

A Concise Review on Liposomes: Novel Drug Delivery System

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Submitted: 10-07-2022

Accepted: 21-07-2022

ABSTRACT: Liposomes are spherical shaped bilayered vesicles that found to show the efficient results in controlled and targeted actions. These lipoidal vesicles are under extensive investigation as drug carriers for improving the bioavailability and delivery of therapeutic agents. Liposomes were the first nanoparticle that to be approved for clinical use in 1995.

Liposomes can be used as therapeutic tool in the fields like tumor targeting, genetic transfer, immunomodulation and in skin therapy. This article is made to provide an overview of liposomal drug delivery system. It has focused on the structure, classification and various applications in pharmaceuticals.

KEYWORDS: Novel drug delivery system, Targeted drug delivery, Liposomes, vesicles, phospholipids.

I. INTRODUCTION :-

Novel Drug Delivery System:(1)

It is a new approach that combines innovative development, formulations, novel technologies and methods for delivering drugs or any pharmaceutical compounds in body as needed to safely achieve its desired pharmacological effects.

It has advantage over the conventional dosage forms.

It minimizes the problems by enhancing efficacy, safety, patient compliance and shelf life of product.

It is one of the important tool expanding drug markets in pharmaceutical industry.

Types of novel drug delivery system:

1. Controlled drug delivery system
2. Microencapsulation
3. Mucosal drug delivery system
4. Transdermal drug delivery system
5. Nasopulmonary drug delivery system
6. Targeted drug delivery system

Advantages of novel drug delivery system:

- Accurate dosing
- Target specific delivery of drug can be achieved
- Controlled delivery by maintaining drug concentration
- Decreased toxicity and side effects

Disadvantages of Novel drug delivery system:

- They have limited potential as carrier to non – phagocyte target tissue.
- Possibility of clumping of cells and dose dumping may be there.

TARGETED DRUG DELIVERY SYSTEM

It is a system of specifying the drug moiety directly into its targeted body part to overcome the aspecific toxic effect of conventional drug delivery, thereby reducing the amount of drug required for therapeutic efficacy.

The goal of targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.

Vehicles used in targeted drug delivery system:

- Liposomes
- Niosomes
- Nanoparticles
- Peptides
- Monoclonal antibodies

APPLICATIONS OF TARGETED DRUG DELIVERY SYSTEM:

- It is used to treat diabetes and cardiovascular diseases.
- Important application is to treat cancerous tumors.
- One of the vehicle that is liposomes can be used as drug delivery for the treatment of tuberculosis.

- Targeted drug delivery system has advantages like convenience in administration, non-invasive, accurate dose and higher compliance.

LIPOSOMES:

Liposomes are spherical, self-closed structures having several concentric lipid bilayers with an aqueous phase inside. The word liposome is derived from two Greek words: lipo means fat and soma means body. That can be produced from cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane proteins.

In early 1970s, it was first proposed and tested as a drug delivery system.

Liposomes are biocompatible and can entrap and protect hydrophilic molecules in the internal water compartment and hydrophobic into the membrane.

Liposomes were first described in 1961 by British dermatologist Dr. Alec D Bangham. Liposomes were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasma lemma and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure.

STRUCTURE:(2-4)

Liposomes are colloidal carriers, having a size range of 0.01 to 5.0 µm. Indeed these are bilayered vesicles that are formed when phospholipids are hydrated in excess of aqueous medium. Liposomes have got potential advantage of encapsulating hydrophilic as well as hydrophobic drugs and targeting them to the required disease site in the body.

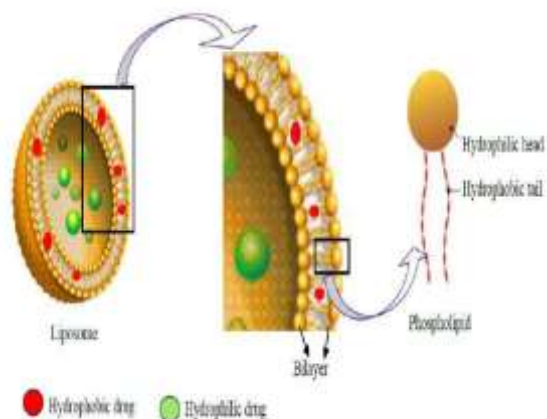


Fig .Structure of liposome and phospholipid

CLASSIFICATION OF LIPOSOMES:(5-7)

1. Classification based on structure

Vesicle type	Abbreviation	Diameter size	No. of lipid layers
Unilamellar	UV	All size ranges	One
Small Unilamellar	SUV	20-100nm	One
Medium Unilamellar	MUV	>100nm	One

Large Unilamellar	LUV	>100nm	One
Giant Unilamellar	GUV	>1.0 μm	One
Oligo Lamellar	OLV	0.1-1. μm	Appx. 0.5
Multi lamellar	MLV	>0.5 μm	5-25
Multi vesicular	MV	>1.0 μm	Multi compartmental Structure

2. Based on method of preparation

Different preparation methods and the vesicles formed by these methods

Preparation method	Vesicle type
Single or oligolamellar vesicle made by reverse phase evaporation	REV
Multilamellar vesicle made by reverse phase evaporation	MLV-REV
Stable pluri lamellar vesicle	SPLV
Frozen and thawed multilamellar vesicle	FATMLV
Vesicle prepared by extrusion technique	VET
Dehydration-rehydration method	DRV

3. Based on composition-

Type	Abbreviation	Composition
Conventional	CL	Neutral or negatively charge phospholipids and cholesterol

Fusogenic	RSVE	Reconstituted dendai virus envelopes
pH sensitive	-	Phospholipids such as per or DOPE with either CHEMS or OA
Cationic	-	Cationic lipid with DOPE
Long circulatory	LCL	Neutral high temp, cholesterol and 5-10% PEG, DSP
Immune	IL	CL or LCL with attached monoclonal antibody

4. Based upon conventional liposome

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

5. Based upon speciality liposome

- Antibody directed
- Methyl x-linked
- Bipolar fatty acid
- Lipoprotein coated
- Carbohydrate coated
- Multiple encapsulated

MECHANISM OF LIPOSOME FORMATION:

The amphiphilic molecules i.e. phospholipids are the basic part of liposome, having hydrophilic part that is phosphoric acid bound to water soluble molecule, whereas the hydrophobic part consists of two fatty acid chains with 10-24 carbon atoms and 0-6 double bonds in each chain.

When these phospholipids are dispersed in aqueous medium, they form lamellar sheets by organizing in a such a way that, the polar head group faces outwards to the aqueous region while the fatty acid groups face each other and finally form spherical/vesicle like structures called as liposomes.

METHOD OF PREPARATION OF LIPOSOMES/VESICLES:

1) Passive loading technique

- Mechanical dispersion
- Solvent dispersion
- Detergent removal

2) Active loading technique

- Proliposome
- Lyophilization

PASSIVE LOADING TECHNIQUE: (8-10)

1. Mechanical dispersion:

In these method, lipid is solubilized in an organic solvent, the drug to be entrapped is solubilized in an aqueous solvent, the lipid phase is hydrated at high speed stirring and due to affinity of aqueous phase to polar head is entrapped in lipid vesicle. For example, lipid film hydration, micro-encapsulation, sonication.

- Liquid hydration method-

The method involves the formation of a film by adding aqueous buffer and vortexing the dispersion. the hydration step is done at a temperature above the gel liquid crystalline transition temperature of the lipid or above the transition temperature of the highest melting component in the lipid mixture. Depending upon the solubilities the compounds to be encapsulated are added either to aqueous buffer or to organic solvent containing lipids.

- **Micro emulsification-**
small lipid vesicles are prepared by these method. This can be achieved by microemulsifying lipid compositions using high shearing stress generated from high pressure homogenizer. Microemulsion for biological applications can be produced by adjusting the speed of rotations from 20-200.

- **Sonication -**
in these method MLV_s are sonicated either with a bath type sonicator or probe sonicator. the main drawback of this method are very low internal volume /encapsulation efficiency ,degradation of phospholipids ,exclusion of large molecules ,metal contamination from probe tip and presence of MLV along with SUV.

- **French pressure cell method-**
The method has several advantages over sonication method. This method involves the extrusion of MLV through small orifice at 20,000 psi at 4^oc. It is simple ,rapid and reproducible method that involves gentle handling of unstable materials. The resulting liposomes are larger than sonicated SUV_s

- **Membrane extrusion-**
it is a technique where the liposome suspension is passed through a membrane filter of defined pore size. The processed liposomes have a narrow size distribution and selected average size less than about 0.4 microns.

2. SOLVENT DISPERSION:

In this method, lipids are dissolved in an organic solvent and then brought into contact with an aqueous phase that contains the material to be entrapped under rapid dilution and rapid evaporation of organic solvent.

- **Ethanol injection method-**
In this process an ethanolic solution of lipids is rapidly injected into an aqueous medium through a needle, dispersing the phospholipids through the medium and promoting the vesicle formation.

- **Ether infusion method-**
A solution of lipids dissolved in diethyl ether or ether-methanol mixture is slowly injected to an aqueous solution of the drug, to be encapsulated at a temperature of 55-65°C under reduced pressure. The liposomes reformed by subsequent removal of ether under vacuum. The

main drawbacks of the method are exposure of drugs and lipids to organic solvents and high temperature which may cause degradation.

- **Double emulsification-**
A primary emulsion is prepared by dissolving the drug in an aqueous phase (w₁) which is then emulsified in an organic solvent of a polymer to make a primary w₁/o emulsion. This primary emulsion is further mixed in an emulsifier-containing aqueous solution (w₂) to make a w₁/o/w₂ double emulsion. The removal of the solvent leaves microspheres in the aqueous continuous phase, which are collected by filtering/centrifuging.

3. DETERGENT REMOVAL:

In this method, phospholipids are brought into contact with an aqueous phase via detergent that associates with phospholipid molecules and screen the hydrophobic portions of the molecules from water. The advantages of detergent analysis method are outstanding reproducibility and production of liposomes population of homogenous size.

ACTIVE LOADING TECHNIQUE(11-13)

- **Proliposome**
Lipid and drug are coated onto a soluble carrier to form free-flowing granular material in pro-liposome which forms an isotonic liposomal suspension on hydration. The pro-liposome approach may provide an opportunity for cost-effective large scale manufacture of liposomes containing particularly lipophilic drugs.

- **Lyophilization**
The removal of water from products in the frozen state at extremely reduced pressure is called lyophilization. The process is generally used to dry products that are thermo labile which may be destroyed by heat-drying. This technique has a great potential to solve long term stability problems with respect to liposomal stability. Leakage of entrapped materials may take place during the process of freeze- drying and on reconstitution.

APPLICATIONS OF LIPOSOMES:

- **Liposomes for brain targeting:**
Liposomes are one of the most promising approaches in brain targeting .they are able to incorporate hydrophilic therapeutic agents in the aqueous core ,and lipophilic ones in the lipid bilayer .they also presents good biodegradability and biocompatibility ,low toxicity and controlled drug release.(14)

- Liposomes in cancer therapy:**
 Doxil ,aPEGylated liposomal formulation ,is the first liposomal product that was approved by FDA for the treatment of Kaposi’s sarcoma in AIDS patients.
 Nowadays many anti-cancer herbal drugs also formulated into liposomes to provide better targeting with enhanced bioavailability.(15)
- Liposome for respiratory drug delivery:**
 Liposome is widely used in several types of respiratory disorders. Liposomal aerosols can be formulated to achieve sustained release, prevent local irritation, reduced toxicity and improved stability. Whilst preparing liposomes for lung delivery, composition, size, charge, drug/lipid ratio and drug delivery method should be considered.

The liquid or dry form is taken for the inhalation during nebulisation. Drug powder liposome is produced by milling or by spray drying.(16)

- Liposomes as vaccine adjuvants**
 Liposome has been established firmly as immune-adjuvant that is potentiating both cell mediated and non-cell mediated immunity. Liposomal immuno-adjuvant acts by slow release of encapsulated antigen on intramuscular injection and also by passive accumulation within regional lymph node. The accumulation of liposome to lymphoid is done by the targeting of liposome with the help of phosphotidyl serine. Liposomal vaccine can be prepared by inoculating microbes, soluble antigen and cytokines of deoxyribonucleic acid with liposome.(17)

LIST OF LIPOSOMAL PRODUCTS APPROVED FOR COMMERCIAL USE: (18)

PRODUCT	DRUG	ADMINISTRATION	INDICATION
Ambisone	Amphotericin B	Intravenous	Severe fungal infection
Amphotec	Amphotericin B	Intravenous	Severe fungal infection
DaunoXome	Daunorubicin	Intravenous	Blood tumors
Doxil	Doxorubicin	Intravenous	Kaposi’s sarcoma, ovarian/breast cancer
DepoCyte	Cytarabine	Spinal	Neoplastic meningitis and lymphomatous meningitis
DepoDur	Morphine sulphate	Epidural	Pain
Lipoplatin	Cisplatin	Intravenously	Epithelial malignancies
Myocet	Doxorubicin	Intravenous	With cyclophosphamide in metastatic breast cancer
Visudyne	verteporfin	Intravenous	Macular degeneration

II. CONCLUSION:

Liposomes are one of the classical specific drug delivery system that is used for controlled and targeted actions. The wide range of selection of administration route which are parenteral, oral, topical makes it more flexible in designing the drug delivery system.

Nowadays liposomes are used as carrier for wide variety of drugs. In spite of its few disadvantages liposomes serve as versatile carrier for wide range of drugs.

Over a dozen of liposome-based drug delivery systems is currently approved by the FDA. The liposomal approach can be successfully utilized to improve the pharmacokinetics and therapeutic efficacy.

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