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Review Article

LIPOSOME A NOVEL DRUG CARRIERAkshay R. Birgad¹, Swati M. Kanoje², Dr. Swati P Deshmukh³¹Student of Shraddha Institute of Pharmacy, Washim²Associate Professor, Department of Pharmaceutics, Shraddha Institute of Pharmacy, Washim³Principal, Department of Pharmacology, Shraddha Institute of Pharmacy, Washim**Abstract:**

Liposomes are the most explored nanocarriers used in targeted drug delivery systems. Liposomes are spherical lipid vesicles (usually 50–500 nm in diameter particle size) composed of one or more lipid bilayers, as a result of emulsifying natural or synthetic lipids in an aqueous medium. There are many drug molecules which are having good pharmacological action but their use is limited due to the toxicity, they possess.

Such drugs can be brought into use by reducing its toxicity and enhancing its pharmacological action. Liposome formulation is an appropriate approach to achieve the therapeutic action of such drugs. Liposome composition has made it more reliable as it is inert and resembles a cellular membrane which makes it an interesting field of research for scientists. A liposome is a good carrier of drugs in the treatment of cancer and it is gaining popularity in the field of chemotherapy.

Keywords: Liposome, Components, Types, Classification, Methods, Application.

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INTRODUCTION:

Liposome was first discovered by Alec Douglas Bangham, a British hematologist in 1961 at the Babraham Institute, in Cambridge, England. He published his work in 1964. They were discovered when A.D. Bangham and R.W. Horne was testing a new electron microscope in the institute with a dry phospholipid and gram-negative stain. They found that on the hydration of phospholipid, it results in the formation of phospholipid bilayer vesicles, which resemble the structure of the cell membrane. Lateron, it becomes a wide research component by scientists for the drug delivery system because of its biocompatibility and its capability to entrap both hydrophilic and lipophilic drugs. In 1974, Geordies et al. proposed the use of liposomes in chemotherapy, and liposome was considered as a good candidate because of safety, size controllability, and easy functionalization. PEG can help its escape from the reticuloendothelial system and reduce its distribution to different organs of the body. Hence, reducing the toxicity of cytotoxic drugs. Liposomes regaining their popularity due to their contribution to varied areas like drug delivery, cosmetics, and the structure of the biological membrane. Liposomes are a term derived from the Greek word: where 'Lipos' meaning 'fats' and 'Somas' meaning 'body'. A. D. Bangham first described liposome in 1964 with his colleagues. His close colleague Gerald Weissman suggested the term "liposomes", which he defined as "microscopic vesicles composed of one or more lipid layer". Liposomes are colloidal particles formed when a phospholipid is hydrated in access to water, resulting in the formation of liposomes of size ranging from 0.01-0.5 μ m in diameter.

Liposomes, due to their biphasic environment, can act as a carrier for both hydrophilic and lipophilic drugs.

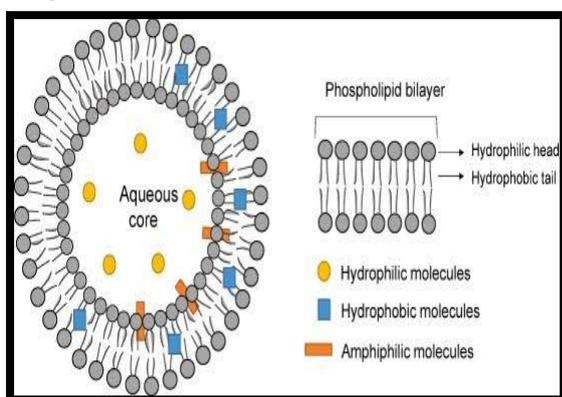


Fig.1: structure of liposome

❖ **Components of liposomes**

1) Phospholipids

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-

Phosphatide choline (Lecithin) PC

Phosphatide ethanolamine (Cephalin)-PE

Phosphatide serine (PS)

Phosphatide 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. 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.

2.1. Attractive biological properties of liposomes:

Liposomes are biocompatible.

Liposomes can entrap water-soluble (hydrophilic) pharmaceutical agents in their internal water compartment and water-insoluble (hydrophobic) pharmaceuticals into the membrane.

Liposome-incorporated pharmaceuticals are protected from the inactivating effect of external conditions; yet do not cause undesirable side reactions.

❖ **Advantages of Liposomes:**

- 1) Provide controlled drug delivery
- 2) Biodegradable, biocompatible, flexible
- 3) Non ionic
- 4) Can carry both water and lipid soluble drugs
- 5) Drugs can be stabilized from oxidation

❖ **Disadvantages of liposomes**

1. Production cost is high.
2. Leakage and fusion of encapsulated drug / molecules.
3. Sometimes phospholipid undergoes oxidation and hydrolysis-like reactions.
4. Short half-life.
5. Low solubility.

❖ **Other problems related to liposomes are as following:**

1. Sterilization: Sterilization of liposomes is a complicated process. Because it is unstable in heat and certain methods of radiation. Sterilizing with chemicals may affect stability problems.

2. Short self-life and stability: It is very difficult to achieve the stability of liposomal formulation due to chemical and physical degradation. Chemically, they are prone to oxidation and hydrolysis and they can physically fuse forming larger vesicles.

3. Entrapment efficacy: The amount of drug a liposome can entrap is often low and sometimes leakage of drugs takes place.

4. Removal from circulation by the reticuloendothelial system (RES): The major drawback of liposomes as a drug carrier is that they are rapidly cleared by a phagocytic cell of the Mononuclear Phagocytic System (MPS).

4.1. MECHANISM ACTION OF LIPOSOMES

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

1. Endocytosis – This takes place by phagocytic cells of reticuloendothelial system such as neutrophils.

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

❖ TYPES OF LIPOSOMES

Liposomes are classified based on their structural properties, methods of preparation and composition, and application. Their properties such as the size of liposomes, number, the position of lamellae depend widely on the method of preparation, types of lipids used, and preparation condition of liposomes.

5.1. CLASSIFICATION OF LIPOSOMES

1. Multilamellar liposomes

Multilamellar vesicle (MLV) is a liposome composed of a number of concentric lipidic bilayers with size range 0.1–0.5 μm . MLVs have onion

structure. Their main advantage is That they are easy to form and have a stable building. The major Disadvantage of these liposomes is limited space for loading Compounds.

2. Unilamellar liposomes

Unilamellar vesicles have a single phospholipid bilayer Sphere enclosing aqueous solution. Unilamellar vesicles can Be divided into small Unilamellar vesicles (SUV), which their Size range is 0.02–0.05 μm .

3. Multivesicular liposome

A vesicle is composed of several non-concentric vesicles Encapsulated within a single bilayer known as a multivesicular Vesicle (MVV). These can be multifunctional liposome Ranging in size from 2 um to 40 um.

4. Oligolamellar liposome

The oligolamellar liposome contains less layers of lamella Compared to the multilamellar liposome. Their size ranges from 0.1 to 10 um in size.

5. Giant liposome (GL)

These are the largest size liposome ranging in size of 10–1000 μm . This GL can be used for different diagnostic and medical Purposes. They can be both SUV and LUV.

1. Classification Based on Structure Vesicle Types with their Size and Number of Lipid Layers

Vesicle type	Abbreviation	Diameter Size	No. of Lipid Layers
Unilamellar	UV	All size ranges	One
Small Unilamellar	SUV	20-100nm	One
Medium Unilamellar	MUV	More than 100nm	One
Large Unilamellar	LUV	More than 100nm	One
Giant Unilamellar	GUV	More than 1.0 μm	One
Oligo lamellar	OLV	0.1-1.0 μm	Approx 0.5
Multi lamellar	MLV	More than 0.5 μm	5-25
Multi vesicular	MV	More than 1.0 μm	Multi compartmental structure

Fig 2. Structure of vesicles

2. Based on Method of Preparation Different Preparation Methods and the Vesicles Formed By these Methods

a. Multilamellar Liposomes (MLV)

1. Lipid Hydration Method: This is the most widely used method for the preparation of MLV. The method involves drying a solution of lipids so that a thin film is formed at the bottom of round bottom flask and then hydrating the film by adding aqueous

buffer and vortexing the dispersion for some time. The drawbacks of the method are low internal volume, low encapsulation efficiency and the size distribution is heterogeneous.

MLVs with high encapsulation efficiency can be prepared by hydrating the lipids in the presence of an immiscible organic solvent (petroleum ether, diethyl ether). The contents are emulsified by vigorous vortexing or sonication.

Table 2: Based on the method of preparation

Type	Abbreviation	Composition
Conventional	CL	Neutral or negatively charge phospholipids and cholesterol
Fusogenic	RSVE	Reconstituted sendai virus envelops
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
Immuno	IL	CL or LCL with attached monoclonal antibody or recognition sequences

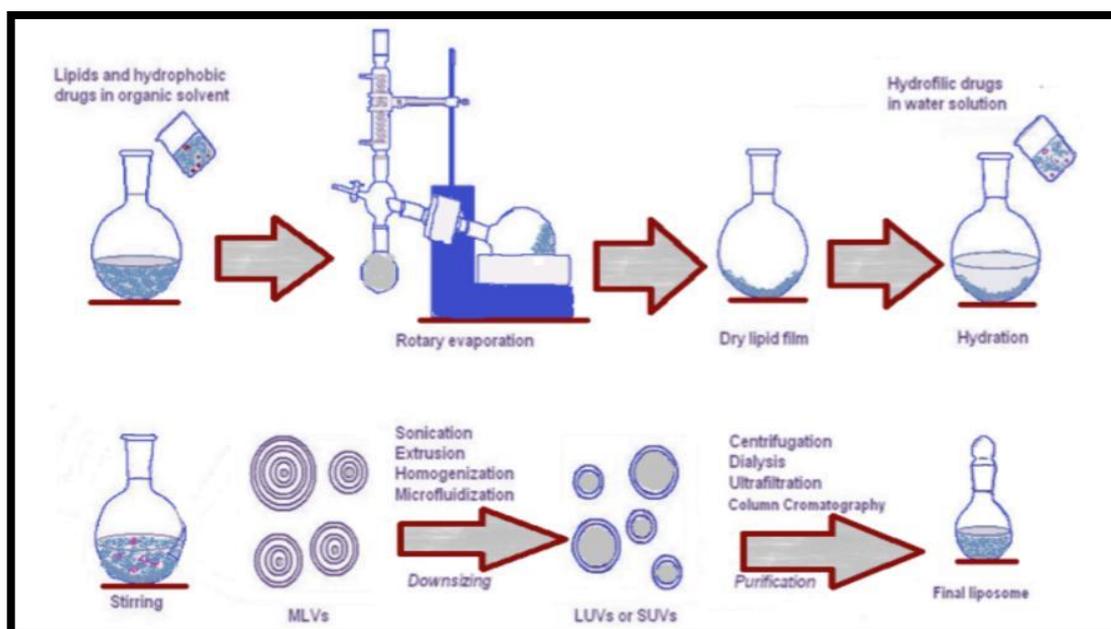


Fig 3. Lipid hydration method

3. Based on Composition Different Liposome with their Compositions

1. Conventional liposomes:

Composed of neutral or negatively charged phospholipids and cholesterol. Subject to coated pit endocytosis, contents ultimately delivered to Lysosomes if they do not fuse with the endosomes, useful for E.E.S targeting; rapid and saturable uptake by R.E.S; shortcirculationhalf-life, dose dependent pharmacokinetics

2. Cationic Liposomes:

Composed of cationic lipids. Fuse with cell or endosome Membranes; suitable for delivery of negatively charged macromolecules (DNA, RNA); ease of formation, structurally unstable; toxic at high dose, mainly restricted to local administration.

3. pH sensitive liposomes:

Composed of phospholipids such as phosphatides Ethanolamine, dioleoyl phosphatidyl ethanolamine. Subjected to coated Pit endocytosis at low pH, fuse with cell or endosomes membrane and release their contents in cytoplasm; suitable for intra cellular delivery of Weak base and macromolecules.

4. Long circulating or stealth liposomes:

Composed of neutral high transition temperature lipid, Cholesterol and 5-10% of PEG-DSPE. Hydrophilic surface coating, low Opsonization and thus low rate of uptake by RES long circulating half Life (40 hrs.); Dose independent Pharmacokinetics

5. Immuno liposomes:

Conventional or stealth liposomes with attached Antibody or Recognition Sequence. Subject to receptor mediated endocytosis, cell Specific binding

(targeting); can release contents extracellularly near the target tissue and drugs diffuse through plasma membrane to Produce their effects.

Table 3: Based on composition and application.

Type	Abbreviation	Composition
Conventional	CL	Neutral or negatively charge phospholipids and cholesterol
Fusogenic	RSVE	Reconstituted sendal virus envelops
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
Immuno	IL	CL or LCL with attached monoclonal antibody or recognition sequences

❖ METHOD OF PREPARATION

The conventional method for the preparation of liposomes Includes the solubilization of lipids in the organic solvent, Drying down the lipids from organic solution, dispersion of Lipids in aqueous media, purification of resultant Liposomes, and analysis of the final product. All the method for the preparation of liposomes involves Four steps:

1. Drying down lipids from an organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product

6.1. Techniques used for the preparation of liposomes are Described below;

1. Hand Shaking method: In this method, the lipid is Solubilized in an organic solvent (mainly ethanol) in a Round bottom flask with constant shaking in a circular Manner, when the organic solvent evaporates, it forms A thin film of lipid on the RBF which on hydrated with Purified water, with constant shaking, form a liposome.

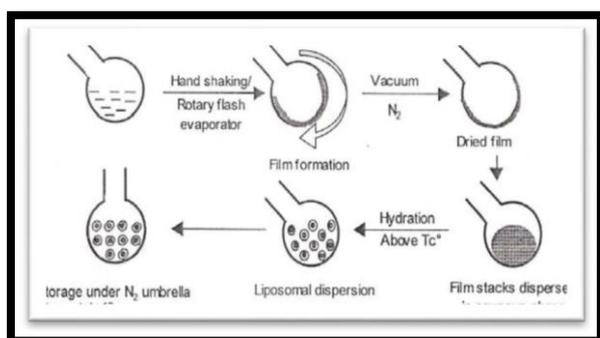


Fig 4. Hand Shaking method

2. Sonication Method:

This is the most widely used Method for the preparation of SUV from MLV, Prepared from the handshaking method and rotary Evaporator method. There are two types of sonication Methods used in the preparation of SUVs.

A). Probe Sonication method: In this method, the tip of the titanium probe is directly dispersed into

liposome Dispersion for the production of SUVs. In this method, the energy input is high due to which there is the Generation of heat.

B) Bath sonication: In this method, liposome dispersion in a container is placed on the sonication bath. This Method is more convenient as compared to probe Sonication for the production of SUVs because the Temperature can be controlled easily. The sterilized Liposome can be obtained, there is no titanium Contamination.

3. French Press method: In this method, unstable MLVs are converted to SUVs and LUVs bypassing Then through a small orifice of equipment. Liposomes Produced through this method are more reliable, as it Has good stability as compared to those prepared by Sonication method. The drawback of this method is That it has a small working volume of a maximum of 50 ml and a high temperature is hard to manage.

4. Freeze Thawed liposomes:

Here, SUVs formed by the Sonication method is frozen and thawed slowly and continuously, resulting in the formation of LUVs due to aggregation of SUVs during the thawing process. By This method, the encapsulation efficacies increase by 20%-30%.

5. Solvent Dispersion method:

A) Ether injection (solvent evaporation): In this method, lipid dissolved in a diethyl-ether or ether-methanol mixture is gradually injected in an aqueous medium containing drug at the temperature of 50 to 65 °c or reduced pressure. The removal of ether under vacuum results formation of liposomes.

B) Ethanol injection: To a buffer a solution of lipid and Ethanol is injected, resulting in the formation of MLVs. The drawback is the formation of a heterogeneous Population of liposomes (30-110 nm). It is also Difficult to remove ethanol from a solution Consequently increasing the chances for the Inactivation of biologically active macromolecule

6. Reverse Phase evaporation method:

This method has Brought a breakthrough in the history of liposomes. The aqueous and lipid ratio used in this method is high, About four times higher than the handshaking method Or MLVs.

7. Detergent removal method (removal of non-Encapsulated material)

A) Dialysis:

In this method, detergent is used to dissolve Lipids at Critical Micelles Concentration (CMC). When it is removed by dialysis, using a commercial device Such as LipoPrep (Diachema AG, Switzerland) which Is a version of the dialysis method.

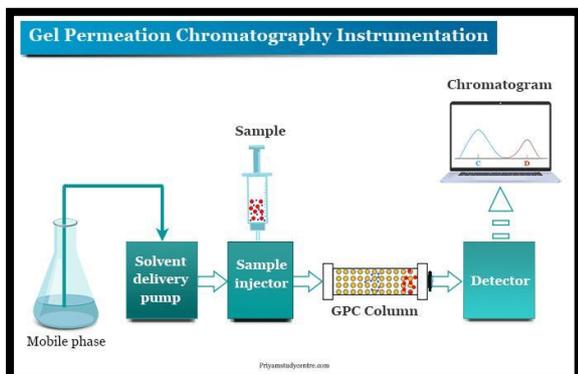
B) Detergent

(cholate, alkyl glycoside, Triton X-100) Removal of mixed micelles (absorption): In this Method, removal of detergent in achieved by shaking Mix micelle with beaded organic polystyrene absorbers Such as XAD-2 beads (SERVA Electrophoresis

GmbH, Heidelberg, Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA)

C) Gel-permeation chromatography:

Sephadex G-50, Sephadex G-1 00 (Sigma-Aldrich,



MO, USA), Sepharose 2B-6B, and Sephacryl S200-S100 (General Electric Company).

Fig 5. Gel permeation chromatography instrumentation

❖ Application of Liposomes

1. The therapeutic value of liposomes as drug carriers, particularly for anticancer, antifungal, and antibacterial agents.
2. As anticancer, cytotoxic drugs like Cytarabine, alkylating agents.
3. As vaccine adjuvants i.e., when administered by IM route, they slowly release the antigens and accumulate in lymph nodes.
4. In ophthalmic drug delivery systems, Idoxuridine used in acute & chronic keratitis.

❖ Limitations Of Liposomes

1. Stability
2. Sterilization
3. Encapsulation efficiency
4. Lysosomal degradation

1. Stability

• One of the major problems limiting the widespread use of liposomes is stability--both physical and chemical.

2. Sterilization

Identification of a suitable method for sterilization of liposome formulations is a major challenge because phospholipids are thermolabile and sensitive to sterilization procedures involving the use of heat, radiation and/or chemical sterilizing agents.

3. Encapsulation efficiency

Liposome formulation of a drug could only be developed if the encapsulation efficiency is such that therapeutic doses could be delivered in a reasonable amount of lipid, since lipids in high doses may be toxic and also cause non-linear (saturable) pharmacokinetics of liposomal drug formulation.

4. Lysosomal degradation

Once the liposome has reached the target cell the efficacy is determined not only by the amount of

drug associated with the cell, but also by the amount of drug reaching the 'target molecule inside the cells.

❖ Marketed Preparation Of Liposome

Liposome (Doxil™) Doxorubicin = Kaposi sarcoma

Liposome (EVACT) = breast cancer

Liposome (DaunoXome) Daunosome = Advanced Kaposi' sarcoma, small cell lung cancer, leukemia& solid tumor.

Liposome (VincaXome) Vincristine = Solid tumor

❖ Summary

Liposomes are microscopic, spherical vesicles composed of lipid bilayers. They are widely used in various fields, including pharmaceuticals and cosmetics, due to their unique properties. Liposomes can encapsulate both hydrophilic and hydrophobic substances, making them excellent drug delivery vehicles. Their biocompatibility and ability to protect and transport drugs to target cells make them valuable in medicine. Liposomes also find applications in cosmetics for controlled release of active ingredients. Their versatility and ability to improve the efficacy and safety of drug formulations make liposomes a subject of ongoing research and development.

❖ CONCLUSION:

Liposomes are the most explored nanocarriers used in targeted drug delivery systems. Liposomes are spherical lipid vesicles (usually 50–500 nm in diameter particle size) composed of one or more lipid bilayers, as a result of emulsifying natural or synthetic lipids in an aqueous medium. There are many drug molecules which have good pharmacological action but their use is limited due to the toxicity they possess. Such drugs can be brought into use by reducing their toxicity and enhancing their pharmacological action. Liposome formulation is an appropriate approach to achieve the therapeutic action of such drugs. Liposome composition has made it more reliable as it is inert and resembles a cellular membrane which makes it an interesting field of research for scientists. A liposome is a good carrier of drugs in the treatment of cancer and it is gaining popularity in the field of chemotherapy. Researchers are developing liposomal technology for improving its therapeutics and pharmacokinetic efficacy. At the same time, reducing the toxicity of potent drugs.

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