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Liposomes as a novel drug delivery system

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Abstract

Liposome is a microparticulate colloidal vesicle, in which aqueous medium is surrounded by single or multiple concentric layers of phospholipids. Both hydrophilic & hydrophobic drug can be incorporated, water soluble drug being trapped in aqueous core and fat soluble drug in phospholipids. It offers controlled release, targeted drug delivery thus enhanced therapeutic efficacy and reduced dosing frequency. Several liposome based drug formulation are approved for clinical use and many are under extensive investigation. Therapeutically, these are used as carrier for drugs, viruses, bacteria, antigen, peptides (antibiotic), vaccines, genes and diagnostic agents. This review discusses about the method of production and extensive therapeutic potential of liposomes as carriers for targeted and controlled delivery.

Keywords: Liposomes; Novel drug; Controlled release; Currier; Drug targeting

1. Introduction

Liposomes were spherical shaped concentric vesicles derived from two Greek words lipos means fat and soma means body[1] Liposome were first made by Bangham et al in 1961, it was an accidental discovery in which he scattered the phosphatidyl choline molecule in water, during this he found that the molecule was forming a closed bilayer structure having an aqueous phase which were entrapped by a lipid bilayer[2]. Liposome very useful because act as a carrier for a variety of drugs, having a potential therapeutic action or other properties. Liposome is colloidal carriers, having a size range of 0.01–5.0μm in diameter. Drug encapsulated by liposome achieve therapeutic level for long duration as drug must first be release from liposome before metabolism and excretion[3]. They are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposome's are promising systems for drug delivery[4]. There is a unique ability of liposomes to entrap drugs of both aqueous and the lipid phase and it makes them attractive drug delivery systems for hydrophilic and hydrophobic drugs[5] Liposomes are the novel drug delivery system that aims to deliver the drug directly to the place of action. They have potential to accommodate both hydrophilic and lipophilic compounds to protect the drug from degradation and release the active ingredients in a controlled manner. It has been found that glycerol is the backbone of a molecule that's why phospholipid containing glycerol were found to be an essential component of liposomal formulation and it represents 505 of lipid weight.

A liposome is a tiny bubble (vesicle), with a membrane composed of a phospholipid bilayer. Membranes are usually made of phospholipids like phosphatidylethanolamine and phosphatidylcholine. Phospholipids are amphiphilic with its polar head as hydrophilic and hydrocarbon tail as hydrophobic.

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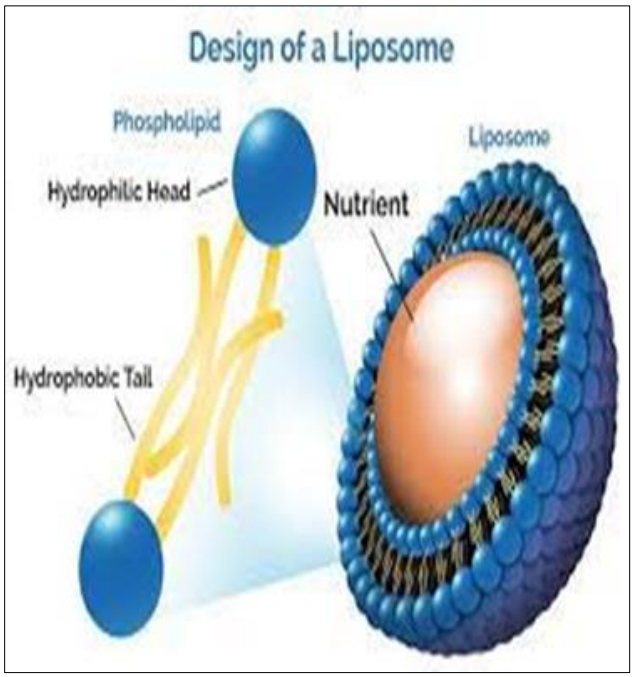

Figure 1 Desing of Liposome

1.1. Advantage

- They offer targeted drug delivery.
- They are biocompatible, biodegradable and biologically inert.
- They are no antigenic, nonpyrogenic and non toxic.
- They can encapsulate both water soluble and water insoluble drugs.
- Drug toxicity is removed as other tissues and cells are protected.
- Cellular uptake of drug is enhanced.
- Size can be varied to incorporate smaller or larger drug molecules.

1.2. Disadvantages

- Liposomes are less stable.
- They are rapidly removed by cells of reticuloendothelial system (RES) from blood after iv injection.
- Drug release is slow and influenced by phagocytes
- Low solubility
- Less stable
- Production cost is high
- Short half life

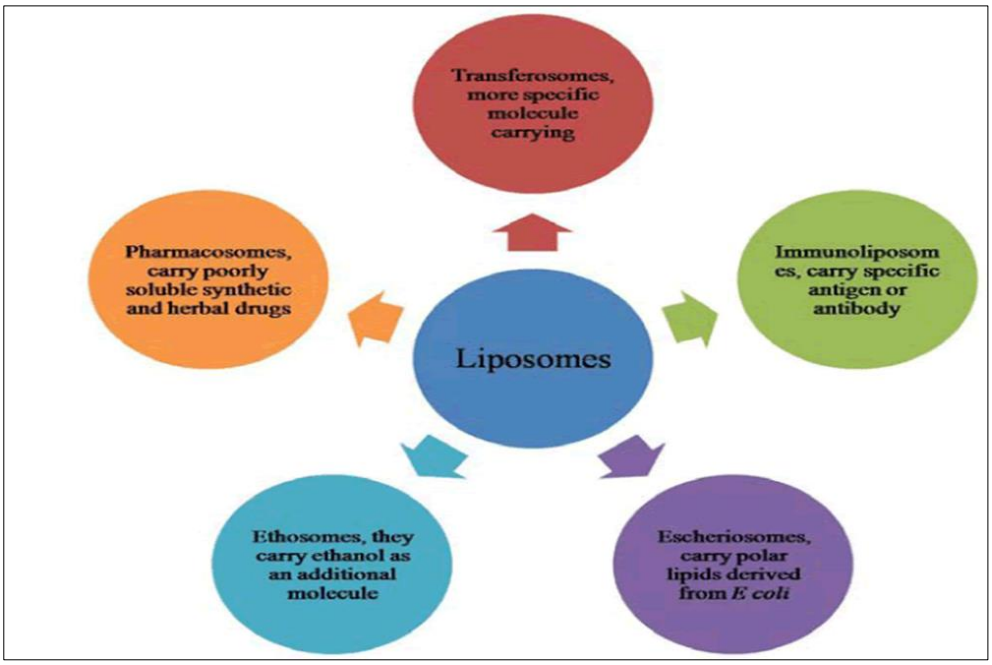

Figure 2 Different type of Liposomes

1.3. Classification of liposomes

Liposomes are effective carriers for drug delivery, including small and large molecules (proteins, peptides, and DNA). Generally, we can classify liposomes based on the preparation method, the number, and size of vesicle bilayers, etc.

1.3.1. Classification based on Structure:

According to the size and number of bilayer membranes (lamellarity) forming vesicles, liposomes can be divided into the following categories:

- Small unilamellar vesicles (SUV): 20-100 nm.
- Large unilamellar vesicles (LUV): >100 nm.
- Giant unilamellar vesicles (GULV): >1000 nm.
- Oligolamellar vesicles (OLV): 100-1000 nm.
- Multilamellar large vesicles (MLV): >500 nm.
- Multivesicular vesicles: >1000 nm.

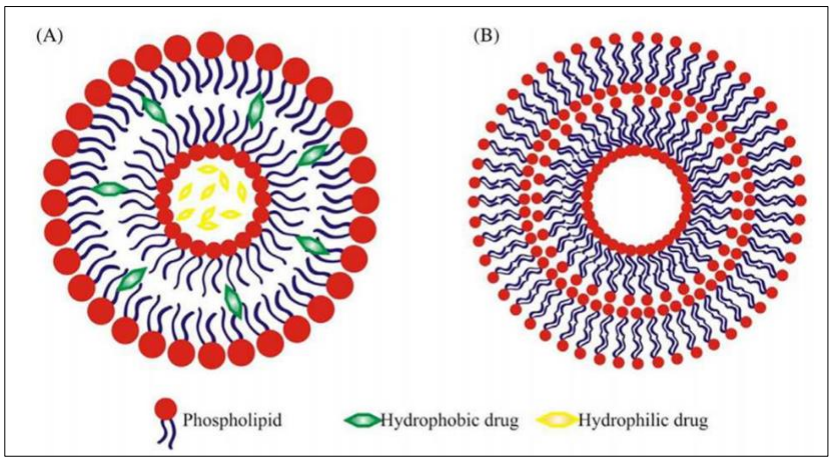

Figure 3 The schematic representation of (A) unilamellar and (B) multilamellar liposome vesicles

1.4. Classification based on Composition and Application

Liposomes can be divided into several different types according to their composition and application, including:

1.4.1. Conventional liposomes

Conventional liposomes are the first generation of liposomes. They are lipid bilayer molecules surrounding the aqueous chamber and are the basis of all subsequent liposomes.

1.4.2. Immunoliposomes

Immunoliposomes are vesicles specially designed for active targeting of the drug substances inside the body.

1.4.3. Long circulating liposomes

The surface modification or PEG modification of liposomes is called PEGylation of liposomes, and the modified liposomes are called long circulating liposomes or stealth liposomes. Compared with conventional liposomes, PEG liposomes can avoid phagocytosis and circulate for a long time in systemic circulation.

1.4.4. Cationic liposomes

Cationic liposomes can be prepared by adding cationic phospholipid into bilayer membrane. This allows high rates of DNA incorporation, and for this reason, such liposomes may be more suitable for gene and antisense therapy.

1.4.5. Stimuli-responsive

Liposomes can be easily functionalized through the introduction of functional materials, such as stimulus-response materials. Their structure, configuration, and other properties can be changed under certain *in vivo* or *in vitro* stimulation, such as the change of heat, light, magnetism, and pH value.

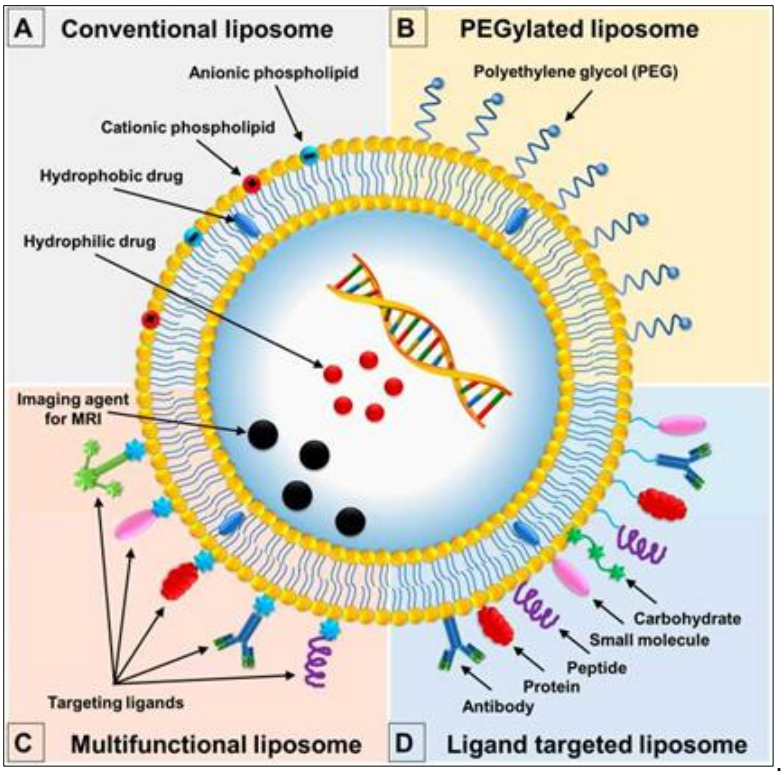

Figure 4 A) Conventional liposome,B) PEG latedliposome,C) Multifunctional liposome, D) Ligand targeted liposome

1.5. Classification based on Preparation Method

In addition to the above two classification methods, liposomes will also be classified according to their preparation methods. This classification depends on using the organic solvents, obtaining different lamellarity of liposomes, changing the size and applications of liposomes.

REV SUVs/OLVs/MLVs: made by reverse-phase evaporation method

- SPLV: stable plurilamellar vesicle
- DRV: made by dehydrated rehydrated method
- VET: vesicles prepared by extrusion technique
- FATMLVs: frozen and thawed MLVs.

2. Methods of preparation of liposomes

Thin- film hydration method/Hand shaking method This method was developed by Bangham et al, for the preparation of multilamellar vesicles. Briefly, phospholipids are dissolved in a mixture of organic solvents (chloroform and methanol). The lipids are deposited as stacks of film from the organic solvents on the wall of round bottom flask by the process of rotary evaporation under reduced pressure. Upon hydration of lipids by addition of aqueous buffer containing the drugs, lipids tend to swell and peel off from the walls of round bottom flask results in the formation of multilamellar vesicle. A mechanical energy is required to cause swelling of lipids and dispersion of lipids film by simple hand shaking technique. Alternatively, exposing lipid film into a water saturated nitrogen for a stipulated period of time usually 15 minutes also results in the swelling of lipids without the use of agitation.

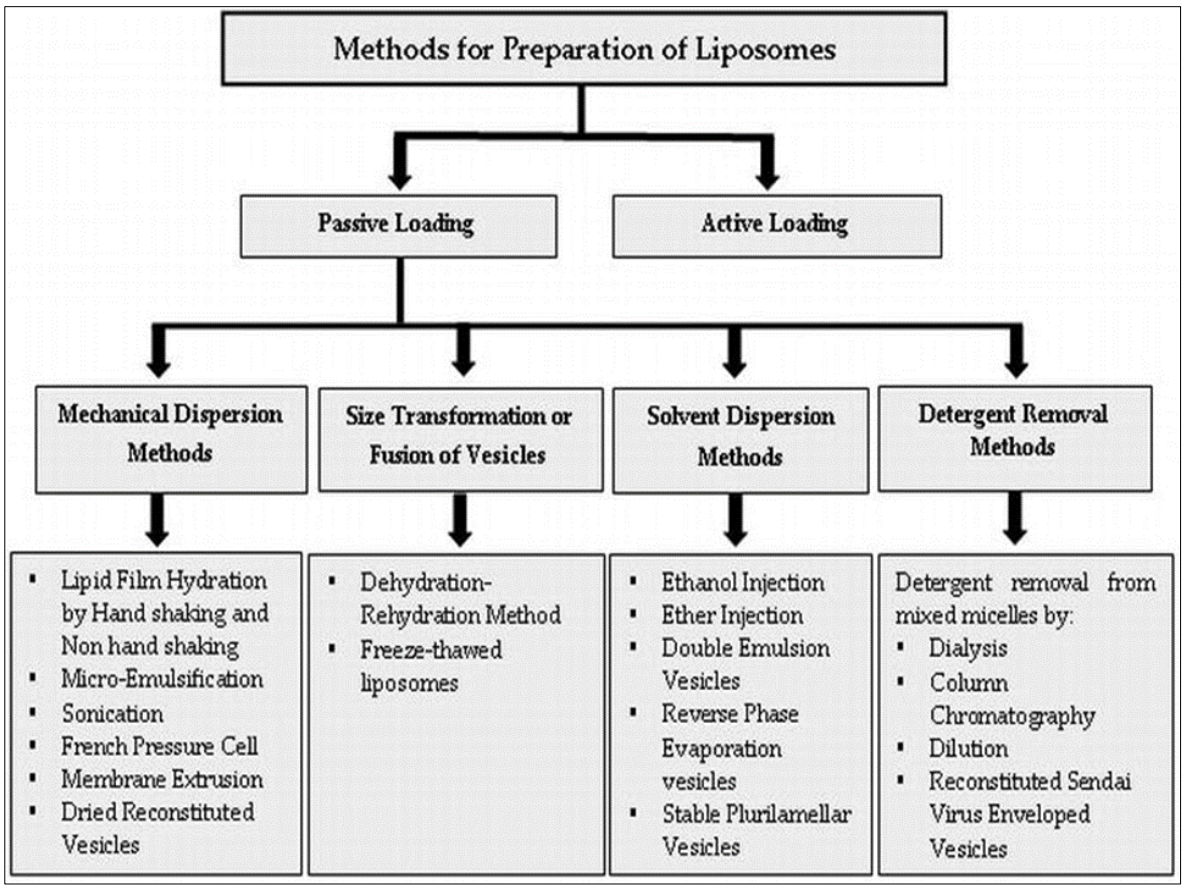

Figure 5 Method for Preparation of Liposome

3. Mechanism of action of liposomes

Liposome performs their action by four different mechanism .They are as follows:

- **Endoytosis**-This take place by phagocytic cells of reticuloendothelial system such as neutrophills.
- **Adsorption** – It occurs to the cell surface by non specific electrostatic forces or by interaction with cell surface components.
- **Fusion**- It occurs by the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm.
- **Lipid exchange** - In this transfer of liposomal lipids to the cellular membrane without association of liposomal contents.

4. Evaluations of liposomes

- **Vesicle shape and lamellarity:** The shape of the vesicles were studied by using electron microscope.
- **Particle size and distribution:** The size analysed by an analyzer based on laser diffraction theory focused with minimum power of 5MW.
- **Entrapment Efficiency:** It determines amount and rate of entrapment of water soluble agents in aqueous compartment of liposomes.
- **Trapped Volume:** It is an important parameter related to liposomes .It is aqueous entrapped volume per quantity of lipids. This can vary from 0.5 to 30 microlitre/micromol.
- **In vitro drug release :** This can be carried by using Franz Diffusion cell which has a diameter of 25 mm .It contains reservoir compartment of 22 ml which was filled with buffer which contains 20%v/v methanol to maintain sink condition.

5. Marketed formulations of liposomes

In 1995, Doxil (PEGylated liposome-encapsulate doxorubicin) became the first liposome drug delivery system approved for human use by the US FDA. There was list of marketed formulations of liposomes.

Table 1 Market Product of Liposomes

Sr. No.	Name of drug	Name of Product	Current status
1.	Doxorubicin	Lipodox	Marketed
2.	Doxorubicin	Myocet	Marketed
3.	Doxorubicin	Doxil/Caelyx	Marketed
4.	Mitoxantrone	LEM-ETU	Phase I
5.	Doxorubicin	MM 302	Phase I
6.	Docetaxel	Doxorubicin	Phase I
7.	Annamycin	Liposome-Annamycin	Phase II
8.	Cisplatin	Lipoplatin	Phase II
9.	Doxorubicin	ThermoDox	Phase II

Figure 6 Marketed Liposomes

6. Applications

- Liposomes as drug or protein delivery vehicles.
- Liposome in antimicrobial, antifungal (lung therapeutics) and antiviral (anti HIV) therapy.
- In tumour therapy.
- In gene therapy.
- In Immunology.
- Liposomes as artificial blood surrogates.
- Liposomes as radiopharmaceutical and radio diagnostic carriers.
- Liposomes in cosmetics and dermatology.

7. Conclusion

The potential use of liposomes in man necessitates the production of sterile, pyrogen free preparations of liposomes which requires specific conditions for their preparation. For use as drug carriers, liposomes should be able to fuse with the arbitrary cells in a spontaneous and controllable manner. One major drawback of liposomal drug delivery system is poor encapsulation of certain drugs in which case the drug is derivised. Application of liposomes medicine include encapsulation of both Lipid and water soluble drugs. Apart from use as drug carrier perhaps the most promising immunological property of liposomes is their cation as adjuvants. The development of 'pharmaceutical' liposomes is currently a growth area.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

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