Review Article

Liposomes: A Versatile Drug Delivery System

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ABSTRACT

Liposomes are microscopic vesicles composed of lipid bilayers that have emerged as a Versatile drug delivery system. Since their discovery in 1961 by Alec Douglas Bangham, liposomes have undergone significant advancements, offering a versatile platform for encapsulating hydrophilic, hydrophobic, and amphiphilic substances. This review highlights the classification, properties, mechanism of action, and preparation methods of liposomes. Various types of liposomes, including conventional, pH-sensitive, cationic, immune, and long-circulating liposomes, have been developed to cater to specific therapeutic needs. Liposomes have demonstrated enhanced therapeutic performance in treating cancer, fungal infections, and other diseases. The surface modification of this review highlights the classification, properties, mechanism, preparation methods, and clinical applications of liposomes, emphasizing their versatility and potential as a drug delivery system.

Keywords: Liposomes, Drug Delivery, Phospholipids, Conventional liposomes.

INTRODUCTION

In 1961, British hematologist Alec Douglas Bangham of the Babraham Institute in Cambridge, England, made the initial discovery of the liposome. In 1964, he published his work. They were found when a gram-negative stain and a dry phospholipid were used by A.D. Bangham and R.W. Horne to test a new electron microscope at the institution [1]. They are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid bilayers [2]. The initial closed bilayer phospholipid structures are referred to as liposomes. The liposome, an innovative delivery mechanism, has demonstrated potential for medicinal administration [3]. These spherical vesicles have a lipid bilayer shell surrounding an aqueous core, forming spontaneously when amphiphilic lipids are dispersed in water [4].

Liposomes are used for drug delivery due to their unique properties, and liposome nanoformulations have shown enhanced therapeutic performance [5]. They act as carriers for a variety of drugs. Various carriers such as nanoparticles, microparticles, polysaccharides, lectins, and liposomes can be used to target drug to a specific site [6]. Liposomes may contain a single lipid bilayer or multiple bilayers around the inner aqueous cube and are thus classified as unilamellar and multilamellar, respectively [7]. Cholesterol is a common component of liposomal drug delivery systems, contributing to mechanical strength and reduced biomembrane permeability[8]. Originally designed for intravenous delivery, liposomes have proven to be versatile drug delivery systems for various routes of administration [9]. In its liposomal system, it may entrap lipophilic as well as h ydrophilic medicines [10]. Phosphatidylserine, a source of negative charge, has been utilized in liposomes [11]. Since liposome-based drug delivery systems are administered systematically, their interaction with cells needs to be considered [12]. Liposomes have a low volume of distribution, resulting in high and sustained plasma concentration, making their distribution into tissues slow, both for therapeutic focus and potentially toxic tissues [13].

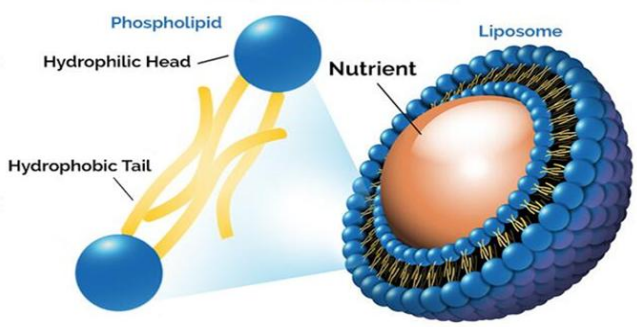

Figure 1: Design of liposomes [14].

1. Classification of liposomes

Liposomes can be categorized based on their preparation methods, with distinctions in the number of bilayer shells [15]. Another classification criterion for liposomes is their composition and functionalization. In addition to the traditional, stealth, and targeted liposomes, recent advancements in liposome design have led to the development of various types, such as immunoliposomes and stimuli-responsive liposomes [16]. Liposomes can also be classified based on their lamellarity, leading to terms like unilamellar, multilamellar, and oligolamellar vesicles [17]. Conversely, giant unilamellar vesicles find common usage as models for cell membranes due to their suitability for optical imaging and micromanipulation of specific vesicles [18]. Liposomes are typically classified based on their lamellae and size or the method of their preparation [19].

Liposomes can be classified in terms of work and mechanism of intracellular delivery into five types as:

1) Conventional liposomes
2) PH sensitive liposomes
3) Cationic liposomes
4) Immune liposomes [5].
5) Long circulating liposomes [20].

1) Conventional liposomes

"The conventional liposome-based approach represents the initial utilization of liposomes for pharmaceutical purposes. These traditional liposome formulations primarily consist of natural phospholipids or lipids, including 1,2-distearoyl-sn-glycero-3-phosphatidylcholine (DSPC), sphingomyelin, egg phosphatidylcholine, and Monosialoganglioside. Conventional liposomes typically comprise phospholipids and/or cholesterol. In an early study by Layton et al. in 1980, vincristine was first encapsulated within liposomes to mitigate its toxicity. However, the results demonstrated that liposomal vincristine did not show a reduction in toxicity or enhanced therapeutic effects compared to vincristine solution in the treatment of lymphocytic leukemia. This lack of improvement may be attributed to potential toxicity resulting from the inclusion of stearylamine in the lipids. However, it's important to note that liposomal vincristine did exhibit a reduction in plasma clearance rate [21].

2) PH sensitive liposomes

Liposomes with diverse compositions have the capability to strongly adhere to cell membranes. In the context of gene delivery, it has been acknowledged that dioleoylphosphatidylethanolamine (DOPE) stands out as the most efficient lipid for in vitro gene transfection, particularly in pH-sensitive liposomes or as an adjunct lipid in cationic liposomes [5]. In the case of viral infections, the fusion of virus envelopes with cell membranes is facilitated under mildly acidic conditions. This discovery has led to the development of pH-sensitive liposomes, which release their encapsulated therapeutics in response to acidic pH levels. Research has also shown that serum albumin and protein fragments can enhance liposome fusion at a lower pH of 6.5. pH-sensitive liposomes offer a bioresponsive drug delivery system to specific tissues. Lower pH values can disrupt the lipid bilayer, leading to rapid drug release within seconds [22].

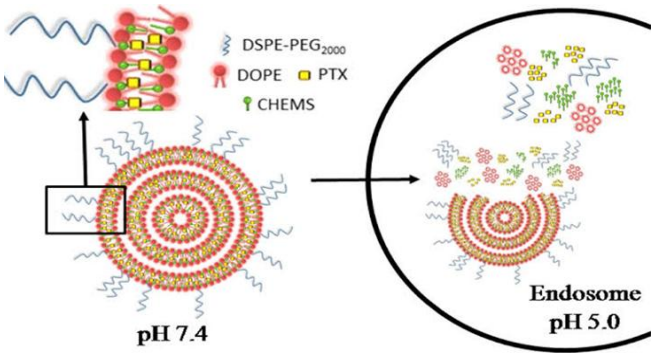

Figure 2: pH sensitive liposomes[5]

3) Cationic liposomes

This procedure is generally simple, involving the mixing of cationic lipids with the DNA and subsequently adding them to the cells. This leads to the formation of collectives made up of DNA and cationic lipids. The cationic lipid DOTMA was first synthesized and described by Feigner et al. in 1987 [5].

4) Immune liposomes

Another potential role of liposomes in the field of medicine is their ability to enhance the immune response by serving as an immunological adjuvant [5].

5) Long circulating liposomes

Increasing the liposomes circulation period in the systemic circulation is a novel strategy to improve their delivery to a particular organ site. The combined action of two distinct pharmacokinetic processes that of the liposome, which initially determines the pharmacokinetics of the associated drug, and that of the drug itself, after it is released from the liposome complicates studies on the pharmacokinetics of drugs associated with carriers like liposomes. Pharmacokinetics becomes comparatively simple at the two extremes. The kinetics will virtually be the same as those of the free drug if a drug is released from the liposome quickly. The kinetics of medications with a high degree of liposome latency will essentially be the same as those of the liposome. Therefore, if there is little to no drug leakage from the liposomes, the liposomes can be utilized to ensure extended plasma half-lives of the encapsulated medications, which may be quickly removed from plasma when given in the free form [23]. Doxorubicin-loaded long-circulating liposomes used for cancer therapy [20].

2. PROPERTIES OF LIPOSOMES:

Liposomes, or lipid vesicles, are colloidal particles primarily composed of (phospho)lipid molecules, forming bilayers or lipid-drug complexes. While the specific lipid composition may vary, many formulations utilize synthetic derivatives of natural phospholipids, particularly phosphatidylcholine [24]. Lipid vesicles and liposomes are colloidal particles constructed from phospholipid molecules, capable of encapsulating solutes within their bilayers. While liposomes and lipid nanoparticles can be prepared with non-phospholipid molecules like cardiolipin and other synthetic derivatives, most core lipids are based on phospholipid structures. In contrast, lipid nanoparticles may include a substantial fraction of drug and other lipid-bound molecules, leading to the formation of thermodynamically stable lipidic nanoparticles. These particles may or may not securely encapsulate solutes within their aqueous compartments.

Although the precise composition varies for each liposome or lipid nanoparticle, most pharmaceutical formulations use synthetic versions of natural phospholipids and their derivatives. Major phospholipids commonly employed in pharmaceutical applications are outlined. Liposome and lipid nanoparticle-based therapeutic drugs approved for human use typically incorporate phosphatidylcholine (PC)

as a primary membrane component, with fatty acyl chains of different lengths and degrees of saturation. In some instances, approximately 30% of total lipids consist of cholesterol to enhance rigidity and reduce serum-induced membrane instability due to serum protein binding. Cellular and physiological factors can also influence the surface charge, membrane fluidity, surface hydration, size, and distribution, as well as the clearance of lipid-associated drugs from the body [25].

2.1 Structure and characteristics of liposomes:

Liposomes are tiny, spherical vesicles made up of aqueous units or compartments surrounded by one or more phospholipid bilayers. Their capacity to encapsulate hydrophilic medications in the aqueous compartment and/or hydrophobic medications in the lipid bilayer sets them apart from other nanoparticles and significantly expands the range of medications that can be included. Size (small unilamellar vesicles (SUVs) < 100 nm, large unilamellar vesicles (LUV) > 100 nm), number of lamellae (unilamellar or multilamellar vesicles), lipid composition, bilayer charge (anionic, cationic, or neutral), and surface functionalization with polymers or ligands are the main characteristics of liposomal formulations. Both in vitro and in vivo, these characteristics are known to affect their stability and biological function [26].

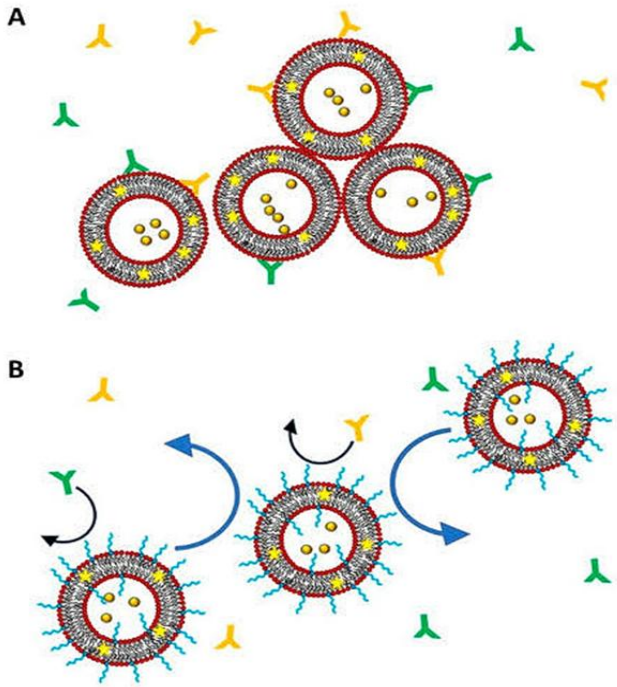

Figure 3: Scheme representing the mechanism for increased circulation time of PEG-decorated liposomes. (**A**) Conventional liposomes, bearing hydrophilic (orange balls) and hydrophobic (yellow stars) loads, aggregated and attacked by plasma proteins (Y-shaped antibodies in yellow and green); (**B**) stealth liposomes with PEG functionalization (cyan "hairs") whose surface cannot be reached by plasma proteins [27].

Important benefits of liposomes include their capacity to encapsulate hydrophilic, hydrophobic, and amphiphilic substances as well as their biocompatibility and biodegradability. However, the quick removal of traditional liposomes from the bloodstream is one of their main disadvantages. Modifying the liposomes' surface has been found to be an effective way to get around this problem and increase the liposomes stability and half-life in the blood. To increase the liposome blood circulation half-life from a few minutes to several hours, hydrophilic polymers like polyethylene glycol (PEG) are specifically utilized as surface coatings. Steric hindrance caused by PEG, which stops them from aggregating and hinders the absorption of plasma proteins and reticuloendothelial system uptake, is the mechanism responsible for extending their circulation duration [27].

3. MECHANISM OF ACTION OF LIPOSOMES

Liposomes work through four distinct mechanisms. They are as follows:

Endocytosis: This is carried out by neutrophils and other phagocytic cells of the reticuloendothelial system. **Adsorption:** It forms on the cell surface by interaction with components of the cell surface or non-specific electrostatic forces.

Fusion: This occurs when the liposomal bilayer is inserted into the plasma membrane and the liposomal content is continuously released into the cytoplasm.

Lipid exchange: This involves the transfer of liposomal lipids to the cellular membrane without affecting the liposomal contents [28].

3.1 Mechanism of drug release and delivery of lipoplex

The drug release mechanism in this type of liposome complex relies on magnetic field technology. Magnetic nanoparticles (MNPs) are commonly utilized as drug delivery systems because their release and targeting to specific tissues can be regulated using external magnetic fields. The release of drugs from MNPs follows both a time-dependent and concentration-dependent pattern. To incorporate magnetic nanoparticles into liposomes, two methods are often employed: the thin-film hydration method and the reverse-phase evaporation method. Hydrophobic magnetic nanoparticles are integrated into the liposome's bilayer membrane, whereas hydrophilic magnetic nanoparticles are enclosed within the liposome's core. The magnetic behavior of the magnetoliposome is influenced by the size of the magnetic nanoparticles; larger nanoparticles produce stronger magnetic signals [29].

4. METHODS OF PREPARATION OF LIPOSOME

Liposomal preparation techniques can be categorized into two primary groups: [30]

1) Active loading techniques
2) Passive loading techniques.

Active encapsulation involves methods where drugs are introduced after liposome formation, often utilizing gradient loading techniques with buffer or ammonium

sulfate gradients. In contrast, passive loading techniques encompass methods in which a drug is encapsulated during the liposome's formation.

The methods of preparation can be classified into three major categories: [19].

I. Mechanical dispersion,

II. Solvent dispersion,

III. Detergent removal

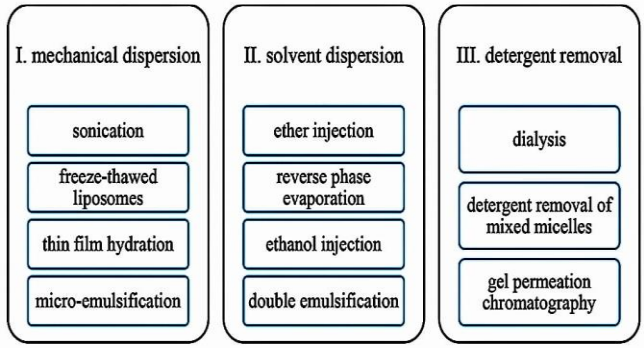

Figure 4: Classification of liposome preparation methods. Each method creates a different type of liposomes [19].

I. Mechanical dispersion methods

A. Film method

"The original method developed by Bangham et al. remains one of the simplest procedures for formulating liposomes, but it has certain limitations due to its low encapsulation efficiency. In this technique, liposomes are prepared by hydrating a thin lipid film in an organic solvent, and the organic solvent is subsequently removed through vacuum-assisted film deposition. After the complete removal of the solvent, the solid lipid mixture is hydrated using an aqueous buffer. The lipids spontaneously expand and hydrate, forming liposomes. However, this method results in a heterogeneous population of multilamellar vesicles (MLVs) with diameters exceeding 1 micrometer [31,32].

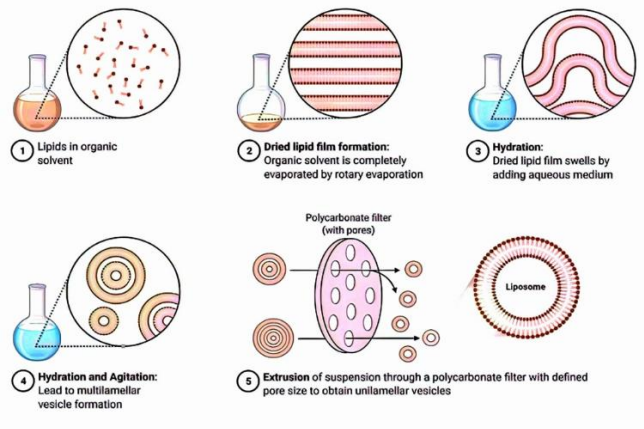

Figure 5: Liposome preparation via thin film hydration [32].

B. Ultrasonic method

This method is employed to create small unilamellar vesicles (SUVs) with diameters ranging from 15 to 25 nanometers. The process involves ultrasonication of an aqueous dispersion of phospholipids using two types of sonicators: probe sonicators and bath sonicators. Probe sonicators are utilized for small volumes that demand high energy input, while bath sonicators are suitable for processing larger volumes [31].

II. Solvent dispersion method

A. Ether injection method

The ether injection method involves slowly injecting a lipid solution that has been dissolved in ether or a diethyl ether/methanol mixture into an aqueous solution of the material that needs to be capsulated. Liposomes formulated when the organic solvent is subsequently removed under lower pressure. The method's main disadvantages are the diverse population and the compounds that need to be encapsulated being exposed to high temperatures or organic solvents [33].

B. Reverse-Phase evaporation method

In this technique, lipids are dissolved in an organic solvent that promotes the development of inverted micelles, such as a 1:1 v/v mixture of diethyl ether and chloroform, diethyl ether and isopropyl ether, or chloroform and methanol. The solution is then mixed with a specified amount of an aqueous phase (buffer). A water-in-oil (W/O) microemulsion is produced when the lipids reorganize at the water-oil interface. To help create a uniform dispersion, the W/O microemulsion can be emulsified using sonication or mechanical techniques. A phosphate saline buffer, also known as citric-Na2HPO4 buffer, is frequently added to the aqueous phase to increase the liposomes' efficiency. The organic solvent can be eliminated by using a continuous rotational evaporation process (at lower pressure) until a thick gel forms. The inverted micelles are more likely to be disrupted and subsequent liposome production (LUVs) is encouraged by the gradual removal of organic solvents. When the gel reaches a certain critical point, the excess phospholipids in the solution environment disperse around the inverted micelles to create a lipid bilayer surrounding the (residual) water droplets, which leads to the production of liposomes [34].

C. Ethanol injection method

The ethanol injection method involves quickly injecting an ethanolic lipid solution into a large volume of hot TRIS-HCl buffer or distilled water. The drug's hydrophilic or hydrophobic properties determine whether it may be incorporated into a liposomal vesicle. 5-fluorouracil migrates to the exterior aqueous phase, whereas nimesulide, a lipid-soluble component, integrates better in liposomes. The primary benefits of the ethanol injection method are its easy scalability and the use of ethanol, a non-toxic solvent. Its application is diminished by the potential for azeotrope production with water [33].

III. Detergent removal method (removal of non-encapsulated material)

a. Dialysis:

This technique dissolves lipids at the Critical Micelles Concentration (CMC) using detergent. When dialysis is used to remove it, a commercial device like LipoPrep (Diachema AG, Switzerland), which is a dialysis variant is used.

b. Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption):

Using beaded organic polystyrene absorbers like Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA) and XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany), the detergent is removed by shaking a mixture of micelles.

c. Gel-permeation chromatography:

Gel filtration can be performed using Sephadex G-50, Sephadex G-l 00 (Sigma-Aldrich, MO, USA), Sephacryl S200-S1000 (General Electric Company, Tehran, Iran), and Sepharose 2B-6B. It is easier to get liposomes since they cannot pass through this packing [35].

5. APPLICATIONS

Several liposomal-based formulations have been effectively used as analgesics, antifungal treatments, and anticancer treatments in clinical fields [36]. Liposome-based therapy has seen remarkable progress, particularly in the treatment of cancer and systemic fungal infections. Presently, there are two distinct doxorubicin formulations, one for daunorubicin, and liposomal AmpB available on the market. Anthracyclines like doxorubicin and daunorubicin are potent anticancer agents, while AmpB is the preferred polyene antibiotic for systemic fungal infection treatment [37]. Liposomal amphotericin B injection is highly successful in treating black fungal disease. Although this disease is uncommon, thousands of infected cases were reported during the second wave of COVID 19 in India, and few of cases were reported in Bangladesh. The black fungus infects the brain, sinuses, stomach, intestine, skin, and lungs. In addition to post-COVID-19 therapy, liposomal drug delivery is used in analgesics, viral vaccines, cancer treatment, various fungal diseases, and photodynamic therapy. Lung disease and pulmonary arterial hypertension are also associated with the liposomal dosage form [38].

Liposome-based drug delivery systems have successfully transitioned to clinical applications, with diverse applications in the medical field, such as anti-cancer, anti-fungal, anti-inflammatory drugs, and therapeutic gene delivery. Several clinical products, including DoxilTM, AmBisome®, and DepoDur, have been developed using liposomes for various clinical purposes. The therapeutic use of various agents has been enhanced through alterations in their pharmacokinetics and pharmacodynamics, achieved by encapsulating drugs within liposomes. Multiple liposome-based drug formulations have gained approval for human use, and numerous other products are currently under evaluation in various clinical trials [39]. These applications span treatments for skin and eye diseases, antimicrobial and anticancer therapies, metal chelation, enzyme and hormone replacement therapies, vaccines, diagnostic imaging, and more [40].

CONCLUSION

Liposomes have emerged as a promising and versatile drug delivery system, offering a wide range of applications in the medical field. Their unique properties, such as biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic substances, make them an attractive option for delivering therapeutic agents. The classification of liposomes into different types, including conventional, pH-sensitive, cationic, immune, and long-circulating liposomes, has expanded their potential applications. Liposomes have shown significant promise in clinical applications, particularly in cancer treatment and systemic fungal infections. Several liposome-based products have already been approved for human use, and numerous others are under evaluation in clinical trials. Further research is needed to fully exploit the potential of liposomes and overcome the challenges associated with their transition from laboratory to clinical use. Nevertheless, liposomes remain a valuable tool in the field of drug delivery, with ongoing developments and advancements expected to enhance their efficacy and therapeutic potential. With their ability to improve the pharmacokinetics and pharmacodynamics of therapeutic agents, liposomes are poised to play a significant role in shaping the future of medicine.

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