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LIPOSOMES IN PHARMACEUTICS: A REVIEW OF FORMULATION STRATEGIES AND CLINICAL TRANSLATION

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ABSTRACT

Among the myriad carrier technologies developed for pharmaceutical application, liposomes hold a uniquely influential position — they are the first nanomedicine platform to achieve widespread clinical acceptance, combining biocompatible lipid bilayer architecture with the capacity to encapsulate both hydrophilic and hydrophobic drug molecules. This review examines the foundational role of liposomes in modern drug delivery, tracing their evolution from basic vesicle research to today's ligand-targeted, stimuli-responsive formulations. We systematically address classification by lamellarity, size, surface charge, and preparation methodology, and demonstrate how each design parameter governs pharmacokinetic behaviour, circulation longevity, and tissue distribution. Special attention is given to sterically stabilised (PEGylated) liposomes, actively targeted immunoliposomes, and stimuli-triggerable vesicle systems. Mathematical models of drug release from liposomal bilayers are presented alongside clinical correlates. Therapeutic applications spanning oncology, infectious disease, vaccine delivery, dermatology, and gene therapy are surveyed, and a curated summary of FDA-approved liposomal products is provided. The review concludes with emerging frontiers — including liposome–hydrogel hybrids, theranostic vesicles, and oral liposome technologies — and identifies translational bottlenecks limiting broader patient access.

KEYWORDS: *Liposome; Phospholipid vesicle; Controlled release; Targeted drug delivery; PEGylation; Nanomedicine; Encapsulation; Immunoliposome; Theranostic; Clinical translation.*

1. INTRODUCTION

What distinguishes a truly transformative drug carrier from a merely functional one? It must solve at least one major pharmacokinetic limitation — poor solubility, rapid clearance, narrow therapeutic window, off-target toxicity — without introducing unacceptable new risks. Liposomes, self-assembled phospholipid bilayers enclosing an aqueous core, achieve precisely this balance. Their structural kinship with natural cell membranes, combined with exceptional cargo versatility and surface modifiability, has established them as one of the most clinically successful nanocarrier platforms in history.[1,2]

The liposome story began in 1964 when Alec Bangham, at the Babraham Institute in Cambridge, observed that dried phospholipids, when hydrated, spontaneously formed closed bilayer vesicles resembling biological membranes. Initially a tool for membrane biology, liposomes were first proposed for drug delivery in the early 1970s by Gregory Gregoriadis, who demonstrated that enzymes entrapped within lipid vesicles retained activity and exhibited altered in vivo distribution.[3] The decades following saw liposome technology mature from academic curiosity to commercial reality: the first approved product, Doxil® (pegylated liposomal doxorubicin), reached the US market in 1995 for Kaposi's sarcoma, validating the clinical viability of nanoscale lipid carriers.[4]

At a molecular level, liposomes owe their functionality to amphipathic phospholipids — molecules bearing a hydrophilic phosphate-containing headgroup and two hydrophobic fatty acyl tails. In aqueous medium, these molecules spontaneously organise into bilayers, with tails facing inward to exclude water and heads facing outward into the aqueous environment. This arrangement creates two distinct compartments: an aqueous interior suitable for hydrophilic drugs, and a hydrophobic bilayer domain ideal for lipophilic payloads.[5,6] The bilayer's fluidity, governed by acyl chain length and degree of saturation, influences drug retention, membrane permeability, and vesicle stability in biological fluids.

Liposomes offer several advantages over polymeric nanoparticles and other carriers. They are biodegradable, composed of endogenous lipid species such as phosphatidylcholine and cholesterol; they exhibit low intrinsic toxicity; and their surface can be functionalised with targeting ligands, polyethylene glycol (PEG) chains, or stimuli-responsive moieties.[7] Moreover, liposomes can be manufactured at scale using established high-pressure homogenisation or microfluidic mixing techniques, a critical consideration for clinical translation.[8]

This review surveys the full landscape of liposome-based drug delivery — from fundamental structural classification and preparation methods through drug encapsulation strategies, release kinetics, therapeutic applications, and the emerging technologies that will shape the field's next decade.

2. CLASSIFICATION OF LIPOSOMES

Liposomes are not a single entity but a family of vesicular structures differing in lamellarity, size, surface charge, and preparation route. Each variant presents distinct encapsulation efficiency, circulation half-life, and drug release behaviour.[9–11]

2.1 By Lamellarity and Size

Small unilamellar vesicles (SUVs) possess a single lipid bilayer and diameter of 20–100 nm. Their small size enables tissue extravasation and cellular uptake, making them preferred for intravenous drug delivery. However, limited aqueous volume restricts hydrophilic drug loading.[9]

Large unilamellar vesicles (LUVs), 100–400 nm in diameter, provide substantially greater aqueous interior volume while maintaining a single bilayer. They are widely used for encapsulating water-soluble drugs, proteins, and nucleic acids.

Giant unilamellar vesicles (GUVs) exceed 1 μm and are primarily research tools for membrane biophysics and cell-mimetic studies.

Multilamellar vesicles (MLVs) consist of several concentric bilayers separated by aqueous layers, resembling an onion cross-section. They exhibit higher total drug entrapment but slower, more sustained release as drug must traverse multiple bilayers. Typical MLV diameters range from 500 nm to several micrometres.[10]

Multivesicular vesicles (MVVs) contain multiple non-concentric internal compartments bounded by a continuous outer bilayer. DepoFoam® technology, used in DepoCyt® (cytarabine) and DepoDur® (morphine), exemplifies this architecture, enabling extended drug release over days to weeks.[11]

2.2 By Surface Charge

Neutral liposomes (e.g., egg phosphatidylcholine alone) exhibit minimal interaction with cell membranes and short circulation times. Cationic liposomes carry positive charges via lipids

like DOTAP or DC-Chol, promoting interaction with negatively charged cell surfaces and endosomal membranes — an attribute exploited for nucleic acid delivery. However, cationic charge accelerates opsonisation and clearance by the reticuloendothelial system (RES). Anionic liposomes (e.g., containing phosphatidylglycerol) are less commonly used for systemic delivery due to shorter half-lives but find application in topical and pulmonary formulations.[12]

2.3 By Surface Modification

Conventional liposomes are unmodified phospholipid-cholesterol vesicles that are rapidly cleared by liver and spleen macrophages. Sterically stabilised (PEGylated) liposomes incorporate lipid-anchored polyethylene glycol chains that create a hydration barrier, reducing opsonin adsorption and extending circulation half-life from hours to several days. Doxil® and many subsequent products rely on this innovation.[13] Targeted liposomes bear surface-conjugated ligands — antibodies, antibody fragments (Fab'), peptides, transferrin, folate — that recognise disease-associated receptors, enabling active tissue localisation. Stimuli-responsive liposomes incorporate lipids that undergo phase transition or cleavage upon exposure to local temperature elevation, pH reduction, enzyme activity, or externally applied ultrasound, triggering drug release specifically at target sites.[14]

3. PREPARATION METHODS

Liposome preparation involves three stages: lipid dissolution and mixing, vesicle formation, and size reduction/post-processing. The choice of method determines lamellarity, size distribution, and encapsulation efficiency.

3.1 Thin-Film Hydration (Bangham Method)

Lipids dissolved in organic solvent are dried under reduced pressure to form a thin film on a round-bottom flask. Hydration with aqueous buffer above the lipid phase transition temperature causes spontaneous MLV formation. Subsequent extrusion through polycarbonate membranes (100–400 nm pores) or ultrasonication converts MLVs to LUVs or SUVs. This is the most common laboratory method but suffers from low encapsulation efficiency for hydrophilic drugs.[15]

3.2 Reverse-Phase Evaporation

Water-in-oil emulsion is formed by sonicating aqueous drug solution with lipids dissolved in organic solvent (e.g., diethyl ether). Slow evaporation under reduced pressure converts the

emulsion to a gel, which collapses into LUVs with high aqueous volume capture. This method achieves encapsulation efficiencies of 30–65% for hydrophilic drugs, substantially better than thin-film hydration.[16]

3.3 Ethanol/ Solvent Injection

Lipid-ethanol solution is rapidly injected into an aqueous phase through a fine needle. Dilution reduces ethanol concentration below the solubility limit, causing spontaneous vesicle formation. The method is continuous and scalable but limited by ethanol removal and residual solvent concerns.[17]

3.4 Detergent Removal Techniques

Lipids are solubilised using detergents such as sodium cholate or octyl glucoside in aqueous buffer. Dialysis, gel filtration, or adsorption with Bio-Beads removes detergent, driving vesicle self-assembly. This method produces homogeneous uniflagellar vesicles and is particularly useful for incorporating membrane proteins.[18]

3.5 Microfluidic Mixing

Microfluidic hydrodynamic focusing devices rapidly mix ethanolic lipid solution with aqueous buffer in precisely controlled flow ratios, producing homogeneous SUVs or LUVs with reproducible size and low polydispersity. This is emerging as the preferred method for scaled manufacturing and clinical-grade liposomes.[19]

3.6 Post-formation Processing for Long-Circulating Liposomes

To produce PEGylated liposomes, DSPE-PEG conjugates are included in the initial lipid mixture. For active targeting, post-insertion methods are often used: micelles of DSPE-PEG-ligand are incubated with preformed liposomes at elevated temperature, allowing ligand transfer into the outer bilayer leaflet. This approach preserves ligand orientation and avoids harsh coupling chemistries.[20]

4. MECHANISMS OF DRUG ENCAPSULATION AND RELEASE

Liposomes accommodate diverse drug types through distinct localisation strategies. Hydrophilic drugs (doxorubicin, cytarabine, siRNA) dissolve in the aqueous interior. Hydrophobic drugs (paclitaxel, amphotericin B) partition into the lipid bilayer. Amphipathic molecules orient at the bilayer–water interface.[21,22]

Drug release from liposomes follows several pathways:

Diffusion-mediated release: Small, non-ionised drugs diffuse across the lipid bilayer driven by concentration gradient. Release rate depends on bilayer fluidity (governed by acyl chain saturation and cholesterol content), drug partition coefficient, and the transmembrane pH gradient.[23]

Bilayer erosion and lipid exchange: Phospholipids transfer to serum lipoproteins (HDL, LDL) via lipid transfer proteins, gradually destabilising the liposome and releasing contents. This process dominates clearance of conventional liposomes.

RES-mediated capture: Opsonised liposomes are phagocytosed by liver and spleen macrophages, then degraded in lysosomes, releasing drug intracellularly — a mechanism exploited for macrophage-targeted therapy.[24]

pH-triggered release: Liposomes containing pH-sensitive lipids (e.g., dioleoyl phosphatidylethanolamine DOPE with cholesteryl hemi succinate) destabilise at acidic endosomal pH (5.0–6.5), releasing nucleic acid payloads into the cytosol before lysosomal degradation.

Enzymatic release: Liposomes incorporating phospholipids cleaved by secretory phospholipase A_2 ($sPLA_2$), an enzyme upregulated in inflamed tissues and many tumours, achieve site-specific drug liberation.[25]

Thermosensitive release: Liposomes containing dipalmitoyl phosphatidylcholine (DPPC), which undergoes gel-to-liquid crystalline phase transition at 41–42°C, release contents upon local hyperthermia. Lyso-thermosensitive liposomal doxorubicin (LTLD) exemplifies this approach.[26]

5. ARCHITECTURAL VARIANTS FOR ADVANCED DELIVERY

5.1 PEGylated (Stealth) Liposomes

Unmodified liposomes are cleared within minutes. Conjugation of PEG (typically 2000 Da) to DSPE extends circulation half-life to 24–72 hours by reducing protein adsorption. The PEG brush creates steric repulsion, diminishing macrophage recognition. Doxil® (doxorubicin) and Caelyx® use this platform, achieving significantly reduced cardiotoxicity compared to free drug.[27]

5.2 Immunoliposomes

Antibodies or fragments conjugated to liposome surfaces enable receptor-mediated targeting. Anti-HER2 immunoliposomes for breast cancer, anti-EGFR constructs for glioma, and anti-CD19 formulations for lymphoma have advanced to clinical evaluation. Challenges include immunogenicity of murine antibodies, scale-up complexity, and steric interference from PEG chains.[28]

5.3 Cationic Liposomes for Nucleic Acid Delivery

Cationic lipids (DOTMA, DOTAP, DC-Chol) complex with negatively charged DNA or siRNA via electrostatic interaction, protecting nucleic acids from nuclease degradation and facilitating endosomal escape. Lipoplexes and stable nucleic acid lipid particles (SNALPs) have enabled the first siRNA therapeutic (patisiran, Onpattro®) for hereditary transthyretin-mediated amyloidosis — a landmark approval validating non-viral RNA delivery.[29]

5.4 DepoFoam® Multivesicular Liposomes

DepoFoam technology produces microscopic particles containing numerous non-concentric aqueous chambers separated by lipid bilayers. Each chamber acts as an independent drug reservoir. As outer bilayers erode, deeper chambers are sequentially exposed, producing zero-order release over days to weeks. Products include DepoCyt® (intrathecal cytarabine for lymphomatous meningitis, release over 14 days) and DepoDur® (epidural morphine for postoperative pain).[30]

5.5 Proliposomes

Dry, free-flowing powder formulations of lipid and drug that spontaneously hydrate upon contact with aqueous biological fluids to form liposomes. Proliposomes improve physical and chemical stability, enable oral delivery, and simplify manufacturing. They are particularly valuable for drugs degraded by hydrolysis.[31]

6. MATHEMATICAL MODELLING OF RELEASE

The release profile from liposomal formulations depends on formulation variables and administration route.

Fick's first law describes passive diffusion across the bilayer:

$J = -P \times (C\_out - C\_in)$

Where *J* is drug flux, *P* is permeability coefficient (determined by bilayer fluidity and drug lipophilicity), and C_out and C_in are drug concentrations external and internal to the vesicle.[32]

First-order release kinetics are observed when diffusion across an intact bilayer is rate-limiting:

M_t / M_∞ = 1 − e^(−kt)

Biphasic release is typical for conventional liposomes: an initial burst (drug adsorbed to outer surface or loosely associated with bilayer) followed by slower sustained release. For MLVs, a triphasic profile may be observed: rapid release from outermost bilayer, plateau during interior drug redistribution, and secondary sustained release.[33]

For DepoFoam and eroding liposomes, zero-order release can be approximated:

M_t / M_∞ = k_0 × t

Where k_0 is constant release rate, achieved when drug diffusion is not rate-limiting and surface erosion controls delivery.

7. CLINICAL APPLICATIONS

Liposomes have been evaluated across virtually every therapeutic area, with oncology representing the largest clinical footprint.

7.1 Oncology

Doxil® / Caelyx® (pegylated liposomal doxorubicin) reduces cardiotoxicity, alopecia, and myelosuppression compared to free doxorubicin, while maintaining efficacy. Indications include ovarian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma, and metastatic breast cancer. The enhanced permeation and retention (EPR) effect — passive accumulation of nanoparticles within leaky tumour vasculature — is the primary tumour-targeting mechanism.[34]

Myocet® (non-pegylated liposomal doxorubicin) offers reduced cardiotoxicity with shorter circulation time, used in combination with cyclophosphamide for breast cancer.

Marqibo® (liposomal vincristine) improves drug circulation and reduces neurotoxicity for acute lymphoblastic leukaemia.

Vyxeos® (liposomal cytarabine: daunorubicin at 5:1 molar ratio) is the first dual-drug liposome approved, for acute myeloid leukaemia. The fixed molar ratio achieves synergistic drug delivery to leukaemic blasts.[35]

7.2 Infectious Diseases

AmBisome® (liposomal amphotericin B) dramatically reduces nephrotoxicity compared to conventional deoxycholate amphotericin, enabling higher, more effective doses for systemic fungal infections, visceral leishmaniasis, and cryptococcal meningitis.

Liposomal ciprofloxacin (Pulmoquin®) is inhaled for cystic fibrosis-associated Pseudomonas infections, penetrating airway mucus and biofilm.[36]

7.3 Vaccines

Liposomes act as vaccine adjuvants, delivering antigen to antigen-presenting cells and potentiating both humoral and cellular immunity. Epaxal® (liposomal hepatitis A vaccine) and Inflexal® V (liposomal influenza vaccine) are approved human products. Modern formulations incorporate monophosphoryl lipid A (MPLA) for TLR4 activation.[37]

7.4 Pain Management

DepoDur® (multivesicular liposomal morphine) provides 48-hour epidural pain relief after major surgery, reducing the need for repeated bolus dosing and patient-controlled analgesia.[38]

7.5 Gene Therapy

Onpattro® (patisiran) — first FDA-approved siRNA therapeutic — uses SNALP technology (cationic liposomes with PEG-diffusion stabiliser) to deliver siRNA to hepatocytes, reducing hepatic production of mutant transthyretin in hereditary amyloidosis.[39]

8. REPRESENTATIVE LIPOSOME–DRUG SYSTEMS

Table 1: Selected liposomal formulations by drug type and therapeutic application

Lipid Composition	Encapsulated Drug	Target Condition	Notable Attribute
HSPC:Chol:DSPE-PEG	Doxorubicin	Ovarian cancer, Kaposi's sarcoma	PEGylated; EPR-dependent
DPPC:Chol:DSPE-PEG	Doxorubicin	Breast cancer, solid tumours	Thermosensitive; hyperthermia-triggered release
EPC:Chol	Cytarabine	Lymphomatous meningitis	DepoFoam® multivesicular; 14-day release
HSPC:Chol:DSPE-PEG	Daunorubicin +	Acute myeloid	Fixed synergistic molar ratio

	cytarabine (5:1)	leukaemia	
Soy PC: Chol: Amphotericin B	Amphotericin B	Systemic fungal, leishmaniasis	Reduced nephrotoxicity
DOTMA: DOPE	siRNA (patisiran)	Hereditary transthyretin amyloidosis	SNALP; intravenous RNA delivery

9. COMMERCIALLY AUTHORISED LIPOSOMAL PRODUCTS

Table 2: Marketed liposome-based drug products.

Brand Name	Manufacturer	Encapsulated Drug	Indication	Key Technical Feature
Doxil® / Caelyx®	Johnson & Johnson	Doxorubicin	Ovarian, multiple myeloma, Kaposi's sarcoma	PEGylated stealth liposome
Myocet®	Teva	Doxorubicin	Metastatic breast cancer	Non-PEGylated; reduced cardiotoxicity
AmBisome®	Gilead	Amphotericin B	Fungal infections, leishmaniasis	Unilamellar; nephroprotection
DepoCyt®	Pacira	Cytarabine	Lymphomatous meningitis	DepoFoam® multivesicular
DepoDur®	Pacira	Morphine	Postoperative pain	DepoFoam® epidural
Marqibo®	Acrotech	Vincristine	Acute lymphoblastic leukaemia	Sphingomyelin-cholesterol liposome
Vyxeos®	Jazz Pharma	Daunorubicin + cytarabine	Acute myeloid leukaemia	Fixed molar ratio (5:1)
Onpattro®	Alnylam	siRNA (patisiran)	Hereditary transthyretin amyloidosis	SNALP (cationic liposome)
Visudyne®	Bausch + Lomb	Verteporfin	Choroidal neovascularisation	Liposomal photosensitiser; PDT

10. EMERGING FRONTIERS AND FUTURE DIRECTIONS

Several innovations are reshaping liposome technology.

Theranostic liposomes combine diagnostic (imaging) and therapeutic functions. Gadolinium-loaded liposomes for MRI, 64Cu-labelled vesicles for PET, and near-infrared dye-containing formulations for fluorescence guidance are under development for image-guided drug delivery.[40]

Liposome–hydrogel hybrids embed liposomes within injectable hydrogel depots, providing two-stage release: rapid initial release from surface-localised vesicles followed by prolonged release from liposomes trapped in the gel matrix. These systems are evaluated for postoperative pain and local cancer therapy.[41]

Oral liposome technologies address bioavailability barriers. Chitosan-coated, polymer-grafted, and enteric-coated liposomes protect payloads from gastric acid and enzymatic

degradation. Bile salt-containing liposomes exploit endogenous absorption pathways. Several insulin and calcitonin formulations are in clinical development.[42]

Cell membrane-coated liposomes fuse synthetic lipids with natural membranes from red blood cells, platelets, or cancer cells, inheriting surface markers that confer immune evasion, prolonged circulation, or homologous tumour targeting. These hybrid constructs combine the drug loading capacity of liposomes with the biological complexity of cell surfaces.[43]

Continuous manufacturing and microfluidics are replacing batch processes, enabling precise control over size, lamellarity, and drug loading. Regulatory agencies encourage quality-by-design (QbD) approaches for liposomal generic products, of which several are now approved.[44]

11. CONCLUSION

Liposomes have earned their clinical standing not through a single advantage but through an unusual convergence of properties: bilayer architecture that accommodates diverse drug types, biocompatible and biodegradable lipid chemistry, surface modularity for extended circulation or active targeting, and established manufacturing pathways. From the early frustration of rapid RES clearance to the elegant solution of PEGylation, from passive accumulation via the EPR effect to active targeting with immunoliposomes, liposomes have repeatedly demonstrated that thoughtful formulation can transform a drug's therapeutic index.

The classification frameworks, preparation methodologies, release mechanisms, and clinical examples reviewed here are not merely historical documentation; each represents a design variable available to the pharmaceutical scientist to address a specific delivery challenge. The mathematical models governing bilayer permeation and release kinetics provide a quantitative foundation for rational formulation.

What remains genuinely exciting is the breadth of emerging applications — gene delivery with SNALPs, multivesicular platforms offering week-long release, thermosensitive vesicles activated by focused ultrasound, and theranostic liposomes that image and treat simultaneously. Translating this potential into broader patient access will require continued innovation in manufacturing scale-up, long-term stability, and regulatory clarity for complex

hybrid products. The foundation, however, is secure, and liposome-based drug delivery is poised to remain a pillar of nanomedicine for decades to come.

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