

“Review On: Liposomes A Novel Drug Delivery System”

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ABSTRACT: Novel drug delivery systems play a major role in providing an optimum dose at a right time and to the right location. Liposomes are the novel drug delivery systems consisting of an aqueous compartment enclosed by means of one or more phospholipid bilayers. It is spherical sac vesicle it consists at least one lipid bilayer. Liposomes are the most successful drug delivery systems which uses nanotechnology to potentiate therapeutic efficacy and reduces the toxicities that occurs due to conventional medicines. The ability of liposomes to encapsulate both hydrophilic and lipophilic drugs have allowed these vesicles to become useful drug delivery systems. The present article gives an idea regarding the classification of liposomes, mechanism of vesicle formation, advantages, disadvantages, methods of preparation of liposomes, novel liposomes, applications and marketed products. The aim of the present study was conduct to investigate as drug carriers for improving the drug delivery of therapeutic agent. The objective of the present article is to discuss the advances in liposomes assisted drug delivery, biological challenges that remain and current clinical and experimental use of liposomes for biomedical applications. To study classification of liposomes advantages, dis-advantages and its application & To study method of preparation of liposomes.

KEYWORDS: Liposomes, novel drug delivery system, phospholipid, vesicles, lipid bilayer.

I. INTRODUCTION

Liposomes were spherical shaped concentric vesicles derived from two Greek words lipos means fat and soma means body. 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. 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. 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. 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. 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 of lipid weight It is use as vehicle for administration of nutrients as well as pharmaceutical drugs. It shows both characteristics.

- 1) Hydrophilic head
- 2) Lipophilic tail.

Structural component of liposome-

Liposomes are composed lipid bilayer size:- 50-1000 nm in diameter that serve as targeted delivery vehicle that contain active biological compound. Liposome most often composed of phospholipid and cholesterol.

1) Phospholipids

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

Phosphatidylcholine. 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 molecules. 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 behavior 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 structure. 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 structure. 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 cholesterol.

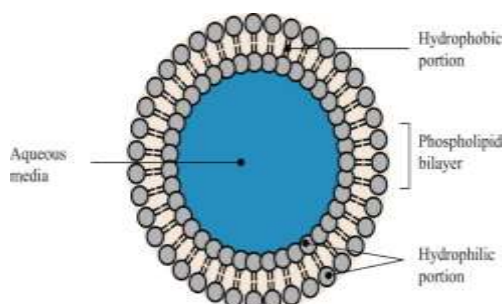


Figure 1:- Structure of Liposome

ADVANTAGES OF LIPOSOMES

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

- 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 biodegradable.
- Biocompatible
- Liposome increases stability of drug.
- Site avoidance effect.
- Improve protein stabilization.
- Provide sustained release.
- Direct interaction of drug with cell.
- Site avoidance effect.

DISADVANTAGES OF LIPOSOMES

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

MECHANISM OF ACTION OF LIPOSOMES

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

1.Endoytosis – This take place by phagocytic cells of reticuloendothelial system such as neutrophills.

2.Adsorption – It occurs to the cell surface by non specific electrostatic forces or by interaction with cell surface components.

3.Fusion- It occurs by the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm.

4.Lipid exchange- In this transfer of liposomal lipids to the cellular membrane without association of liposomal contents.

CLASSIFICATION OF LIPOSOMES

There are various classification of liposome based on-

A.Structural features

B.Based upon Conventional Liposomes

- Natural lecithin mixtures
- Liposome with glycolipids
- Synthetic identical chainphospholipids

C. Based on method of preparation of liposomes

D.Based upon Specialty liposomes

- Lipoprotein coated
- Carbohydrate coated

- Bipolar fatty acid
- Antibody direct

Table 1: Liposomes based on vesicle type

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 100 nm.	1
Large Uni lamellar vesicles (LUV)	More than 100 nm.	1
GaintUni lamellar vesicles (GUV)	More than 1.0 µm	1
Multi Vesicular vesicles (MVV)	More than 1.0 µm	Multicompartmental structure

II. MATERIALS & METHOD

All the methods of preparing the liposomes involved are given below-

1. Passive loading techniques
2. Active loading techniq

1.Passive loading techniques:-

Passive loading techniques include three different methods :-

- A. Mechanical dispersion method
- B. Solvent dispersion method
- C. Detergent removal method (removal of non- encapsulated material)

A. Mechanical dispersion method.

Thin film hydration technique:MLVs are produced by this technique. This method involves the dissolution of phospholipids in an organic solvent like Chloroform: Methanol in the ratio of 2:1 v/v in a round bottomed flask. The RBF is then attached to rotary evaporator and is allowed to rotate at a speed of 60rpm. As a result, evaporation of organic solvent occurs. This leads to the formation of thin and homogeneous lipid film on sides of RBF. Nitrogen gas is used to remove the residual solvent. The so formed lipid film is hydrated using an aqueous media. This results in the formation of milky white suspension which is kept aside for 2h at room temperature or above the transition temperature of lipid. Hence, complete swelling of particles occurs which leads to the formation of MLVs.

Microemulsification method: Microemulsification method yields small MLVs. This method involves the usage of Microfluidizer, wherein the lipids are introduced into it either as large MLVs or as slurry of unhydrated lipids in an organic medium. Microfluidizer pumps the fluid through an orifice (5µm) at a pressure of 10,000 psi. Due to this high pressure, the fluid passes through the microchannels which directs the two streams of fluid to collide with each other at right angles with higher velocity. The so formed fluid is collected and recycled through the pump and interaction chamber until the spherical vesicles are produced. After a single pass, the size of vesicles gets reduced to a diameter of 0.1 and 0.2µm.

Ultrasonication method: This method involves preparation of SUVs from MLVs. Bath type or probe type sonicators are generally used under an inert atmosphere of nitrogen or argon.Principle: Pulsed, high frequency sound waves are used to agitate MLVs suspension.

probe type sonicator:This method involves the usage of titanium probe which delivers high energy to the liposomal suspension.

Disadvantages:Thermo labile materials like proteins or DNA gets denatured or inactivated.Degradation of liposomal suspension may occur due to the release of titanium particles into it.

Bath type sonicator: To overcome the drawbacks associated with the probe type sonicator; bath type sonicators are majorly preferred. In this method, test

tube containing MLV dispersion is placed in a bath type sonicator. MLV dispersion is subjected to sonication for about 5-10 min at a temperature above the transition temperature of the lipid. Due to this, slightly hazy transparent solution is obtained which is then subjected to centrifugation in order to produce SUV dispersion. Upon centrifugation, MLVs and titanium particles form a sediment. Later, the tube is removed from the rotator and by using the Pasteur pipette, top clear liquid layer is decanted leaving behind the central layer having MLVs and pellet. The top layer constitutes the pure SUVs dispersion. Both bath and probe type sonicators.

French pressure cell: French pressure cell is made up of stainless steel and is capable of withstanding pressures of 20,000–40,000psi. The body of cell contains pressure chamber, pressure relief valve, piston, bottom seal and valve closure. Both piston and bottom seal have rubber O-ring each. This method is expensive, and cleaning of cell is difficult. This method involves addition of liposomal suspension to the pressure chamber and the piston is pushed into the body. Then the cell is turned at an angle of 180°. After filling, the bottom seal is pressed down and the pressure chamber is closed. Later, the cell is brought back to upright position and inserted in a hydraulic press due to which pressure is developed. Finally, the valve is opened slowly and the product (liposomes) is allowed to exit in a drop-wise manner. ULVs or OLVs having a size of 30-80nm are obtained.

High pressure extrusion method: This method offers advantages like large capacity, simple and rapid. It is used to produce SUVs and LUVs. The mechanism of action appears like peeling of an onion. This involves the usage of polycarbonate filter membranes. MLV suspension is passed through the filter at a pressure of 250psi. During this process, the successive layers get peeled off, there

II. Ethanol Injection method.

Ethanol solution containing lipids is injected into excess of saline or aqueous solution through fine needle. Then mixing is done to produce SUVs.

III. Reverse Phase Evaporation techniques.

This method is generally used to encapsulate RNA and various enzymes. This technique involves injection of aqueous solution of drug into an organic solvent containing lipid followed by sonication of the biphasic mixture. This leads to the formation of water-in-oil type of emulsion. Later, the emulsion is dried in a rotary

by leaving only a single layer. Hence, uniform sized liposomes are obtained. Liposomes produced by this technique are known as LUVETs. High pressure extrusion technique.

Freeze thaw sonication: This technique involves series of steps like freezing, thawing and sonication. This method involves freezing of unilamellar dispersion (SUV). Then the frozen dispersion is allowed for thawing at room temperature for about 15min. Later, sonication is done. Hence, aggregation of SUVs occurs leading to the formation of LUVs.

B. Solvent Dispersion Method:

- I. Ether injection method.
- II. Ethanol Injection method.
- III. Reverse Phase Evaporation techniques.

I. Ether injection method.

This method involves dissolution of lipids in diethyl ether or ether/methanol. This lipid mixture is then injected into an aqueous solution containing material to be encapsulated. This is performed at a temperature of 55-65°C or under reduced pressure. Evaporation of organic solvent is brought about by vacuum application. Finally, liposomes are obtained.

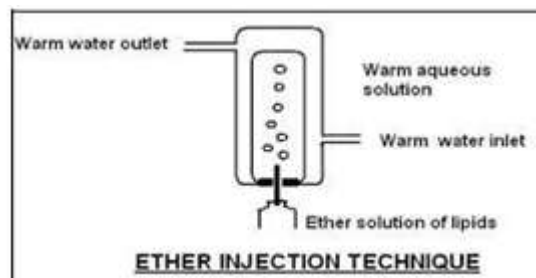


Fig: Ether injection method

evaporator to obtain semisolid gel. The gel is then agitated mechanically due to which phase inversion occurs i.e., water- in-oil turns to oil-in-water type of emulsion. During the process of agitation, some of the water droplets collapses to form the external phase, while remaining portion forms the entrapped aqueous volume.

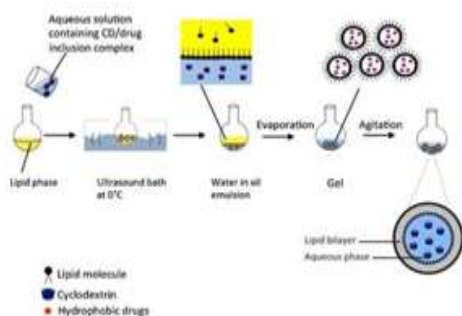


Fig: Reverse Phase Evaporation

C. Detergent removal method (removal of non-encapsulated material):

At low concentration detergent equilibrates between vesicular lipid and water phase. After reaching a critical detergent concentration, membrane structure tends to unstable and transform gradually in to micelles and all lipids exists in mixed micelle form.

2. Active loading techniques

In active loading, liposomes are first generated containing a transmembrane gradient, i.e. aqueous phase inside and outside the liposomes are different. Subsequently, an amphipathic drug is dissolved in exterior aqueous phase can permeate the phospholipid bilayer. After permeation interaction with trapping agent and core to lock- in the drug. In 1976, Deamer and Nicols demonstrate that a pH gradient could be utilized to load catecholamine into liposomes, Resulting stable drug retention in vitro.

III. PURPOSE OF STUDY

The aim of any Drug Delivery System is to modulate the pharmacokinetics and distribution of the drug in a beneficial way. liposome-based formulations and products are extremely wide, because of ability of liposomes to carry a wide variety of substances large number of drugs Antimicrobial agents, drugs against cancer, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials, their structural versatility and the innocuous nature of their compound. there are lots of applications of

liposomes in various fields.

This Review paper contain following information about liposomes a novel drug delivery system:

To study classification of liposomes advantages, dis-advantages and its application.

To study method of preparation of liposomes.

To discuss the advances in liposomes assisted drug delivery, biological challenges that remain and current clinical and experimental use of liposomes for biomedical applications.

IV. CONCLUSION

It was concluded from the review that liposomes can be a promising carrier for improving targeted delivery of a large number of drugs. Liposomes are administrated orally, parenterally and topically as well as employed in a broad range of pharmaceutical and pharmacology applications with therapeutic and diagnostic purposes and as good carriers in gene delivery various drugs. Liposomal delivery systems have been approved as a suit carrier for therapeutic effectiveness in terms of duration of action and decrease in dose frequency and delivering drugs at higher efficiency and lower toxicity. The use of liposomes in the delivery of drugs and genes is promising and is sure to undergo further developments in the future. From this article we conclude that the new studies should be done on the parameters.

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