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A Review on Liposome Technology

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ABSTRACT:

Liposomes remain a vital nano-sized drug delivery system, known for their bilayer structure mirroring cellular membranes, ease of preparation, and high biocompatibility. Significant efforts have been dedicated to developing liposome-based drug delivery systems, encapsulating various drug candidates to reduce toxicity and prolong therapeutic effects. This approach spans hydrophilic and hydrophobic small molecules, as well as large molecule biologics, with numerous FDA-approved liposomal therapeutics and ongoing clinical trials across diverse applications such as anticancer, antibacterial, and antiviral therapies. Recent advancements aim to optimize liposomal delivery systems, ensuring reproducible preparation techniques and expanding applications to novel modalities like nucleic acid therapies, CRISPR/Cas9 therapies, and immunotherapies. This review highlights recent techniques in liposome preparation, excipients used in novel studies, and routes of administration, offering insights into evolving research in liposomal delivery and future nanotechnological approaches.

Introduction:

Liposomes, stemming from the Greek words for fat and body, represent microscopic vesicles characterized by a lipid bilayer enclosing an aqueous volume. They can manifest as uni-lamellar or multi-lamellar constructions, with their nomenclature reflecting their structural components, primarily phospholipids, rather than their size. Amphipathic molecules serve as the building blocks of liposomes, facilitating their formation. Within the liposome, drug molecules can either be encapsulated within the aqueous space or intercalated into the lipid bilayer. Functionally, liposomes act as spherical vesicles, employed to deliver drugs or genetic material into cells.

In terms of advantages, liposomes offer increased drug efficacy and therapeutic index, exemplified by Actinomycin-D. They contribute to stability through encapsulation, enhancing the biocompatibility of drugs while maintaining flexibility and non-immunogenicity for both systemic and non-systemic administration. Liposomal delivery systems also play a pivotal role in reducing the toxicity of encapsulated agents such as Amphotericin B and Taxol, thereby mitigating exposure of sensitive tissues to harmful drugs and exhibiting a site-avoidance effect.

However, liposomal technology also entails certain drawbacks. Production costs can be prohibitive, and there is a risk of leakage and fusion of encapsulated drug molecules.

Additionally, phospholipids may undergo oxidative and hydrolytic reactions, leading to instability and a short half-life of liposomal formulations. Moreover, liposomes may face challenges related to low solubility, limiting their applicability in certain contexts.

Structural Components of Liposomes:

a. **Phospholipids:** Phospholipids constitute the primary structural component of biological membranes, including liposomes. Two main types of phospholipids, phosphodiglycerides, and sphingolipids, are present. The most prevalent phospholipid in liposomes is phosphatidylcholine (PC). These molecules, insoluble in water, align themselves in planar bilayer sheets in aqueous media to minimize unfavorable interactions between hydrocarbon fatty chains. Glycerol- containing phospholipids, derived from phosphatidic acid, represent over 50% of the lipid weight in biological membranes.

b. **Cholesterol:** While cholesterol does not independently form bilayer structures, it can be integrated into phospholipid membranes at high concentrations, with ratios of up to 1:1 or even 2:1 molar ratio of cholesterol to phosphatidylcholine. Cholesterol inserts into the membrane, with its hydroxyl group oriented toward the aqueous surface and its aliphatic chain aligned parallel to the acyl chains in the bilayer. The solubility of cholesterol in phospholipid liposomes is attributed to both hydrophobic and specific headgroup interactions, although the exact arrangement of cholesterol within the bilayer remains uncertain.

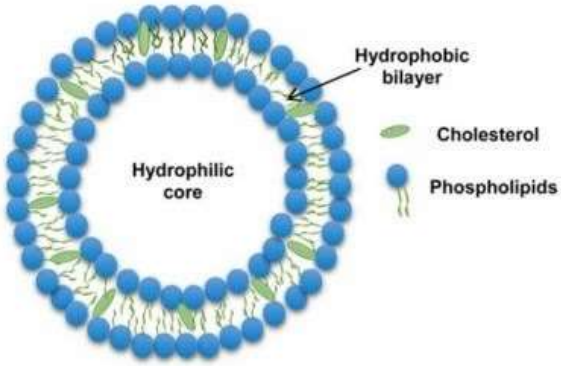

Fig. 1 Structure of Liposome

Mechanism of Liposome Formation:

Phospholipids are amphipathic molecules, possessing affinity for both aqueous and polar moieties due to their hydrophobic tails and hydrophilic or polar heads. These molecules typically consist of two fatty acid chains containing 10-24 carbon atoms and 0-6 double bonds in each chain. Common phospholipids, such as phosphatidylcholine, are amphipathic, with a glycerol bridge linking hydrophobic acyl hydrocarbon chains to a hydrophilic polar head group, phosphocholine. The amphipathic nature of phospholipids enables them to form closed concentric bilayers in the presence of water. Liposomes are formed when thin lipid films or lipid cakes are hydrated, causing stacks of lipid crystalline bilayers to become fluid and swell. During agitation, the hydrated lipid sheets detach and self-close, forming large, multilamellar vesicles that prevent water interaction with the hydrocarbon core of the bilayer at the edges.

Methods Used for Preparation of Liposome:

(A) Mechanical Dispersion Method:

1. Hand-Shaken Multilamellar Vesicles:

- Lipid mixture is dissolved in a chloroform: methanol solvent mixture, then evaporated under vacuum to form a lipid film.
- Nitrogen is introduced to achieve equilibrium pressure inside and outside the flask.
- The flask is then removed and either fixed on a manifold or subjected to lyophilization to remove residual solvents.

2. Non-Hand Shaking or Freeze Drying:

- Lipid hydration and swelling occur in two separate steps.
- Lipid solution is spread in a conical flask and dried under nitrogen.
- After hydration, lipids are swelled by adding bulk fluid, resulting in a milky suspension that is centrifuged to obtain liposomes

3. Sonication:

- Disruption of liposome suspensions using sonic energy typically produces small, unilamellar vesicles (SUV) with diameters of 15-50nm.
- Common instrumentation includes bath and probe tip sonicators.

4. French Pressure Cell Method:

- Involves extrusion of multilamellar vesicles (MLV) at high pressure through a small orifice.
- Results in liposomes somewhat larger than sonicated SUVs.

5. Freeze-Thaw Method:

- SUVs are rapidly frozen and thawed, leading to the formation of unilamellar vesicles due to fusion of SUVs

B) Solvent Dispersion Methods:

1. Ether Injection Method

A solution of lipids dissolved in diethyl ether or an ether/methanol mixture is slowly injected into an aqueous solution of the material to be encapsulated.

The subsequent removal of ether under vacuum leads to the formation of liposomes.

Drawbacks include heterogeneous population (70-190 nm) and exposure of compounds to organic solvents or high temperature

2. Ethanol Injection Method

A lipid solution in ethanol is rapidly injected into a large excess of buffer, forming multilamellar vesicles (MLVs) immediately.

Drawbacks include heterogeneous population (30-110 nm), dilute liposomes, difficulty in removing all ethanol due to azeotrope formation, and potential inactivation of biologically active macromolecules in the presence of ethanol.

3. Reverse Phase Evaporation Method:

Initially, a water-in-oil emulsion is formed by brief sonication of a two-phase system containing phospholipids in an organic solvent (diethyl ether, isopropyl ether, or a mixture).

Organic solvents are removed under reduced pressure, resulting in the formation of a viscous gel.

Liposomes are formed as residual solvent is removed by continued rotary evaporation under reduced pressure.

This method can achieve high encapsulation efficiency (up to 65%) in low ionic strength mediums.

Disadvantages include exposure of materials to organic solvents and brief periods of sonication.

C) Detergent Removal Method:

The detergent removal method utilizes detergents at their critical micelle concentrations to solubilize lipids, forming micelles rich in phospholipids that eventually combine to form large unilamellar vesicles (LUVs). Detergents are removed through dialysis, ensuring homogeneity in liposome size. However, traces of detergent may remain within the liposomes. Alternative techniques for detergent removal include gel chromatography, adsorption to Bio-Beads SM-2, or binding to Amberlite XAD-2 beads.

D) Industrial Production of Liposomes

Various methods are employed for the preparation and stabilization of liposomal formulations. Detergent dialysis, facilitated by the LIPOPREP device, allows for efficient detergent removal through dialysis, resulting in reproducible and homogeneous liposome populations. Microfluidization, utilizing technology such as the MICROFLUIDIZER by Microfluids Corporation, can produce liposomes with high efficiency, reaching up to 20 gallons per minute, and in a size range of 50-200 nm. Proliposomes involve coating lipid and drug onto a soluble carrier, forming granular material that hydrates into an isotonic liposomal suspension, offering cost-effective large-scale manufacturing of liposomes containing lipophilic drugs. Lyophilization, or freeze-drying, addresses long-term stability concerns by removing water from liposomal products under low pressures while in a frozen state, with trehalose emerging as a promising cryoprotectant.

COMPANIES INVOLVED:

- ADD Drug Delivery Technologies AG (Switzerland)
- DepoTech Corporation (USA)
- Nexstar Pharmaceuticals (USA)
- Novavax Inc. (USA)
- The Liposome Company Inc. (USA)
- Sequus Pharmaceuticals Inc. (USA).

Applications of Liposomes:

Protecting drugs from degradation is crucial for ensuring their efficacy and safety. Liposomal formulations offer a robust solution by utilizing lipids that resist enzymatic degradation, thereby safeguarding the encapsulated drug during circulation. This protection extends to various administration routes, including oral, topical, pulmonary, and more, where liposomes excel in enhancing drug stability and bioavailability.

In oral administration, liposomes shield drugs from the harsh gastrointestinal environment, enhancing their absorption and effectiveness. Topical application benefits from liposomal formulations, which not only reduce side effects but also improve skin permeability for better drug delivery. Pulmonary administration is particularly suitable for sensitive drugs, as liposomal formulations prolong therapeutic effects while minimizing tissue irritation and toxicity.

Moreover, liposomes enhance antibiotic efficacy by preventing enzymatic degradation and increasing cellular uptake, thus reducing required doses and toxicity. In cancer therapy, liposomal delivery mitigates toxicities associated with conventional treatments while improving drug concentration at tumor sites, leading to enhanced therapeutic outcomes.

At CD Formulation, we specialize in advancing pharmaceutical formulation development, leveraging cutting-edge science and technology to provide tailored drug delivery system development services. Committed to innovation, we strive to overcome pharmaceutical challenges and contribute to the advancement of global medical solutions.

Conclusion:

twenty-five years of research into liposomes for drug delivery have demonstrated their unique potential in controlling and targeting drug delivery. Liposomes can be administered orally, parenterally, and topically, and they have applications in cosmetic and hair technologies, sustained release formulations, diagnostics, and gene delivery. Various drugs delivered through liposomal systems have been approved, showcasing their versatility as carriers for targeted drug delivery.

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