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Liposomal Drug Delivery: A Promising Approach for Targeted and Sustained Therapy

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Abstract:

Liposomes are thought to be a promising and adaptable form of drug delivery. Site-targeting, sustained or controlled release, protection of drugs from degradation and clearance, superior therapeutic effects, and fewer toxic side effects are some of the better qualities liposomes have over conventional drug delivery systems. Self-generated bilayer lipid hydrations were used to search for lipids or liposomes. The development of potent medications to enhance treatment has been greatly aided by the liposome drug delivery system. Liposome formulations have recently been shown to reduce symptoms and improve conservation at the target site. Cosmetic formulations also make use of liposomes. Biological, chemical, and physical characteristics are used to characterize liposomes. The unique binding characteristics of agglutinating liposomes with target cells, including tumor cells and particular molecules in the body, are recent advancements in this field. Liposome-encapsulated drug candidates have been studied for their longer duration of therapeutic effect and decreased toxicity. Various academic and industrial research groups have established the liposomal encapsulation of hydrophilic and hydrophobic small molecule therapeutics and other large molecule biologics. As of right now, there are a growing number of liposomal-based treatments that have received FDA approval and are also undergoing clinical trials. These treatments have a variety of uses in antiviral, antibacterial, and anticancer treatments. Recent developments have looked into improving the liposomal-based drug delivery system with a more repeatable preparation method. The excipients of liposomal formulations used in numerous novel studies, the most recent methods for preparing liposomes, and the administration routes utilized to deliver liposomes to specific disease areas are the main topics of this review.

Keywords: liposomes, drug delivery system, recent approaches, polymers.

Introduction:

The spherical concentric vesicles known as liposomes were created by combining the Greek words "Lipos," which means fat, and "Soma," which means body. Liposomes are phospholipid molecules in a round sac. It contains a water droplet that is specifically shaped to transport the drug into the tissue membrane. Liposomes are 100 nm-sized nanoparticles. [1] The British scientist Alec Bangham and associates founded the field of liposomology at Babraham Cambridge in the middle of the 1960s, and 1964 they published the structure of liposomes. [3] Liposomes are self-assembled drug vesicles based on phospholipids that enclose a central aqueous compartment in a bilayer (uni-lamellar) or a concentric series of multiple bilayers (multilamellar). The phospholipid bilayer of liposomes is 4–5 nm thick, and their sizes range from 30 nm to the micrometer scale. [3] Natural, non-toxic phospholipids and cholesterol can be combined to form liposomes. In addition to being biocompatible, liposomes' size and hydrophobic and hydrophilic properties make them promising drug delivery vehicles. Lipid composition, surface charge, size, and preparation technique all have a significant impact on liposome characteristics. [2] Because of its contributions to several fields, including drug delivery, cosmetics, and biological membrane structure, liposomal drug delivery is gaining attention. [1] Liposomes are appealing drug delivery vehicles for both hydrophilic and hydrophobic medications due to their special capacity to entrap medications in both the lipid and aqueous phases. A novel drug delivery method called liposomes seeks to deliver the medication straight to the site of action. They may be able to hold both lipophilic and hydrophilic substances, preventing the drug from breaking down and allowing the active ingredients to be released gradually. [4]

Structure of Liposomes:

The structural components of liposomes are:

1. Phospholipid: The main structural elements of liposomes are phospholipids. Phosphatidylcholine is the most often utilized phospholipid in liposomal preparation. The amphipathic molecule phosphatidylcholine is made up of two hydrophobic acyl hydrocarbon chains, a glycerol bridge, and a hydrophilic polar head group. [4] The phospholipids phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine are found naturally and are utilized in liposomes. The liposomes contain synthetic phospholipids such as dioleoyl phosphatidylcholine, dioleoyl phosphatidylcholine, and dioleoyl phosphatidylethanolamine. [1]

2. Cholesterol: Another crucial element of the liposome's structure is cholesterol. It is a sterol that is frequently used. Sterols are added, which lengthens the bloodstream's circulation time and modifies the function of stability and rigidity. It doesn't create a bilayer structure on its own. [4] The membrane of phospholipids can contain cholesterol at very high levels, up to 1:1 or 2:1 molar ratios of cholesterol to phosphatidylcholine. [1]

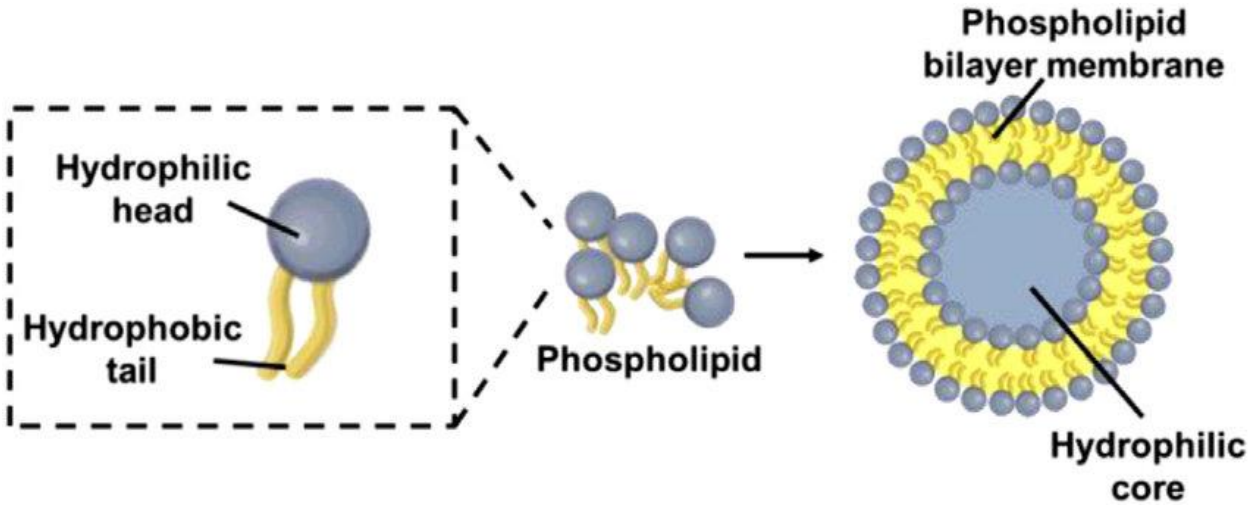

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Fig. The basic structure of liposome[6]

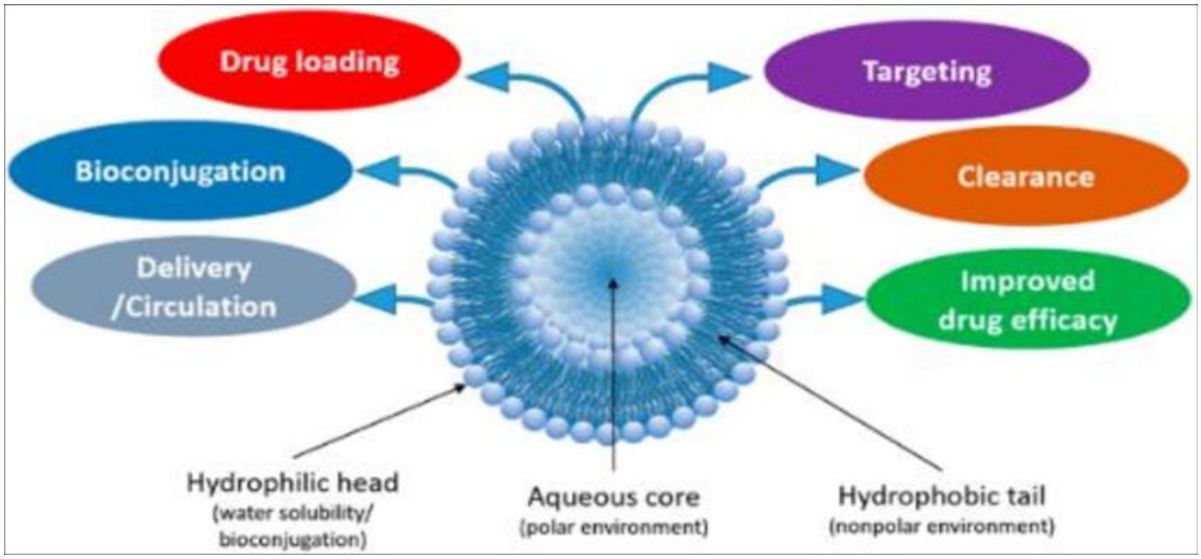

Fig. Structure and function of liposomes[1]

Classification of Liposomes:

1) Based on size and number of bilayers:

- Multilamellar vesicles(MLV)

- Unilamellar vesicles(ULV)[7]

2) **Based on the method of preparation:**
   - Single or Oligolamellar vesicles
   - Vesicles prepared by dehydration-rehydration method
3) **Based on composition and application:**
   - Conventional liposomes
   - Fusogenic liposomes
   - pH-sensitive liposomes
   - Cationic liposomes
   - Long circulatory liposomes
   - Immuno liposomes
4) **Conventional liposomes:**
   - Lecithin mixture containing liposomes
   - Glycolipids containing liposomes
5) **Specialty liposomes:**
   - Antibody directed liposomes
   - Lipoprotein coated liposomes
   - Carbohydrate coated liposomes
   - Multiple encapsulated liposomes[1]

Advantages And Disadvantages of Liposomes:

Advantages:

- It provides targeted medication delivery.
- A higher drug's therapeutic index and efficacy.
- They are non-ionic. [4]
- Flexibility, biocompatibility, and total biodegradability. [2]
- Sensitive tissues are less exposed to harmful medications thanks to liposomes. [4]
- In cosmetics, liposomes are used to improve the skin's absorption of active ingredients. [1]
- The tumor tissue can be selectively targeted passively. [4]

Disadvantages:

- They have low solubility. [4]
- They have a short circulation half-life.
- They provide limited drug loading. [1]
- The cost of production is high. [2]
- The encapsulated drug can leak or fuse.
- Phospholipids can oxidize.
- Liposomal constituents may cause allergic reactions. [4]

Methods of Preparation of Liposomes:

A) **General preparation techniques:**

B) There are four fundamental steps involved in all liposome preparation techniques:

C) 1. Lipids are dried out using an organic solvent.

D) 2. Lipid dispersion in aqueous media.

E) 3. Cleaning the liposome that is produced.

F) 4. Examining the finished item. [7]

G) Methods of liposome preparation and drug loading:

1. **Thin film hydration method:**

   This is one of the most popular techniques for making liposomes. [1] A conventional method that works well for loading the lipophilic drug is thin-film hydration. The lipid–solvent solution is evaporated while the flask rotates under vacuum to produce a thin film. [3]

2. **Reverse phase evaporation:**

   This technique advanced the technology of liposomes. [4] Liposomes with a high encapsulation efficiency are prepared using this technique. [1] The foundation of reverse phase evaporation is the formation of inverted micelles, which are formed by sonicating a mixture of an organic phase that solubilizes the amphiphilic molecules and a buffered aqueous phase that contains the water-soluble molecules to be encapsulated into the liposomes. [4]

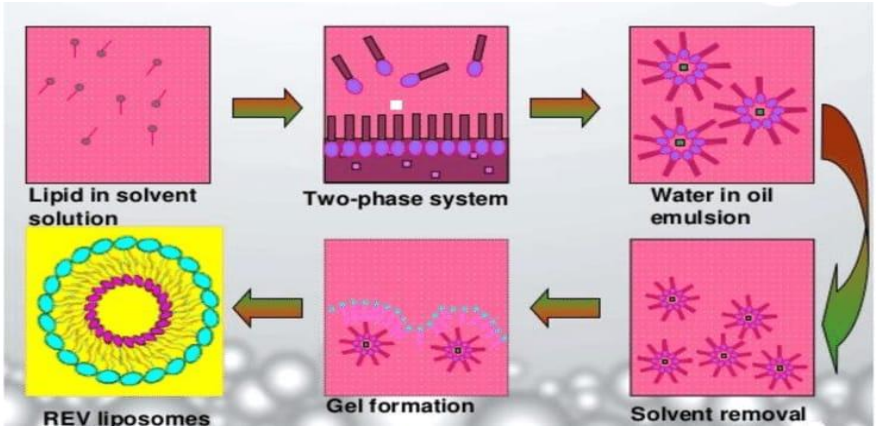

Fig. Reverse phase evaporation method[8]

3. Sonication method:

Sonication is arguably the most widely used technique for SUV preparation. In this case, MLVs are sonicated in a passive atmosphere using either a bath-type sonicator or a probe sonicator. [7] This technique is used to create small unilamellar vesicles (SUVs) or reduce the size of liposomes. [1] This method's primary drawbacks include its extremely low internal volume/encapsulation efficacy, the potential for phospholipid and compound degradation, the removal of large molecules, metal contamination from the probe tip, and the presence of MLV in addition to SUV.[2]

There are two techniques of sonication:

a) **Probe sonication:** The liposome dispersion is directly engrossed in the sonicator tip. This method requires a very high energy input for lipid dispersion. [7]

b) **Bath sonication:** The cylinder containing the liposome dispersion is put inside a bath sonicator. Compared to sonication by dispersal directly using the tip, this method typically makes it easier to control the temperature of the lipid dispersion. [7]

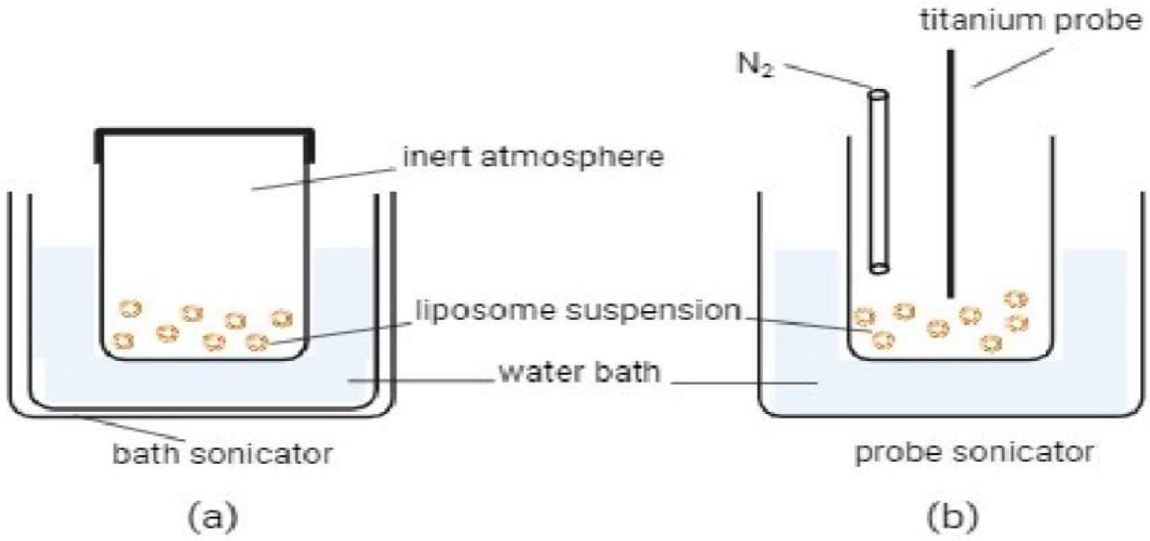

Fig Sonication method. [9]

Marketed Formulation of Liposomes:

Product	Drug	Company
Abelcet™	Amphotericin B	The liposome company, NJ
Doxil™	Doxorubicin	Sequus Pharmaceuticals, Inc., CA
DC99™	Doxorubicin	Liposome CO., NJ, USA
Epaxel™	Hepatitis A Vaccine	Swiss Serum Institute, Switzerland.

Application of Liposomes:

- **Liposomes in medicine and pharmacology:**

  The diagnostic and therapeutic uses of liposomes containing different drugs or markers, as well as their use as a tool, model, or reagent in the fundamental research of cell interactions, recognition mechanisms, and mechanism of action of specific substances, are the two main categories of liposome applications in medicine and pharmacology. [2]

- **Liposomes in gene therapy:**

  Drug and gene delivery, as well as the analytical sciences, have made extensive use of liposomes. [4] For gene therapy applications, liposomes can be used to transport genetic material, such as DNA and RNA. They safeguard and make it easier for genetic cargo to enter target cells. [1]

- **Liposomes in vaccines:**

  Liposomes are a well-established immune adjuvant that enhances immunity mediated by cells as well as immunity mediated by noncells. [4] To increase immunogenicity, liposomes are employed as adjuvants or vaccine carriers. They can strengthen the immune response by enhancing the delivery of antigens to immune cells. [1]

- **Liposomes in cosmetics and skin care:**

  Because they release materials into the cells and have physiologies similar to those of cell membranes, they are used in cosmetics. [4]

  Liposomes are used in skincare and cosmetics products to release active ingredients like vitamins and antioxidants in a controlled manner. [1]

Polymers Used in Liposomes:

The primary methods for incorporating polymers into liposomes are "grafting" and "coating," which are determined by the surface configuration of the polymers. The benefits of liposomes as drug delivery vehicles are maintained by polymer-modified liposomes, which also have unique properties from the polymers, including prolonged circulation, accurate targeting, and stimulus responsiveness. These properties lead to better pharmacokinetics, biodistribution, toxicity, and therapeutic efficacy. [10] Conventional liposomes are difficult to use for delivery through certain routes, like the oral and systemic routes, because they are biodegradable and rapidly eliminated. Complexation with polymers, also known as a liposome complex, is one method of resolving this issue. The stability of liposomes about pH, chemicals, enzymes, and the immune system can be improved by using polymers. [11]

- **Polymer-“grafted” liposomes:**

The "gold standard" for steric protection of liposomes has been identified as PEGylation. Hydrophilic, highly flexible, and reasonably priced is PEG ((-O-CH2-CH2-)n). Hydrophilic polymers with one nonadsorbing end

affixed to the liposome surface via the "grafting to" technique are used to create polymer-grafted liposomes. Since the 1995 approval of Doxil®, Since the 1995 approval of Doxil, the first nanosized drug delivery system based on poly(ethylene glycol)-modified (PEGylated) liposome, several liposomal formulations have been authorized for clinical use by the European Medicines Agency (EMA) of Europe and the Food and Drug Administration (FDA) of the United States. (10)

Recent Approaches and Future Perspectives:

Liposomes can encapsulate hydrophilic and lipophilic medications and shield them from deterioration, making them acceptable and effective carriers.

Additionally, it can penetrate deeper into the skin and has an affinity for the keratin of the horny layer of skin, which improves absorption. (4) For many years, liposomes have been researched and employed as drug delivery vehicles, and their prospects for the future remain bright. As drug carriers, they provide several benefits that support their continued applicability and promise in the drug delivery industry. (1) In total liposomal publications, the use of liposomes as drug carriers has grown over time, reaching 50% in 2000, 70% in 2010, and 74% in 2020. Since the 1995 approval of Doxil's first liposome product, liposome techniques have been refined for over two decades. The number of publications about nanomedicine has been growing exponentially over time, even though its development began later than the use of liposomes. (3) The failure simply indicates that the liposomal product did not work as intended under the specific clinical design. These clever strategies will open up a lot of new possibilities for liposomes to improve therapeutic efficacy and reduce side effects. (3)

Conclusion:

With a variety of uses in the pharmaceutical industry, liposomes are a novel and promising drug delivery system. Numerous studies conducted over the years have shown their potential to address several issues related to conventional drug delivery techniques. (1) These days, a large range of medications are delivered by liposomes. Despite their limited drawbacks, liposomes are effective delivery systems for a variety of medications. Numerous formulations based on liposomes have demonstrated the effectiveness of liposomes as drug carriers. (4) However, we can conclude that liposomes have unquestionably cemented their place in contemporary delivery systems based on the pharmaceutical applications and products that are currently on the market. (3)

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