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Liposome: A novel formulation

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Abstract
Liposome's are acceptable and superior carriers and have ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. Liposome's are microparticulate lipoidal vesicles which are under extensive investigation as drug carriers for improving the delivery of therapeutic agents. Due to new developments in liposome technology, several liposome-based drug formulations are currently in clinical trial, and recently some of them have been approved for clinical use. Reformulation of drugs in liposomes has provided an opportunity to enhance the therapeutic indices of various agents mainly through alteration in their biodistribution. This review discusses the potential applications of liposomes in drug delivery with examples of formulations approved for clinical use, their preparation method, targeting, mechanism of formation, liposome component and the problems associated with further exploitation of this drug delivery system.

Keywords: liposome, classification, preparation method, application, limitation

Introduction: Liposome

Liposomes are microscopic vesicles composed of one or more lipid bilayers arranged in concentric fashion enclosing an equal number of aqueous compartments. Various amphipathic molecules have been used to form the liposomes and the method of preparation can be tailored to control their size and morphology. Drug molecules can either be encapsulated in the aqueous space or intercalated into the lipid bilayer; the exact location of a drug in the liposome will depend upon its physicochemical characteristics and the composition of the lipids [1, 2].

Liposomes, i.e., phospholipid vesicles, are widely applied for the topical treatments of diseases in dermatology. Many drugs encapsulated into liposomes show enhanced skin penetration. Because of their ability to provide a sustained and controlled release of the incorporated material, liposomes also have a potential for being applied vaginally. The major disadvantage of using liposomes topically and vaginally lies in the liquid nature of the preparation. To achieve the viscosity desirable for application, liposomes should be incorporated into a suitable vehicle. It has been well established that liposomes are fairly compatible with viscosity increasing agents (methylcellulose) and polyacrylic acid. (Carbopol) [3, 4].

Liposomes are frequently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to particular skin layers. Liposomes are spherical vesicles whose membrane consists of amphiphilic lipids (i.e., lipids that are hydrophilic on one side and lipophilic on the other side) that enclose an aqueous core, similar to the bilayer membranes of living cells. Because liposomes offer an amphiphilic environment, they may encapsulate hydrophilic substances in their aqueous core and lipophilic substances in their lipid bilayer. This unique dual release capability enables the delivery of 2 types of substances once they are applied on the skin; each differs in its effects on skin permeability, which may enhance the desired therapeutic benefit [2]. Classification of liposome [5]

Table 1

Type-1	Specification
Based on structure Parameter	
MLV	Multilamellar large vesicle->0.5µm
OLV	Oligolamellar vesicle-0.1-0mm
UV	Unilamellar vesicle (all range size)
SUV	Small sized unilamellar vesicle
MUV	Medium sized unilamellar vesicle
LUV	Large unilamellar vesicle-> 100mm
GUV	Giant unilamellar vesicle- >1mm
MV	Multivesicular vesicle >1mm
Type-2	
Based on liposome preparation	
REV	Single or oligolamellar vesicle made by reverse phase evaporation method
MLV-REV	Multilamellar vesicle made by reverse phase evaporation method
SPLV	Stable plurilamellar vesicle
FATMLV	Frozen and thawed MLV
VET	Vesicle prepared by extrution technique
DRV	Dehydration rehydration method
Type-3	

Based Upon Composition And application	Neutral or negatively charged
Conventional liposome	Phospholipid
Fusogenic liposome Cationic liposome	Reconstitute sendai virus envelop Cationic lipid
Long circulatory liposome	Neutral high Transition temprature liposme
pH sensitive liposome	Phospholipid like Phosphatidyl ethanolamine
Immuno liposome	Long cerculatory liposome with attached monoclonal antibody

Method of Liposome

Preparation and Drug Loading [6]

Liposome may be prepared by two techniques

a) Passive loading technique.

b) Active loading technique.

1 Passive loading technique

A) Mechanical dispersion method

- Lipid hydration by hand shaking or freeze drying
- Micro emulsification
- Sonication
- French pressure cell
- Membrane extrusions
- Dried reconstituted vesicle
- Freeze thawed liposome

B) Solvent dispersion method

- Ethanol injesction
- Ether injection
- Double emulsion vesicle
- Reverse phase evaporation vesicle
- Stable plurilamellar vesicle

C) Detergent removal method

- Detergent (cholate, alkyl glycoside, Tritonx-100) removed from mixed micelles
- Dialysis
- Column chromatography
- Dilution
- Reconstituted sendai virus enveloped vesicle

2 Active loading technique

Passive loading techniques include three different group of method working on different
principles namely mechanical dispersion, solvent dispersion and detergent solubilization.

A) Mechanical dispersion method of passive Loading

All method covered under this category begin with a lipid solution in organic solvent and end up with lipid dispersion in water. The various components are typically combined by codissolving the lipid in organic solvent and organic solvent is then removed by film diposition under vacuum. When all solvent is removed, the solvent dispersion mixture is hydrated using aqueous buffer. The film spontaneously swell and hydrate to form liposomes. At this point method incorporate some diverge processing parameters in various way to modify their ultimate properties. The post hydration treatments include vortexing, sonication, freeze thawing and high- pressure extrusion.

B) Solvent dispersion method of passive loading

In solvent dispersion method, lipid a is first dissolved is an organic solution, which is then brought into contact with an aqueous phase containing materials to be entrapped within the liposome. The lipid allign themselves at the interface of organic and aqueous phase forming monolayer of phospholipids, which form the half of the bilayer of the liposome method employing solvent dispersion can be categorized on the
basis of the miscibility of the organic solvent and aqueous solution. These include condition where the organic solvent is miscible with aqueous phase, the organic solvent is immiscible with the aqueous phase, the latter being in excess and the case where the organic solvent is in excess, and immiscible with the aqueous phase.

C) Detergent removal method of passive loading

In this method the phospholipids are brought into intimate contact with the aqueous phase via detergent, which associate with phospholipids molecule and serve to screen the hydrophobic portion of the molecule from water. The structure formed as result of this association is known as micelles, and can be composed of several hundreds of component molecule. Their size and shape depend on the chemical nature of detergent, the concentration and other lipid involved. The concentration of detergent of in water at which micelles just start to form is known as 'critical micelle concentration'. Below the critical micelle concentration, micelle the detergent molecule exists entirely in free solution.

As detergent is dissolved in water in concentration higher than the CMC, micelle form in more and more numbers, while the concentration of detergent in the free from remain essentially the same as it is at the CMC. Micelle containing other participating component in addition to detergent (or composed of two or more detergent in their formulation known as "mixed micelle". Invariably in all method, which employed detergent in the preparation of liposome, the basic feature is to remove the detergent from preformed mixed micelle containing phospholipids, where upon uni lamellar vesicle formed spontaneously

2) Active loading technique

The utilization of liposomes as drug delivery system is stimulated with the advancement of efficient encapsulation procedures. The membrane from the lipid bilayer is in general impermeable to ions and larger hydrophilic molecules. Ions transport can be regulated by the
ionophores while permeation of neutral and weakly hydrophobic molecule can be controlled by concentration gradients. Some weak acid or bases however, can be transported through the membrane due to various transmembrane gradient, such as electric, ionic (pH) or specific salt (chemical potential) gradient. Several method exist for improved loading of drugs, including remote

(active) loading method which load drug molecules into preformed liposome using pH gradient and potential difference across liposomal membrane. A concentration difference in proton concentration across the membrane of liposomes can drive the loading of amphipathic molecule. Active loading methods have the following advantages over passive encapsulation technique:

- A high encapsulation efficiency and capacity.
- A reduced leakage of the encapsulated compounds.
- Bed side" loading of drugs thus limiting loss of retention of drugs by diffusion, or chemical degradation during storage.
- Lexibility of constitutive lipid, as drug is loaded after the formation of carrier unit.
- Avoidance of biological active compounds during preparation step in the dispersion thus reducing safety hazards. The transmembrane pH gradient can be developed using various method depending upon the nature of drug to be encapsulated.

Example of drugs in liposomal formulation [9]

Table 2

Drug	Application	Commercial Name	Composition of Liposomes
Amikacin	Bacterial Infection	MiKa some	HSPC/CH/DSPG
Adriamycin	Stomach Cancer	-	DPPC/CH
Ampicillin	Listeria monocytogenesis	-	CH/PC/PS
Annamycin	Breast Cancer Leukemia	Annamycin	Liposomes
Amphotericin B	Systemic Fungal Infection	Am Bi some	HSPC/CH/DSPG
All-*trans*retionic acid	Prostate Cancer, Leukemia	Atragen	Liposomes
Muramyl dipeptide	Immunostimulator	-	DSPC/PS 1:1
Ciprofloxacin	*Pseudomonas aerogonisa*	-	DPPC
Clodronate	Macrophage suppresion	-	PC/CH
Cyclosporin	Immunosuppresor	-	PC/CH
Chloroquinine	Malaria	-	PC/PG/CH
Doxorubicin	Cancer	Doxil	Doxil HSPC/CH/PEG
Streptosotocin	Lymphocyte activator	-	DMPC/CH
Suramin	Trypanosomes	-	DPPC
Lurotecon	Cancer	NX211	Liposomes

Advantage of liposome [7]

- Non ionic
- Can carry both water and lipid soluble drugs
- Biodegradable drugs can be stabilized from oxidation
- Improve protein stabilization
- Controlled hydration
- Provide sustained release
- Targeted drug delivery or site-specific drug delivery
- Stabilization of entrapped drug from hostile environment
- Alter pharmacokinetics and pharmacodynamics of drugs
- Can be administered through various Routes
- Can incorporate micro and macro molecules
- Act as reservoir of drugs
- Therapeutic index of drugs is increased
- Site avoidance therapy
- Can modulate the distribution of drug
- Direct interaction of the drug with cell
- Biodegradable and flexible

Disadvantages [7]

- Less stability
- Low solubility
- Short half life
- Phospholipids undergoes oxidation, hydrolysis
- Leakage and fusion
- High production cost
- Quick uptake by cells of R.E.S
- Allergic reactions may occur to liposomal constituents
- Problem to targeting to various tissues due to their large size

Characterization of liposomes [8]

Table 3

Size and its distribution	Microscopy. Laser light scattering
Surface charge	Gel electrophoresis
Entrapped volume	NMR
Lamellarity	Freeze electron microscopy, 31P-NMR
Phase behavior of liposomes	DSC
Drug release	In vitro diffusion cell
Encapsulation efficiency (% capture)	Mini column centrifugation, protamine aggregation

a) Physical properties
b) Chemical properties

Table 4

Quantitative determination of phospholipids	Barlett assay, Stewart assay, TLC
Phospholipid hydrolysis	HPLC
Phospholipid oxidation	UV, GLC, TBA

Application of liposomes [8]

1. Liposome as drug/protein delivery vehicle:
2. Controlled and sustained drug release in situ Enchaned drug solubilization Altered pharmacokinetic and biodistribution
3. Enzyme replacement therapy and lysosomal disorders
4. Liposome in antimicrobial, antifungal and antiviral therapy Liposomal drugs Liposomal biological response modifier
5. Liposomes in tumour therapy Carrier of small cytotoxic

molecule Vehicle for macromolecule as cytokines or genes
6. Liposome in gene therapy Gene and antisence therapy Genetic (DNA) vaccination
7. Liposome in immunology Immunoadjuvant Immunomodulator Immunodiagnosis
8. Liposome as artificial blood surrogates
9. Lipososmes as radiopharmaceutical and radio diagnostic carrier Liposomes in cosmetics and dermatology Liposomes in enzyme immobilization and bioreactor technology

Limitation in liposome technology
1. Stability
2. Sterilization
3. Encapsulation efficiency
4. Active targeting
5. Gene therapy
6. Lysosomal degradation

Conclusion
Liposome carriers, well known for their potential application. Liposomes are acceptable and superior carriers and have ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. There are a number of methods available by which liposomes can be manufactured separately depending on the property of molecule. The liposomes containing drugs can be administrated by many routes (intravenous, oral inhalation, local application, ocular) and these can be used for the treatment of various diseases. A number of problems associated with drug molecule such as bioavailability, degradation, stability, site effect can be overcome by incorporating it into liposome. As a novel carrier system liposome provide controlled and sustained release.

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