STM JOURNALS

Trends in
Drug Delivery

ISSN: 2394-7268
Volume 11, Issue 2, 2024
May–August
DOI (Journal): 10.37591/TDD

https://journals.stmjournals.com/tdd

Review TDD

Liposomes Innovative Role as a Drug Delivery System: A Detailed Analysis

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Abstract

The first nanomedicine to be approved for use in clinical settings was liposomes. These are the spherical vesicles with a bilayer of phospholipids enclosing a middle empty aqueous region. Because of their extraordinary potential to stop medication deterioration and lessen unwanted effects, liposomes are being utilized more and more for targeted drug distribution. For targeted drug delivery, the pharmaceuticals can be integrated into the liposomes' aqueous space or phospholipid bilayer. In order to target a medication or substance to the active site at a predetermined rate and time range without impacting other body parts in the process, liposomes are available in a range of sizes to treat different sorts of diseases. Vesicular systems, as they are often called, are colloidal spheres composed of cholesterol, sphingolipids, glycolipids, long-chain unsaturated fats, layer proteins, and active atoms. They are also constituted of non-poisonous surfactants. Liposomes are one of the most often utilized methods in biological, pharmaceutical, medical, and nutritional research for the encapsulation and transport of a wide range of different compounds, including bioactive substances, benefits and drawbacks, as well as different approaches to preparation, assessment, etc. This paper examines the liposomal vesicles' classification, manufacturing and encapsulating techniques, and uses in the food, cosmetics, and pharmaceutical industries. Furthermore, this section presents the primary analytical techniques utilized to investigate the properties of liposomes, including their size, stability, fluidity, lamellarity, surface charge, and encapsulation efficiency.

Keywords: Liposome, evaluation, drug delivery system, vesicles, MLV, SUV

INTRODUCTION

The age of development for targeted delivery began in 1906 when Paul Ehrlich conceived of a drug delivery device. Liposomes are small vesicles with a spherical form that can be made of membrane proteins, sphingolipids, glycolipids, cholesterol, and non-toxic surfactants. He referred to them as "magic bullets" because they would deliver drugs directly to damaged cells. Phospholipids dissolve in water and spontaneously create a closed structure with an aqueous environment inside and phospholipid bilayer membranes on the outside. This makes medicine distribution easier [1, 2].

The word liposome is derived from the Greek words lipo, which means "fat," and soma, which means "body." According to Figure 1, a liposome is a drug delivery system consisting of enzymes, antibiotics, antifungals, and anticancer agents. It is structurally similar to a colloidal, vesicular substance and composed of one or more lipid bilayers (the "outer layer") surrounded by an equal number of water layers (the "inner layer"). This

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Received Date: May 03, 2024
Accepted Date: May 13, 2024
Published Date: May 22, 2024

Citation: Satbir Singh, Kehar Singh, Hemant Rana, Jaikaushik, Yakshita Saini. Liposomes Innovative Role as a Drug Delivery System: A Detailed Analysis. Trends in Drug Delivery. 2024; 11(2): 25–32p.

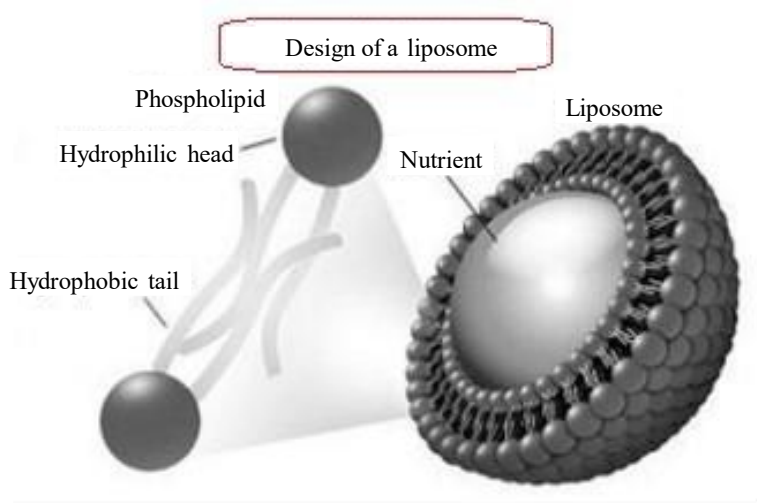

Figure 1. Design of liposome.

delivery method allows the medication to treat a specific condition for an extended period of time without affecting other body parts [3].

A cutting-edge method of medicine administration called liposomes seeks to get the medication right to the site of action. They can hold both lipophilic and hydrophilic molecules, preventing the medication from breaking down and allowing the active ingredients to be released gradually. Since glycerol has been shown to be a molecule's backbone, phospholipid, which contains glycerol, has been identified as a crucial component of liposomal formulation as shown in Figure 1.

Structural Components of Liposome

1. *Phospholipids:* The primary structural constituents of liposomes are phospholipids. The most widely utilized phospholipids in liposomal getting ready are phosphatidylcholine. An amphipathic molecule called phosphotidyl-choline is made up of the following components: a hydrophilic polar head group called phosphocholine; a glycerol bridge; and two hydrophobic acyl hydrocarbon chains.
2. *Cholesterol:* Another crucial liposome structural element is cholesterol. It is a sterol that is often utilized. The incorporation of sterols alters the prolongs, the period that blood is in circulation in the bloodstream as a consequence of stiffness and stability. It doesn't create a bilayer structure by itself [4].

Advantages of Liposomes

1. It provides non-ionic targeted medication delivery;
2. It boosts the medicine's efficacy and therapeutic index;
3. Provides targeted passive targeting to tumor tissue; reduces exposure of delicate tissues to harmful medications. Medication can be kept from oxidizing;
4. They can be made biodegradable and biocompatible;
5. Liposome helps to keep medications stable; and side effects can be avoided [5, 6]

Disadvantages of Liposomes

1. Less solubility
2. Half – life is shorter
3. High cost
4. Leakage of encapsulation drug may occur
5. Phospholipid undergoes hydrolysation and oxidation [7].

Application of Liposomes

- *Tumor therapy:* Transporter of macromolecules like cytokines and tiny cytotoxic molecules in vesicles.
- *Immunological adjuvants in vaccines:* Liposomes for immune diagnosis and immune adjuvant applications.
- *Liposomes as protein drug delivery:* They are used to enhance drug solubilization.
- *Pulmonary Application:* Their solubility makes them effective tools for medication administration to the lungs.
- *Liposomes in cosmetics:* They release materials to the cell employed in cosmetics, and their physiology is comparable to that of a cell membrane.
- *Gene therapy:* Liposomes are used widely in gene application to cure disease.
- *Site specific targeting:* More specifically, the immune liposomes may identify and attach to target cells [8–10].

Classification

The size of liposomes can range from tiny (0.1/2 μm) to large (2.5 μm) vesicles. Furthermore, liposomes consist of one or two layers. Each size and type of bilayer affects the amount of medicine exemplification inside the liposome, and the estimate of the vesicles is a crucial parameter in understanding the stream half-life of liposomes. Because of their length and diverse range of bilayers, liposomes can also be arranged in each of the following directions: [1] Unilamellar vesicles and Multilamellar vesicles (MLV) [2]. Additionally, unsealed vehicles can be divided into two categories: (1) tiny unsealed vehicles and (2) massive unsealed vehicles, sometimes known as SUVs and MUVs. Vesicles in multilamellar liposomes are shaped like an onion. A unit phospholipid bilayer circle surrounds the fluid arrangement of the vesicle in a unilamellar liposome. Similarly, additional unilamellar vesicles will form within the distinct vesicle, with smaller diameter, developing a multilamellar state with circles of concentric phospholipids separated by water layers. They are categorized as pH-delicate liposomes, immuno-liposomes, cationic liposomes, customary liposomes (CL), and lengthy flowing liposomes (LCL) based on organizational structure. They are arranged as French press vesicles (FPV), turn around stage vanishing vesicles (REV), and ether infusion vesicles (EIV) mostly based on the direction method. In this instance, the class that is entirely determined by the length and range of bilayers is MLV, which has an additional 0.1 μm of length and is composed of layers. Flowchart of structural based classification shown in Figure 2.

METHOD PREPARATION

General Method of Preparation

It involves four steps for the preparation of liposomes as shown in the Figure 3.

Passive Loading Techniques

Figure 4 shown the loading of drug by active and passive technique.

Mechanical Dispersion

This is the most popular and extensively utilized technique for making MLV. You can use a flask with a circular bottom for getting ready. By drying the lipid solution and adding an aqueous buffer, the technique creates a thin film, which is subsequently hydrated by vortexing the dispersion. The hydration procedure is conducted at a temperature greater than the lipid combination's greatest melting point or its gel liquid crystalline transition temperature. Depending on how soluble they are, the molecules to be encapsulated are introduced to either an aqueous buffer or an organic solvent containing lipids.

Hydration of Lipid Film

All that has to be done to hydrate the dry lipid film or cake is to add an aqueous medium to the container and stir.

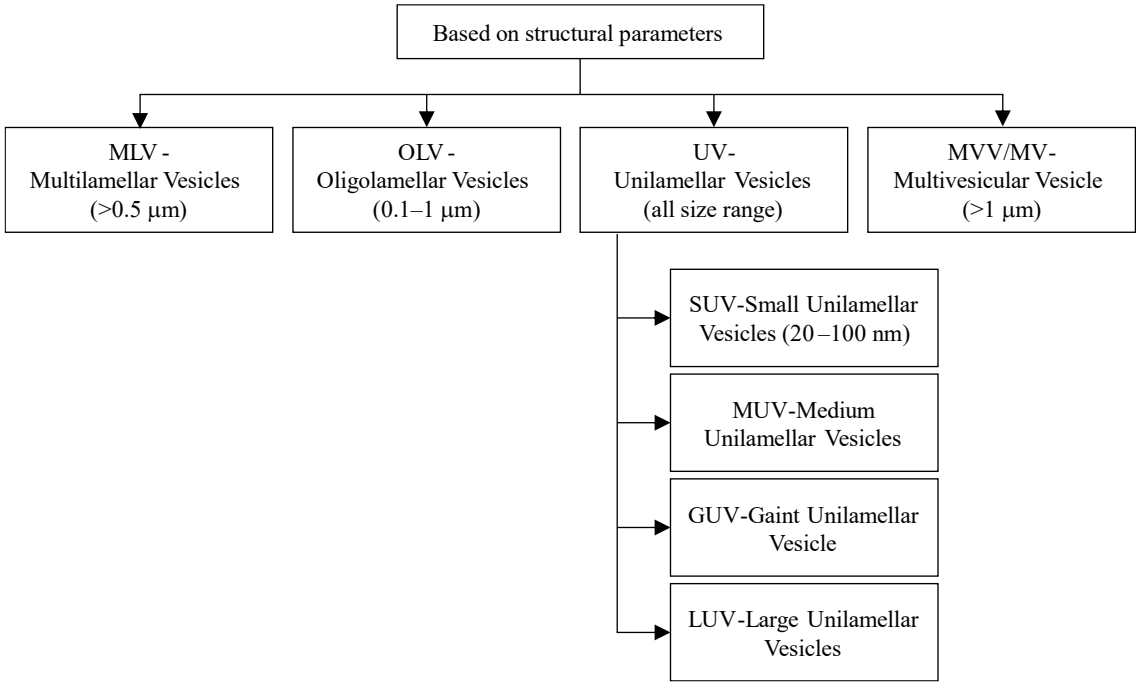

Figure 2. Classification of liposomes [11–14].

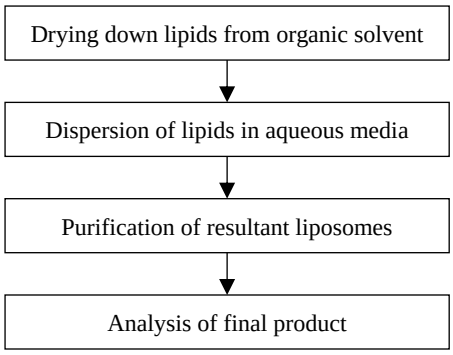

Figure 3. General method of preparation.

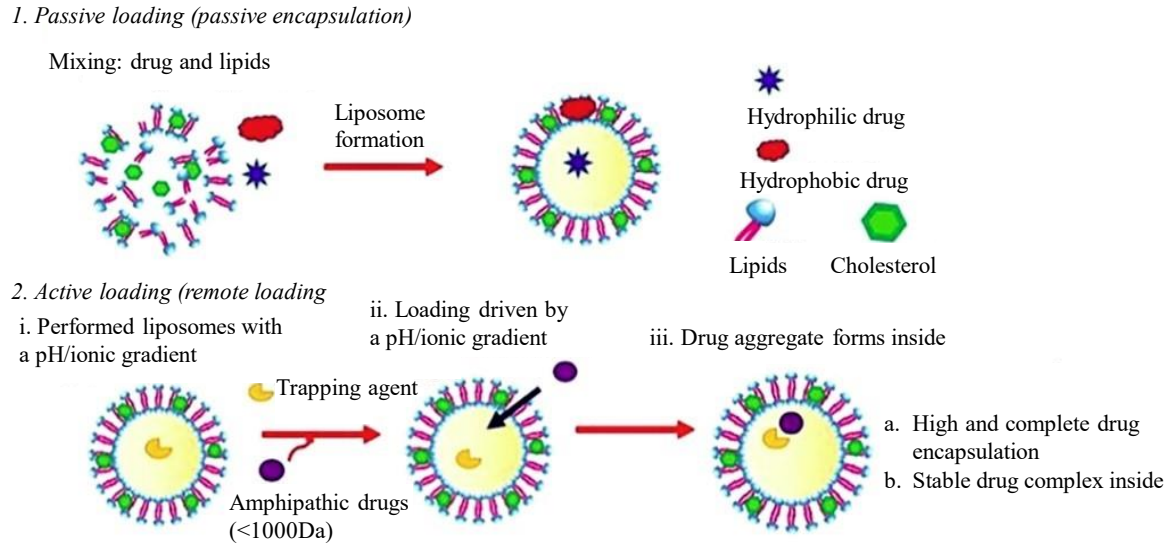

Figure 4. Passive and active loading techniques.

Sizing of Lipid Suspension

Sonication

Small unilamellar vesicles (SUV) with diameters ranging from 15 to 50 nm are usually produced when LMV suspensions are disrupted with sonic energy, a process known as sonication. The most popular pieces of equipment for preparing sonicated particles are sonicators for baths and probe tips. Even though they are less common, cup-horn sonicators have effectively created SUVs.

French Pressure Diffusion Cell Method

MLV is extruded through a tiny hole at 4°C and 20,000 high pressure using this approach. The approach is superior to the sonication method in a number of ways. The procedure handles unstable materials gently and is quick, easy, and repeatable. The ensuing liposome resembles sonicated SUVs in size, but slightly bigger.

Solvent Dispersion

Ether and Ethanol Injection

Ethanol injection: The process entails the extrusion of MLV via a tiny aperture at 4°C and 20,000 pressures. The technique has multiple benefits over the use of sonication. The procedure is straightforward, quick, repeatable, and calls for careful handling of unstable materials. A large amount of buffer is quickly injected with an ethanol lipid solution as shown in Figure 5. The MLVs come into being right away with size range of 30 to 110 nm.

Reverse Phase Evaporation Method

For the achievement of high encapsulation effectiveness of up to 65%, two-phase solution system phospholipids in an organic solvent like diethyl ether, isopropyl ether in combination with chloroform and an aqueous buffer is briefly sonicated to create a viscous gel. When the remaining solvent is eliminated by continuous rotating evaporation at low pressure, liposomes are created. Both tiny and big macromolecules have been encapsulated using this technique.

Detergent Removal Method

Solubilization and Detergent Removal Method

This procedure, which is used to prepare LUVs, involves solubilizing the lipids with a detergent (surfactant). Utilized detergents comprise the following surfactants: cationic (like hexadecyl trimethyl ammonium bromide), anionic (like dodecyl sulphate), and nonionic (like n-octyl beta and D-glucopyranose

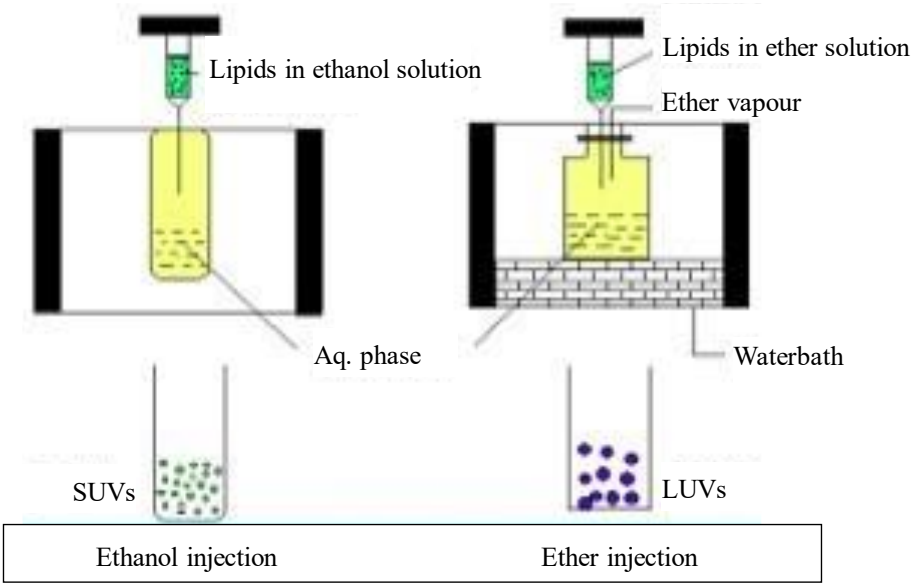

Figure 5. Method of preparation of liposomes by solvent dispersion.

octyl gluside). For the detergent to be removed with ease, it must have a high critical micelle concentration (CMC). The detergent is then eliminated using column chromatography or dialysis. When the detergent is removed, LUVs with a diameter of 0.08–0.2 μm are created.

Detergent Dialysis

A pilot plant is offered by Diachema, AG, and Switzerland under the trade name LIPOPREPR II-CIS. The production capability is 30 milliliters of liposome per minute at a higher lipid content of 80 mg/ml. However, up to many liters of liposome can be formed when the lipid concentration is between 10 and 20 mg/ml [15].

Micro Fluidization Technique

To make liposomes, a technique based on microfluidization, microemulsification, and homogenization was created. The Microfludics Corporation in Massachusetts in the USA sells MICROFLUIDIZERR. There are two suggested solutions:

Pro-liposome

Lipid and medication are coated onto a soluble carrier to create pro-liposome, which are free-flowing granules that, when hydrated, form an isotonic liposomal suspension [14].

Lyophilization

Water is extracted from frozen items at very low pressures using a process called freeze-drying, also known as lyophilization. The method is typically used to dry goods that would not survive heat-drying because they are thermolabile.

Active Loading Technique

Advances in effective encapsulation have promoted the use of liposomes as a medication delivery mechanism protocols. Ions and bigger hydrophilic molecules are generally unable to get through the lipid bilayer's membrane. While concentration gradients can govern the penetration of neutral and weakly hydrophobic compounds, ionospheres can control the transport of ions. On the other hand, a variety of transmembrane gradients, such as electric, ionic (pH), or particular salt (chemical potential) gradients, might cause some weak acids or bases to pass across the membrane. There are a number of techniques for better drug loading, such as the distant (active) loading approach, which uses the pH gradient and voltage difference across the liposomal membrane to load drug molecules into manufactured liposomes [15–23].

MARKETED PHARMACEUTICAL PRODUCT OF LIPOSOMES

Table 1 lists the liposome formulations that are commercially available [24, 25].

EVALUATION OF LIPOSOMES

1. *Vesicle shape and lamellarity:* By using electron microscope for the study of liposome shape.
2. *Particle size and distribution:* By using compound microscopy.
3. *Entrapment efficiency:* This calculates out how much drug hold by the liposome for later release in blood circulation. This can be calculated by a given formula

$$\%\ \text{Entrapment efficiency} = \frac{\text{Entrapped drug} \times 100}{\text{Total drug}}$$

4. *Trapped volume:* This can range between 0.5 and 30 microns/micro ml.
5. *In vitro drug release:* Franz Diffusion Cells can be used for this.
6. *Percentage yield of liposome:* The liposome that was created was collected. The weight that was measured and the total quantity of medicine and ingredient utilized to make the liposome were divided [26].

Table 1. Marketed formulation of liposomes.

Product	Administration	Drug	Particle type	Lipid composition	Indication
Ambisome	Intravenous	Amphotericin B	Liposome	HSPC, DSPG, cholesterol and amphotericin B in 2:0.8:1:0:4 molar ratio	Fungal infections
Abelcet	Intravenous	Amphotericin B	Lipid complex	DMPC and DMPG in 7:3 molar ratio	Fungal infection
Amphotec	Intravenous	Amphotericin B	Lipid complex	Cholesteryl sulfate	Fungal infection
DaunoXome	Intravenous	Daunorubicin	Liposome	DSPC and cholesterol (2:1 molar ratio)	Blood tumors
Doxil	Intravenous	Doxorubicin	PEGylated Liposome	HSPC:Cholesterol:PEG2000-DSPE(56:39:5 molar ratio)	Kaposi's sarcoma, Ovarian/Breast Cancer
Epaxal	Intramuscular	Inactivated hepatitis A virus	Liposome	DOPC:DOPE (75:25 Molar ratio)	Hepatitis A
Visudyne	Intravenous	Verteporfin	Liposome	EPG and DMPC	Macular degeneration

CONCLUSION

One of the most effective and well-known carrier systems for regulated and focused medication delivery is liposome technology. Liposome is useful and effective carriers that can encapsulate both lipophilic and hydrophilic medications and shield them from deterioration. Additionally, it may penetrate deeper into the skin and has a stronger affinity for the keratin in the horny layer of skin, improving absorption. When applied topically, liposome has the potential to function as a local depot, penetration enhancer, and solubilizing matrix for poorly soluble medications while also reducing their adverse effects. Oral, parenteral, and topical administration are available for these systems. Its extensive selection of administration routes allows for flexibility in the design of the medication delivery system.

Acknowledgement

Author expresses his sincere thanks to Professor RP Arya, Pt. LR College of Pharmacy, Faridabad for providing support to carry out this review work.

Conflict of Interest

The authors declare that they have no conflict of interest.

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