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Liposomes A Vesicular Drug Delivery System

Alok Kumar Dash*
*Institute of Pharmacy, VBS Purvanchal University, Jaunpur, India

***Corresponding Author-** Dr. Alok Kumar Dash,
*Institute of Pharmacy, VBS Purvanchal University, Jaunpur, India, E-mail: alokjina@gmail.com

ABSTRACT
Liposomes are self-assembling, phospholipid-based vesicles that have revolutionized drug delivery by improving solubility, stability, targeting, and reducing toxicity of therapeutics. Since their discovery in the 1960s, liposomes have transitioned from laboratory curiosities to clinically approved formulations (e.g., Doxil®, Ambisome®). This review covers liposome classification, methods of preparation, physicochemical characteristics, in vitro and in vivo behavior, strategies for targeting and controlled release, applications in various therapeutic areas, regulatory status, challenges, and future perspectives.

Keywords: Liposomes; vesicular systems; drug delivery; targeting; controlled release; nanomedicine; phospholipids; clinical applications.

1-INTRODUCTION

Liposomes are vesicular drug delivery methods that optimize the administration of medications by enhancing their solubility, stability, and bioavailability. They have the ability to form encapsulations for both hydrophilic and hydrophobic medicines, safeguarding them from degradation and enabling regulated release. Drug distribution to specific cells or tissues is facilitated by the fusion of the phospholipid bilayer of liposomes with biological membranes, making them valuable for targeted therapy. Liposomes find use in various medical contexts, such as cancer treatment, by facilitating the targeted delivery of chemotherapeutic pharmaceuticals to malignant cells, mitigating systemic toxicity.[1,2]
Liposomes were first identified in the early 1960s by Alec D. Bangham and his colleagues and became the most thoroughly investigated method for delivering drugs. They are concentric bilayer vesicles where an aqueous volume is completely surrounded by a membraneous lipid bilayer mostly made of natural or semisyntheic phospholipids. The fundamental components of these bilayer vesicles consist of glycerol-based amphiphatic phospholipids, mostly lecithin, and sterols, namely cholesterol and its derivatives. These componentry serve as a fluidity buffer to maintain the stability of the bilayer membrane when exposed to biological fluids.[3,4]

Liposomes have garnered significant interest as prospective drug carriers for enhancing the intestinal absorption of medications when administered orally and for regulating the delivery of pharmaceuticals to pathological locations such as tumors and inflammatory regions via intravenous administration by drug encapsulation. However, their efficacy as medication carriers for intravenous injection is limited by their poor stability in the bloodstream.[5,6]

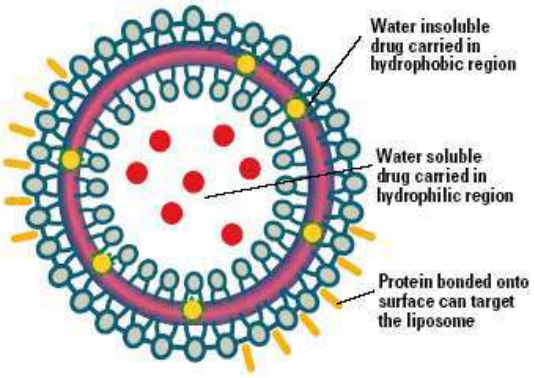

Image of liposome

The evolution of liposomes has a significant heritage characterised by important breakthroughs and achievements in the domains of biochemistry, pharmacology, and medicine. The initial conceptualization in the 1960s was proposed by Alec D. Bangham and his colleagues at the Babraham Institute in Cambridge, UK. Gregory Gregoriadis, a researcher at the Royal Free Hospital in London, identified the considerable potential of liposomes as effective medication delivery vehicles during the early 1970s.

Innovations in liposome formulation throughout the 1980s included the development of stealth liposomes, which are liposomes with polyethylene glycol (PEG) modifications, to avoid being detected by the immune system. The initial approval of liposomal drug Doxil in 1995 marked a significant achievement in the clinical use of liposomal technology by demonstrating that liposomes could effectively mitigate the adverse effects of chemotherapy without compromising its therapeutic effectiveness.[7,8]

Current cutting-edge research is focused on investigating sophisticated uses of liposomes, such as targeted delivery, gene therapy, and imaging agents. The continuing research in the field of customized medicine employing liposome technology reflects the continuously evolving nature of this adaptable drug delivery platform.

1.1Historical Background

Bangham and Horne first described multilamellar phospholipid vesicles—liposomes—in the early 1960s. Initially pursued as cell-membrane models, the potential for encapsulating both hydrophilic and hydrophobic drugs quickly attracted pharmaceutical interest (Gregoriadis, 1976).[9]

1.2Definition and Basic Architecture

A liposome consists of one or more concentric phospholipid bilayers surrounding aqueous compartments. Phospholipids (e.g., phosphatidylcholine, phosphatidylglycerol) self-assemble in water to minimize free energy, with hydrophilic heads interfacing aqueous media and hydrophobic tails buried inside.

1.3Advantages of Liposomal Drug Delivery

Liposomal drug delivery systems offer several key advantages that make them highly effective in modern therapeutics. One of the foremost benefits is their ability to encapsulate both hydrophilic and hydrophobic drugs, thereby improving the solubility and bioavailability of poorly water-soluble compounds [11]. Liposomes also protect encapsulated drugs from enzymatic degradation and premature metabolism, leading to enhanced stability and prolonged circulation time [12]. By modifying the lipid composition and surface characteristics—such as PEGylation—liposomes can evade the reticuloendothelial system, reducing clearance and enhancing accumulation in target tissues via the enhanced permeability and retention (EPR) effect [13]. Furthermore, surface functionalization with ligands allows for active targeting, thereby increasing drug accumulation at disease sites while minimizing systemic toxicity (Pattni . This targeted approach is particularly beneficial in cancer therapy, where liposomal formulations like Doxil® have demonstrated reduced cardiotoxicity and improved therapeutic outcomes compared to conventional chemotherapy [14]. Thus, liposomes serve as versatile and biocompatible carriers that enhance drug delivery efficacy, reduce side effects, and enable controlled and site-specific release.

- **Enhanced solubility** of poorly water-soluble drugs
- **Protection** of labile drugs from degradation
- **Reduced toxicity** by altering biodistribution
- **Passive targeting** via the enhanced permeability and retention (EPR) effect in tumors

- **Active targeting** by surface functionalization with ligands
- **Controlled release** by lipid composition and membrane engineering

2. Classification of Liposomes

Liposomes can be categorized by size, lamellarity, charge, and function:[15,16]

- **By Lamellarity**
  - Multilamellar Vesicles (MLV, >0.1 µm, many bilayers)
  - Small Unilamellar Vesicles (SUV, 20–100 nm, single bilayer)
  - Large Unilamellar Vesicles (LUV, >100 nm)
- **By Surface Charge**
  - Neutral (e.g., phosphatidylcholine)
  - Anionic (e.g., phosphatidylserine)
  - Cationic (e.g., DOTAP)
- **By Function/Modification**
  - **Stealth (PEGylated)**: surface grafted polyethylene glycol for long circulation
  - **Targeted**: conjugated antibodies, peptides, sugars
  - **Stimuli-responsive**: pH, temperature, redox, enzyme-sensitive liposomes

3. Liposome Preparation Methods

3.1 Thin-Film Hydration

The classic Bangham method: dissolve lipids in organic solvent, evaporate to form a thin film, hydrate with aqueous buffer under agitation to form MLVs. Downsides: heterogeneous size, needs downsizing (sonication or extrusion).[17,18]

3.2 Reverse-Phase Evaporation

Generates large unilamellar vesicles with high encapsulation efficiency for hydrophilic drugs. An emulsion of water-in-organic solvent containing lipids is created, then the solvent is slowly evaporated under reduced pressure.

3.3 Detergent-Removal

Lipids solubilized in detergent micelles; removal of detergent (e.g., dialysis) induces vesicle formation, allowing incorporation of sensitive proteins but requires complete detergent removal.

3.4 Ethanol/Propanol Injection

Rapid injection of lipid–alcohol solution into aqueous media yields small vesicles; suitable for scale-up.

3.5 Microfluidics and Supercritical Fluid Methods

Modern approaches for precise size control and continuous manufacturing: rapid mixing in microchannels or using supercritical CO_2 to precipitate lipids around aqueous droplets.

4. Physicochemical Characterization

4.1 Particle Size & Distribution

Dynamic light scattering (DLS) measures hydrodynamic diameter and polydispersity index (PDI). Target PDI < 0.2 for monodispersity.

4.2 Zeta Potential

Assesses surface charge; influences stability (electrostatic repulsion) and interactions with cells and proteins.

4.3 Encapsulation Efficiency (EE%)

Percentage of drug entrapped versus total drug added. Determined by separation of free drug (ultracentrifugation, dialysis) and quantification (HPLC, UV).

4.4 Membrane Fluidity & Phase Transition

Differential scanning calorimetry (DSC) and fluorescence anisotropy gauge lipid phase behavior, affecting leakage and release kinetics.

4.5 Morphology

Transmission electron microscopy (TEM) or cryo-EM visualizes vesicle lamellarity and shape.

5. In Vitro and In Vivo Behavior

5.1 Stability Studies

Evaluate size, EE, leakage over time under storage conditions. PEGylation and cholesterol incorporation (30–50 mol%) enhance membrane rigidity and reduce leakage.[19,20]

5.2 Serum Protein Interaction ("Opsonization")

Binding of opsonins leads to rapid clearance by the mononuclear phagocyte system (MPS). Stealth liposomes (PEG) minimize protein adsorption.

5.3 Pharmacokinetics & Biodistribution

Comparison between free drug and liposomal formulation:

- Increased plasma half-life
- Altered tissue distribution: accumulation in liver, spleen, tumors (EPR effect)
- Reduced off-target exposure (e.g., cardiotoxicity of doxorubicin)

6. Targeting Strategies

6.1 Passive Targeting

Relies on leaky vasculature in tumors and inflamed tissues. Liposomes ~100 nm extravasate and accumulate.

6.2 Active Targeting

Surface functionalization with:

- Antibodies (immunoliposomes)
- Peptides (RGD for integrins)
- Aptamers
- Small molecules (folate for cancer cells)

These ligands bind receptors on target cells, enhancing uptake via receptor-mediated endocytosis.

6.3 Stimuli-Responsive Release

- **pH-sensitive** liposomes destabilize in acidic endosomes/tumor microenvironment
- **Thermosensitive** liposomes release payload at mildly elevated temperatures (42 °C)
- **Enzyme-sensitive** (e.g., MMP-cleavable lipids)

7. Therapeutic Applications[21]

7.1 Oncology

- **Doxil®/Caelyx®** (PEGylated liposomal doxorubicin): first FDA-approved nanodrug; reduced cardiotoxicity, pegylation extends circulation.
- **Lipodox®, LipoDox®**: generics.
- **DaunoXome®** (liposomal daunorubicin) for Kaposi's sarcoma.

7.2 Antifungal

- **AmBisome®** (liposomal amphotericin B): dramatically reduced nephrotoxicity compared to free drug.

7.3 Vaccines and Gene Delivery

- **mRNA vaccines (COVID-19)**: lipid nanoparticles (LNPs) are essentially ionizable lipid-based liposomes optimized for nucleic acid delivery (Pfizer/BioNTech, Moderna).
- **DNA vaccines** and **siRNA** delivery are ongoing areas.

7.4 Anti-inflammatory and Pain Management

- Liposomal formulations of NSAIDs (e.g., liposomal diclofenac) for local injection.
- Experimental intra-articular liposomal steroids.

7.5 Other

- Ophthalmic (e.g., liposomal cyclosporine)
- Transdermal and topical applications.

8. Regulatory and Manufacturing Considerations

8.1 Quality by Design (QbD)

Critical Quality Attributes: size, PDI, zeta potential, EE, residual solvents, sterility. Critical Process Parameters: hydration rate, mixing shear, temperature.

8.2 Scalability

Traditional methods (film hydration) have scale-up challenges. Microfluidic and ethanol-injection platforms offer continuous, reproducible manufacture, with inline monitoring.

8.3 Sterilization

Terminal filtration (0.22 μm) possible for small vesicles; larger liposomes require aseptic processing.

8.4 Regulatory Guidelines

- ICH Q5C for biotechnological products
- FDA's guidance on liposomal products emphasizes detailed characterization, stability, immunotoxicity.

9. Challenges and Limitations

- **Shortcomings of Passive Targeting**: heterogeneous EPR across patients and tumor types.
- **Immunogenicity**: repeated doses of PEGylated liposomes can elicit anti-PEG antibodies ("accelerated blood clearance").
- **Complexity and Cost**: sophisticated manufacturing and characterization increase cost.
- **Drug Loading**: high loading of water-soluble drugs remains challenging.
- **Storage Stability**: aggregation, leakage over time.

10. Emerging Trends and Future Directions

Emerging trends in liposomal drug delivery are focused on enhancing precision, responsiveness, and multifunctionality to meet the evolving needs of personalized medicine. One of the most significant advancements is the development of stimuli-responsive liposomes, which release their payload in response to specific triggers such as pH, temperature, redox gradients, or enzymes, allowing for spatiotemporal control of drug release .Additionally, targeted liposomes functionalized with antibodies, peptides, or aptamers are being designed to improve site-specific delivery and cellular uptake, especially in cancer therapy and immunotherapy Lipid-based nanoparticles for gene delivery, including mRNA vaccines (e.g., Pfizer-BioNTech and Moderna COVID-19 vaccines), represent a revolutionary application of liposomal technologies in nucleic acid delivery .Future directions also include the integration of theranostic agents, combining therapeutic and diagnostic functions in a single liposome for real-time monitoring of treatment efficacy .Moreover, scalable and green manufacturing techniques, including microfluidics and solvent-free methods, are being explored to ensure reproducibility and regulatory compliance for clinical translation. Collectively, these innovations are poised to transform liposomes from traditional drug carriers into intelligent, multifunctional platforms central to next-generation nanomedicine.

10.1 Next-Generation Liposomes

- **Exosome-mimetic** vesicles for improved biocompatibility.
- **Multi-functional platforms** co-delivering drugs + imaging agents (theranostics).

10.2 Personalized Nanomedicine

- Patient-specific EPR profiling to predict liposome accumulation.
- On-demand triggered release using external stimuli (ultrasound, light).

10.3 Combination Therapies

- Co-encapsulation of chemotherapeutics and immunomodulators to synergize anti-tumor immunity.

10.4 Green Manufacturing

- Use of biodegradable, natural lipids; solvent-free processes.

11-Summary

Liposomes are vesicular drug delivery methods that optimize medication administration by enhancing solubility, stability, and bioavailability. They can form encapsulations for both hydrophilic and hydrophobic medicines, safeguarding them from degradation and enabling regulated release. Liposomes are useful for targeted therapy, such as cancer treatment, where they facilitate the targeted delivery of chemotherapeutic pharmaceuticals to malignant cells, mitigating systemic toxicity. Liposomes were first identified in the early 1960s by Alec D. Bangham and his colleagues and have since been extensively researched. They are concentric bilayer vesicles surrounded by a membraneous lipid bilayer made of natural or semisyntheic phospholipids. The fundamental components of these bilayer vesicles consist of glycerol-based amphiphatic phospholipids, mostly lecithin, and sterols, namely cholesterol and its derivatives. Liposomes have gained significant interest as drug carriers for enhancing intestinal absorption of medications and regulating the delivery of pharmaceuticals to pathological locations. However, their efficacy as intravenous injection carriers is limited by their poor stability in the bloodstream. Current research is focused on investigating sophisticated uses of liposomes, such as targeted delivery, gene therapy, and imaging agents. Liposomes can be categorized by size,

lamellarity, charge, and function. They can be Multilamellar Vesicles (MLV), Small Unilamellar Vesicles (SUV), Large Unilamellar Vesicles (LUV), and Surface Charge (neutral, anionic, or cationic). They can also be stimuli-responsive, such as pH, temperature, redox, or enzyme-sensitive. Liposome preparation methods include Thin-Film Hydration, Reverse-Phase Evaporation, Detergent-Removal, Ethanol/Propanol Injection, Microfluidics, and Supercritical Fluid Methods. Physicochemical characterization includes particle size, distribution, zeta potential, encapsulation efficiency, membrane fluidity, morphology, stability studies, and pharmacokinetics. Targeting strategies include passive targeting, active targeting, stimuli-responsive release, and therapeutic applications. Oncology uses liposomal formulations for drug delivery, such as Doxil®/Caelyx®, Lipodox®, LipoDox®, DaunoXome®, antifungal applications like AmBisome®, vaccines and gene delivery like mRNA vaccines, anti-inflammatory and pain management like liposomal formulations of NSAIDs, and ophthalmic applications like transdermal and topical applications. Regulatory and manufacturing considerations include quality by design, scalability, sterilization, and regulatory guidelines. Challenges include heterogeneous EPR across patients and tumor types, immunogenicity, complexity and cost, drug loading, and storage stability. Emerging trends in liposomal drug delivery focus on precision, responsiveness, and multifunctionality to meet personalized medicine needs. Stimuli-responsive liposomes release their payload in response to specific triggers, allowing spatiotemporal control of drug release. Targeted liposomes functionalized with antibodies, peptides, or aptamers improve site-specific delivery and cellular uptake, especially in cancer therapy and immunotherapy. Lipid-based nanoparticles for gene delivery, including mRNA vaccines, represent a revolutionary application of liposomal technologies in nucleic acid delivery.

12. Conclusion

Liposomes remain at the forefront of nanomedicine, with proven clinical successes and ever-expanding applications—from classical chemotherapeutics to cutting-edge mRNA vaccines. Ongoing innovations in lipid chemistry, targeting ligands, and manufacturing promise to overcome current limitations, delivering safer, more effective therapies tailored to individual patient needs.

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