lattice disruption. The vast surface area of sub-micron vesicles accelerates molecular transfer into the surrounding microenvironment or directly into epithelial cell membranes, enhancing the apparent aqueous solubility and kinetic dissolution rate [29].

3.2. Protection Against Enzymatic and Chemical Degradation

The gastrointestinal tract exposes therapeutics to harsh conditions, including acidic gastric pH, proteolytic enzymes, and bile salts. Hydrophobic drugs with susceptible ester, amide, or lactone structures undergo rapid degradation prior to absorption [30].

Liposomal vesicles serve as protective barriers. The hydrophobic core isolates sensitive drug domains from external hydronium ions, oxidative species, and digestive enzymes [31]. Enclosing vulnerable molecules within the lipid matrix preserves chemical stability during transit through the stomach and upper intestine, ensuring intact active drug reaches primary absorption sites.

3.3. Membrane Permeation, Endocytosis, and Epithelial Transport

The structural similarity between liposomal bilayers and biological membranes facilitates drug transport across mucosal barriers [32]. Liposomes enhance epithelial transport via four primary pathways as shown in Figure 2:

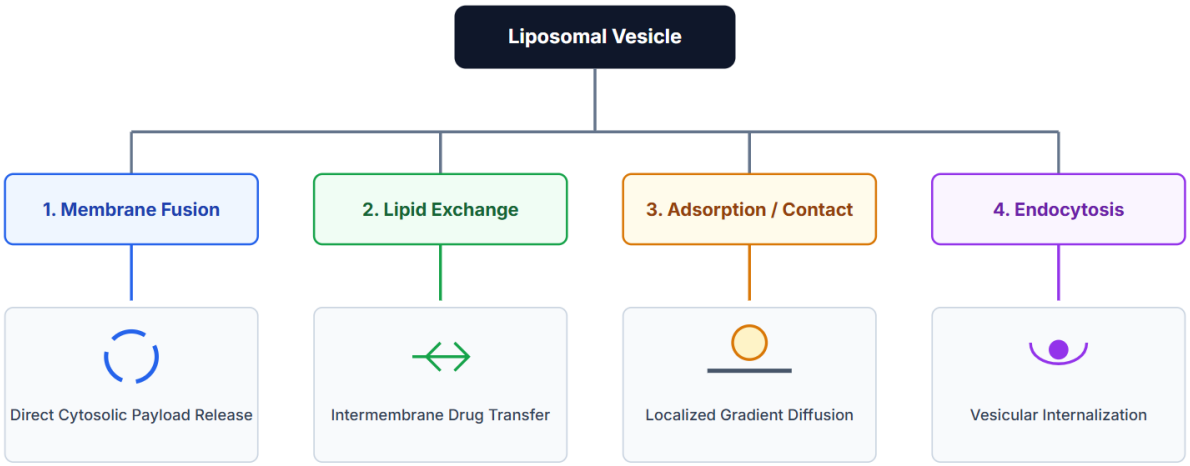

Figure 2. Mechanisms of Cellular Interaction & Epithelial Transport

3.3.1. Membrane Fusion

Direct merging of the liposomal lipid bilayer with the enterocyte plasma membrane releases the encapsulated payload directly into the cytoplasm, bypassing active efflux transporters [33].

3.3.2. Lipid Exchange

Inter-membrane exchange of phospholipids between liposomes and cell membranes destabilizes the liposomal matrix, promoting drug partitioning into the lipid-rich enterocyte membrane [34].

3.3.3. Adsorption and Contact

Vesicles adhere to the mucosal surface, generating a localized concentration gradient that accelerates passive diffusion across enterocytes [35].

3.3.4. Endocytic Uptake

Intact nanosized vesicles undergo clathrin- or caveolae-mediated endocytosis, transporting the carrier and its drug payload across the apical membrane [36].

3.4. Intestinal Lymphatic Transport and First-Pass Metabolism

Orally administered liposomal formulations can access systemic circulation through the intestinal lymphatic system [37]. Following liposomal lipid digestion by pancreatic lipase, lipid breakdown products, exogenous phospholipids, and lipophilic drugs form mixed micelles within the intestinal lumen. Enterocytes re-esterify these lipids into triglycerides, assembling them into chylomicrons within the endoplasmic reticulum.

Lipophilic molecules with high log P values (≥ 5) and substantial triglyceride solubility incorporate into the hydrophobic core of chylomicrons. These chylomicrons pass into the lacteals the specialized lymphatic capillaries of the intestinal villi rather than entering the hepatic portal vein [38]. Transport through the lymphatic system empties directly into the subclavian vein via the thoracic duct, bypassing primary hepatic first-pass metabolism and markedly increasing systemic drug availability.

3.5. Passive and Active Targeting Mechanisms

Parenterally administered liposomal formulations alter tissue disposition through passive and active targeting [39]. Passive targeting relies on the Enhanced Permeability and Retention (EPR) effect, characteristic of solid tumors and inflamed tissues. Tumor microvasculature displays structural abnormalities, including wide endothelial fenestrations (100-780 nm) and impaired lymphatic drainage. Long-circulating liposomes (100-150 nm) extravasate through these fenestrations, selectively accumulating within target tissues while sparing healthy organs [40].

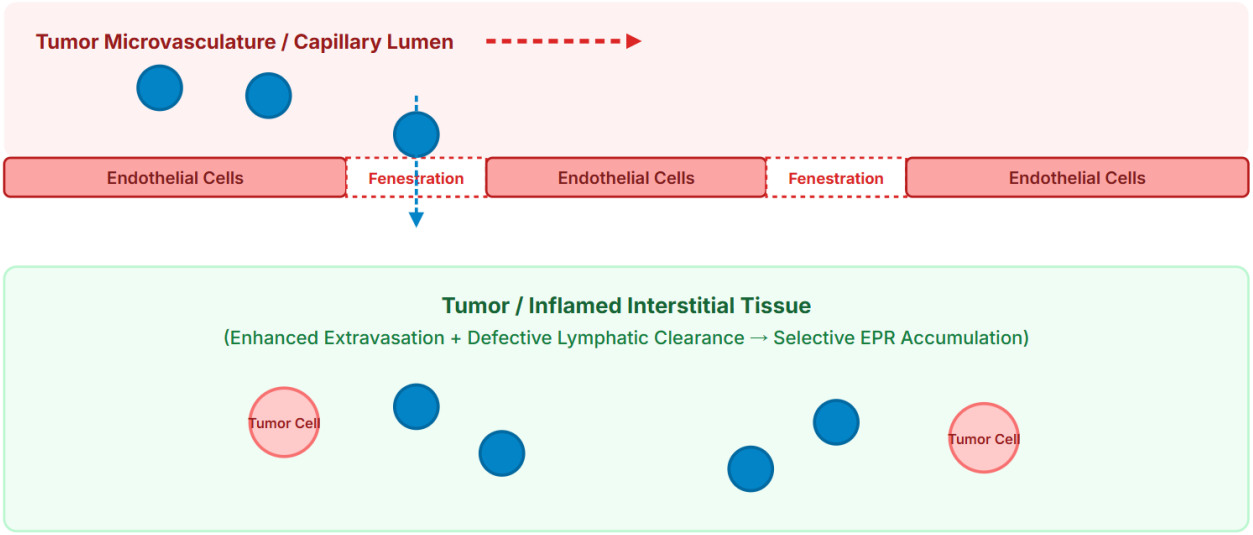

Figure 3. Targeting Mechanism of Enhanced Permeability and Retention (EPR)

Active targeting modifies the surface of long-circulating liposomes with specific targeting ligands such as monoclonal antibodies, antibody fragments, peptides, aptamers, or small molecules like folic acid and transferrin [41]. These ligands bind to receptors overexpressed on diseased cell surfaces, triggering receptor-mediated endocytosis. This approach increases intracellular drug accumulation within target cells while minimizing off-target exposure.

4. Fabrication and Manufacturing Methods

4.1. Conventional Preparation Techniques

4.1.1. Thin-Film Hydration Method

The thin-film hydration method (Bangham method) remains a standard laboratory technique for liposome preparation [6]. Phospholipids, cholesterol, and lipophilic drugs are dissolved in an organic solvent mixture (e.g., chloroform, methanol, or dichloromethane). The solvent is removed under reduced pressure using rotary evaporation at a temperature above the highest lipid Tm, yielding a thin lipid film on the inner wall of the flask.

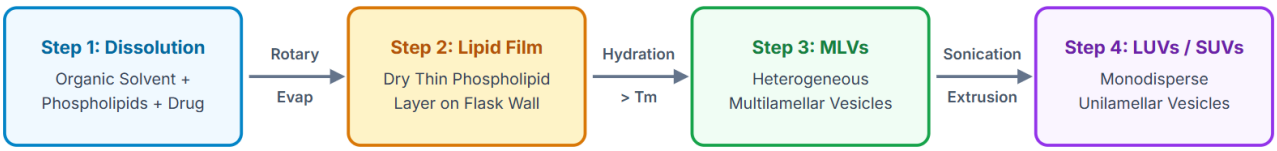

Figure 4. Method of Thin-Film Hydration

Hydration of the dried film with an aqueous buffer above Tm causes the lipid layers to swell and peel away, spontaneously forming heterogenous multilamellar vesicles (MLVs). To obtain uniform unilamellar vesicles, the resulting suspension undergoes mechanical size reduction using membrane extrusion or probe sonication [42].

4.1.2. Reverse-Phase Evaporation

The reverse-phase evaporation method achieves high encapsulation efficiencies for hydrophilic and macro-molecular compounds [43]. Lipids are dissolved in an organic phase (such as diethyl ether or isopropyl ether), followed by the addition of an aqueous phase containing the drug. The mixture is sonicated to yield a stable water-in-oil emulsion.

The organic solvent is slowly evaporated under reduced pressure, causing the inverted micelles to gel and transform into a continuous viscous matrix. Upon reaching a critical state, the gel structure collapses, forming large unilamellar vesicles (LUVs) with high aqueous-to-lipid entrapment ratios.

4.1.3. Solvent Injection

Solvent injection techniques including the ethanol injection and ether injection methods involve dissolving lipids in a water-miscible organic solvent and injecting the solution into an aqueous phase [44]. In ethanol injection, rapid diffusion of the solvent into the aqueous medium causes local lipid supersaturation, driving spontaneous lipid self-assembly into small unilamellar vesicles (SUVs). This process avoids aggressive mechanical homogenization, though residual solvent removal requires downstream processing such as diafiltration or vacuum distillation.

4.2. Scalable and High-Throughput Manufacturing Technologies

4.2.1. High-Pressure Homogenization and Microfluidization

Transitioning liposomal formulations from bench scale to commercial manufacturing requires continuous processing technologies [45]. Microfluidization forces coarse liposomal dispersions under extreme pressure (up to 20,000 psi) through micro-engineered interaction chambers.

Inside these micro-channels, fluid streams split and collide at high velocities, subjecting lipid aggregates to intense shear forces, cavitation, and impact stresses [46]. This energy input disrupts large MLVs into uniform nanoscale vesicles. Particle size and polydispersity are controlled by adjusting operational pressure, chamber geometry, and pass number.

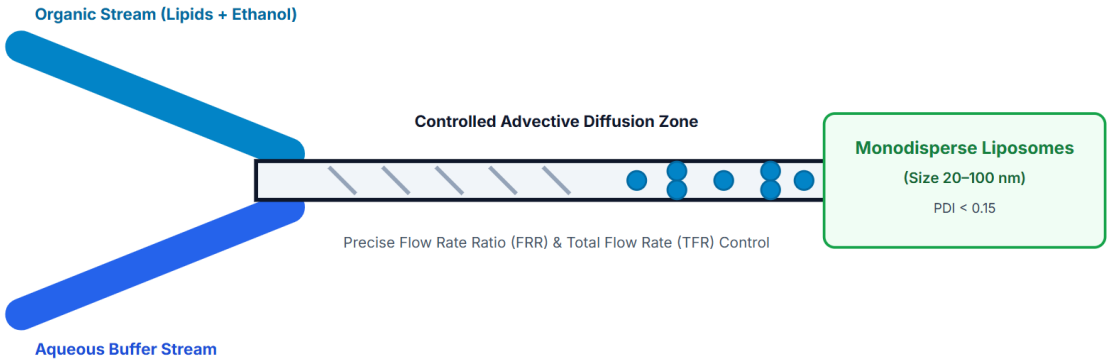

Figure 5. Mechanism of Microfluidic Channel Synthesis & Self-Assembly

4.2.2. Microfluidic Mixing and Microchannel Assembly

Microfluidic mixing enables precise control over nanoparticle assembly [47]. Lipids dissolved in an organic solvent (typically ethanol) and an aqueous stream are introduced into micro-channels featuring staggered herringbone or spatial toroidal geometries.

The micro-channel geometry induces chaotic advection, driving rapid mixing of the fluids on sub-millisecond timescales. Diffusive mass transfer generates a controlled, reproducible supersaturation gradient, forcing self-assembly into monodisperse liposomes [48]. Microfluidic platforms allow fine control over vesicle size (20-150 nm) by altering total flow rates (TFR) and flow rate ratios (FRR), ensuring high batch-to-batch reproducibility. Table 1 provides the operational parameters, vesicle size outcomes, encapsulation capacities, and scalability profiles across primary conventional and industrial liposome fabrication methods.

Table 1. Comparison of Conventional and Advanced Liposome Fabrication Techniques

Fabrication Technique	Vesicle Type	Particle Size Range (nm)	Encapsulation Efficiency (%)	Advantages	Limitations
Thin-Film Hydration (Bangham Method)	Multilamellar (MLVs) / Large Unilamellar (LUVs)	100 - 5000	10 - 40% (Hydrophilic) > 80% (Lipophilic)	Simple experimental setup; high lipid loading capacity; adaptable to diverse lipid ratios.	Broad size distribution; requires downstream size reduction (extrusion/sonication); batch-to-batch variation.
Reverse-Phase Evaporation	Large Unilamellar (LUVs)	100 - 1000	60 - 80% (Hydrophilic)	Exceptionally high aqueous entrapment volume; ideal for macromolecular payloads.	Organic solvent contact can denature labile proteins/peptides; difficult solvent elimination.
Ethanol Injection Method	Small Unilamellar (SUVs)	50 - 150	20 - 50%	Single-step spontaneous assembly; mild operating conditions; no aggressive mechanical shear.	Dilute final dispersions; requires downstream diafiltration for residual ethanol removal.
High-Pressure Microfluidization	Small Unilamellar (SUVs) / LUVs	50 - 200	Variable (Payload Dependent)	Uniform size reduction; solvent-free physical processing; excellent batch reproducibility.	High energy consumption; risk of sample heating requiring active temperature control loops.
Microfluidic Channel Mixing	Small Unilamellar (SUVs) / LUVs	20 - 100	> 80%	Precise control over vesicle diameter and PDI (<0.1); ultra-high batch-to-batch reproducibility.	High specialized equipment cost; potential for microchannel clogging at high lipid concentrations.

5. Physicochemical Characterization and Evaluation Metrics

5.1. Hydrodynamic Diameter and Polydispersity Index

Particle size directly governs the in vivo fate, clearance kinetics, mucosal transport, and tissue permeability of liposomes [33]. Dynamic Light Scattering (DLS), or Photon Correlation Spectroscopy, measures the hydrodynamic diameter of vesicles suspended in aqueous media by analyzing intensity fluctuations in scattered light caused by Brownian motion. The Stokes-Einstein equation relates the diffusion coefficient (D) directly to hydrodynamic radius (r_h):

$$D = \frac{k_B T}{6\pi\eta r_h}$$

where k_B represents the Boltzmann constant, T denotes absolute temperature, and η corresponds to medium viscosity.

The Polydispersity Index (PDI) reflects the breadth of the particle size distribution. PDI values below 0.2 indicate a monodisperse sample suitable for parenteral administration, whereas values above 0.3 signal size heterogeneity and potential physical instability [34].

5.2. Surface Charge and Zeta Potential Determination

Zeta potential (ζ) measures the electrical charge at the stern layer-diffuse layer boundary of the double layer surrounding a colloidal particle [35]. Electrophoretic Light Scattering determines zeta potential by applying an electric field across the suspension and measuring particle electrophoretic mobility (μ_e). Zeta potential is calculated using the Smoluchowski approximation:

$$\mu_e = \frac{\epsilon_r \epsilon_0 \zeta}{\eta}$$

where ϵ_r represents the relative permittivity of the liquid, ϵ_0 is the vacuum permittivity, and η is dynamic viscosity.

Absolute zeta potential values greater than $|30|mV$ provide sufficient electrostatic repulsion to overcome van der Waals attractive forces, preventing particle aggregation during storage [36].

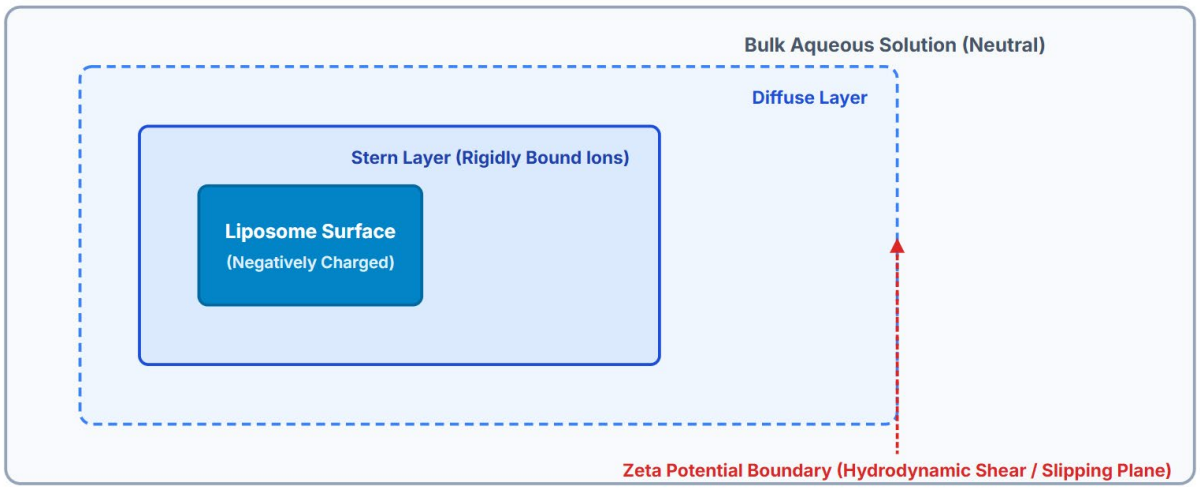

Figure 6. Colloidal Electrical Double Layer Structure & Zeta Potential

5.3. Morphological Analysis and Cryo-TEM Techniques

Direct visualization of liposomal structure confirms vesicle shape, surface topology, and lamellarity. Conventional Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) require staining and drying procedures that can introduce structural artifacts [37].

Cryogenic Transmission Electron Microscopy (Cryo-TEM) preserves native morphology by rapidly vitrifying the aqueous suspension in liquid ethane. Cryo-TEM imaging reveals bilayer thickness, distinguishes unilamellar from multilamellar architectures, and detects drug crystallization within the core or membrane. Atomic Force Microscopy (AFM) complements Cryo-TEM by providing three-dimensional surface topology and mechanical elasticity measurements under native hydrated conditions [38].

5.4. Encapsulation Efficiency and Drug Loading Capacity

Encapsulation efficiency (EE%) and drug loading (DL%) define drug entrapment capacity:

$$\text{EE\%} = \left(\frac{W_{\text{encapsulated}}}{W_{\text{total}}}\right) \times 100 \text{DL\%} = \left(\frac{W_{\text{encapsulated}}}{W_{\text{total lipid}} + W_{\text{encapsulated}}}\right) \times 100$$

where $W_{encapsulated}$ represents the mass of entrapped drug, W_{total} is the total drug added, and W_{total} lipid denotes total lipid mass.

Separation of free, unencapsulated drug from intact liposomes is achieved using ultracentrifugation, gel filtration chromatography (e.g., Sephadex columns), or tangential flow ultrafiltration [39]. Quantitation of drug concentrations in isolated fractions is subsequently performed using validated High-Performance Liquid Chromatography (HPLC) or UV-Visible spectrophotometry.

5.5. *In Vitro* Dissolution and Release Kinetic Modeling

In vitro dissolution testing evaluates drug liberation dynamics under simulated physiological conditions [39]. Standard techniques utilize membrane dialysis sacks, continuous flow-through cells (USP Apparatus 4), or reverse dialysis methods. Dialysis media must maintain sink conditions, often requiring the addition of biorelevant surfactants (such as sodium taurocholate and lecithin) or non-ionic surfactants to emulate intestinal fluid environments [42].

Mechanistic mathematical models quantify drug release mechanisms:

1. Zero-Order Model: $Q_t = Q_0 + K_0 t$ (describes constant drug release profiles).
2. First-Order Model: $\ln Q_t = \ln Q_0 - K_1 t$(describes concentration-dependent release kinetics).
3. Higuchi Model: $Q_t = K_H t^{1/2}$ (describes diffusion-controlled release from matrix networks).
4. Korsmeyer-Peppas Model: $M_t/M_\infty = Kt^n$(where n indicates the transport mechanism: n ≤ 0.45 corresponds to Fickian diffusion, while 0.45 < n < 0.89 indicates anomalous non-Fickian transport) [43].

6. Therapeutic Applications

6.1. Cancer and Tumor-Targeted Therapy

Liposomal formulations have achieved widespread clinical adoption in oncology [9]. Doxorubicin encapsulated in PEGylated liposomes shows altered pharmacokinetics compared to conventional doxorubicin formulations. Polymer-mediated steric stabilization reduces MPS clearance, extending elimination half-life to approximately 55 hours in humans [20].

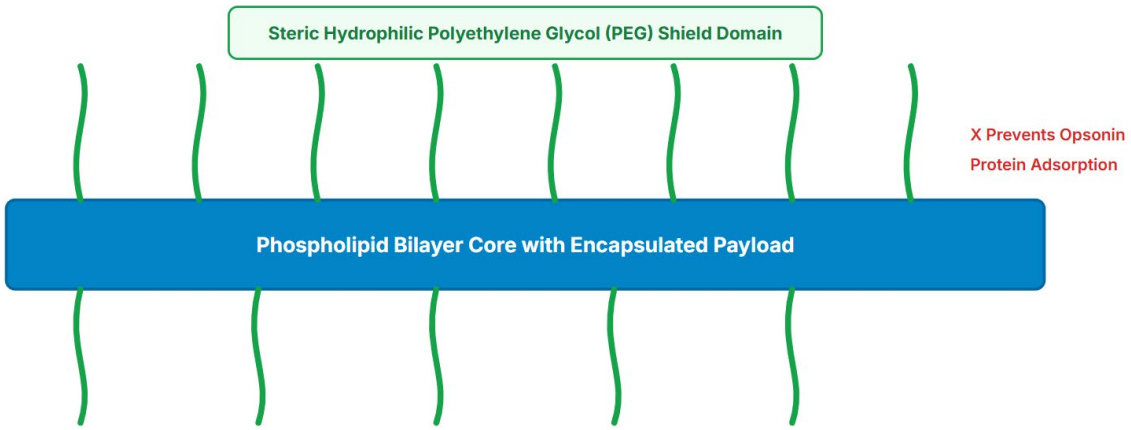

Figure 7. Steric Stabilization of PEGylated (Stealth) Liposomes

Extravasation through fenestrated tumor capillaries accumulates the carrier within tumor interstitium via the EPR effect. Controlled drug liberation within tumor tissue yields significant reductions in peak plasma concentrations of free drug, mitigating severe cardiotoxicity and alopecia [28]. Additional clinical oncology formulations include liposomal irinotecan (Onivyde®), liposomal vincristine (Marqibo®), and liposomal daunorubicin (DaunoXome®) [40]. Table 2 provides clinically approved and commercialized liposomal drug delivery platforms, detailing their lipid compositions, structural characteristics, and primary bioavailability enhancement mechanisms.

6.2. Antimicrobial and Antifungal Therapy

Treating systemic fungal infections and intracellular bacterial pathogens presents drug delivery challenges, as conventional hydrophobic anti-infective formulations often induce systemic toxicity [41]. Liposomal amphotericin B (AmBisome®) shows the utility of lipid complexation for poorly soluble anti-infectives [36]. Amphotericin B inserts directly into the liposomal lipid bilayer,

reducing free drug interaction with cholesterol in human cell membranes while preserving high binding affinity for ergosterol in fungal cell walls. This alteration reduces nephrotoxicity compared to conventional sodium deoxycholate solubilized formulations, permitting higher daily dosing regimens [37]. In intracellular bacterial infections such as tuberculosis, brucellosis, and listeriosis macrophages endocytose administered liposomes, delivering encapsulated antibiotics directly to phagolysosomes where intracellular pathogens reside [46].

Table 2. Clinically Approved and Commercialized Liposomal Nanocarrier Products

Product Name (Brand)	Active Drug	Lipid Matrix Composition & Molar Ratios	Hydrodynamic Diameter (nm)	Clinical Indications	Mechanism of Bioavailability & Disposition Enhancement
Doxil® / Caelyx®	Doxorubicin HCl	MPEG2000-DSPE / HSPC / Cholesterol (5: 56: 39)	~ 80 - 100 nm	Ovarian cancer, Metastatic breast cancer, Kaposi's sarcoma	Extended circulation half-life (~ 55 h) via PEG steric shielding; selective EPR accumulation in tumor tissue; decreased cardiotoxicity.
AmBisome®	Amphotericin B	Hydrogenated Soy PC / Cholesterol / DSPG / α-Tocopherol (2: 1: 0.8: 0.01)	~ 80 nm	Systemic fungal infections, Visceral leishmaniasis	Bilayer intercalation reduces free drug interaction with human cholesterol membranes; selectively delivers payload to fungal ergosterol.
Onivyde®	Irinotecan Trihydrate	DSPC / Cholesterol / MPEG2000-DSPE (3: 2: 0.015)	~ 110 nm	Metastatic pancreatic adenocarcinoma	Intravesicular triethylammonium sucrose octasulfate gradient yields ultra-high drug retention and sustained plasma exposure.
Marqibo®	Vincristine Sulfate	Sphingomyelin / Cholesterol (55: 45)	~ 100 nm	Acute lymphoblastic leukemia (ALL)	Rigid sphingomyelin membrane prevents premature systemic leakage; enhances accumulation in bone marrow and lymphoid tissues.
DepoCyt®	Cytarabine	DOPC / DPPG / Cholesterol / Triolein	10 - 30 μm (Multivesicular)	Lymphomatous meningitis	DepoFoam® multivesicular matrix provides sustained intrathecal drug release over 14 days post-single injection.
Onpattro®	Patisiran (siRNA)	DLin-MC3-DMA / DSPC / Cholesterol / PEG2000-C-DMG (50: 10: 38.5: 1.5)	~ 80 - 100 nm	Hereditary transthyretin-mediated amyloidosis	Ionizable lipid nanoparticle enables hepatocyte targeting via ApoE binding and endosomal release via pH-triggered charge conversion.

6.3. Vaccine Delivery and Immunomodulatory Agents

Liposomes function as effective vaccine delivery platforms and immunological adjuvants [43]. Incorporating recombinant proteins, peptide antigens, or carbohydrate antigens within liposomal architectures protects vulnerable epitopes from enzymatic processing while facilitating uptake by antigen-presenting cells (APCs), such as dendritic cells and macrophages [47].

Co-encapsulating lipophilic immunostimulatory adjuvants such as monophosphoryl lipid A (MPLA) within the lipid membrane triggers Toll-like receptor signaling, inducing robust cell-mediated and humoral immune responses. Liposomal adjuvant technology forms the foundation of commercial vaccines, including herpes zoster (Shingrix®) and hepatitis A (Epaxal®) [44].

6.4. Nucleic Acid Delivery and Gene Therapy

Delivering fragile nucleic acids such as messenger RNA (mRNA), small interfering RNA (siRNA), and plasmid DNA (pDNA) requires protection from serum nucleases and assistance crossing anionic cell membranes [48]. Lipid Nanoparticles (LNPs), an advanced evolution of cationic liposomal technology, utilize ionizable lipids that remain neutral at physiological pH but become protonated within acidic endosomes (pH 5.5-6.0) [49, 50].

Ionizable lipid structures facilitate endosomal membrane disruption, releasing nucleic acid payloads into the cytosol. This platform enabled the rapid development of mRNA vaccines targeting SARS-CoV-2 (Comirnaty® and SPIKEVAX®) and systemic siRNA therapeutics targeting hereditary transthyretin-mediated amyloidosis (Onpattro®) [51, 52].

7. Limitations and Challenges

7.1. Physical and Chemical Instability Mechanisms

Translating liposomal formulations into stable commercial products requires addressing distinct physical and chemical destabilization pathways [49]:

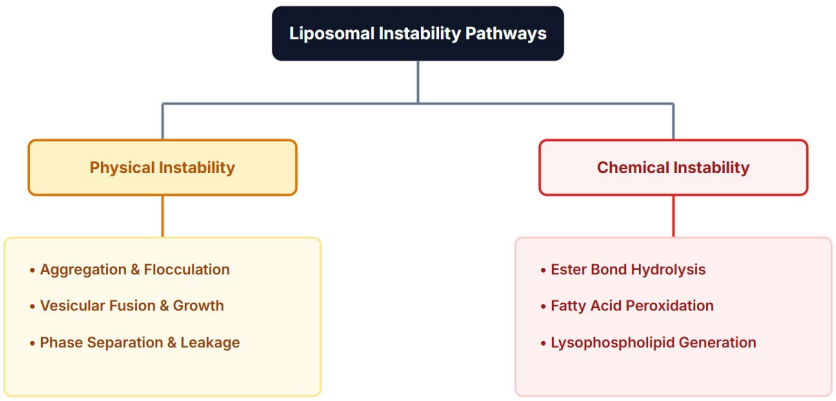

Figure 8. Classification of Physical and Chemical Instability

7.1.1. Physical Instability

Vesicles suspended in liquid media undergo collision events driven by Brownian motion. Insufficient repulsion allows attractive van der Waals forces to dominate, causing aggregation and flocculation. Over time, aggregated vesicles fuse into larger multilamellar structures, reducing surface area and triggering premature drug leakage [27].

7.1.2. Chemical Instability

Phospholipids containing ester linkages undergo hydrolysis in aqueous environments, yielding lysophospholipids and free fatty acids that disrupt bilayer integrity [20]. Unsaturated fatty acid acyl chains are also susceptible to free-radical peroxidation, which generates polar hydroperoxides that increase membrane permeability. To mitigate these instability pathways, commercial formulations are processed using lyophilization (freeze-drying) with lyoprotectants such as sucrose, trehalose, or mannitol to preserve vesicular structure in dry powder forms [21].

7.2. Scale-Up Obstacles and Regulatory Considerations

Industrial scaling of liposomal products requires strict control over critical quality attributes (CQAs) across manufacturing batches [29]. Minor variations in mixing shear, temperature profiles, lipid purity, or solvent removal rates can alter particle size distributions, encapsulation efficiencies, and release profiles [30]. Regulatory frameworks demand detailed characterization of lipid raw materials, residual solvent levels, sterilization validation (typically achieved via 0.22 μm sterile filtration for particles under 150 nm), batch-to-batch reproducibility, and long-term physical stability [14].

8. Emerging Trends

8.1. Smart Stimuli-Responsive Liposomal Systems

Next-generation liposomes incorporate stimuli-responsive elements that trigger selective payload release in response to physiological signals or external physical triggers [19].

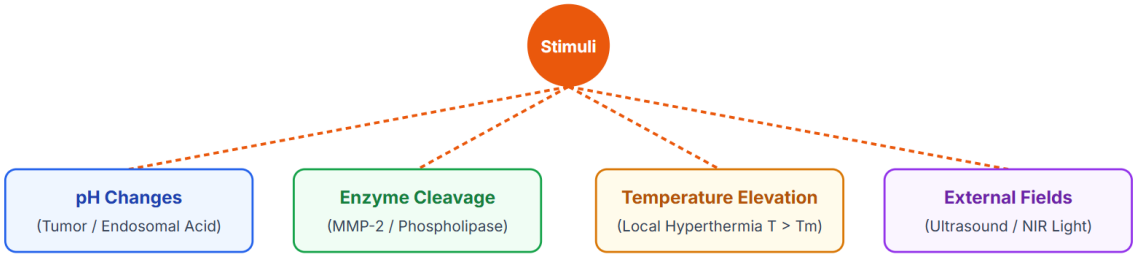

Figure 9. Mechanisms of Stimuli-Responsive Triggered Release

1. pH-Sensitive Liposomes: Incorporate lipids such as dioleoylphosphatidylethanolamine (DOPE) modified with protonatable heads. In acidic tumor or endosomal environments (pH 5.0-6.5), conformational changes trigger rapid membrane destabilization and cytosolic release [27].
2. Enzyme-Responsive Liposomes: Utilize lipid conjugates cleaved by overexpressed disease-associated enzymes, such as matrix metalloproteinases (MMPs) or phospholipase A_2, directing localized payload release at inflammatory or tumor sites [19].
3. Thermo-Sensitive Liposomes: Formulated with lipids like DPPC (Tm = 41°C), these nanocarriers release their payload when exposed to localized mild hyperthermia [43].

8.2. Artificial Intelligence and Computational Formulation Design

Integrating artificial intelligence (AI), machine learning (ML), and molecular dynamics (MD) simulations is reshaping liposomal design pipelines [38]. High-throughput computational modeling predicts drug-lipid miscible interactions, bilayer insertion energies, and encapsulation parameters prior to physical synthesis [51]. Machine learning algorithms trained on quantitative composition-property datasets optimize formulation variables including lipid ratios, cholesterol fractions, microfluidic flow rates, and processing temperatures accelerating formulation development and improving product reproducibility [48].

9. Conclusion

Liposomal drug delivery systems are novel drug delivery systems with a potential to address biopharmaceutical limitations associated with poorly soluble compounds. Enclosing hydrophobic active pharmaceutical ingredients within phospholipid bilayers or hydrophilic compounds within aqueous cores improves apparent solubility, protects fragile molecules from chemical and enzymatic degradation, and alters systemic disposition profiles. Controlled release profiles, combined with passive and active targeting techniques, broaden therapeutic windows while reducing off-target toxicities across oncological, anti-infective, immunomodulatory, and gene delivery applications. Advances in scalable microfluidic manufacturing, cryo-characterization, stimuli-responsive lipid architectures, and predictive computational modeling continue to support the clinical translation of advanced liposomal therapeutics.

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