GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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A comprehensive review on liposomes: A vesicular system for drug delivery

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GSC Biological and Pharmaceutical Sciences, 2022, 18(02), 331–337

Publication history: Received on 19 January 2022; revised on 24 February 2022; accepted on 26 February 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.18.2.0084

Abstract

In the last few years, many techniques have been utilized to enhance the pharmacological activity of any Active Pharmaceutical Drug [API] resulting in better bioavailability and lesser side effects. Liposomal drug delivery has evolved in this manner to increase the drug effect and reduce side effects. This review article focuses on all the aspects of liposomes with formulation methodology and characterization. Liposomes seem the first choice for designing a drug delivery system.

Keywords: Liposomes; Bioavailability; Liposomal drug delivery; API

1. Introduction

Many drugs experience very low bioavailability, poor pharmacokinetic profile, and high side effects which may be because of poor solubility of the drug or because of the physicochemical nature of the drug. To get better results and boost the therapeutic efficacy of the narrow range drugs nanotechnology has shown significant outcomes. Liposomes are one of the parts of the Nano-system with notable outcomes [1-4].

Liposomes are colloidal vesicles made up of one or more lipid bilayers surrounded by aqueous compartments. Liposomes encapsulate different types of drugs like antibiotics, antifungal, anticancer, proteins, hormones, peptides etc. Many drugs achieve therapeutically level for very less time because of metabolism of drug Liposomes can act as a promising carrier to delivery of drugs and to archives therapeutics level [5].

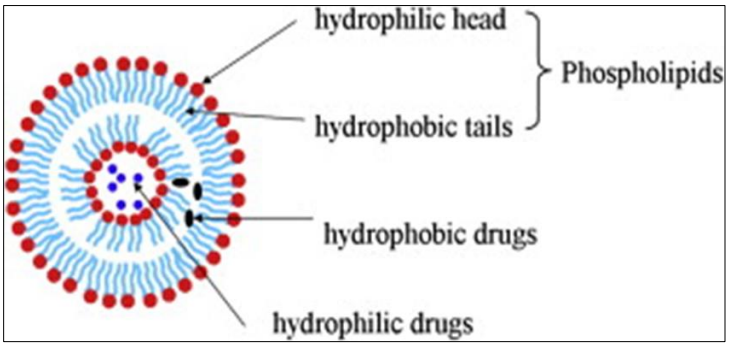

Figure 1 Liposome

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1.1. Advantages of liposomes [6-9]

- Liposomes act with the following benefits
- Liposomes can deliver a wide range of drug candidates (e.ghydrophilic, hydrophobic and amphipathic)
- Completely biodegradable, biocompatible, and non-toxic
- Reduces side effects especially in the case of chemotherapeutics agents wherein very low concentration drug show harmful effects.
- Minimizes contact of sensitive tissues to harmful drugs.

1.2. Limitations of liposome

- Manufacturing is very costly.
- Leaking and fusion of incorporated drug is a measure problem with liposomes.

2. Types of liposomes [10-13]

Liposomes are classified into different categories.

2.1. Based on Vesicle size

2.1.1. Unilamellar vesicles

- Small unilamellar vesicles (SUV) (Size- 40-80nm)
- Medium unilamellar vesicles (MUV)(Size -40-80 nm)
- Large unilamellar vesicles (LUV)(Size100 nm-1,000 nm)

2.1.2. Oligolamellar vesicles (OLV)

OLVs are made up of 10-20 lipid bilayers enclosed by internal volume.

2.1.3. Multilamellar vesicles (MLV)

They have many lipid bilayers. MLVs are prepared in a different manner. The structure is like layers of an onion. The central part is made up of LUV/MLV.

2.2. Based on techniques of liposome preparation

- REV: Reverse Phase Evaporation Method. This method is used to prepare Single or oligo lamellar and Multilamellar vesicles [14].
- SPLV: Stable Plurilamellar Vesicles
- FATMLV: Frozen and Thawed method used to prepare MLV.
- VET: Extrusion technique used to prepare different types of vesicles
- DRV: Dehydration-rehydration method is used to prepare different type of vesicles.

2.3. Based upon composition and application

- Conventional Liposomes (CL): Made up of neutral and negatively charged cholesterol and phospholipids[15].
- Fusogenic Liposomes (RSVE)
- pH sensitive Liposomes: Phospholipids such as DOPE with either
- Long Circulatory (Stealth) Liposomes (LCL): LCL contains PEG (polyethylene glycol) which is termed pegylation.Pegylation increases circulation of liposomes in the body by reducing its body clearance[16].

3. Methods of preparation of liposomes [17-22]

Different methods are utilized to prepared liposomes.

3.1. General method of liposomes preparation

It involves following steps

Drying of lipid from organic solvent followed by lipid dispersion in aqueous media followed by liposomes purification. At last analysis of liposomes.

3.2. Passive Loading Techniques

3.2.1. Mechanical dispersion methods

Lipid hydration method

Most common method of MLV formation.

This method involves drying of lipid solution to form a thin layer at the bottom of RBF. This film is further hydrated using aqueous buffer and overtaxing the mixture. The drug compound to be used to form liposomes is added either in that buffer or in organic solvent as per their solubility profile [2]3.

3.2.2. Micro emulsification

High pressure homogenizer is used for this method. This method is used to prepare SLVS. By using high shear stress lipid composition is micro emulsified.

3.2.3. Dried reconstituted vesicles

This method involves liposomes are mixed in an aqueous solution having drug or a mixture of lyophilized protein which is further dehydrated.

3.2.4. Freeze thaw method

Results in formation of SUVs using slow thawing method [24].

3.2.5. Solvent Dispersion

Ethanol injection

A lipid solution of ethanol is mixed into aqueous buffer resulting formation of MLVs.

Ether infusion

A lipid solution is added in diethyl ether and injected slowly to a solution of drug compound to be encapsulated.

Detergent

Detergents can solubilize lipids at CMC. After removal of detergents micelles becomes rich in phospholipids and join together to form LUVs.

3.3. Active Loading Techniques

3.3.1. Proliposomes

In this method drug molecules and lipid both are coated with soluble carrier to form freely flowing granules in pro-liposomes. When hydrated results in an isotonic liposomal suspension [25].

3.3.2. Lyophillization

Lyophilization is the process of water removal under reduced pressure in a frozen state. This method is utilized for drying of thermolabile products.

4. Evaluation parameters of liposomes

- Particle Size Determination
- Surface Charges
- Encapsulation Efficiency (EE)
- Phase Behavior
- Drug Release Study

4.1. Particle Size Determination

Both particle size and particle size distribution of liposomes can be determined by using following methods;

- Laser light scattering
- Transmission electron microscopy

4.2. Surface charges

The method involved in the measurement of surface charge is based on free-flow electrophoresis of Multi-Layer Varistors (MLVs).

- It utilizes a cellulose acetate plate dipped in sodium borate buffer of pH 8.8.
- About 5N moles of lipid samples are applied on to the plate, which is then subjected to electrophoresis for 30 minutes.
- The liposomes gel gets bifurcated depending on their surface charges.

This technique can be used for determining the heterogeneity of charges in the liposomes suspensions as well as to detect any impurities such as fatty acids [26].

4.3. Encapsulation Efficiency (EE)

The quantity of drug entrapped in the liposomes helps to estimate the behavior of the drug in a biological system. The % of drug encapsulation is done by first separating the free drug fraction from encapsulated drug fraction. The encapsulated fraction is then made to leak off the liposomes into an aqueous solution using suitable detergents [27].

4.4. Phase Behavior

The phase behavior of liposomes can be determined by using differential scanning calorimetry (DSC). Around 2 mg sample is taken out and placed in a sealed aluminum pot. And an empty aluminum pot is used as a reference. The impurities determination is performed by using a heating rate of 10 °C/min. DSC equipment should be 1° calibrated.

4.5. Drug Release Study

500 ml 20% ethanol was used as the release medium; 10 ml release medium was drawn and placed into a dialysis bag The dialysis bag was then clamped and attached on the paddle of a dissolution apparatus; 5 ml drug-containing liposomes and 5 ml ethanol solution of drug with the same drug content as the liposomes, were respectively dissolved in the dialysis vessel, with stirring at 37°C and 300 × g. A sampling of 100 µl liquid from the dialysis bag was conducted at 1, 2, 4, 6, 8, 10, 12 and 24 h for sample determination and calculation of the accumulative release rate. A release curve was drawn using the time (t) [28].

5. Marketed formulations of liposomes

In 1995, Doxil (PEGylated liposome-encapsulated doxorubicin) was the first liposomal formulation approved by the US FDA. There are some liposomal formulations available in market for human use (table1).

5.1. Applications of Liposomes [9-13]

Liposomes already established a wide are of applications. Some of them are discussed here as follows.

5.1.1. Respiratory Disorders

Liposomes found very beneficial in respiratory disorders with sustain release, better stability of drug product with minimum side effects in comparison of convention aerosols. Liquid and dry both forms can be taken in liposomal form with nebulization.

5.1.2. Tumor therapy- Carrier

Liposomes have already been established as nanocarrier in chemotherapy treatment. Many drug formulations have already been approved for chemotherapy.

5.1.3. Immunological adjuvants in vaccines

The liposomal formulation are used as immunoadjuvant and in immunodiagnostic.

5.1.4. Ophthalmic Disorders

Liposomes have shown positive results against many eye disorders, including dryness of eyes, corneal transplant rejection etc. Drug verteporfin has been approved as a liposomal formulation for eye disorders.

5.1.5. Pulmonary Application

Liposomes are one of the best tools for pulmonary delivery of drugs because of their better solubility profile.

5.1.6. Liposomes in Cosmetics-

Liposomes are also used in the cosmetic industry because of their release pattern and similarity to the cell membrane.

5.1.7. Site specific targeting

The immunoliposomes are capable to identify and binding to target cells with higher affinity.

5.1.8. Liposomes as protein drug delivery-

Liposomes are utilized in increase drug solubilization.

5.1.9. Gene therapy

Liposomes a reutilized widely in gene applications to cure diseases.

Table 1 Market Formulations of liposomes

S. No	Product Name	Drug Name	Manufacturer
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.
5	Daunoxome	Daunorubicin	Nexstar Pharmaceuticals Inc.CO
6	Mikasome	Amikacin	Nexstar Pharmaceuticals Inc.CO
7	DC99	Daxorubicin	The Liposome company N.J.
8	Epaxel	Hepatitis A vaccine	Swiss Serum institute Switzerland
9	ELA max	Lidocaine	Biozone Labs, Ca, USA

6. Advancements in liposomes

6.1. Ethosomes

They are well-organized to deliver to the skin made up of soya phosphatidylcholine and 30% ethanol·

6.2. Immuno liposomes

They were improved with antibodies.

6.3. Niosomes

Small unilamellar vesicles made from non- ionic surfactants.

6.4. Stealth liposomes

Stealth liposomes possess modified and long half-life in circulation. PEG coating is used to prepare these liposomes.

7. Conclusion

Tradition pharmaceutical doses forms have many limitations which can be overcome by use of a liposomal drug delivery system. Nano carriers systems are developed as a potential system in the delivery of drugs. Liposomes act as a Nano carriers system that can act and reach to a specific site, tissue, or organ. As mentioned in the above discussion many anti-cancerous drugs are now available in liposomal form. To get better results from liposomal formulation it should be designed properly resulting in better bioavailability of and lesser side effects. Liposomes are one of the best choices of Nano carrier in drug delivery, site-specific drug delivery, specific organ, and receptor targeting.

Compliance with ethical standards

Acknowledgments

Authors are thankful for the management of the institute to provide necessary facilities for this work.

Disclosure of conflict of interest

No conflict of interest is associated.

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