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Review Article

A comprehensive review on Liposomes: a novel drug delivery system

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ABSTRACT

Liposome was derived from two Greek words “**Lipos** meaning fat and **Soma** meaning body”. Liposome were spherical shaped vesicles consist of phospholipids and cholesterol. Due to their size hydrophobic and lipophilic character they are very promising system for drug delivery. This novel drug delivery system aims to target the drug directly to the site of action. Liposomes are very biocompatible and stable and have unique property to entrap both hydrophilic drug and lipophilic drug (amphiphatic nature) to its compartment and lead to controlled release effect. They are of 0.05- 5.0 micrometer in diameter. Liposomes are used for the treatment of various diseases like tumors or cancer. This article provides an overview of Liposomal Drug Delivery System and various aspects related to liposome that can be studied.

Keywords: Liposomes, novel delivery, amphiphatic, controlled release.

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INTRODUCTION

Liposomes were spherical shaped concentric vesicles derived from two Greek words lipos means fat and soma means body¹. 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 bilayer². 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 excretion³. 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 delivery⁴. 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 drugs⁵.

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 manner⁶. 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 50% of lipid weight⁷.

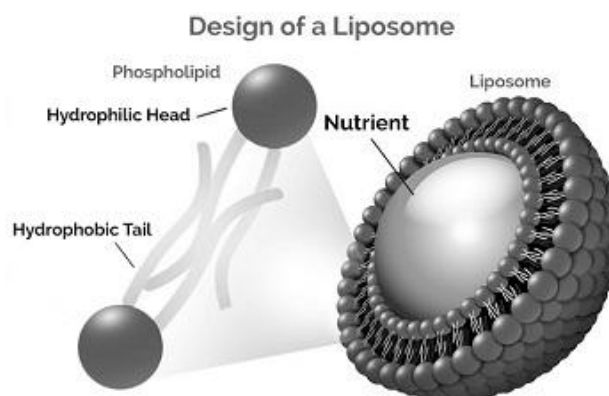


Figure 1: Design of liposome

The structural components are:

1) Phospholipids

Phospholipids are the major structural components of liposome. The most common phospholipids used in liposomal preparation are Phosphatidylcholine (PC⁸).

Phosphatidyl-choline is an amphiphatic molecule consist of-

- A hydrophilic polar head group, phosphocholine
- A glycerol bridge
- A pair of hydrophobic acyl hydrocarbon chains

The chemical structure of naturally occurring Phosphatidylcholine has a glycerol moiety attached to two acyl chains which may be saturated or unsaturated. The stability of liposome membrane depends on the packing of hydrocarbon chains of the lipid molecules⁹. The nature of the fatty acid in lipid molecule, such as number of double bonds in the chain, is responsible for bilayer properties such as elasticity and phase behavior¹⁰. Phospholipids are very abundant in nature and which contains choline is used for the preparation of liposomes.

Examples of phospholipids are-

- Phosphatidyl choline (Lecithin) PC
- Phosphatidyl ethanolamine (Cephalin)-PE
- Phosphatidyl serine (PS)
- Phosphatidyl Glycerol (PG)

2) Cholesterol

Cholesterol is another important structural component of liposome. It is a commonly used sterol. The addition of sterols modulates the function of stability and rigidity. It does not by itself form a bilayer structure¹¹. It gets incorporated into phospholipids in a very high concentration up to 1:1 or 2:1 molar ratio of cholesterol to phosphatidyl choline. The presence of cholesterol in the lipid bilayer enhances the stability and form highly ordered and rigid membrane structure¹².

Cholesterol reduces the permeability of water soluble molecules and improves the fluidity and stability of biological membrane. The interaction and destabilization of liposomes was prevented by cholesterol¹³.

ADVANTAGES OF LIPOSOMES

- Amphiphatic in nature so entrap both kind of drugs either water soluble or insoluble
- Increased efficacy and therapeutic index of drug¹⁴.
- Non ionic

- Liposome helps to reduce exposure of sensitive tissues to toxic drugs.
- Provides selective passive targeting to tumor tissues.
- Prevent oxidation of drugs.
- Liposomes are biodegradable¹⁵.
- Biocompatible
- Liposome increases stability of drug¹⁶.
- Site avoidance effect.
- Improve protein stabilization¹⁷.
- Provide sustained release.
- Direct interaction of drug with cell.
- Site avoidance effect.

DISADVANTAGES OF LIPOSOMES

- Low solubility.
- Short half life.
- Production cost is high¹⁸.
- Leakage and fusion of encapsulated drug may occur.
- Oxidation of phospholipids may occur¹⁹.
- Less stable.

MECHANISM OF ACTION OF LIPOSOMES

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

1. **Endocytosis** – This take place by phagocytic cells of reticuloendothelial system such as neutrophils²⁰.
2. **Adsorption** – It occurs to the cell surface by non specific electrostatic forces or by interaction with cell surface components²¹.
3. **Fusion**- It occurs by the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm²².
4. **Lipid exchange**- In this transfer of liposomal lipids to the cellular membrane without association of liposomal contents²³.

CLASSIFICATION OF LIPOSOMES

There are various classification of liposome based on-

a) Structural features

Table 1: Liposomes based on vesicle type²⁴

Vesicle type	Diameter Size	No. of Lipid Layer
Multi lamellar large vesicles (MLV)	More than 0.5 µm	5-25
Oligo lamellar vesicles (OLV)	0.1-1.0 µm	Approx 0.5
Uni lamellar vesicles (UV)	All size ranges	1
Small Uni lamellar vesicles (SUV)	20-100 nm	1
Medium sized uni lamellar vesicles (MUV)	More than 100nm	1
Large Uni lamellar vesicles (LUV)	More than 100nm	1
Giant Uni lamellar vesicles (GUV)	More than 1.0 µm	1
Multi Vesicular vesicles (MVV)	More than 1.0 µm	Multicompartmental structure

b) Based upon Conventional Liposomes²⁵

- Natural lecithin mixtures
- Liposome with glycolipids
- Synthetic identical chain phospholipids

c) Based on method of preparation of liposomes²⁶

Table 2: Liposomes based on vesicle type

Vesicle Type	Method of preparation
REV	Prepared by Reverse phase evaporation method
MLV	By Reverse phase evaporation method
VET	Prepared by extrusion method
FUV	Vesicles prepared by fusion
FPV	Vesicles prepared by French press

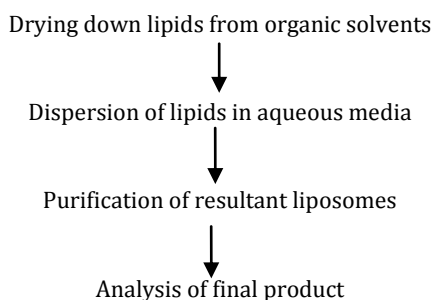
d) Based upon Specialty liposomes

- Lipoprotein coated
- Carbohydrate coated
- Bipolar fatty acid
- Antibody directed

METHODS OF PREPARATION OF LIPOSOMES

There are different methods involved in the preparation of liposomes

- **General method of preparation** – It involves four steps for the preparation of liposomes²⁷.



I) Passive Loading Techniques

A) Mechanical dispersion methods

Lipid hydration method: This is the most common method of preparing MLV.

In this method lipid solution was dried so that a thin film was formed at the bottom of RBF and then film was hydrated by adding aqueous buffer and vortexing the mixture. The hydration step is done at a temperature above the gel liquid crystalline transition temperature. The compound to be encapsulated are added either to aqueous buffer or organic solvent depending upon their solubility²⁸.

Micro emulsification: This method is used for preparing SLV. It can be achieved by microemulsifying lipid compositions using high shearing stress generated from high pressure homogenizer.

Dried reconstituted vesicles: In this method liposomes are added to an aqueous solution containing drug or mixed with lyophilized protein, followed by dehydration of mixture.

Freeze thaw method- In this method SUVs were frozen rapidly by slow thawing technique. The formation of unilamellar occurs due to this reason.

B) Solvent Dispersion –

Ethanol injection: A lipid solution of ethanol was added to an aqueous buffer which immediately forms MLV.

Ether infusion: A solution of lipids dissolved in diethylether and is slowly injected to a solution of the material to be encapsulated at temperature 55-60° C²⁹.

C) Detergent: Lipids were solubilized by detergents at their critical micelles concentration. As detergent is removed, micelles become richer in phospholipids and finally combine to form LUVs.

II) Active Loading Techniques

Proliposomes: In this method lipid and drug were coated onto a soluble carrier to form free flowing granular material in pro-liposome which forms an isotonic liposomal suspension on hydration³⁰.

Lyophilization: The removal of water from products in a frozen state at a reduced pressure is called Lyophilization. This method is generally used to dry the products that are thermolabile

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 3: Market product of liposomes

S.NO	PRODUCT NAME	DRUG	COMPANY
1.	Ambisome	Amphotericin B	NeXstar pharmaceuticals Inc.CO
2.	Abelcet	Amphotericin B	The Liposome company N.J.
3.	Amphocil	Amphotericin B	Sequus pharmaceuticals Inc.CA
4.	Doxil	Doxorubicin	Sequus pharmaceuticals Inc.CA
5.	DaunoXome	Daunorubicin	NeXstar pharmaceuticals Inc.CO
6.	Mikasome	Amikacin	NeXstar pharmaceuticals Inc.CO
7.	DC99	Doxorubicin	Liposome CO.,NJ,USA
8.	Epaxel	Hepatitis A vaccine	Swiss Serum Institute,Switzerland
9.	ELA max	Lidocaine	Biozone Labs,CA,USA

EVALUATIONS OF LIPOSOMES

- 1) **Vesicle shape and lamellarity:** The shape of the vesicles were studied by using electron microscope.
- 2) **Particle size and distribution:** The size analysed by an analyzer based on laser diffraction theory focused with minimum power of 5MW³¹.
- 3) **Entrapment Efficiency** – It determines amount and rate of entrapment of water soluble agents in aqueous compartment of liposomes.

This can be calculated by a given formula

$$\% \text{ Entrapment Efficiency} = \frac{\text{Entrapped Drug} \times 100}{\text{Total Drug}}$$

- 4) **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/micromol³².
- 5) **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.

- 6) **Percentage yield of liposomes**- The prepared liposomes were prepared and collected. The measured weight was divided by the total amount of drug and ingredients which were used for the preparation of liposomes³³.

STABILITY OF LIPOSOMES

Therapeutic efficacy of drug molecule is governed by stability of liposomes. There are two types of stability-

Physical Stability- There are various physical processes which effects the shelf life of liposomes like fusion , aggregation and shape and size .The general problem that occurs is leakage of drug material. The morphology and size distribution are important parameters for accessing stability.Physical stability can be maintained by avoiding excess unsaturation in the phospholipids. They must be stored at 4°C with no freezing and light exposure³⁴.

Chemical Stability- Phospholipids are unsaturated fatty acids prone to hydrolysis alter the stability of drug product. Liposomes can be prevented from oxidative degradation by adding antioxidants such as butylated hydroxy anisole³⁵.

APPLICATIONS OF LIPOSOMES

- **Respiratory Disorders**- The liposomes have been found to possess beneficial effects in the treatment of several respiratory disorders, reason being their better sustained release, improved stability and reduced toxicity than ordinary aerosols. Liquid or dry form can be taken for inhalation of liposome and release of drug has been reported to occur during nebulization .
- **Ophthalmic Disorders**- Dry eyes, keratitis, corneal transplant rejection, uveitis, ondothelmitis and proliferative *vitro* retinopathy are the examples of eye disorders against which liposomes have been found to possess beneficial effects. The drug verteprofin that is

found to be effective against eye disorders has been recently approved as liposomal formulation³⁵.

- **Tumor therapy- Carrier** of small cytotoxic molecule and vehicles used for macromolecule such as cytokines.
- **Immunological adjuvants in vaccines** - Liposomes used in immunoadjuvant, immunodiagnosis .
- **Liposomes as protein drug delivery**- They are used to enhanced drug solubilization
- **Pulmonary Application** – They are useful tools for pulmonary delivery of drugs due to their solubilization capacity¹².
- **Liposomes in Cosmetics**- They are used in cosmetics because their physiology is similar to the cell membrane and they release materials to the cells¹⁶.
- **Site specific targeting**- The immunoliposomes are able to recognize and binds to target cells with greater specificity.
- **Gene therapy**- Liposomes are used widely in gene applications to cure diseases.

ADVANCEMENTS IN LIPOSOMES

- **Ethosomes**- They are efficient at delivering to the skin composed of soya phosphatidylcholine and 30% ethanol³⁶.
- **Immuno liposomes**- They were modified with antibodies.
- **Niosomes**- They is small unilamellar vesicles made from non ionic surfactants⁷.
- **Stealth liposomes**- They are new type of liposomes which were prepared to improve stability and lengthen their half life in circulation. Coating of liposomes should be done by poly ethylene glycol (PEG) for preparing these liposomes⁸.

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