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A Review on Liposomal Drug Delivery System

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Abstract:- In 1961, Bangham and his team invented liposomes, which are concentric bilayer vesicles. They are quite effective and have a high potential for drug entrapment. They are the most often employed drug delivery vehicles due to their size, hydrophobic, and lipophilic nature. Direct drug delivery to the site of action is the major goal of this drug delivery system, which will extend and increase the effects of the treatment. Both hydrophilic and lipophilic drugs can be contained inside liposomes, which are biocompatible and stable. The range of sizes is from 0.05 to 5.0 mm in diameter. Some conventional methods used for liposomal manufacturing and size reduction include mechanical dispersion, solvent dispersion, and detergent removal techniques. Liposomes can be divided into categories based on their size, charge, state, and other characteristics due to variations in the manufacturing process and lipid composition. A liposome is a drug delivery system used to administer various types of medications or active substances, both of which are necessary for the treatment of various diseases. The reason a liposome is also known as a targeted drug delivery system is that it is a very effective drug delivery system for delivering active medication to a specific area of the body without entrapping or impacting other areas of the body. To treat specific diseases, liposomes are available in a range of sizes to serve as the carrier for medications or drugs targeted to the active site at a specific rate and time without damaging other body parts. Colloidal spheres containing cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long-chain unsaturated fats, layer proteins, and active atoms are also present in this system, which is also known as a vesicular system. They are an extremely helpful copy, reagent, and tool in many domains of modern study, including maths and theoretical physics, biophysics, chemistry, colloid science, biochemistry, and biology. Liposomes have since made their way onto the market. This page gives a general review of liposomes, including their benefits, drawbacks, mode of action, classification, structural makeup, preparation, uses, and future implications.

Keywords:- *Liposomes, Classification, Preparation, Mechanism, Purification, Applications.*

I. INTRODUCTION

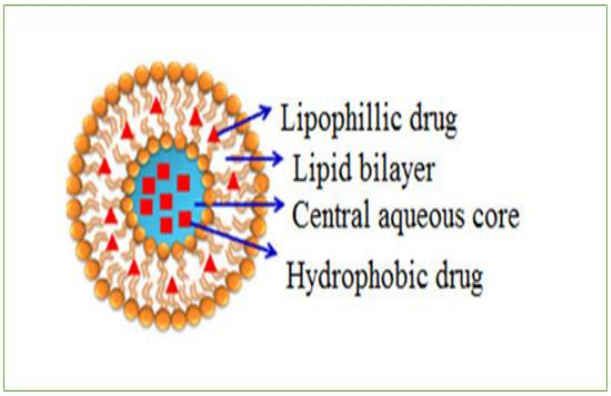

Fig No. 1– Structure of Liposome.

When Paul Ehrlich researched a drug delivery method that would direct medication to damaged cells, or what he called "magic bullets," he launched an era of development for targeted delivery.[1] In a colloidal, vesicular structure known as liposomes, an equal number of aqueous compartments are surrounded by one or more lipid bilayers. The liquid interior of the sphere-shaped shell contained peptides and proteins, hormones, enzymes, antibiotics, antifungal agents, and anticancer agents. Due to metabolism and elimination, a free medication injected into the bloodstream often only maintains therapeutic levels for a short time. Drugs enclosed in liposomes maintain therapeutic levels for a long time because the medication must be released from the liposome before it can be metabolized and excreted. [2-3]

The Greek words “lipo”, which means "fat," and “soma”, which means "body," are combined to form the name liposome. A liposome is a type of drug delivery system that represents a colloidal, vesicular structure and is made up of one or more lipid bilayers (the outer layer), as shown in Figure 1, and an equal number of aqueous layers (the inner layer), which contains peptides, proteins, hormones, enzymes, antibiotics, antifungals, and anticancer agents. With the help of this delivery method, drugs can effectively treat a specific ailment for a long time without having any adverse effects on the body as a whole.[4]

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Liposomes are small, spherical vesicles that can be made from a variety of substances, including membrane proteins, non-toxic surfactants, sphingolipids, glycolipids, and fatty acids with long chains. When phospholipids are dissolved in water, they naturally form a closed structure with an internal aqueous environment enclosed by phospholipid bilayer membranes. This vesicular system is known as a liposome.[5] Liposomes are a type of drug delivery system that may carry a wide range of materials, including plasmids, proteins, nucleotides, and tiny drug molecules. In 1961, Dr. Alec D. Bangham, a British hematologist, published the first description of liposomes. When Bangham and R. W. Horne were experimenting with the institute's new electron microscope by adding negative dye to dried phospholipids, they discovered liposomes. The first definite proof that the cell membrane is a bilayer lipid structure was provided by the similarity to the plasma lemma and the microscopy images. The size, content, charge, and lamellarity of liposomes can be altered during formulation and processing. [6] Commercialized medicinal medication compositions in liposomal form exist.

II. THE FOLLOWING OPTIMAL QUALITIES ARE ACHIEVED THROUGH LIPOSOME DESIGN.

- Liposomes have features similar to those of a biofilm at the nanoscale.
- Liposomes are also possessing excellent biocompatibility, becoming more & more useful in drug development as the delivery system.
- Hydrophilic medications may be contained in liposomes' aqueous phase, and lipophilic drugs should be targeted by the phospholipid bilayer of the liposomes.
- Drug loading and drug release rate management.
- Overcoming liposomes' quick clearance.
- Drug delivery inside cells.
- Ligand-targeted liposome endocytosis by receptors.
- Triggered discharge.
- Delivery of DNA and nucleic acids.[7]

➢ *Advantages of liposomes: -*

For systemic and non-systemic applications, liposomes are non-toxic, totally biodegradable, biocompatible, adaptable, and nonimmunogenic.

- Deliver a controlled, prolonged release.
- Drugs that are soluble in lipids, as well as water, are carried.
- From oxidation, the medication can be stabilized.
- Controlled hydration; site-specific or targeted medication administration.
- For systemic and non-systemic administrations, biocompatible, non-toxic, adaptable, biodegradable, and non-immunogenic materials.
- Passive targeting that is specific for tumor tissues & reduced toxicity.
- Enhanced therapeutic effectiveness and therapeutic index.
- A controlled, sustained release, side effect avoidance.
- The stability of encapsulation is improved.
- Appropriate for medications that are hydrophobic, amphipathic, and hydrophilic.[8]

➢ *Disadvantages of liposomes: -*

- Decrease solubility.
- A relatively short half-life.
- High cost of production.
- Drug/molecule encapsulation leakage and fusing.
- Decrease stability.
- Phospholipids may undergo oxidation or hydrolysis.[9]

➢ *Classification of liposomes: -* [10]

The liposomes may be classified based on

- Structure
- Method of preparation
- Composition
- D. Conventional liposome
- E. Specialty liposome

A. *Based on their structural parameters-*

1. **Unilamellar vesicles (ULV): It consists of a single lipid bilayer further divided into giant unilamellar liposomes/vesicles (GUV) groups, large unilamellar liposomes/vesicles (LUV), medium unilamellar vesicles (MUL), and small unilamellar liposomes/vesicles (SUV).**
   - Giant unilamellar vesicles (GUV) - Size range from 1-200 µm.
   - Small unilamellar vesicles (SUV) - Size ranges from 20-40 nm.
   - Medium unilamellar vesicles (MUV) - Size ranges from 40-80 nm.
   - Large unilamellar vesicles (LUV) - Size ranges from 100-1000nm.
2. **Oligolamellar vesicles (OLV): Oligolamellar vesicles are defined as those that have two to five concentric lamellae. These have two to ten lipid bilayers enclosing a large internal volume.**
3. **Multilamellar vesicles (MLV):** They contain several bilayers. There are lots of other ways they can divide up the aqueous volume. Their differences are based on how they are made. The structure can be like an onion, with several SUVs being enclosed by concentric spherical bilayers of LUV/MLV.

B. Based on the method of preparation-

1. **Reverse Phase Evaporation:** A process used to create single or oligolamellar vesicles.
2. **MLV-REV:** Reverse phase evaporation-produced multilamellar vesicles.
3. **SPLV:** Stable puri-lamellar Vesicles.
4. **FATMLV:** Frozen & Thawed MLV.
5. **VET:** Vesicles prepared by Extrusion Technique.
6. **DRV:** Dehydration-Rehydration Method.

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C. Based upon composition & application-

1. **Conventional Liposomes (CL):** Cholesterol and neutral or negatively charged phospholipids.
2. **Liposomes that are pH sensitive**: Phospholipids like PE or DOPE with either CHEMS or OA.
3. **Fusogenic Liposomes:** Reconstituted Sendai virus envelopes
4. **Cationic Liposomes:** Cationic lipids with DOPE
5. **Long Circulatory (Stealth) Liposomes (LCL):** To reduce phagocyte system detection, they have derivatives of polyethylene glycol (PEG) linked to their surface (reticuloendothelial system; RES). The presence of PEG in liposomes slows their removal from the bloodstream and prolongs their duration in circulation. Pegylation is another name for the process of PEG attachment.
6. **Immuno-Liposomes:** CL or LCL that have a monoclonal antibody or recognition sequence attached.

D. Conventional liposome-

1. Natural lecithin mixtures.
2. Synthetic identical, chain phospholipids.
3. Liposome with Glycolipids.

E. Specialty liposome-

1. Bipolar fatty acid.
2. Antibody directed.
3. Methyl/ Methylene x- linked.
4. Lipoprotein coated.
5. Carbohydrate coated.
6. Multiple encapsulated.

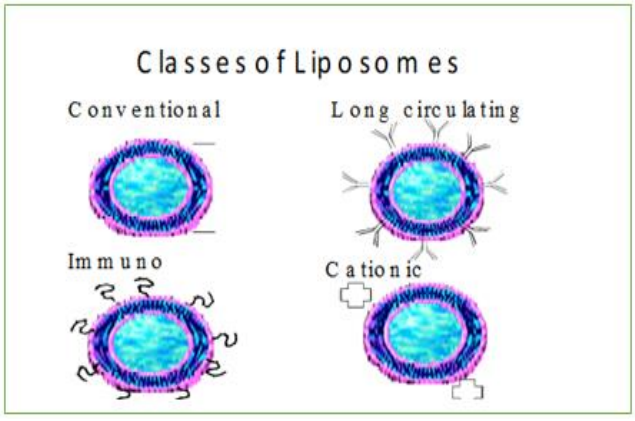

Fig No. 2 - Classes of Liposomes.

❖ **Structural components of liposomes: -** [11]

1. Phospholipids-

- The primary structural elements of biological membranes are phospholipids. Phosphatidylcholine is the most prevalent phospholipid utilized in liposomal preparation (PC). A pair of hydrophobic acyl hydrocarbon chains, a hydrophilic polar head group, a glycerol bridge, and phosphatidylcholines make up the amphipathic molecule phosphatidylcholine. Phosphatidylcholine molecules are not water-soluble. They firmly organize themselves in planar bilayer sheets in aqueous conditions to reduce the unfavorable interaction between the long hydrocarbon fatty chain and the bulk aqueous phase. The sheets then fold back on themselves to create sealed, closed vesicles.
- For the preparation of liposomes, a variety of phospholipids can be used, including Di-lauryl phosphatidylcholine (DLPC), Dimyristoyl phosphatidylcholine (DMPC), Dipalmitoyl phosphatidylcholine (DPPC), Di-stearoyl phosphatidylcholine (DSPC), Di-lauryl phosphatidyl ethanolamine, Di-myristoyl phosphatidyl ethanolamine, di-stearoyl phosphatidyl ethanolamine, and di-oleoyl phosphatidyl ethanolamine are some examples of phosphatidyl ethanolamine (DOPE).

2. Cholesterol-

Following are some details on how cholesterol affects liposome formulation:

- The preparation of these membranes is significantly altered when sterols are added to the liposome bilayer.
- The structure of a bilayer is not created by cholesterol by itself.
- A fluidity buffer, however, is provided by cholesterol. Under the phase transition, the membrane becomes slightly more disorganized and permeable, whereas, above the phase transition, the membrane becomes more stable and organized. Up to 1:1 or even 2:1 molar ratios of cholesterol to phospholipids, it can be incorporated into phospholipid membranes at very high concentrations.

III. MECHANISM OF ACTION OF LIPOSOMES: - [12]

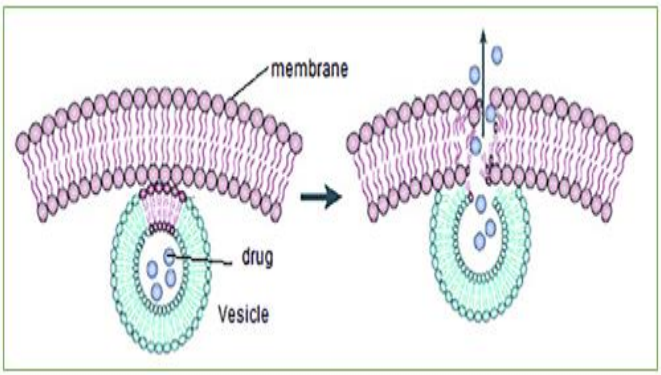

Fig No. 3– Mechanism of action of liposomes.

A region of aqueous solution enclosed in a hydrophobic membrane makes up a liposome. Due to the ease with which hydrophobic substances can be dissolved into the lipid membranes, liposomes are capable of transporting both hydrophilic and hydrophobic molecules. While the drug's physiochemical properties and lipid composition will determine its location and spread. The lipid bilayers combine with other bilayers of the cell (cell membrane) to release the liposomal content, which then transports the required drug molecules to the site of action.

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The following steps are involved in drug delivery by liposomes:
1. Adsorption: When liposomes adhere to cell membranes, they come into contact with the membrane.
2. Endocytosis: The process by which liposomes adhere to the cell surface membrane before being engulfed by the cell and internalized into the liposomes.
3. Fusion: Direct delivery of liposomal contents into the cytoplasm is achieved by the fusion of the lipid bilayers of liposomes with the lipoidal cell membrane through lateral diffusion and lipid mixing.
4. Lipid exchange: Since the phospholipids in cell membranes and the liposomal lipid membrane are similar, lipid transfer proteins in the cell membrane have an easy time identifying liposomes and causing lipid exchange.
For example, cancer cells, which need to use a lot of fat to grow quickly, see liposomes (which are packed with an anti-cancer medicine) as a potential source of nutrition. They are absorbed when a liposome targets them. Cancer cells are killed by anti-cancer medications as soon as they are released from the liposome and reach the location.

❖ **Characterization of liposomes-** [13,14,15]

When describing liposomes, it is important to consider their stability, composition, size distribution, concentration, turbidity, and presence of degradation products. These elements determine how liposomes behave in physical and biological systems; as a result, liposomes are classified according to their physical characteristics and chemical composition.

A. Biological characterization
- Sterility - Aerobic/anaerobic culture.
- Pyrogenicity - Temperature (Rabbit) response.
- Animal toxicity - Monitor animal survival (rats).

B. Chemical characterization
- Phospholipids concentration - HPLC/Barrlet assay.
- Cholesterol concentration - HPLC or cholesterol oxide assay.
- Drug concentration - Assay method
- Phospholipids peroxidation - UV observance
- Phospholipids hydrolysis - HPLC/ TLC
- Cholesterol auto-oxidation - HPLC/ TLC
- Anti-oxidant degradation - HPLC/TLC
- PH - PH meter
- Osmolarity - Osmometer

C. Physical Characterization
- Surface morphology and vesicle form - SEM / TEM
- Size and dispersion of the vesicles using TEM and dynamic light scattering.
- Surface charge - Free flow electrophoresis
- Lamellarity - NMR
- Drug release - Diffuse cell/dialysis
- pH and Zeta potential-sensitive sensors for electrical surface potential
- Electron microscopy, DSC, and phase behavior
- Centrifugation of a small column with gel exclusion, percentage capture

1. Visual Appearance

The liposomal suspension's appearance might range from clear to milky depending on the particle size and composition. Flat, grey color, most likely an inverse hexagonal phase or dispersed microcrystallites, indicates the presence of a non-liposomal dispersion. If the turbidity has a bluish tint, the samples are homogeneous. Larger liposomes greater than 0.3 μm and contamination with other particles can both be found using an optical microscope.

2. Determination of Liposomal Size

Size Distribution

Typically, dynamic light scattering is used to measure it. For this approach, liposomes with a comparatively homogenous size distribution are reliable. Gel exclusion chromatography is an easy approach to identifying a hydrodynamic radius. Liposomes with a size range of 30-300 nm can be separated using sepharyl-S100. SUV and micelles can be separated using Sepharose -4B and -2B columns.

3. Determination of lamellarity

The lamellarity of liposomes can be measured by using spectroscopic or electron microscopy methods. Most typically, the liposome NMR spectrum is captured both with and without the addition of a paramagnetic substance that changes or bleaches the signal of the detected nuclei on the liposome's outer surface.

4. Liposome Stability

Physically, chemically, and physiologically stable liposomes are ideal. Physical stability reflects the medicinal drug-to-lipid ratio and size stability. The oxidative and hydrolytic breakdown mechanisms both have the potential to alter chemical stability. Most phospholipids in liposomes that transport unsaturated fatty acyl chains undergo phospholipid oxidation. In the absence of certain oxidants, these chains oxidize. Protection against light and oxygen, as well as low storage temperatures, helps reduce oxidation.

5. Entrapped Volume

To ensure that the concentration of solute in the aqueous medium inside liposomes remains the same after separation from unentrapped material, measurements of the total amount of solute entrapped inside liposome can frequently be used to determine the entrapped volume of liposome (in L/ mg phospholipids). For example, in a two-phase preparation procedure, water from the internal compartment may be lost when it is being dried down to remove the organic solvent.

$$\% \text{ Entrapment Efficiency} = \frac{\text{Entrapped drug}}{\text{Total added drug}} \times 100$$

6. Surface Charge

It is important to understand the charge on the vesicle surface since lipids that transfer or constitute charge are typically used to create liposomes. Free flow electrophoresis and zeta potential measurement are the two techniques typically employed to evaluate the charge.

❖ *Methods of preparation of liposomes: -* [16,17,18]

For the formation of liposomes, two techniques are used: -

1. A general method of preparation
2. A specific method of preparation: - are of two types-

A. Passive loading technique: -

1. Mechanical dispersion
a) Lipid hydration method.
b) Micro emulsification.
c) Sonication.
d) French pressure cell method.
e) Membrane extrusion.
f) Dried reconstituted vesicles.
g) Freeze-thaw method.

2. Solvent dispersion
a) Ethanol injection method.
b) Ether infusion method.
c) Double emulsification.
d) Reverse-phase evaporation.
3. Detergent removal.

B. Active loading technique: -

1. Prollposome.
2. Lyophilization.

A. Passive loading technique: -

1. Mechanical dispersion

a) Lipid hydration method.

The most typical and popular way for creating MLV is this one. For the preparation, a flask with a round bottom might be utilized. The process involves drying the lipid solution to produce a thin film, hydrating the film by adding an aqueous buffer, and vertexing the dispersion. The hydration process is carried out at a temperature greater than the lipid's gel-liquid-crystalline transition temperature or greater than the transition temperature of the lipid mixture's greatest melting point. The molecules to be encapsulated are added to an organic solvent containing lipids or an aqueous buffer, depending on how soluble they are. The approach has drawbacks such as poor interior capacity, ineffective encapsulation, and fluctuating size. By hydrating the lipids in the presence of immiscible organic solvents such as petroleum ether and diethyl ether, the lower encapsulation efficiency can be overcome. Sonication is then used to emulsify it. MLVs are created by flowing nitrogen over the organic layer to remove it.

b) Micro emulsification

Small lipid vesicles are made using this technique in industrial volumes. This can be done by applying high-shearing stress produced by a high-pressure homogenizer to micro-emulsify lipid compositions. The production of microemulsion for biological purposes can be accomplished by changing the rotational speed from 20 to 200.

c) Sonication

This technique uses either a probe sonicator or a bath-type sonicator to sonicate MLVs. Very low internal volume/encapsulation efficiency, phospholipid breakdown, exclusion of big molecules, metal contamination of the probe tip, and the presence of MLV together with SUV are the main downsides of this approach.

d) French pressure cell method

The process entails forcing MLV at 20,000 pressure and 4°C through a tiny hole. The approach provides several benefits over sonication. The process is quick and easy to repeat, and it handles unstable materials gently. The final liposomes are bigger than Vehicles that have been sonicated. Less working volume and difficulties achieving temperature are some of the drawbacks (about 50 mL maximum).

e) Membrane extrusion

This technique involves passing a solution of liposomes of different sizes through a polymer filter with a web-like design that creates a tortuous-path capillary hole, a network of interconnected pores, and a membrane thickness of at least 100 microns. The size distribution of the treated liposomes is restricted, with the chosen average size being less than 0.4 microns. dried-up reconstituted vesicles. This approach involves mixing a lyophilized protein with premade liposomes, which are then added to an aqueous solution containing a medication. The mixture is then dehydrated.

f) Freeze-Thaw Method

The SUVs are quickly frozen in this way, then slowly thawed. Aggregated materials are dispersed by sonication to LUV. ULV is created when an SUV fuses during the freezing and thawing cycles. By boosting the medium's ionic strength and phospholipid concentration, this form of fusion is severely prevented. This approach resulted in an entrapment efficiency of 20 to 30%.

2. Solvent dispersion

a) Ethanol Injection Method

Rapid injection of an ethanol-lipid solution into a buffer overflow results in the instantaneous production of MLVs. The key downside of the approach is that the particles may be with heterogeneous size distribution (30-110 nm). Another downside is that it is difficult to eliminate all ethanol, which could result in the formation of an azeotrope with water.

b) Ether Infusion Method

At a temperature of 55–65°C and low pressure, an aqueous solution of the medication is slowly injected with a solution of lipids dissolved in diethyl ether or ether–methanol combination. After the ether was removed under vacuum, the liposomes were once again produced. Drug and lipid exposure to organic solvents and high temperatures,

which may lead to deterioration, are the method's principal downsides. Moreover, the size can range from 70 to 190 nm.

c) Double emulsification

The medication is dissolved in an aqueous phase (w1) using this approach, and the resulting primary w1/o emulsion is subsequently emulsified in an organic solvent of a polymer. This primary emulsion is then combined with an aqueous solution (w2) that contains an emulsifier to create a w1/o/w2 double emulsion. Microspheres are left in the aqueous continuous phase after the solvent is removed, and they are collected by centrifuging or filtering.

d) Reverse-phase evaporation

The lipid mixture is placed in a flask with a flat bottom, and then the solvent is removed using a rotary evaporator while the pressure is decreased. The lipids are redissolved in the organic phase when nitrogen is used to purge the system. In this phase, the reverse phase vesicles will form. Diethyl ether and isopropyl ether are the most frequently used solvents. After the lipids in this phase are re-dispersed, an aqueous phase containing the medicine to be encapsulated is added. The two-phase system is sonicated until the combination becomes a distinct one-phase dispersion while the system is kept under continuous nitrogen. After that, the mixture is placed on a rotary evaporator, where the organic solvent is eliminated till a gel forms and the unencapsulated substance is eliminated. Reverse-phase evaporation vesicles are the name given to the liposomes that arise.

3. Detergent removal

When detergents reach their critical micellar concentrations, lipids are solubilized. The micelles' phospholipid content increases over time as the detergent is removed by dialysis, and they eventually gather together to form LUVs. Detergent dialysis's benefits include exceptional repeatability and the creation of homogeneous-sized liposome populations. The method's primary flaw is the retention of detergent impurities.

B. Active loading technique: -

1. Proliposome-

A soluble carrier is coated with lipids and medication to make a pro-liposome, which is a free-flowing granular substance that, when hydrated, becomes an isotonic liposomal solution. The pro-liposome strategy might make it possible to produce liposomes containing especially lipophilic pharmaceuticals on a big scale and at a low cost.

2. Lyophilization

Lyophilization is the process of removing water from frozen items under very low pressure (freeze-drying). The method is typically used to dry thermolabile materials that could be ruined by heat-drying. This method has a tremendous deal of promise to address issues with liposomal stability over the long run. Leakage of entrapped components is possible both during the freeze-drying process and after reconstitution.

❖ **Purification of liposomes: -** [19,20]

Centrifugation, gel filtration chromatography, and dialysis are the typical methods used to purify liposomes. The most popular chromatographic separation material is Sephadex-50. A hollow fiber dialysis cartridge may be used in the dialysis procedure. SUVs in normal saline can be isolated using the centrifugation method by centrifuging at 200000 g for 10–20 hours. Centrifuging at 100,000 g for less than an hour separates MLVs.

❖ **Evaluation of liposomes: -** [21, 22, 23]

To ensure that it predicted in vitro and in vivo performance for a given application, liposome formulation and processing are outlined. Physical, chemical, and biological parameters make up the three basic categories into which the evaluation's characterization parameters can be divided.

- Physical characterization evaluates various parameters including size, shape, surface features, lamellarity, phase behavior, and drug release profile.
- Studies that determine the potency and purity of various lipophilic are included in chemical characterization.
- The use of biological characterization factors can help determine a formulation's appropriateness and safety for therapeutic use.

1) Shape and lamellarity of the vesicles

The average particle size can be calculated from the vesicle shape using different types of electron microscopic techniques. Using Freeze-fracture electron microscopy and 31P nuclear magnetic resonance analysis, the lamellarity of the vesicle, or the number of bilayers present in the liposomes, is evaluated.

2) The size and dispersion of the vesicles

The literature describes a variety of techniques for estimating size and size distribution. Light microscopy and fluorescence microscopy are some of these techniques. Zetasizer, Gel Permeation and Gel Exclusion, Photon Correlation Spectroscopy, Laser Light Scattering, and Electron Microscopy. Although electron microscopy is the most accurate method, it takes a lot of time.

3) Surface charge

To investigate charge on the vesicle surface, zeta potential, and free flow electrophoresis are performed. Vesicle surface charge is calculated based on the liposomal dispersion's mobility in a suitable buffer.

4) Encapsulation efficiency

It controls how much and how quickly water-soluble substances are trapped in the liposomes' aqueous compartment.

5) Drug release

Using highly aligned in vitro dispersion cells, the component of the drug released from liposomes can be examined. By using in vitro experiments to predict the pharmacokinetics and bioavailability of drugs before using

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pricey and time-consuming in vivo tests, the liposome-based definition can be aided.

IV. FUTURE SCOPE: - [24]

Future drug formulations may be transformed into convectional liposomes with improved circulation when considering liposomal drug delivery systems. Future delivery of oligonucleotides and ribozymes is also guaranteed. Future candidates for development include artificial liposomes based on blood and encapsulated allergens, which are employed in allergy treatment as desensitizers. Three key areas for development in the future are immunotherapy, diagnostic tests, and targeted drug delivery. Using a liposomal kit with a synthetic lipid bilayer composition allows for the assessment of repeatable results. Future applications for liposomal development include the food, cosmetics, nutrition, and coating sectors, among others. One of the approaches that call for future development in therapies is the spatial and temporal release of medications encapsulated in liposomes at the site of action.

Table 1 Liposomal product list for commercial use and their indications.

Drug	Product	Indication
Amphotericin B	Ambisome™	Fungal Infections
Daunorobucin	Daounoxome™	Kaposi's sarcoma
Doxorubicin	Doxil™	Refractory Kaposi's Sarcoma
Verteporfin	Visudyne®	Age Related Macular Degeneration, Pathologic Myopia and Ocular Histoplasmosis
Cytarabine	Depocyt®	Neoplastic and Lymphomatous Meningitis
Cisplatin	Lipoplatin®	Epithelial Malignancies
Morphine Sulphate	Depodur®	Postoperative Pain Following Major Surgeries

A. Liposomal formulations in the market: -

We discovered that 14 different types of liposomal products have been approved by the FDA and EMA after searching the approved medicine database on their websites (Table 1). This list does not include generic medications, lipid complexes (such as Abelcet, Amphotec, and Onpattro), or legally approved liposomal products in Europe. In 1995, the FDA approved the first liposomal product, Doxil (doxorubicin HCl liposome injection). A whopping 43% of the marketed products were approved before the year 2000, and 57% were approved before the year 2010. Although other fields, including infection, anesthetic, vaccination, lung illness, and photodynamic therapy, are also included in the therapeutic field, cancer therapy is the primary focus. The major dosing forms are lyophilized powder and sterile suspension. Intravenous infusion, intramuscular and intrathecal injection, epidural, local infiltration, and oral inhalation are some of the administration methods.

Table no. 2 The FDA and EMA have authorized a list of liposomal products.

Product Name	API	Approved Year/Area	Dosage Form	Adm. Route	Indication
Doxil Caelyx	Doxorubicin hydrochloride (DOX·HCl)	1995, US 1996, EU	Suspension	IV	Ovarian cancer, Kaposi's sarcoma, myeloid melanoma
Daunoxome	Daunorubicin	1996, US	Suspension	IV	Kaposi's sarcoma
Ambisome	Amphotericin B (AmpB)	1997, US	Lyo	IV	Systemic fungal infection
Depocyt	Cytarabine	1999, US 2001, EU	Suspension	IT	Lymphomatous meningitis
Myocet	DOX·HCl	2000, EU	3 vials	IV	Breast cancer
Visudyne	Verteporfin	2000, US 2000, EU	Lyo	IV	Wet AMD
Depodur	Morphine	2004, US	Suspension	Epidural	Postoperative pain
Mepact	MTP-PE	2009, EU	Lyo	IV	Osteosarcoma
Exparel	Bupivacaine	2011, US 2020, EU	Suspension	Local infiltration	Post-surgical analgesia
Marqibo	Vincristine Sulfate	2012, US	3 vials	IV	Leukemia
Onivyde	Irinotecan hydrochloride trihydrate	2015, US 2016, EU	Suspension	IV	Pancreatic adenocarcinoma

Product Name	API	Approved Year/Area	Dosage Form	Adm. Route	Indication
Vyxeos	Daunorubicin, cytarabine	2017, US 2018, EU	Lyo	IV	Leukemia
Shingrix	Recombinant varicella-zoster virus glycoprotein E	2018, EU	2 vials (powder and suspension)	IM	Against shingles and post-herpetic neuralgia
Arikayce	Amikacin sulfate	2018, US 2020, EU	Suspension	Oral inhalation	Lung disease

This list only includes liposomal dosage forms that have been approved by the FDA and EMA; it leaves out generic versions of drugs like doxorubicin hydrochloride (liposomal), lipid complexes like Abelcet, Amphotec, and Onpattro, as well as liposomal medications that are sold legally across Europe. Abbreviations: intrathecal injection (IT), muramyl tripeptide phosphatidyl ethanolamine, intravenous infusion (IV), intramuscular injection (IM), and lyophilization (Lyo) (MTP-PE).

B. Therapeutic applications: - [25]

- Cancer chemotherapy
- Gene therapy
- Liposomes as carriers for vaccines
- Liposomes as a drug delivery system for oral therapy
- Liposomes for topical applications
- Liposomes for pulmonary delivery
- Lysosomal storage disease
- Cell biological application
- Metal storage disease
- Ophthalmic delivery of drug

➢ *Liposomes in anticancer therapy* [26]

It has been demonstrated that multiple anticancer drugs in various liposome formulations are less hazardous than free medication. Anthracyclines are medications that kill mostly quickly dividing cells by intercalating into the DNA to limit the growth of dividing cells. This family of drugs is particularly harmful because these cells can also be found in blood cells, gastrointestinal mucosa, hair, and cancers. Adriamycin is the most widely used and researched (commercial name for doxorubicin HCl). Its dosage is constrained by its rising cardiotoxicity in addition to the aforementioned acute toxicities. There were several different formulas tested. The toxicity was typically decreased by roughly 50%. Because liposome encapsulation decreases the transport of the drug molecules to those tissues, these include both acute and chronic toxicities.

➢ *Immunological adjuvant in vaccines* [27]

Depending on how lipophilic the antigen is, liposomes can either absorb it into the bilayer or encapsulate it in their watery area. Initially, liposomes were utilized as immunological adjuvants to boost the immune response to diphtheria toxoid that had been encapsulated. As nontoxic adjuvants for bacterial, viral, protozoan, tumor, and other antigens, liposomes have also been employed. While Cervarix®, Inflexal®, and Epaxal® are commercially available liposome vaccines, several liposome formulations are currently undergoing clinical trials as adjuvants for prophylactic as well as therapeutic vaccines against malaria, influenza, tuberculosis (TB), human immunodeficiency virus (HIV), and dengue fever.

➢ *Liposome as Anti-Infective Agents* [28]

By integrating and concentrating the medication using a liposomal carrier, disorders like leishmaniasis, candidiasis, aspergillosis, histoplasmosis, erythrocytosis, giardiasis, malaria, and tuberculosis can be treated. Amikacin, Amphotericin B, and Nystatin are some examples of active liposomes used as antifungals.

➢ *Liposome in Eye Disorders* [29]

Several eye problems have been treated using liposomes. Dryness, keratitis, corneal transplant rejection, endophthalmitis, and proliferative vitriol retinopathy are all symptoms of eye disease. Blindness is frequently caused by retinal disorders. Recent strategies for treating selective cancer and neo-vascular vessel blockage, angiography, and retinal and choroidal blood vessel stasis use a focal laser for the heat-induced release of liposomal medicines and dyes. In the area of ocular medication delivery, coating nanocarriers with chitosan, especially liposomes, received considerable consideration. Chitosan gives liposomes a positive charge and a coating on their surface, enabling them to interact with the surface of the eye through electrostatic contact.

➢ *Liposome for Respiratory Drug Delivery System* [30]

Many different forms of respiratory illnesses are treated with liposomes. Liposomal aerosols can be designed for continuous release, to stop local irritation, to have lower toxicity, and to have better stability. Composition, size, charge, drug/lipid ratio, and drug delivery technique should all be taken into account while making liposomes for lung distribution. For inhalation during nebulization, either the liquid or dry form is used. The production of drug powder liposomes involves milling or spray drying. For instance, two antibacterial formulations now under development are Arikace® (liposomal amikacin) and Pulmaquin® (liposomal ciprofloxacin).

V. CONCLUSION

One of the traditional methods for delivering certain medications with controlled and precise action is the use of liposomes. These systems can be delivered topically, parenterally, or orally. Because there are so many options for administration routes, the medication delivery system

can be designed with flexibility. Moreover, these systems serve as an efficient carrier for compositions used in cosmetics. The stability issue with liposome formulation is the main issue. These issues can be resolved by making changes to the preparation process and using select specialized carriers. Today, a wide range of medications are transported using liposomes. Despite a few drawbacks, liposomes are a flexible drug delivery system for a variety of medications.

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