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Review Article

Liposomes: A Historical Perspective, Classification, Preparation Methods, and Clinical Application

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Abstract

Liposomes, lipid-based vesicles, have evolved significantly since their discovery in the 1960s, becoming indispensable tools in drug delivery and other biomedical applications. This review provides a comprehensive overview of liposomes, covering their historical development, classification, methods of preparation, and diverse clinical applications [1]. Through an examination of seminal studies and recent advancements, this article aims to elucidate the structural intricacies of liposomes, explore their preparation techniques, and highlight their pivotal role in modern medicine [2].

Key words: correlation; nurses' knowledge; practices; fall prevention; elderly women

Introduction

The discovery of liposomes by Alec D. Bangham in the late 1960s marked a paradigm shift in drug delivery research [3]. Initially conceived as model systems for studying cell membranes, liposomes soon found application as drug carriers due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs [4]. Over the decades, extensive research has led to a deeper understanding of liposome structure and function, paving the way for their widespread clinical use [4,5].

Historical Development: The history of liposomes can be traced back to the pioneering work of Bangham and colleagues, who first described the formation of lipid bilayer vesicles in 1965 [5]. Subsequent studies by Gregoriadis and coworkers demonstrated the encapsulation of enzymes and drugs within liposomes, laying the foundation for their therapeutic potential [6]. The development of stealth liposomes, pegylated to evade immune detection, and targeted liposomes, functionalized with ligands for site-specific delivery, further expanded the applicability of liposomal drug delivery systems [7].

Classification of Liposomes: Liposomes can be classified based on size, lamellarity, surface charge, and composition. Common classifications include small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), and surface-modified liposomes. Surface-modified liposomes, such as stealth liposomes and targeted liposomes, are designed to prolong circulation time and enhance tissue specificity, respectively [8,9].

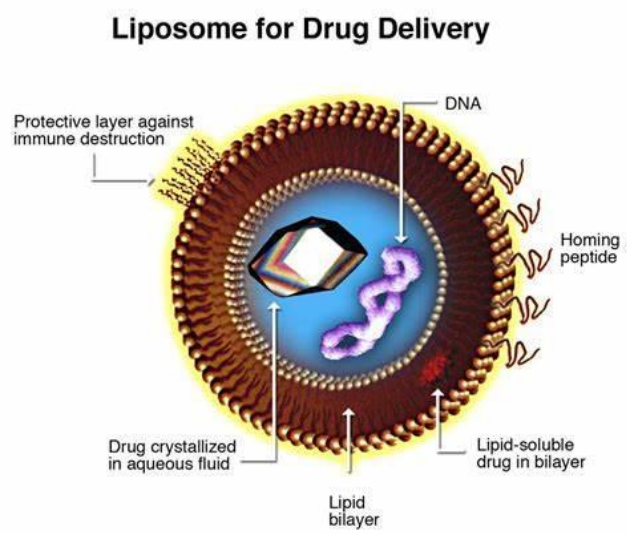

Figure 1: structure of liposome.

Types of liposomes based on Structural parameters	Size (μm)
Multilamellar liposome (MLV)	0.1–0.5 μm
Unilamellar liposome	
Small Unilamellar liposome (SUV)	0.02–0.05 μm
Large Unilamellar liposome (LUV)	more than 0.06 um
Multivesicular liposome (MVV)	2–40 um
Oligolamellar liposome	0.1–10 um in size
GL	10–1000 um

MLV: Multilamellar vesicle, MVV: Multivesicular vesicle, SUV: Small Unilamellar vesicles, GL: Giant liposome, LUV: Large unilamellar vesicle

Table 1: classification of liposomes.

Methods for the preparation of liposomes:

Thin-Film Hydration Method:

1. **Principle**: This is one of the most common methods for liposome preparation. It involves dissolving phospholipids and sometimes cholesterol in an organic solvent (such as chloroform or ether) to form a thin lipid film on the walls of a round-bottom flask [10]. This film is then hydrated with an aqueous solution containing the desired payload (e.g., drugs, nucleic acids) [10].
2. **Procedure**:
   - Dissolve lipids in an organic solvent to form a homogeneous solution.
   - Evaporate the solvent under reduced pressure to form a thin lipid film.
   - Hydrate the lipid film with an aqueous solution by gentle agitation or sonication.
   - Liposomes spontaneously form as the lipid bilayers reassemble in the presence of water.
3. **Advantages**: Simple, widely applicable, and suitable for both small and large-scale production.
4. **Limitations**: Low encapsulation efficiency for hydrophilic drugs, potential lipid degradation during solvent evaporation [10].

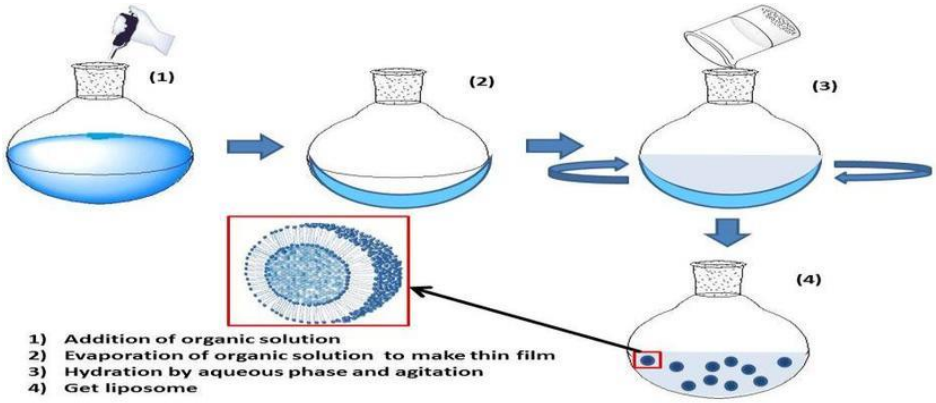

Figure:2 schematic representation of thin film hydration technique.

5. **Reverse-Phase Evaporation Method**:
   - **Principle**: This method is particularly useful for encapsulating hydrophilic drugs [11]. It involves the formation of a water-in-oil emulsion, which is then converted into liposomes by the removal of the organic solvent.
   - **Procedure**:
     - Dissolve lipids and an organic solvent in a round-bottom flask.
     - Add an aqueous phase containing the drug to the lipid solution.
     - Homogenize the mixture to form a water-in-oil emulsion.
     - Remove the organic solvent under reduced pressure, leading to the formation of liposomes.
   - **Advantages**: High encapsulation efficiency for hydrophilic drugs, stable liposome formation.
   - **Limitations**: Requires specialized equipment for homogenization, potential solvent retention.

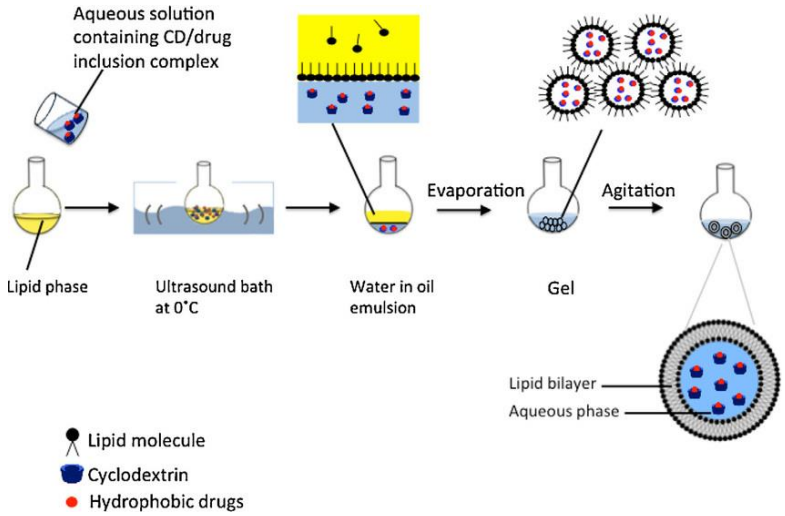

Figure 2: schematic representation of reverse phase evaporation method.

6. Ether Injection Method:

6. **Principle**: This method involves dissolving lipids in diethyl ether and rapidly injecting the lipid solution into an aqueous phase under vigorous stirring.
7. **Procedure**:
   - Dissolve lipids in diethyl ether to form a clear solution.
   - Rapidly inject the lipid solution into an aqueous phase under vigorous stirring.
   - Ether evaporates, leading to the formation of liposomes.
8. **Advantages**: Rapid and straightforward procedure.
9. **Limitations**: Risk of lipid oxidation due to exposure to air, potential residual ether in liposome suspension [9,10].

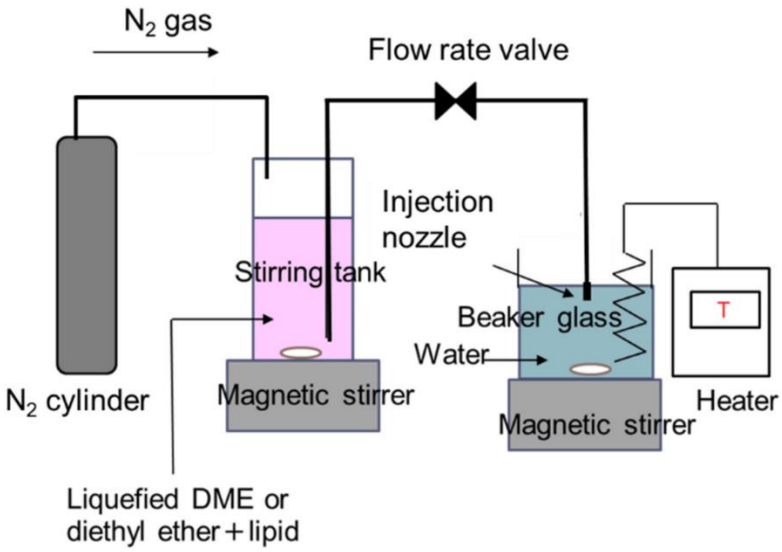

Figure 3: schematic representation of ether injection method.

Detergent Removal Method:

10. **Principle**: In this method, lipids are solubilized in a detergent solution, and liposomes are formed by removing the detergent through dialysis or other means.
11. **Procedure**:
    - Dissolve lipids and a detergent (e.g., Triton X-100) in an aqueous solution.
    - Remove the detergent by dialysis, gel filtration, or other detergent removal techniques.
    - Liposomes form as the detergent concentration decreases below the critical micelle concentration.
12. **Advantages**: High encapsulation efficiency, minimal organic solvent use.
13. **Limitations**: Potential residual detergent in liposome suspension, longer preparation time due to detergent removal [12].

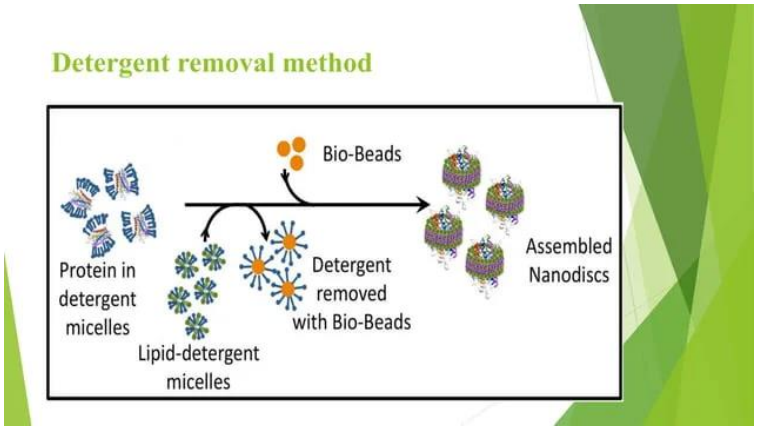

Figure:4 schematic representation of detergent removal method.

These are some of the conventional methods for liposome preparation, each with its own set of advantages and limitations [12]. Researchers often choose a method based on factors such as the desired properties of the liposomes, the nature of the payload, and scalability for large-scale production [12].

Advantages And Disavantages of Liposomes .

Advantages:

14. **Biocompatibility**: Liposomes are composed of natural phospholipids, making them biocompatible and non-toxic [13]. This property reduces the risk of adverse reactions when used for drug delivery in living organisms.
15. **Versatility**: Liposomes can encapsulate a wide range of drugs, including hydrophilic, hydrophobic, and amphiphilic compounds. This versatility makes them suitable for delivering various types of therapeutic agents.
16. **Targeted Delivery**: By modifying the surface properties of liposomes, such as attaching targeting ligands or antibodies, it is possible to achieve targeted delivery to specific cells or tissues [13]. This enhances the therapeutic efficacy of drugs while minimizing off-target effects.
17. **Enhanced Drug Stability**: Liposomes can protect encapsulated drugs from degradation, enzymatic metabolism, and premature clearance. This improves the stability of drugs, particularly those prone to degradation in physiological environments [14].
18. **Controlled Drug Release**: Liposomes can be engineered to release drugs in a controlled manner, allowing for sustained drug release over an extended period. This controlled release profile can improve drug efficacy and reduce dosing frequency.

19. **Reduced Systemic Toxicity**: Liposomal drug delivery systems can reduce systemic toxicity by minimizing drug exposure to healthy tissues and organs. This selective targeting can enhance the therapeutic index of drugs, allowing for higher doses to be administered safely.
20. **Immunogenicity Reduction**: Surface modification of liposomes can help reduce their immunogenicity, thereby minimizing immune recognition and clearance by the reticuloendothelial system. This prolongs circulation time in the bloodstream and enhances drug delivery efficiency.
21. **Encapsulation of Multiple Agents**: Liposomes can encapsulate multiple drugs or therapeutic agents simultaneously, allowing for combination therapy. This approach can synergistically enhance therapeutic outcomes and reduce the development of drug resistance.

Disadvantages:

22. **Limited Stability**: Liposomes are susceptible to aggregation, fusion, and leakage over time, leading to reduced stability and potential loss of encapsulated drugs. This instability can pose challenges for long-term storage and transportation.
23. **Batch-to-Batch Variability**: The reproducibility of liposome preparation methods can vary between batches, leading to inconsistency in particle size, drug encapsulation efficiency, and drug release kinetics. This variability complicates quality control and regulatory approval processes.
24. **High Production Costs**: The production of liposomes on a large scale can be expensive due to the cost of raw materials, specialized equipment, and labor-intensive processes. This high production cost may limit the widespread use of liposomal drug delivery systems, particularly in resource-limited settings.
25. **Limited Drug Loading Capacity**: Despite their versatility, liposomes have a finite capacity to encapsulate drugs, particularly hydrophobic compounds. This limited loading capacity may restrict the use of liposomes for certain drugs with high therapeutic doses.
26. **Recognition by the Immune System**: While surface modification can reduce immunogenicity, liposomes may still elicit immune responses upon administration, leading to clearance by the immune system and reduced circulation time. This immune recognition can limit the effectiveness of liposomal drug delivery systems.
27. **Complexity of Formulation**: The formulation of liposomal drug delivery systems involves multiple parameters, including lipid composition, size, surface charge, and drug-to-lipid ratio. Optimizing these parameters for specific therapeutic applications can be challenging and time-consuming.
28. **Potential for Drug Leakage**: Despite efforts to optimize liposome stability, encapsulated drugs may still leak out of liposomes prematurely, leading to suboptimal drug delivery and efficacy. Strategies to prevent drug leakage, such as modifying lipid bilayer properties, are actively being explored.
29. **Limited Tissue Penetration**: While targeted liposomal drug delivery can enhance drug accumulation at specific sites, liposomes may still face challenges in penetrating deep tissues or crossing biological barriers, such as the blood-brain barrier. This limitation may affect the efficacy of liposomal therapies for certain diseases.

Despite these disadvantages, ongoing research efforts aimed at addressing these challenges and improving liposomal drug delivery systems hold promise for advancing the field and enhancing their clinical utility in various therapeutic applications.

Advantages	Disadvantages
LIPOSOMES	
✓ Entrapment of hydrophilic and hydrophobic compounds separated or simultaneously.	✗ Reduction in encapsulation efficiency due to size enlargement
✓ The increase in number of layers (e.g., kinetic constraints) may be beneficial to prevents or delays the release of active molecules.	✗ Higher physical instability during storage.
✓ Made of natural ingredients	✗ Susceptibility to fast clearance from the bloodstream
✓ Simple fabrication process	✗ Drug leakage
✓ Possibility of surface functionalization	✗ Higher susceptibility to be capture by RES
✓ Cost-effectiveness	✗ Reduced bioavailability compared to nanoliposomes
NANOLIPOSOMES	
✓ Entrapment of hydrophilic and hydrophobic compounds separated or simultaneously.	✗ Manufacturing process usually involves mechanical energy (e.g., sonication, homogenization,

Table:2 tabular form representing advantages and diadvantages of liposomes.

Clinical Application of Liposomes.

Liposomes have found a wide range of clinical applications due to their unique properties as drug delivery vehicles. Here's a detailed exploration of their clinical applications:

30. **Cancer Therapy**:
    - *Chemotherapy*: Liposomal formulations of chemotherapeutic agents, such as doxorubicin (Doxil®), are used in cancer treatment. Liposomes can enhance the efficacy of chemotherapy by increasing drug accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect, while minimizing systemic toxicity.

- *Targeted Therapy*: Targeted liposomal formulations can deliver anticancer drugs selectively to tumor cells by conjugating targeting ligands or antibodies to liposome surfaces. This approach improves drug delivery to tumor sites, reduces off-target effects, and enhances therapeutic efficacy.

31. **Infectious Diseases**:
- *Antibiotic Therapy*: Liposomal formulations of antibiotics, such as amphotericin B (AmBisome®), are used to treat fungal and bacterial infections. Liposomes improve the solubility and stability of antibiotics, allowing for higher doses to be administered with reduced toxicity [14].
- *Antiviral Therapy*: Liposomal formulations of antiviral drugs, such as zidovudine (AZT) and acyclovir, have been explored for the treatment of viral infections, including HIV and herpes simplex virus (HSV).

32. **Vaccines**:
- *Subunit Vaccines*: Liposomes can serve as carriers for vaccine antigens, adjuvants, and immunomodulators, enhancing antigen presentation and immune responses [13,14]. Liposomal vaccines have been developed for diseases such as influenza, hepatitis B, and human papillomavirus (HPV), among others.
- *mRNA Vaccines*: Lipid nanoparticles, a type of liposome, have been utilized as carriers for mRNA-based vaccines, including the mRNA COVID-19 vaccines developed against SARS-CoV-2. Lipid nanoparticles protect mRNA from degradation and facilitate its delivery into host cells to induce immune responses.

33. **Pain Management**:
- *Local Anesthetics*: Liposomal formulations of local anesthetics, such as bupivacaine (Exparel®), are used for prolonged pain relief following surgical procedures. Liposomes provide sustained release of the drug at the site of administration, reducing the need for frequent dosing and improving patient comfort [13,14].

34. **Dermatological Conditions**:
- *Topical Drug Delivery*: Liposomal formulations are used for the topical delivery of drugs to treat various dermatological conditions, including acne, psoriasis, and fungal infections [15]. Liposomes enhance drug penetration into the skin, improving therapeutic efficacy and minimizing systemic side effects [8,9].

35. **Neurological Disorders**:
- *Brain Targeting*: Liposomal formulations are being investigated for the treatment of neurological disorders, such as Alzheimer's disease and brain tumors [2,7]. Targeted liposomes can cross the blood-brain barrier and deliver therapeutic agents to the central nervous system, overcoming a major challenge in neuropharmacology.

36. **Ophthalmic Applications**:
- *Eye Drops*: Liposomal formulations of drugs, such as corticosteroids and antimicrobial agents, are used for the treatment of ocular diseases, including dry eye syndrome, uveitis, and infections [6,7]. Liposomes improve drug retention and bioavailability in the eye, prolonging therapeutic effects [6,7].

37. **Gene Therapy**:
- *Nucleic Acid Delivery*: Liposomes are utilized as carriers for delivering nucleic acids, such as DNA, RNA, and siRNA, in gene therapy applications. Liposomal vectors protect nucleic acids from degradation and facilitate their uptake into target cells, enabling gene expression modulation for therapeutic purposes.

These are just a few examples of the diverse clinical applications of liposomes in medicine [14,15]. Ongoing research continues to explore new formulations, delivery strategies, and therapeutic targets, driving innovation in the field of liposomal drug delivery and expanding its potential impact on patient care.

List of Some clinically approved liposomal drugs

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Depocyt	Pacira (formerly SkyePharma)	Malignant lymphomatous meningitis
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	SkyePharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

Table 3: marketed liposomal drugs and their applications.

Conclusion: Liposomes represent a versatile platform for drug delivery and biomedical applications, offering tunable properties and enhanced therapeutic outcomes. The elucidation of liposome structure, historical evolution, methods of preparation, classification, and clinical

applications underscores their significance in modern medicine [5,6,4]. Continued research efforts aimed at refining liposome formulations and exploring novel applications are essential for advancing the field of nanomedicine and improving patient care [10].

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