INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Liposomes: Versatile Nanocarriers in Modern Drug Delivery Systems - A Comprehensive Review

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ARTICLE INFO

Received: 03 April 2024
Accepted: 07 April 2024
Published: 12 April 2024
Keywords:
Liposomes, Versatile, Nanocarriers, Modern, Drug, Delivery, System
DOI:
10.5281/zenodo.10965869

ABSTRACT

Liposomes are a novel drug delivery system (NDDS), which are vesicular structures consisting of hydrated bilayers which form spontaneously when phospholipids are dispersed in water. The goal of a novel drug delivery system is to route the active ingredient to the site of action and supply the medication at a rate determined by the body's demands during the course of treatment. They are basic microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid bilayers. There has been interest in the creation of NDDS. Liposomes are colloidal spheres of cholesterol non-toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane proteins and drug molecules or it is also called vesicular system delivery system used to target the drug to particular tissue. It has concentrated on the elements influencing how liposomes behave in biological environments. The paper also covered a number of topics pertaining to the stability, characterisation, and mechanism of liposome synthesis in the liposomal medicinal product. Liposomes have therapeutic applications in cosmetics, Cancer therapy, Infection, topical therapy, immunomodulation, Gene genetic transfer, and tumour targeting. [1,2]

INTRODUCTION

The name "liposome" comes from two Greek words: "soma," which denotes body, and "lipos," which signifies fat. Since 1970, liposomes have been studied as a medicine delivery or targeting method for particular bodily locations. Liposomes are composed of biocompatible and biodegradable components, which are able to encapsulate both hydrophilic and lipophilic molecules in one platform. Further, they provide sustained release profile and site-specific delivery of pharmaceuticals into cells and also inside individual cellular compartments. A liposome can have a multi- or uni-lamellar structure and can arise at different sizes. Drugs can be encapsulated in liposomes, either in the phospholipid's bilayer, in the entrapped aqueous volume or at the bilayer interface. They provide selective passive targeting

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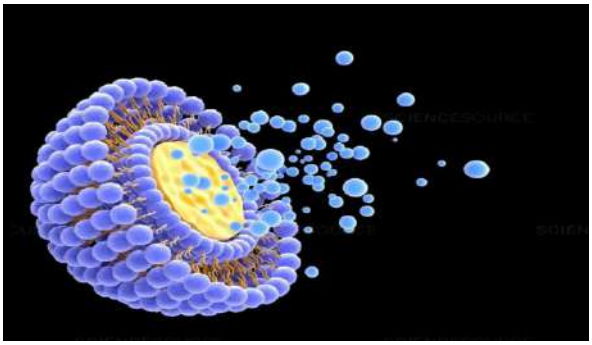
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

to tumour tissues and increase in safety and therapeutic index. Additionally, they serve as a solubilizer, preventing precipitation at the injection site and in the bloodstream. As a result, liposomes are well tolerated when administered intravenously. Liposomes can be prepared as an aerosol, a suspension, or a semisolid material like a gel, cream, or dry powder. In-vivo, they can be administered topically or parenterally. After systemic (usually intravenous) administration, this seems to be the most promising route for this carrier system. Liposomes typically recognized as foreign particles and consequently endocytosis by cells of the mononuclear phagocytic system (MPS), mostly fixed Kupffer's cells in the liver and spleen. Some liposomal drug delivery techniques show better pharmacological characteristics than those found in traditional formulations. In the present review, we will discuss on the various types of liposomes, their production procedures and characterization parameters along with the applications in pharmaceutical field. Also list of clinically approved liposomal products are given to have an updated idea on the current status. [2,3,4,5,6]

Structure Of Liposomes



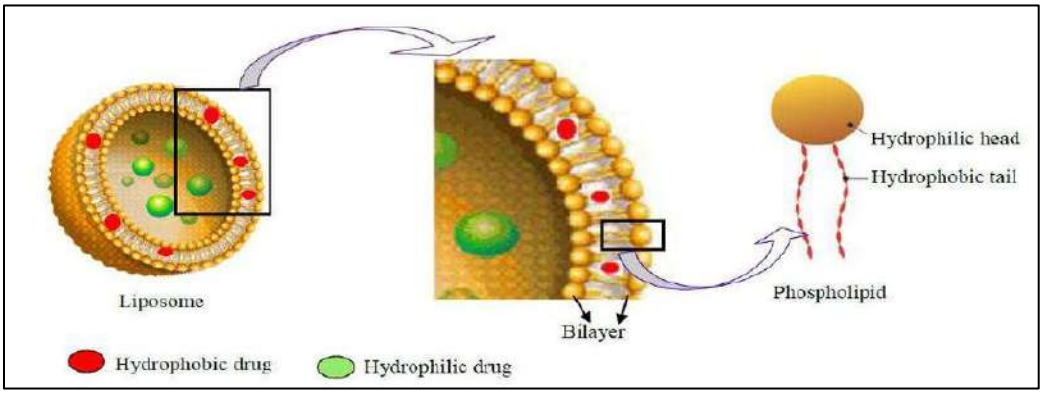


Figure 1: Spherical vesicles with a phospholipid bilayer.[7,8]

STRUCTURAL COMPONENTS

1. Phospholipids:

The most often utilized ingredient in liposome composition is phospholipid. Phospholipids are derived from phosphatidic acid and the responsible part of the molecule is glycerol moiety. At C3 position OH group is esterified to phosphoric acid and OH at C1 & C2 are esterified with long chain. One of the remaining OH group of phosphoric acid may be further esterified to organic alcohols including glycerol, choline, ethanolamine, serine and inositol. Therefore, the phosphoric ester of glycerol is the parent component of the series.

Examples of phospholipids are :

- Phosphatidyl inositol (PI)
- Phosphatidyl choline (Lecithin) – PC
- Phosphatidyl serine (PS

- Phosphatidyl ethanolamine (cephalin) – PE
- Phosphatidyl Glycerol (PG) for stable liposomes, saturated fatly acids are used. Unsaturated fatty acids are not used generally. [3,9,10]

2. Sphingolipids:

Backbone is sphingosine or a related base. These are important constituents of plant and animal cells. This contains 3 characteristic building blocks.

- A mol of F.A
- A mol of sphingosine
- A head category that ranges from highly complex carbohydrates to simple alcohols like choline.[3]

3. Sterols:

Liposomes frequently contain cholesterol and is derivatives to reduce the bilayer's fluidity or microviscocity, which lowers the membrane's permeability to molecules soluble inmaintaining membrane stability when biological fluids like plasma are present (this effect i employed in the formulation of i.v. liposomes). [3]

4. Cationic lipids:

E.g.: For instance, dioctadecyl dimethyl ammonium bromide or chloride, or DODAB/C. Dioleoyl propyl trimethyl ammonium chloride is known as DOTAP. This is a DOTAP analogue, along with a number of others, such as DOTMA analogues and cationic derivatives of cholesterol.[9]

5. Synthetic phospholipids

E.g.: for saturated phospholipids are

- Dipalmitoyl phosphatidyl ethanolamine (DPPE)
- Dipalmitoyl phosphatidyl choline (DPPC)
- Dipalmitoyl phosphatidyl serine (DPPS
- Distearoyl phosphatidyl choline (DSPC)

E.g.: for unsaturated phospholipids

- Dioleoyl phosphatidyl choline (DOPC)
- Dioleoyl phosphatidyl glycerol (DOPG)[3]

6. Polymeric materials:

When exposed to ultraviolet light, synthetic phospholipids containing a diacetylene group in their hydrocarbon chain polymerize, forming polymerized liposomes that have significantly greater permeability barriers to entrapped aqueous pharmaceuticals. E.g.: for other Polymerizable lipids are lipids containing conjugated diene, Methacrylate etc. Also, several Polymerizable surfactants are also synthesized.[3]

7. Polymer bearing lipids:

Stability of repulsive interactions with macromolecules is governed mostly by repulsive electrostatic forces. Applying a charged polymer covering to the liposome surface can cause this repulsion. E.g.: Diacyl Phosphatidyl ethanolamine with PEG polymer linked via a carbon at or succinate bond. [12]

MECHANISM OF LIPOSOME FORMATION

Liposome can interact with cells by four different adsorption mechanisms by specific interactions with cell-surface components, electrostatic forces, or by non-specific weak hydrophobic, which is one of the possible paths. The second possible interaction is endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils. The third mechanism is fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane with simultaneous release of liposomal content into the cytoplasm. And the fourth mechanism is Swap of bilayer components, for instance, cholesterol, lipids, and membrane-bound molecules with components of cell membranes. It is difficult to understand what mechanism is functioning, and more than one may operate at the same time. [13,14,15]

IDEAL PROPERTIES OF LIPOSOMES

- Drug loading and control of drug release rate.
- Overcoming the rapid clearance of liposomes.

- Intracellular delivery of drugs.
- Receptor-mediated endocytosis of ligand targeted liposomes.
- Triggered release.
- Delivery of nucleic acid and DNA.[16]

ADVANTAGES OF LIPOSOMES

- Liposomes improved the drug's therapeutic index and efficacy.
- Liposomes aid in lowering the amount of harmful medication exposure to delicate tissues.
- Liposomes are suitable for controlled release.
- Liposomes can be administered systemically or non-systemically and are flexible, non-toxic, biocompatible, fully biodegradable, and non-immunogenic.
- Liposomes increased stability via encapsulation. [3,17]

DISADVANTAGES OF LIPOSOMES

- Low solubility.
- Liposomes have short half-life.
- Leakage and fusion.
- Difficult in large scale manufacturing and sterilization.
- Phospholipids undergoes oxidation, hydrolysis.
- Possibility of dose dumping due to faulty administration. [17]

CLASSIFICATION OF LIPOSOMES

1. Based on Structural Parameters:

a. Unilamellar vesicles:

- Small unilamellar vesicles (SUV): The size range of SUV is from 20- 40 nm
- Medium unilamellar vesicles (MUV): The size range of MUV is from 40-80 nm.
- Large unilamellar vesicles (LUV): The size range of LUV is from 100 nm-1,000 nm.

b. Oligolamellar vesicles (OLV):

These are consisting of 2-10 bilayers of lipids encircling a large internal volume.

C. Multilamellar vesicles (MLV):

They have several bilayers. They can compartmentalize the aqueous volume in an infinite number of ways. They vary in the method used to prepare them. The arrangements can be onion like arrangements of concentric spherical bilayers of LUV/MLV enclosing a large number of SUV etc. [18,19]

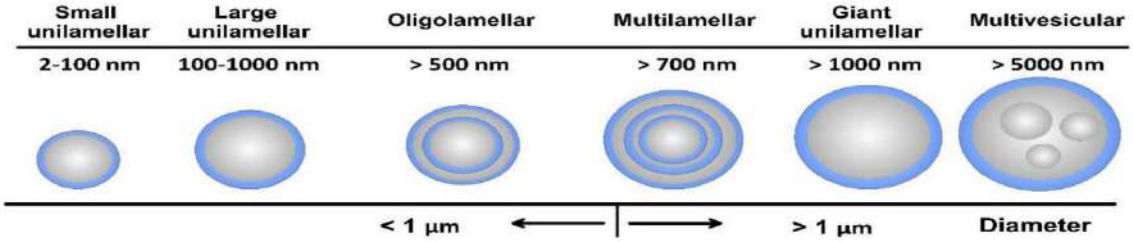


Figure 2 : Classification of Liposomes on the basis of Structural Parameters.[20]

2. Based on composition and mode of drug delivery

a. Conventional liposomes:

It is Composed of neutral or negatively charged phospholipids and cholesterol.

b. Cationic Liposomes:

It is Composed of cationic lipids. Easily form, structurally unstable, fused with cell or endosome membranes, appropriate for transport of negatively charged macromolecules (DNA, RNA); hazardous at high doses, primarily applied topically.

c. PH sensitive liposomes:

It is Composed of phospholipids such as phosphatidyl 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. Biodistribution

and pharmacokinetics similar to conventional liposomes.

d. Long Circulatory (Stealth) Liposomes:

To lessen the phagocyte system's ability to identify them, they have derivatives of polyethylene glycol (PEG) adhered to their surface (reticuloendothelial system; RES).

e. Magnetic Liposomes:

It is made up of P.C., cholesterol, a tiny quantity of a linear chain aldehyde, and magnetic iron oxide colloidal particles. These are liposomes that indigenously contain binding sites for attaching other molecules like antibodies on their exterior surface.

f. **Immuno liposomes:**

Conventional or long circulatory [stealth] liposomes with attached Monoclonal antibody or Recognition Sequence. Subject to cell-specific binding, receptor-mediated endocytosis, and release of contents extracellularly close to the target tissue, medications diffuse through the plasma membrane to exert their effects. [21]

Methods of liposome preparation

All the methods of preparing the liposomes basically involve four basic stages:

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

- **Various method of liposomes preparations is:[22]**

Active or remote loading:

Certain types of compounds with ionisable groups and those with both manufacturing procedure lipid and water solubility can be introduced into the liposomes after the formation of the intact vesicles.

Passive loading:

It involves loading the agents that have become trapped either before or throughout the manufacturing process.

1. **Mechanical dispersion methods**

Lipid film hydration

- Micro emulsification
- Sonication
- French pressure cell
- Membrane extrusion
- Dried reconstituted vesicles
- Freeze thawed liposomes

2. Solvent dispersion methods

- Ethanol injection
- Ether injection
- Double emulsion vesicles
- Vesicles
- Reverse phase evaporation vesicles

3. Detergent removal methods

- Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelle (absorption):
- Dilution
- Column chromatography
- Reconstituted Sendai virus enveloped vesicles [22]

Mechanical dispersion method

1. **Lipid hydration by hand shaking:**

Step (1)

- To prepared firstly lipid mixture of different phospholipid and charge components in chloroform: methanol (2:1 v/v) solvent mixture.
- Then introduce into a round bottom flask a ground glass neck.
- This flask is attached to rotary evaporator (rotated at 60 rpm).
- The organic solvent is evaporated at about 30° C or about transition temperature of lipid. The evaporator is isolated from the vacuum source by close the tip.
- The nitrogen is introduced into the evaporator and the pressure of cylinder is gradually raised up to no difference between inside and outside the flask.

Step (2) - Hydration of lipid layer

- After removal from lyophilizer, the flask flushed with nitrogen; 5ml saline phosphate buffer is added.
- The flask is again attached to evaporator and flushed with dinitrogen (N2).
- The evaporator is rotated at room temperature and pressure at same speed (for below 60 rpm).
- The flask is stop rotate after 30 minute or until all lipid has been removed from the wall of the flask and has given homogeneous milky suspension.
- The suspension is allowed to stand for 2 hours at room temperature or at a temperature above transition temperature of the lipid in order to complete the swelling process to give MLVs (Multilamellar vesicle)
- Remove the flask from the evaporator and fixed on lyophilizer to remove residual solvents.[23]

2. Micro emulsification:

Micro emulsification in mechanical dispersion methods involves the formation of stable microemulsions through the application of mechanical energy.

The process of micro emulsification using mechanical dispersion methods can be described as follows:

a. Selection of Components: Choose suitable water, oil, surfactant, and co-surfactant components based on the desired properties of the microemulsion and the solubility of the active ingredients.
b. Formulation Preparation: Mix the water, oil, surfactant, and co-surfactant components in appropriate ratios to form a pre-microemulsion mixture.
c. Mechanical Dispersion: Apply mechanical energy to the pre-microemulsion mixture using techniques such as stirring, high-pressure homogenization, or ultrasonication. This helps in breaking down the larger droplets into smaller droplets and promotes the formation of a stable microemulsion.
d. Characterization: Characterize the microemulsion for droplet size, stability, viscosity, and other relevant parameters to ensure that it meets the desired specifications.
e. Application: Use the microemulsion in the desired application, such as drug delivery or formulation of cosmetics, taking advantage of its stability and ability to solubilize both hydrophilic and lipophilic compounds.[24]

3. Sonication:

The most widely utilized technique for preparing SUVs is sonication.

a. Probe Sonication:

- The tip of the sonicator is directly engrossed into the liposome dispersion.
- In a probe sonication the energy input into lipid dispersion is very high.
- The coupling of energy at the tip results in local hotness. So, the vessel must be engrossed into an ice or water bath.
- Sonication up to 1 h, more than 5% of the lipids can be de-esterified.
- And also with this method, titanium may slough off and pollute the solution. [25]

b. Bath sonication:

The cylinder containing the liposome dispersion is placed inside a bath sonicator. Usually, this method is easier to control the temperature of the lipid dispersion than sonication by dispersing directly using the tip. In contrast to the probe units, the substance being sonicated can be shielded in a sterile vessel or in an inert environment.[12]

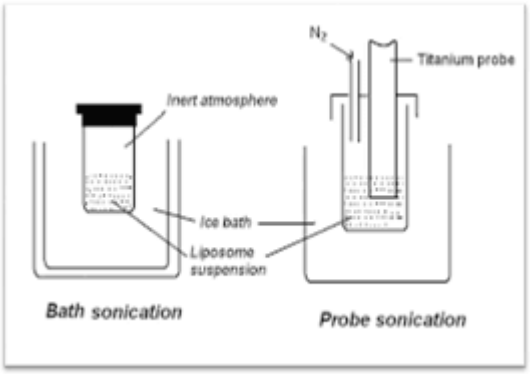


Figure 3: Probe and bath sonicator.[26]

4. French pressure method:

This method is based on mechanism of high pressure Using this process, 1–40 ml of homogeneous, unilamellar liposomes with an intermediate size range of 30-80 nm were prepared. When it comes to stability, this liposome outperforms sonicated liposomes. This method is some drawbacks are that initial high cost for the pressure cell. Liposome prepared by this method having less structural defects compared to sonicated liposome. [27]

5. Freeze-thawed liposomes:

Freeze-thawed liposome Liposomes are rapidly frozen and thawed slowly. The short-lived sonication disperses aggregated materials to LUV. The creation of unilamellar vesicles is as a result of the fusion of SUV throughout the processes of freezing and thawing This type of synthesis is strongly inhibited b. y increasing the phospholipid concentration and by increasing the ionic strength of the medium. The encapsulation efficacies from 20% to 30% were obtained. [28]

Solvent dispersion method

1. Ethanol injection:

A lipid solution of ethanol is rapidly injected to a huge excess of buffer which leads to formation of large size MLVs. The disadvantages of the method are that the population is heterogeneous (30 to 110 nm). The liposomes are very dilute, the removal of all ethanol is difficult and the probability of the various biologically active macromolecules to inactivate in the presence of even low amounts of ethanol is high. [29,30]

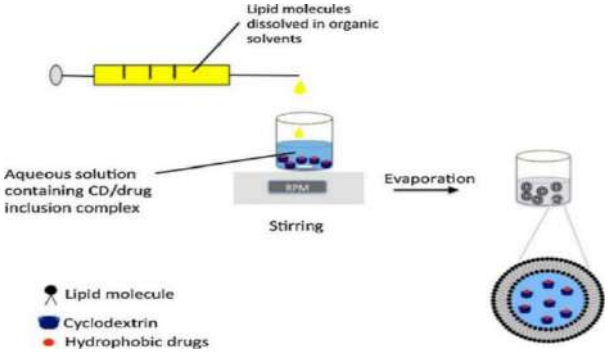


Figure 4: Ethanol injection method[31]

2. Ether injection:

A solution of lipids dissolved in ether methanol mixture or diethyl ether. And the mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°C to 65°C or under reduced pressure removal of ether from the mixture under vacuum leads to the creation of liposomes. The main drawback of the technique is that the exposure of compounds to be encapsulated to organic solvents at high temperature and population is heterogeneous (70 to 200 nm). [3,32]

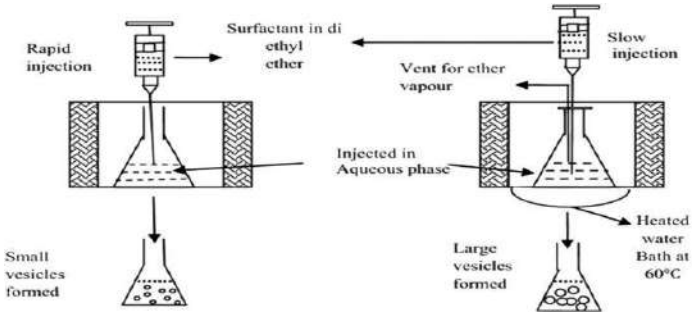


Figure 5 : Ether injection method[33]

3.Reverse phase evaporation vesicles:

Reverse phase evaporation method The water in oil emulsion is formed by sonication of two phase

system. It has phospholipid in an aqueous buffer and an organic solvent (diethyl ether). This mixture of lipid is added to round bottom flask. The organic solvent is removing under pressure by a rotary evaporation. The system is purged with nitrogen and lipids are re-dissolved in the organic phase. Diethyl ether and isopropyl ether are the solvent of choice after the lipids are re-dissolved the emulsion are obtaining and then the solvents are evaporated by evaporation of semi solid gel under reduce pressure, at 20-25°C rotating at approximately 200 rpm. A viscous gel forms and an aqueous suspension appears. Add excess water or buffer and evaporate the suspension for an addition 15 minute at 20°C to remove traces of solvent. Dialyze the preparation, and passthrough 4B column or centrifuge. Resulting liposome are called 'reverse phase evaporation vesicle'. [33]

Detergent removal methods

1. **Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption):**

Detergent absorption is attained by shaking mixed micelle solution with beaded organic polystyrene adsorbers such as XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA). The great benefit of using detergent adsorbers is that they can eliminate detergents with a very low CMC, which are not entirely depleted.[33]

2. **Dilution:**

Upon dilution of aqueous mixed micellar solution of detergent and phospholipids with buffer, the micellar size and the polydispersity increase fundamentally, and as the system is diluted beyond the mixed micellar phase boundary, a spontaneous transition from poly-dispersed micelles to vesicles occurs.[33]

Characteristics of liposomes

Liposomes are spherical vesicles with an aqueous core surrounded by one or more lipid bilayers. They are commonly used as delivery systems for drugs, vaccines, and other bioactive compounds. The characteristics of liposomes can vary depending on their composition, size, and method of preparation. Here are some key characteristics of liposomes:

1. **Structure:**

Liposomes are typically composed of phospholipids, which have a hydrophilic head and hydrophobic tail. This structure allows liposomes to form a bilayer in aqueous environments, with the hydrophobic tails facing inward and the hydrophilic heads facing outward, thereby encapsulating the aqueous core.

2. **Size:**

Liposomes can vary in size from tens to hundreds of manometers in diameter. The size of liposomes can be controlled during their preparation, and different sizes may be used depending on the application.

3. **Encapsulation Efficiency:**

Liposomes can encapsulate both hydrophilic and hydrophobic compounds within their aqueous core or lipid bilayers, respectively. The encapsulation efficiency depends on the physicochemical properties of the encapsulated compound and the liposome composition.

4. **Stability:**

Liposomes are relatively stable structures but can undergo changes in size, shape, and membrane integrity over time. Various factors, such as temperature, pH, and the presence of ions, can affect the stability of liposomes.

5. **Biocompatibility:**

Liposomes are biocompatible and biodegradable, making them suitable for use in drug delivery and other biomedical applications. They are generally non-toxic and well-tolerated in the body.

6. **Surface Properties:**

The surface of liposomes can be modified to alter their properties, such as circulation time, targeting ability, and interactions with biological systems.

Surface modifications can be achieved by incorporating different lipids or attaching functional groups or targeting ligands.

7. **Drug Release:**

The release of encapsulated compounds from liposomes can be controlled by the lipid composition, the size of the liposomes, and external factors such as temperature or ph. This controlled release is advantageous for drug delivery applications.

8. **Versatility:**

Liposomes can be designed to deliver a wide range of compounds, including small molecules, proteins, nucleic acids, and vaccines. They can also be used for imaging, diagnostics, and other applications. Overall, liposomes are versatile and customizable delivery systems with a range of characteristics that make them valuable in various biomedical and pharmaceutical applications.[34]

APPLICATIONS OF LIPOSOMES

Liposomes have a wide range of applications in pharmaceuticals, cosmetics, and research. Some of the key applications include:

1. **Drug Delivery:**

Liposomes are used as carriers for delivering drugs to specific targets in the body. They can encapsulate both hydrophilic and hydrophobic drugs, protecting them from degradation and improving their bioavailability.

2. **Cancer Therapy:**

Liposomes are used in cancer therapy to deliver chemotherapy drugs directly to tumour cells, reducing systemic toxicity and improving therapeutic efficacy.

3. **Vaccines:**

Liposomes are used as adjuvants and delivery systems for vaccines, enhancing the immune response and improving vaccine efficacy.

4. **Cosmetics:**

Liposomes are used in cosmetics for delivering active ingredients such as vitamins, antioxidants, and moisturizers to the skin, improving their penetration and effectiveness.

5. **Gene Delivery:**

Liposomes are used for delivering nucleic acids, such as DNA or RNA, for gene therapy and gene editing applications.

6. **Diagnostic Imaging:**

Liposomes can be loaded with contrast agents for imaging techniques such as magnetic resonance imaging (MRI) and ultrasound imaging, improving the visualization of tissues and organs.

7. **Antibiotic Delivery:**

Liposomes are used for delivering antibiotics to treat infections, particularly in cases where conventional antibiotic therapy is ineffective.

8. **Wound Healing:**

Liposomes loaded with growth factors and other bioactive molecules are used in wound healing applications to promote tissue regeneration and repair.

9. Nutraceuticals:

Liposomes are used to deliver vitamins, minerals, and other nutrients in nutraceutical products, improving their absorption and effectiveness.

10.Research Tools:

Liposomes are used as model membranes in research to study membrane biophysics, drug-membrane interactions, and other biological processes. Overall, liposomes are versatile delivery systems with a wide range of applications, making them valuable tools in pharmaceuticals, cosmetics, and research. [34]

CONCLUSION

It has been established that liposomes are incredibly effective drug delivery vehicles. Liposomes with enhanced drug delivery to disease locations along with long circulation residence times, are now achieving clinical acceptance. Liposomes have been used in a broad range of pharmaceutical applications. Hence the development of deformable liposomes and ethosomes along with the administration of drug

loaded liposomes through inhalation and ocular route are some of the advances in the technology. Drugs encapsulated in liposomes can have a significantly altered pharmacokinetics. The flexibility of their behaviour can be exploited for the drug delivery through any route of administration and for any drug material irrespective of their solubility properties Pharmacokinetics of drugs enclosed in liposomes can be dramatically changed. irrespective of the solubility characteristics of the drug material, the flexibility of their behaviour can be used to administer the medication by any route of administration. The phospholipid bilayers enclose the medications, which are anticipated to gradually diffuse out of the bilayer. The liposomal formulation's efficacy is contingent upon its capacity to transport the drug molecule to the intended place for an extended duration, while concurrently mitigating the drug's harmful effects.

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HOW TO CITE: Shraddha Vaishnav, Kashish Khairnar, Mrunali Kothavade, Liposomes: Versatile Nanocarriers in Modern Drug Delivery Systems - A Comprehensive Review, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 4, 723-734. https://doi.org/10.5281/zenodo.10965869