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# Liposomal Drug Delivery System

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**ABSTRACT:**
Liposomes have been considered promising and versatile drug vesicles. Compared with traditional drug delivery systems, liposomes exhibit better properties, including site-targeting, sustained or controlled release, protection of drugs from degradation and clearance, superior therapeutic effects, and lower toxic side effects. Given these merits, several liposomal drug products have been successfully approved and used in clinics over the last couple of decades. In this review, the liposomal drug products approved by the U.S. Food and Drug Administration (FDA) and European Medicines. Agency (EMA) are discussed. Based on the published approval package in the FDA and European public assessment report (EPAR) in EMA, the critical chemistry information and mature pharmaceutical technologies applied in the marketed liposomal products, including the lipid excipient, manufacturing methods, nanosizing technique, drug loading methods, as well as critical quality attributions (CQAs) of products, are introduced. Additionally, the current regulatory guidance and future perspectives related to liposomal products are summarized. This knowledge can be used for research and development of the liposomal drug candidates under various pipelines, including the laboratory bench, pilot plant, and commercial manufacturing.
**Key words:** Liposome, novel drug delivery, pharmaceutical application

## I. INTRODUCTION:

Liposomes are the drug carried loaded with different variety of molecules such as small drug molecules, proteins, nucleotides and even plasmids. Liposomes were first described in 1961 by British hematologist Dr. Alec D Bangham. Liposomes were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasma lemma and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure. Liposome can be formulated and processed to differ in size, composition, charge and lamellarity[1]. The name liposome is derived from two Greek words: Lipo = "fat" and Soma = "body". A liposome is the drug delivery system which is structurally seeing like a colloidal, vesicular and made up one or more than one lipid bilayer (outer layer) in which the equal number of aqueous layer (inner layer) is inclosed into it shown in which contains a substance like peptides and protein, hormones, enzymes, antibiotics, antifungal and anticancer agent .in this delivery system drug achieve the long therapeutic effect for the treatment of particular disease without affected to another part of the body[2]. Liposomes mostly consist of biocompatible and biodegradable materials capable of encapsulating both hydrophobic and hydrophilic molecules on one platform. The ongoing researches focus more on the growth of long circulating stealth liposomes and multi-functional liposomes with advanced in vitro properties[3].

A majority of anti-neoplastic agents, which are highly cytotoxic to tumor cells in vitro, affect the normal cells also. This is due to their low therapeutic index (TI), i.e., the dose required to produce anti-tumor effect is toxic to normal cells. Such drugs have to be targeted to a specific site (diseased site) in order to reduce their toxic effects to normal tissues[4]. Liposome are also defined as artificial microscopic vesicles consisting of aqueous compartment and surrounded by one or more concentric layer of phospholipid. The sphere like encapsulated a liquid interior contain more substance like peptides, protein, hormones, enzymes, antibiotic, antifungal and anticancer agents. Liposome is small artificial vesicles of spherical shape that can create cholesterol and naturally non-toxic phospholipid. They are depending upon size, hydrophobic and hydrophilic characteristic. Liposome is a spherical vesicles having at least one lipid bilayer. The membrane of liposome is made of phospholipids, which have phosphoric acid sides to form the liposome bilayers.Liposomes can be manufacturing in

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different lipid comopsitions or by different method show variation in par. Size , size distribution, surface electrical potential, no. of lamella, encapsulation efficacy, Surface modification showed great advantage to produce liposomes of different mechanisims, kinetic properties and biodistribution. Products in the market Doxorubicin (Doxil, Myocet) (KS Kaposis sarcoma) Daunorubicin (Dauno Xome) Cytarabin artificial microscopic vesicle consisting of an aqueous core enclosed in one or more phospholipid layers, used to convey vaccines, drugs, enzymes, or other substances to target cells or organs[6].

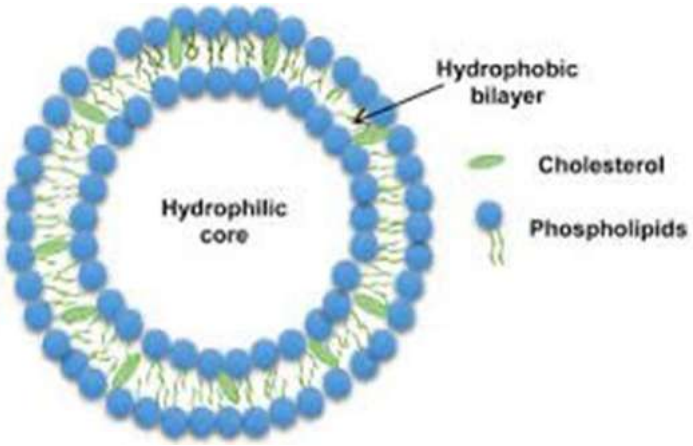


**Fig: Structure of liposome.**

**Advantges of liposome.**

- Liposomes are biocompatible, completely biodegradable, non-toxic, flexible, and nonimmunogenic for systemic and non-systemic administrations.
- Improved solubility of lipophilic and amphiphilic drugs: The hydrophobic anti-cancer drugs can be incorporated in the lipid membrane of liposome that will increase the solubility of poorly soluble anti-cancer drugs[6].
- Liposome provides selective passive targeting to tumor tissues especially cells of the mononuclear phagocytic system, for example, antimonials, amphotericin B, porphyrins, vaccines, and immunomodulators. Improved solubility of lipophilic and amphiphilic drugs.
- Increased potency and efficacy: Nanoliposomes can penetrate most of the biological membranes of the body. This results in higher accumulation of drug at the targeted site of action and increases the therapeutic index and efficacy of drug[7].
- Targeted Drug Delivery: Liposomes can encapsulate drugs and deliver them to specific target tissues or cells, allowing for targeted therapy. This minimizes the exposure of healthy tissues to the drug, reducing side effects.
- Improved Bioavailability: Liposomes can encapsulate poorly water-soluble drugs, improving their solubility and bioavailability, which can be a critical factor in drug effectiveness.
- Sustained Release: Liposomes can release drugs gradually over time, leading to sustained therapeutic effects and reducing the need for frequent dosing.
- Protection of Sensitive Compounds: Liposomes can protect sensitive drugs or bioactive compounds from degradation due to environmental factors, such as enzymes, pH changes, or oxidation[8].
- Versatility: They can be tailored in terms of size, composition, and surface modifications to optimize their performance for specific drugs or therapeutic applications.
- Reduced Toxicity: Liposomal drug delivery can reduce the toxicity of certain drugs by minimizing their exposure to healthy tissues while targeting diseased cells.
- Enhanced Cellular Uptake: Liposomes can improve the cellular uptake of drugs or therapeutic agents, making them more effective in treating diseases.
- Cosmetic Applications: Liposomes are used in cosmetics to enhance the penetration of active ingredients into the skin, improving their efficacy.

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- Food Technology: In the food industry, liposomes are used to encapsulate and protect flavors, vitamins, and nutrients, enhancing the quality and shelf life of food products.
- Vaccine Delivery: Liposomes play a crucial role in vaccine development by improving the stability and delivery of antigens, enhancing immune responses.
- Biocompatibility: Liposomes are generally well-tolerated by the body, making them suitable for various medical and cosmetic applications[9].

**Disadvantages of liposomes.**

- Storage Stability: Liposomes can be prone to instability during storage, leading to aggregation, leakage of encapsulated substances, or changes in size and structure.
- Scalability: Scaling up the production of liposomes can be challenging and costly, which may limit their widespread use in large-scale pharmaceutical manufacturing.
- Uniformity: Achieving uniformity in liposome size and composition can be difficult, affecting their performance and reproducibility.
- Short Circulation Half-Life: Liposomes can be rapidly cleared from the bloodstream by the body's immune system, limiting their time window for drug delivery[6].
- Immunogenicity: Some liposome formulations may trigger an immune response, potentially causing adverse reactions in the body.
- Limited Drug Loading: Liposomes have a finite capacity for drug loading, which can be a limitation when trying to deliver high doses of certain drugs.
- Complexity: The development of liposomal formulations requires expertise and can be a complex process, which may limit their accessibility to researchers and manufacturers.
- Expense: Producing liposomal formulations can be costly, which may lead to higher drug prices for liposome-based therapies.
- Compatibility Issues: Some drugs may not be suitable for encapsulation in liposomes due to compatibility issues, limiting the range of drugs that can benefit from liposomal delivery.
- Clinical Translation: Despite promising results in preclinical studies, not all liposome-based therapies have successfully transitioned to clinical use, highlighting challenges in translating laboratory findings to real-world applications.
- Interaction with Biological Systems: Liposomes may interact with proteins or cells in ways that affect their stability, drug release, or performance.
- Biodegradability: Depending on their composition, liposomes may not be readily biodegradable, which can raise environmental concerns[10].
- Production cost is high.
- Leakage and fusion of encapsulated.
- Short half-life.
- Stability problems.
- Allergic reaction may occur to liposome constituents.
- Problem to targeting to various tissues due to their large size.
- Phospholipid undergoes oxidation, hydrolysis[12].

**Classfication of Liposomes:**

1. Based on Structure
2. Based on Preparation.
3. Based on Composition and Application
4. Based on Conventional liposomes
5. Based on Speciality Liposomes.

**1. Based on Structur[11].**

**Table 1: Diameter Size and number of lipid layers of different vesicles Vesicle type**

| Vesicle type | Abbreviation | Diameter Size | **No. of Lipid** Layers |
|---|---|---|---|
| Unilamellar | UV | All size ranges | One |
| Small Unilamellar | SUV | 20-100nm | One |
| Medium Unilamellar | MUV | More than 100nm | One |
| Large Unilamellar | LUV | More than 100nm | One |

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| | | | |
|---|---|---|---|
| Giant Unilamellar | GUV | More than 1.0 µm | One |
| Oligo lamellar | OLV | 0.1-1.0 µm | Approx 0.5 |
| Multi lamellar | MLV | More than 0.5 µm | 5- 25 |
| Multi vesicular | MV | More than 1.0 µm | **Multi compartmental** structure |

**2. Based on Preparation[13].**

**Table 2: Different methods of preparation and the vesicles developed by those methods**

| **Preparation Method** | **Vesicle Type** |
|---|---|
| Lamellar vesicle of a single or oligo formed by reverse phase evaporation | REV |
| Multi lamellar vesicles formed by the method of reverse phase evaporation | MLV- REV |
| Stable pluri lamellar vesicle | SPLV |
| Frozen and thawed multi lamellar vesicle | FATMLV |
| Vesicle prepared by extrusion technique | VET |
| Dehydration-Rehydration method | DRV |

**3. Based on Composition and Application[14].**

**Table 3: Different Liposome with their Compositions**

| **Type of Liposome** | **Abbreviation** | **Composition** |
|---|---|---|
| Conventional | CL | Neutral or negatively charge phospholipids and cholesterol |
| Fusogenic Table 3: Different Liposome with their Compositions | RSVE | Reconstituted sendai virus envelops |
| pH sensitive | - | Phospholipids such as DOPE or PER with either OA or CHEMS |
| Cationic | - | Cationic lipid with DOPE |
| Long circulatory | LCL | Neutral high temp, cholesterol, and 5-10% PEG, DSP |
| Immuno | IL | CL or LCL with monoclonal antibody linked or sequences of recognition |

**4. Based on Conventional liposomes[15].**

a) Lecithin Mixture containing liposomes.
b) Synthetic identical chain phospholipid containing liposomes
c) Glycolipids containing liposomes.

**5. Based on Conventional liposomes[16].**

a) Antibody directed liposomes
b) Methy/ Methylene X-linked liposomes
c) Lipoprotein coated liposome

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d) Carbohydrate coated liposomes
e) Multiple encapsulated liposomes.

**Mechanism:**

- As liposomes are made up of phospholipids, they are amhpipathic in nature and have ability to binds both aqueous and polar moiety.They have polar head and non polar tail.
- The polar end is mainly phosphoric acid and it will bound to water soluble molecule.
- In aqueous medium the molecules in self-assembled structure are oriented in such way that the polar portion of the molecule remain in contact with in polar environment and at same time shields the non polar part. Liposomes are formed when the thin films are hydrated and stacks of liquid crystalline bilayers become fluid and swells.
- Once these vesicle get formed, a change in vesicle shape and morphology required energy input in the form of …. Sonic energy to get SUVs and mechanical energy to get LUVs.
- However, in aqueous mixtures these molecules are able to form various phases, some of them are stable and other remains in metastable form[17,18]

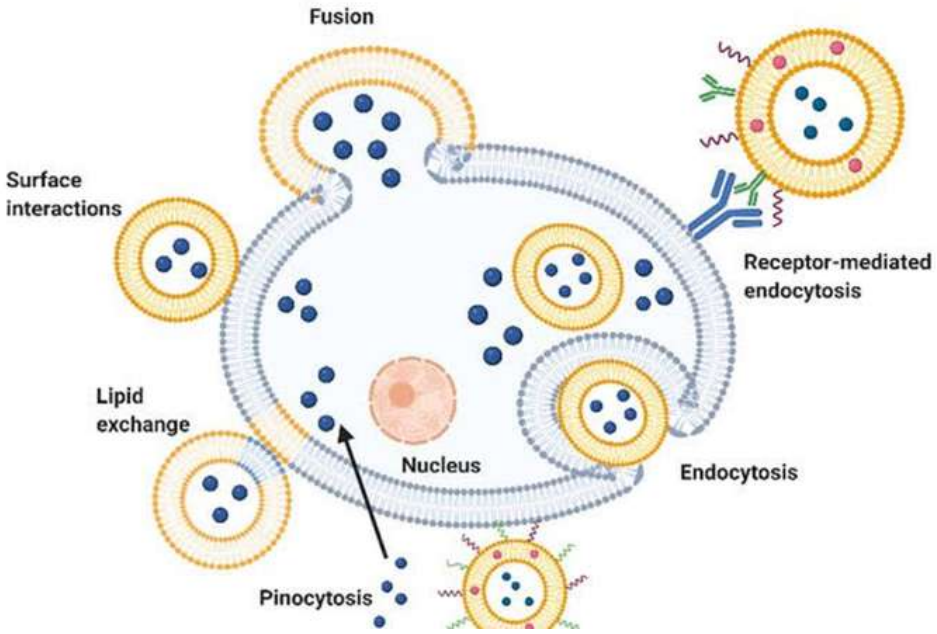


**Fig 2: Mechanism of liposomes[19].**

**Application:**

- **Drug targeting :**

Liposomes can be incorporated with opsonins and ligands (e.g., antibodies, sugar residues, apoproteins or hormones, which are tagged on the lipid vesicles) for site-specific drug delivery system. The ligand recognizes specific receptor sites and, thus, causes the lipid vesicles to concentrate at such target sites. By this approach, the otherwise preferential distribution of liposomes into the reticuloendothelial system (liver, spleen, and bone marrow) is averted and reduces the probabilities of drug-related toxicities[20].

- **Parasitic diseases and infections:**

Liposomes can be made in a particular size and used as a viable target for macrophages. These liposomes may be digested while in the macrophage's phagosome, thus releasing its drug. For this reason, they are suggested as an ideal carrier for treatment parasitic diseases which normally exist in the cell of MPS such as leishmania. Leishmaniasis is a group of endemic diseases caused by the leishmania intramacrophagic parasite and mainly affects the poorest populations. The main therapeutic agents against leishmaniasis are pentavalent antimonials, amphotericin B, pentamidine, paromomycin, and miltefosine, however, the use conventional chemotherapy for leishmaniasis due to high toxicity and serious adverse reactions, e.g., gastrointestinal disorders and cardiac arrhythmias, long duration of treatment and reports of drug-resistance are not appropriate. Liposomal encapsulated drugs appear as an option for the treatment of leishmaniasis, providing greater

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efficacy for the active and reducing its side effects by accumulate at infected macrophages and releasing drug at the desired location[21,22].

- **Liposome for Respiratory Drug Delivery System**.

Liposomes are typically used in many forms of respiratory illnesses. It is possible to formulate liposomal aerosols to develop prolonged release, avoid local inflammation, minimize side effects and improve stability throughout the vast aqueous core. Numerous injectable liposome-based drugs, including ambisome, Fungisome and Myocet, are now available in the market. To be successful, the delivery mechanism of liposomal drugs to the lungs depends on lipid composition, charge, size, drug & lipid ratio and delivery techniques. The emerging application of liposomes for DNA transmission to the lungs indicating that a better knowledge of their usage in macromolecules administration by inhalation is now developing. All of this new expertise can be used to improve liposome-based protein formulations. The liquid or dried form is utilized for liposome inhalation and the pharmaceutical is released during nebulization. Milling or sprays drying have been used to develop drug powder liposomes[23].

- **Liposomes for Brain Targeting**

Liposomes have lately gained popularity as a brain drug delivery mechanism due to their biocompatibility and biodegradability.56 Liposomes with small (100 nm) or even big diameters diffuse freely across the Blood Brain Barrier (BBB). SUVs linked to cognitive drug carriers, on the other hand can be carried across the BBB by receptor-mediated or absorptive-mediated transcytosis. Absorptive mediated endocytosis of cationic liposomes occurs in cells, however it has yet to be proven that absorptive induced transcytosis occurs across the BBB .The mannose-coated liposomes reach the brain and help in drug transport across the BBB. When systemically administered, the Leu-enkephalin, mefenkephalinkyoforphin and neutropeptides do not typically penetrate the blood-brain barrier. Due to the versatility of this approach, the anti-depressant amitriptyline usually penetrates the BBB. Nanoparticles (NP) have been developed from various stabilizers. The amount of amitriptyline was observed to be substantially increased in the brain when the drug was adsorbed to the NP and wrapped or particle remained stable with polyoxyethylene 20 sorbitan trioleate[24].

- **Liposome in Eye Disorders**

Liposomes have long been utilised to treat both the anterior and posterior regions of the eye. Dryness, keratitis, proliferative vitreoretinopathy, endopthelmitis, and corneal graft rejection are all eye diseases. In developing nations retinal abnormalities constitute the single biggest cause of blindness. Liposomes are employed as a genetic transfection vector and a carrier for monoclonal antibodies. In the therapy of targeted tumors and neovascular artery occlusion, angiography, retinal and choroidal blood vessel stasis, recent treatment strategies such as the application of heat-activated liposomes in focused lasers, as well as heat-induced release of liposomal therapeutics and dyes for targeted delivery. To far, two patent medicines have received approval for liposomal drug formulations, and many more are undergoing scientific testing. 'Verteporfin' is a commercially endorsed liposomal medication for ocular usage. The relevance of the liposome will be expanded in the future to include the therapeutic, diagnostic, and research aspects of ophthalmology[25].

## II. CONCLUSION:

A number of drug candidates which are highly potent and have low therapeutic indication can be targeted to the required diseased site using the liposomal drug delivery system. Drugs encapsulated in liposomes can have a significantly altered pharmacokinetics. The efficacy of the liposomal formulation depends on its ability to deliver the drug molecule to the targeted site over a prolonged period of time, simultaneously reducing its (drug's) toxic effects. The drugs are encapsulated within the phospholipid bilayers and are expected to diffuse out from the bilayer slowly. Various factors like drug concentration, drug to lipid ratio, encapsulation efficiency and in vivo drug release must be considered during the formulation of liposomal drug delivery systems. 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. Thus liposomal approach can be successfully utilized to improve the pharmacokinetics and therapeutic efficacy, simultaneously reducing the toxicity of various highly potent drugs.

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