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A Review on – Liposomes as a Novel Drug Delivery System

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ABSTRACT

A flexible and promising drug delivery method are liposomes. Site-targeting, delayed or controlled release, protection of medications from degradation and clearance, increased therapeutic effects, and fewer harmful side effects are some of the advantages of liposomes over alternative drug delivery methods. Liposomes offer numerous advantages and applications due to their efficaciousness as drug carriers in pre-clinical and clinical investigations. Furthermore, problems related to liposomal stabilization, effective targeting strategies, and some of their limitations were covered. The development of liposomes has made it possible to alter the way that many medications are biodistributed, which has improved the substances' medicinal qualities. To sum up, the purpose of this research is to examine the liposomes that are presently available on the market and are employed for a variety of medicinal purposes.

Keywords: Liposomes, Drug delivery, Liposome Production, Applications, Commercialized products.

I. INTRODUCTION

Specific lipids naturally form liposomes, which are colloidal or microparticulate carriers, when they are hydrated in aqueous conditions. [1] Phospholipid layers comprise one or more sphere-shaped vesicles known as liposomes. These are referred to as nano-liposomes and range in size from 10-9 m. [2] Bangham made the initial discovery of the term "liposome" in 1965. The phrase is taken from the Greek words "lipo," which means "fatty constitution," and "soma," which means "structure." [3] Other names for it are lipid vesicles or simply vesicles. Over the years, liposomes have been widely used as model biomembranes and as delivery methods for a range of bioactive compounds due to their size, amphiphilic nature, and biocompatibility. [1] Its special capacity to ensnab both hydrophilic and lipophilic substances. [3]Liposomal drug administration can target tissue on lipid membranes with or without target recognition molecule expression. The most popular medication delivery method for systemic (intravenous) drug administration is liposomes. [2] due to their potential to simplify site-specific medication administration to tumor tissues and their biocompatibility, biodegradability, low toxicity, and capacity to capture

both hydrophilic and lipophilic medicines. [3]Drugs encapsulated in liposomes can be targeted actively and passively in which it reduces target effects and improves efficacy.Encapsulation within liposomes protects compounds from early inactivation,degradation and dilution in the circulation.[2]Various nanocarriers like nanoparticles, microparticles, polysaccharides etc…, can be used to a targeted drug delivery system. [3] It is use as vehicle for administration of nutrients as well as pharmaceutical drugs. It shows both characteristics- A) Hydrophilic head B) Lipophilic tail. [4]

When phospholipids are hydrated in an aqueous media or solution, these vesicles are created. [3]

II. STRUCTURE OF LIPOSOMES: [3,4,5,6,7,8]

Circular soft-matter vesicles called liposomes are created when one or more bilayer membranes split apart to isolate aqueous media from one another. [3] Lipid bilayer size is the component of liposomes. - 50–1000 nm in diameter, which serves as focused delivery vehicles for biological compounds that are active. [4]

The two main components of a liposome are cholesterol and phospholipid.

Phospholipids:

The main structural elements of liposomes are phospholipids. These come from the phosphatidic acid [5]. Glycerol moieties form the backbone of the molecules. [6]

The OH group is esterified to phosphoric acid at position C3. OH is esterified with a lengthy chain at C1 and C2. The lipidic character is due to fatty acids. There are other organic alcohols that can be obtained by further esterifying one of the phosphoric acid's remaining OH groups, such as glycerol, choline, ethanolamine, serine, and inositol. Therefore, the phosphoric ester of glycerol is the parent component of the series. [8]

Example of phospholipids are:

- Phosphatidyl choline (Lecithin)
- Phosphatidyl ethanolamine (Cephalin)
- Phosphatidyl serine (PS)
- Phosphatidyl inositol (PI)
- Phosphatidyl glycerol (PG).

For stable liposomes, saturated fatty acids are used. Unsaturated fatty acids are not used generally. [6]

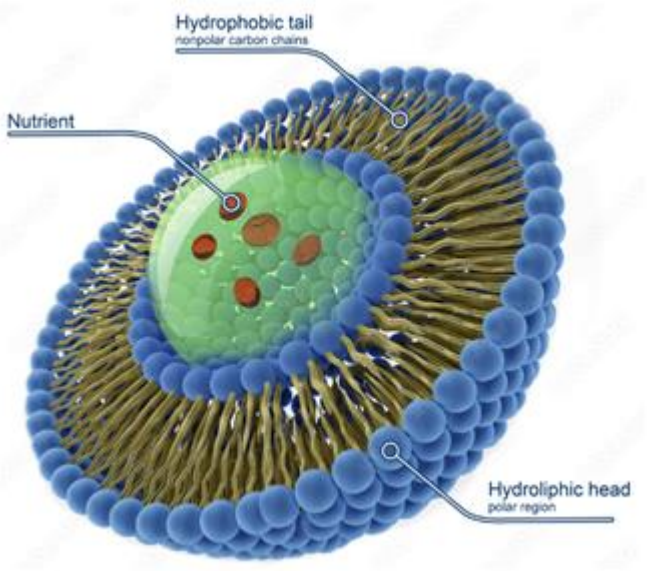

Fig 1. Structure of Liposmes[3]

Cholesterol:

One of the other ingredients in liposomes is cholesterol. [4] It doesn't create a bilayer structure on its own. It is integrated into phospholipids at very high concentrations, up to a molar ratio of 1:1 or 2:1 between phosphatidyl choline and cholesterol. [5] Liposome particle size is influenced by cholesterol content. [4] The lipid bilayer becomes more stable and forms a stiff, highly structured structure when cholesterol is present.Cholesterol increases the fluidity and durability of cellular membranes while decreasing the permeability of molecules that are soluble in water. [5] Low-cholesterol liposomes interact with transferrine, macroglobulin, and albumin, which are plasma proteins. These proteins have a tendency to remove large amounts of phospholipids from liposomes, which weakens the vesicles' monolayer and causes physical instability. [6]

Advantages of Liposomes:[4,9,10,11]

- Liposome is immuneogenic, non-toxic, fully biodegradable, and biocompatible.
- If encapsulation is used to prepare the liposome, stability will increase.
- Targeted drug delivery is made possible by liposomes, which have the ability to encapsulate medications and transfer them to particular target tissues or cells. As a result, there are fewer adverse effects and less exposure of healthy tissues to the medication.
- Able to transport medications soluble in lipids as well as water.
- Liposomes lessen the amount of harmful medications that are exposed to delicate tissues.
- Increased Bioavailability: Drugs that are not very soluble in water can be better dissolved and bioavailable with the help of liposomes, which can play a significant role in the efficacy of the medication.
- Sustained Release: Drugs can be released by liposomes gradually over time, resulting in long-lasting therapeutic effects and a decrease in the frequency of doses required.
- Enhanced Cellular Uptake: Liposomes have the ability to increase the cellular uptake of medications or therapeutic agents, increasing their efficacy in the treatment of illnesses.
- Applications in Cosmetics: Liposomes help cosmetics work more effectively by facilitating the skin's absorption of active substances.
- Food Technology: To improve the quality and shelf life of food items, tastes, vitamins, and nutrients are encapsulated and protected by liposomes in the food business
- Liposomes are essential for the stable transport of antigens, which boosts immune responses and aids in vaccine development.
- Biocompatibility: Liposomes can be used for a variety of medical and cosmetic purposes because they are typically well-tolerated by the body.
- Research Instruments: In biomedical research, liposomes are useful instruments for introducing biomolecules, dyes, or other substances to cells for examination.
- Diagnostic Applications: Drug screening, disease detection, and other diagnostic objectives are served by liposomes in diagnostic assays.
- Immunogenicity: By augmenting the immunogenicity of vaccines, liposomes can provide a more potent and targeted immune response.
- Customization: By altering liposomes' size, charge, and surface functioning, researchers may tailor them for certain uses.

Disadvantages of Liposomes:[9,10,11,12]

- Storage Stability: During storage, liposomes may become unstable and undergo aggregation, encapsulated material leakage, or structural and/or morphological changes.
- The expense of production is substantial.
- They have a brief half-life.
- Uniformity: The performance and reproducibility of liposomes can be affected by the difficulty of achieving consistency in liposome size and composition.
- Restricted Drug Loading: When attempting to provide high dosages of some medications, liposomes' limited ability for drug loading may present a challenge.
- Clinical Translation: Not all liposome-based treatments have made the transition to clinical use smoothly, despite encouraging preclinical study outcomes. This underscores the difficulties in transferring lab discoveries to practical uses.
- Biodegradability: The slow rate of biodegradation of liposomes, which might cause environmental problems, depends on their composition.

- Drug or molecules that are enclosed leaking and fusing.

Classification of Liposomes: [3,4,6,8]

1) **Classification of liposome depending upon size and shape**
   a) Multilamellar vesicles (MLV)
   b) Large unilamellar vesicles (LUV)
   c) Small unilamellar vesicles (SUV)
2) **Classification of liposome according to composition**
   a) Conventional liposome
   b) PH- sensitive liposome
   c) Cationic liposome
   d) Long circulating liposome
   e) Immuno- liposome
3) **Classification of liposome depending upon production method**
   a) Passive loading technique
   b) Mechanical dispersion method
      - Lipid hydration by hand shaking or freeze drying
      - Micro emulsification iii) Sonication
      - French pressure cell
   c) Solvent dispersion method
      - Ethanol injection
      - Ether injection
      - Double emulsion vesicle
      - Reverse phase evaporation
   d) Detergent removal method
      - Dialysis
      - Detergent removal of mixed micellar
      - Dilution
   e) Active loading technique

Mechanism of Formation of Liposomes:[2,3,6]

It is necessary to have a rudimentary understanding of the physiochemical properties of phospholipids in order to comprehend why liposomes form when they are hydrated.

Various tactics such as size transformation, fusing of the produced vesicle, and substitution of organic solvent were also employed in the synthesis of liposomes.

The mechanism involves the following steps:

a) Hydrophilic and hydrophobic chemicals are combined with phospholipids in an aqueous medium.
b) To protect their hydrophobic portions from the water molecules, phospholipids assemble into complexes. Lipid-dissolved hydrophobic substances become retained within liposomal bilayers.
c) When the phospholipids are sufficiently energy-rich, the bilayer sheet organizes into closed, well-organized bilayer vesicles. Liposomes have the ability to ensnare hydrophilic substances from the hydration environment within their watery cores during this process.

Mechanism of Drug Delivery through Liposomes:[2,3,13]

Liposomes hold significant promise for regulating the release of pharmaceuticals at a preset rate and for efficiently delivering medications to their sites of action. Liposomes are lipotropic liquid crystals with an aqueous core encased in one or more bilayers of natural or synthetic lipids. They are made of materials that are biocompatible and generally biodegradable.A chance to improve the therapeutic indices of different agents has been presented, primarily by switching up the bioavailability of medications through reformulation.

The steps involved in the liposome action of drug delivery include:

- Adsorption
- Endocytosis
- Fusion
- Lipid exchange

1. Adsorption:

One of the crucial mechanisms for intracellular drug delivery is liposome adsorption to cell membranes. When cell surface proteins are present, the adsorbed liposomes become brittle and leak the necessary

contents into the cell membrane. leads to an increase in drug concentration at the cell membrane and promotes drug uptake by passive diffusion or transport.

2. Endocytosis:

Following liposome adsorption on the membrane of the cell, endosomes internalize and swallow the liposomes. Liposomes are transported to lysosomes via endosomes. The medication that has been captured is then released into the cytoplasm by lysosomal enzymes breaking down the lipids.

3. Fusion:

Direct transport of liposomal contents into the cytoplasm is achieved by fusing the lipid bilayer of liposomes with the lipoidal cell membrane by lipid intermixing and lateral diffusion.

4. Lipid exchange:

Lipid transfer proteins in the cell membrane identify liposomes and subsequently produce lipid because the phospholipids in the liposomal membrane and the cell membrane are comparable. As a result, drug molecules are released intracellularly and liposomal membranes become unstable.

Knowing the mechanisms underlying liposomes' intracellular drug delivery paves the way for modifying liposome properties to improve the liposomes' favorable interaction with cell membranes and, consequently, drug delivery.

Method of Preparation: [3,5,10,14,15,16]

GENERAL METHOD OF PREPARATION:

Step1: Dissolve 10-20mg/lit of lipids in chloroform.

Step2: Discard the solvent by using rotary evaporator to produce thin film of lipids.

Step3: Desiccate the thin film for required time.

Step4: Hydrate desiccate product for required time. After complete hydration, the liposomes of multilamellar vesicles are produced in the size range of 200-1000nm.

Step5: Reduce the MLVs size by extrusion.

Step6: Purify the resultant liposome.

Step7: Analyse the final product

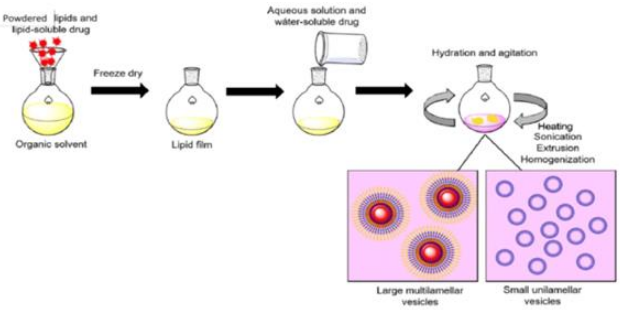

Fig.2 General Method of Preparation of liposomes

OTHER METHODS:

The different methods involved in preparation of liposomes include:

1. **Passive loading techniques:**
   - A. Mechanical dispersion method
     - Sonication
     - French pressure cell
     - Membrane extrusion
     - Microencapsulation
     - Lipid hydration method
     - Membrane extrusion
   - B. Solvent dispersion method
     - Ethanol injection
     - Ether injection
     - Double emulsion
     - Reverse phase evaporation
   - C. Detergent removal method
2. **Active loading techniques:**
   - i. Proliposomes
   - ii. Lyophilization

1. Passive loading techniques:

This method is employed to encapsulate the medication while liposomes are being formed. By combining with the hydrating buffer, which is utilized to hydrate the thin lipid film during liposome synthesis, the hydrophilic medicines are loaded into the interior core of the liposomes. By using gel-filtration chromatography and dialysis, the drug molecules that have become freed are extracted from the liposome suspension.

A. Mechanical Dispersion Method:

Sonication:

The technique most frequently used to prepare SUVs is sonication. Here, MLVs are sonicated in a passive atmosphere using either a bath-style or a probe-style sonicator. This method's primary drawbacks include its extremely tiny internal volume, poor encapsulation effectiveness, phospholipid breakdown and big molecule removal, metal contamination from the probe tip, and the existence of MLV in addition to SUV. Two methods of sonication exist:

a) **Probe sonication:**The liposome dispersion is immediately submerged in this sonicator. This process involves a very high energy input into the lipid dispersion. The vessels must be submerged in an ice or water bath because the coupling of energy at the tip causes localized heat. Over 5% of the lipids can be deesterified during the sonication process for up to one hour. Titanium determination flake off and contaminate the solution while using the probe sonicator.

b) **Bath sonication:**The liposome-containing cylinder is submerged in a bath sonicator at a regulated temperature; this is typically a simpler procedure than sonication by direct dispersion using the tip. The substance is being sonicated and can be shielded by an inert environment, a sterile vessel, or a probe unit.

Advantages:

- This helps in speed dissolution.
- It helps in stirring the sample in NMR tubes.
- It also produce energy for certain chemical reactions to proceed.

Disadvantages:

- Chance of metal pollution.
- Very low internal volume.
- Elimination of large molecules.

- **French Pressure Cell:**

The process of ejection of MLV through a tiny hole is used in French pressure cells. The fact that the proteins appear to be relatively unpretentious while undergoing sonication is a noteworthy aspect of the French press vesicle approach. It's worth noting that French press vesicles, which are generated through sonication or detergent removal, seem to recall encapsulated solutes far longer than SUVs do. The technique calls for handling unstable materials with care. The approach is superior to the sonication method in a number of ways. As a result, the liposomes resemble sonicated SUVs in size. The method's shortcomings are that it can be challenging to reach the high temperature and that the working quantities are very small—the maximum being 50 mL.

- **Membrane extrusion:**

Using this technique, multilamellar vesicles are forced to flow through a polycarbonate membrane at a pressure of about 250 psi. Until only a single, tiny layered vesicle is left, the layers of multilamellar liposomes peel off.

Advantages:

- Produce homogenous size range and suitable to produce stable liposomes with a variety of lipids.

Disadvantages:

- High pressure is required.
- Not effective as sonication and produces relatively larger vesicles.

- **Microemulsification method:**

The commercial development of tiny lipid spheres employs this technique. This could be achieved by micro-emulsifying fatty blends under the shearing stress of a homogenizer. For natural applications, microemulsion can be produced by increasing the rotation rate from 20 to 200.

- **Lipid hydration method:**

The hydration approach is the most common and extensively utilized technique for MLV preparation. The process entails dehydrating the lipid arrangement, vortexing the dispersion, and adding

fluid buffer before hydrating the thin layer. The stage of hydration is finished. Substances that need to be enclosed are either added to an organic solvent containing lipids or a watery buffer, depending on how soluble they are. Hydrating the lipids next to immiscible solvents, including diethyl ether and petroleum ether, can address the decreased application efficacy. After that, it is emulsified using sonication. MLVs are created by releasing a natural layer by the passage of nitrogen.

B. Solid Dispersion Method:

- **Ethanol injection:**

A massive excess of buffer is immediately injected with an ethanol lipid solution. Immediately, the MLVs are produced. The method's drawbacks include the population's heterogeneity (30 to 110 nm), the liposomes' extreme diluteness, the difficulty of removing all of the ethanol because it forms an azeotrope with water, and the high likelihood of the various biologically active macromolecules inactivating in the presence of even minute amounts of ethanol.

- **Ether injection method:**

Lipids are dissolved using this approach in either ether/methanol or diethyl ether. After that, an aqueous solution containing the substance to be encapsulated is injected with this lipid mixture. This is done at lower pressure or at a temperature between 55 and 65 degrees Celsius. The use of vacuum causes organic solvents to evaporate. At last, liposomes are produced.

- **Double-Emulsification Strategy:**

This method, called the Depo Foam platform TM, is used by three commercial products, DepoCyte, DepoDur, and Eliminate, to create MLVs. The composition of a "water-in-oil" emulsion, a "water-in-oil-in-water" emulsion (Ye et al., 2000), soluble extraction using vacuum weight or stripping gas, and microfiltration for the concentration, exchange, and release of that free drug Mantripragada (2002). Aseptic evidence should be supplied during the manufacturing procedure since MLVs resulting from the lower scale molecular measure cannot be created as sterile bunches through the 0.22 m filtering. The drug seeps from the inner fluid stage of the second emulsion due to a few MLVs breaking; this lowers embodiment competency during the dissolvable evacuation. Furthermore, the elevated temperature encourages the flexibility and alteration of the lipid bilayer, leading to lipidcombination and the closure of the fluid compartments.

- **Reverse phase evaporation technique:**

Firstly, a two-phase structure including phospholipids in naturally dissolvable materials such as isopropyl ether, diethyl ether, or a mixture of isopropyl ether and chloroform with aqueous buffer is rapidly sonicated to generate the water-in-oil emulsion. Natural materials crumble under lighter weights, forming a polymer. The primary advantage of this technique is that the liposomes were 80% or more firmly packed.

C. Detergent removal method (removal of non-encapsulated material):

Lipids have been solubilized by dialysis the detergents at their critical micelle concentrations (CMC). The micelles are more richer in phospholipid as the detergent separates from them, and eventually they unite to form LUVs. Through dialysis, the detergents were eliminated. For the removal of detergents, there is a commercial equipment called LipoPrep (Diachema AG, Switzerland) that is a dialysis system version. Dialysis can be carried out in dialysis bags submerged in large buffers devoid of detergent (equilibrium dialysis). Removal of mixed micelles by detergent (cholate, alkyl glycoside, Triton X-100) (absorption) In order to achieve detergent absorption, a mixed micelle solution is shaken with beaded organic polystyrene adsorbers, such as Bio-beads SM2

(Bio-Rad Laboratories, Inc., Hercules, USA) and XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany). Detergent adsorbers have the significant advantage of being able to remove detergents that have a very low CMC and are partially exhausted.

2. Active loading techniques:

During active loading, liposomes with a transmembrane gradient—that is, with distinct aqueous phases inside and outside the liposomes—are first produced. A medication that is amphipathic is then dissolved in the external aqueous phase so that it can penetrate the phospholipid bilayer. contact between the core and the trapping agent after penetration to lock in the medication. Deamer and Nicols showed in 1976 that loading catecholamine into liposomes with a pH gradient could result in stable drug retention in vitro.

Advantages:

- Encapsulation efficiency and capacity is higher.
- Leakage of encapsulated drug is less.
- It gives freedom of using any type of lipid.

Disadvantages:

- This technique is not suitable for hydrophobic drugs.
- It also requires presence of weakly basic functional groups.
- This process requires certain conditions, such as pH or electrostatic gradient which will help the drug to cross the lipid membrane.

Evaluation parameters of liposomes: [3,4,6,17]

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

1. Particle Size Determination:

Size, shape, surface features, release profile, and phase behaviors are just a few of the criteria that are evaluated during physical characterisation.

The methods listed below can be used to determine the liposomes' particle size and particle size distribution:

- Laser light scattering
- Transmission electron microscopy

2. Surface charges:

Surface charge is measured using a technique based on Multi-Layer Varistors (MLVs) free-flow electrophoresis.

- A cellulose acetate plate soaked in a pH 8.8 sodium borate buffer is used.
- After applying roughly 5N moles of lipid samples to the plate, it is electrophoresed for 30 minutes.
- Depending on the charges on their surfaces, the liposome gel splits into two halves. This method can be used to identify any contaminants, such as fatty acids, and to ascertain the heterogeneity of charges in the liposome suspensions.

- **Encapsulation Efficiency:**

The amount of medication included in the liposomes aids in estimating how the medication will behave in a biological system. To determine the percentage of drug encapsulation, the free drug fraction and encapsulated drug fraction must first be separated. Afterwards, using the appropriate detergents, the encapsulated fraction is allowed to flow off the liposomes into an aqueous solution.

3. Phase Behaviour:

At the transition temperature, liposomes experience a reversible phase transition, in which the disordered polar head group of the gel state gives way to the liquid crystalline state. Differential scanning calorimetry can be used to investigate the phase behavior of liposomes. The transition temperature represents the drug entrapment zone as well as the stability and permeability of liposomes.

4. Drug Release Study:

The release medium was 500 ml of 20% ethanol; 10 ml of the release medium was drawn and put into a dialysis bag. After clamping and attaching the dialysis bag to a dissolving apparatus' paddle, 5 ml of drug-containing liposomes and 5 ml of an ethanol solution

containing the same amount of drug were dissolved in the dialysis vessel at 37°C and 300 × g, respectively. 100 µl of the dialysis bag's fluids were sampled at 1, 2, 4, 6, 8, 10, 12, and 24 hours in order to determine the sample and compute the accumulative release rate. To create a release curve, the time (t) was used.

FUTURE SCOPE [16]

Liposome-based formulations may be the best method for delivering vitamins, minerals, phytochemicals, and lipophilic bioactive substances. One possible use of liposomal drug delivery systems in the pharmaceutical industry has been identified via research into the targeted delivery of liposomes to cancer cells or tumors.

Application of Liposomes: [3,4,6, 14,15,16,17]

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

- **Respiratory Disorders:**

As compared to conventional aerosols, liposomes have been proven to be particularly effective in the treatment of respiratory illnesses due to their sustained release, improved medicinal product stability, and minimal adverse effects. Both dry and liquid forms can be nebulized and taken in liposomal form.

- **Tumor therapy :**

It has already been demonstrated that carrier liposomes work as nanocarriers in chemotherapy treatments. For chemotherapy, numerous medication compositions have previously received approval.

- **Food application :**

Nowadays, the food industry uses most microencapsulation techniques based on biopolymer matrices made of sugar, starch, gum, protein, synthetic, dextrin, and alginates. Still, the use of liposomes in food items has started to grow recently.

- **Drug targeting:**

Using ligands (such as antibodies, sugar residues, apoproteins, or hormones) that are tagged on the lipid vesicles is the method for drug targeting via liposomes. Lipid vesicles concentrate at specific target sites because the ligand binds to those receptor sites. This method avoids or reduces the liposomes' otherwise preferred distribution into the reticuloendeothelial system (RES), which includes the liver, spleen, and bone marrow.

- **Diagnostic imaging :**

In addition to technique, proper signal intensity from an area of interest is required in diagnostic imaging to distinguish particular structures from surrounding tissues. However, molecular imaging plays a significant part in illness diagnosis and treatment tracking. When liposomes are combined with certain targeting ligands and imaging molecular probes, they can be directed to particular disease tissues. These probes are liposome-loaded in four different ways: (i) by integrating into the liposome as it forms, (ii) by penetrating the preformed liposome's lipid bilayer, (iii) by encapsulating the liposome using a variety of active techniques, and (iv) by adhering to the liposome's surface.

- **Ophthalmic Disorders:**

Liposomes have demonstrated efficacy against a variety of ocular conditions, such as corneal transplant rejection and dry eyes. For eye conditions, the liposomal version of the medication verteporfin has been licensed.

- **Gene therapy:**

Liposomes a reutilized widely in gene applications to cure diseases.

III.CONCLUSION:

Liposomes have found widespread use in medicinal applications. As intracellular delivery methods for anti-sense compounds, ribosomes, proteins/peptides, and DNA, liposomes are demonstrating particular

potential. Additionally, liposomes facilitate the targeting of specific diseased cells at the site of the illness. In summary, liposomal medications demonstrate decreased toxicity and maintain higher efficacy when compared to free complements. Which of the aforementioned applications and theories will turn out to be effective is a question best answered in time.However, we may conclude that liposomes have cemented their place in contemporary delivery systems based on the pharmacological uses and products that are currently accessible.

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