

Liposomes Used As a Drug Delivery System: Preparation Method, Application, Current Status of Approved Products, Regulatory Environments and Future Directions

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ABSTRACT

Liposomes are most promising and versatile platform drug delivery which are compared with traditional drug delivery systems gives benefits like sustained and controlled release drug. Which has been protect from degradation and also this gives superior therapeutic effects and less toxic side effects. Liposome was first discovered in 1964 by Bangham and his colleagues. Since then, liposomes have extensive research which has prime aim to optimize encapsulation, stability and target specific drug delivery. These advancements have link the successful approval of different liposomal drug products and now they are widely utilized in clinical settings around in the world.

It highlights key chemistry knowledge and also advanced pharma technologies used in marketed products, such as lipid excipient and critical quality attributions. Additionally, the review summarizes recent regulatory guidelines and future motive for marketed products. Which providing valuable insights for the research of liposomal drug products across different kind of stages, from pilot plants to commercial manufacturing processes.

I. INTRODUCTION

Liposomes are lipid-based drug vesicles that self-assemble and create a bilayer unilamellar structure as well as a multilamellar one, surrounding a central aqueous space.^[1] Liposomes have different in size from 30 nm to the micrometer range.^[2] The liposomes were identified by British scientist Alec Bangham along with colleagues at Babraham Cambridge during the 1960s.^[3] Since that time, liposomes have been extensively studied as delivery systems for small molecular drugs, proteins, and nucleic acids.^[4-8] There are different administration routes that can be we used such as parenteral, pulmonary, oral, transdermal, ophthalmic, and nasal routes this route can be help to improve therapeutic efficacy and patient compliance.^[9-13] In the field of food^[14] and

cosmetics liposomes have been most widely used.^[15] As drug carriers, liposomes demonstrate exceptional qualities, including shielding the enclosed compounds from biological breakdown, extending the drug's half-life, and possessing excellent biocompatibility and safety characteristics.^[16]

In addition to the specific drugs, liposomes serve as an outstanding method for routes of drug delivery. Nevertheless, just 14 varieties of liposome products in the market, indicating that advantage of liposomes have not completely leveraged or utilized. Consequently, in this review, we compiled information regarding mercantile liposomal products authorized by Food Drug Administration and European Medicine Agency. The primary motive of this article is offer valuable reference knowledge that support advancement of liposomes as therapeutic tools which can be used for treating various disease.

Structures and Main Components of Liposomes

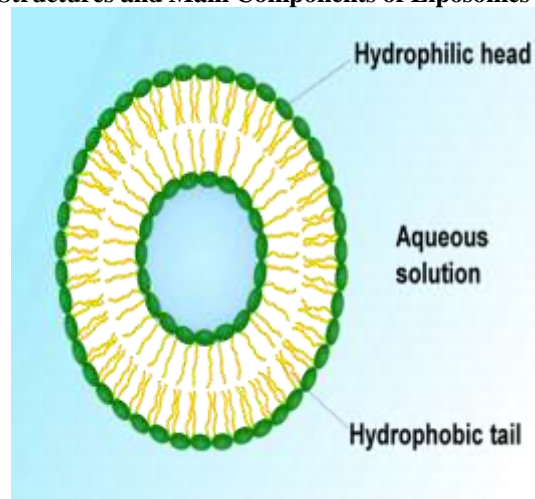


Fig.1. Structure of Liposomes and its structural component

Classification of Liposomes

Liposomes can be categorized based on their compartment structure and lamellarity into unilamellar vesicles (ULVs), multilamellar vesicles (MLVs), oligolamellar vesicles (OLVs), and multivesicular liposomes (MVLs) as illustrated in Fig 2.^[17] oligolamellar vesicles and multilamellar vesicles exhibit an onionlike structure, featuring 2–6 and over 5 concentric lipids in bilayers, respectively.

Depending on particle size, ULVs can be categorized into small unilamellar vesicles (SUVs) with a size range of 30–100 nm, large unilamellar vesicles (LUVs) with a size range of over 100 nm, and giant unilamellar vesicles (GUVs) which have a size range exceeding 1000 nm.^[18] Various size categories of ULVs have been noted, with SUVs ranging in size from less than 200 nm and LUVs having a size range of 200 to 500 nm.^[19]

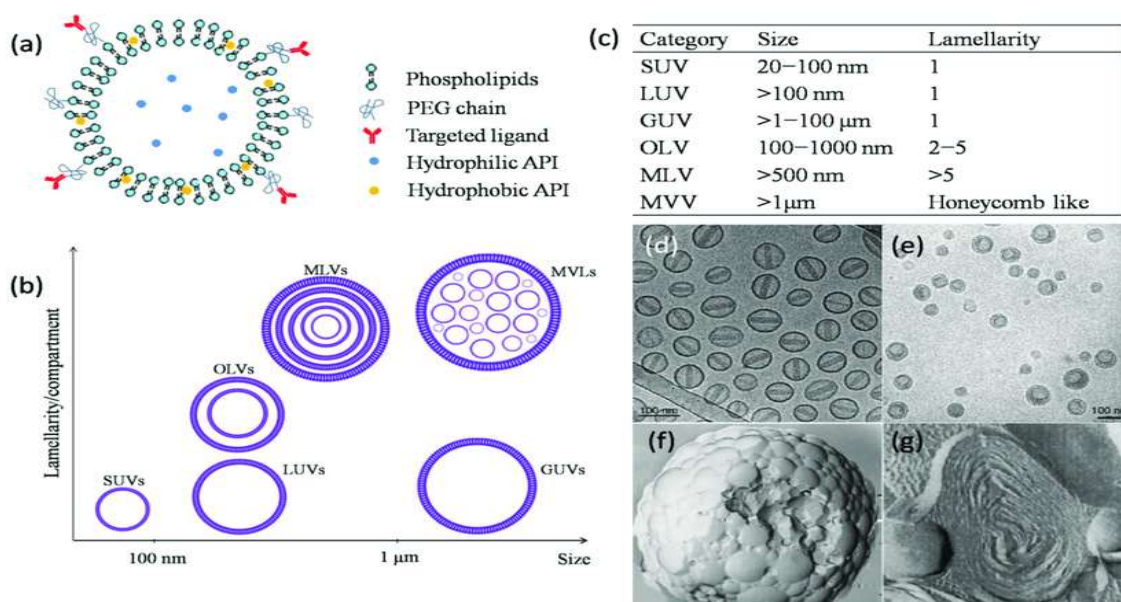


Fig.2. Category and structures of liposomal drug.

- i. Structured demonstration for liposomal structure. Size of a phospho lipid bilayer is 4.6 nm,
- ii. Classification of liposomal vesicles according to their lamellarity and particle size,
- iii. The size and lamellarity of liposomes has different types such as cryo-transmission electron microscopy of Doxil^[20] and Vyxeo^[21]s, electron micrographs of Depo Foam particles with typical diameter of 1–100 μm and MLVs with a typical diameter of 0.2–5 μm.^[22]

Properties of Liposomes

Liposomes can differ significantly in size and structure:

- They are amphiphilic and osmotically sensitive.
- They also permeable to water.
- It has +ve charged membranes are impermeable to cations, while -ve charged membranes show increased permeability to anions.
- The extensive sizes range of liposomes are:^[23]

Liposomes Type	Size range	Layers
Small Unilamellar Vesicles(SUV)	20nm-100nm	Single
Large Unilamellar Vesicles(LUV)	100nm-400nm	Single
Giant Unilamellar Vesicles(GUV)	1 μm and larger	Single
Large Unilamellar Vesicles(LUV)	200nm- 3μm	Multiple
Multivesicular Vesicles(MV)	200nm- 3μm	Multiple

- These properties make it versatile tools in drug delivery used.

Benefits of Liposomes^[24]

The primary benefits of liposomes include their application in drug formulation and delivery. Additionally, following are their benefits:

- Liposomes transporting both water and lipidsoluble medications.
- Liposomes are made of suitable to biocompatible components ideal for drug delivery.
- It decomposes naturally and has reduced systemic toxicity.
- Liposomes exhibit enhanced pharmacokinetic properties and are also biocompatible.
- Liposomes additionally aid in safeguarding delicate molecules from degradation.
- Liposomes help minimize negative interactions and reduce the toxic effects with drug absorption.

- Liposomes also inhibit oxidation of medications while they are being delivered.
- Liposomes possess enhanced stability and decrease the adverse effect of encapsulated substances (e.g. amphotericin B).
- Also it do not trigger an immune response for both systemic and non-systemic administration routes.
- Liposomes prevent sensitive tissues from being exposed to harmful drugs.
- Liposomes are not harmful.

Drawbacks of Liposomes^[24]

- Its solubility in water-based solutions is minimal.
- Brief half-life within the body environment.
- Additionally, the manufacturing costs are elevated.
- The substantial sizes of liposomes pose various challenges when used, including drug leakage or fusion of the encapsulated substances.

Preparation Method of Liposomes

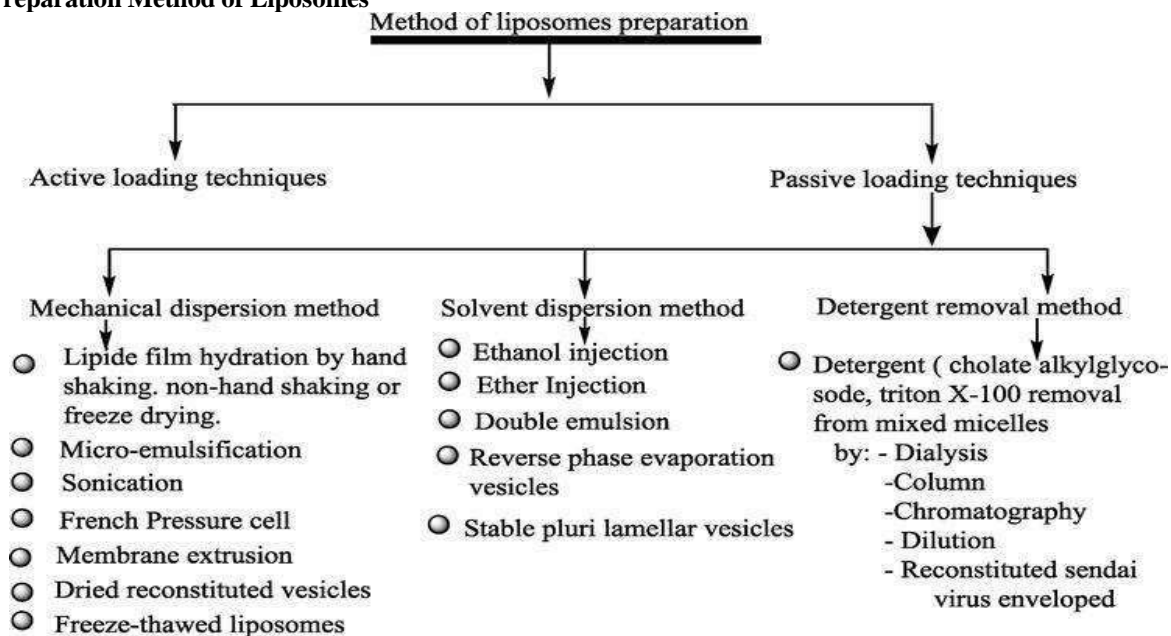


Fig.3. Different methods for preparation of Liposomes^[25]

Thin Fluid Film Technique:

The thin film technique is that commonly used method for preparing liposomes. This relies on formation of thin film that can be developed on inner surface of rotary evaporator flask. Film produced from the rotary evaporator is subsequently hydrated with a buffer solution. This combined with the intense shaking and then sonicate in an ultrasonic bath. It enables the film to separate from the flask and form

liposomes. The enclosing material mixed with lipids prior to the creation of the thin film. Initially, 3–30 mg of lipids are measured inside the pre-weighed 10 mL rotary flask and subsequently dissolved in a 2–6 mL mixture of methanol and chloroform (3:8 v/v). The solvent is subsequently removed by evaporation at 200–300 mbar while being heated in water bath at 35–45 °C, adjusting rotation speed to create a thin film. Prior to liposome formation, the thin film and buffer solution undergo preheating

above the T_m of the selected lipids. Ultimately, the created MLVs undergo sonication in ultrasonic bath for 5 minutes and are then preserved at $-80\text{ }^\circ\text{C}$ within plastic microcentrifuge tubes. For the creation of liposomes incorporating additional substances like polyphenols. The substances may

be incorporated into the lipids prior to the liposome assembly (i.e., they can be dissolved in the hydration solution). The technique is primarily beneficial for producing large volumes of liposomes on a pharmaceutical industrial level^[26,27,28].

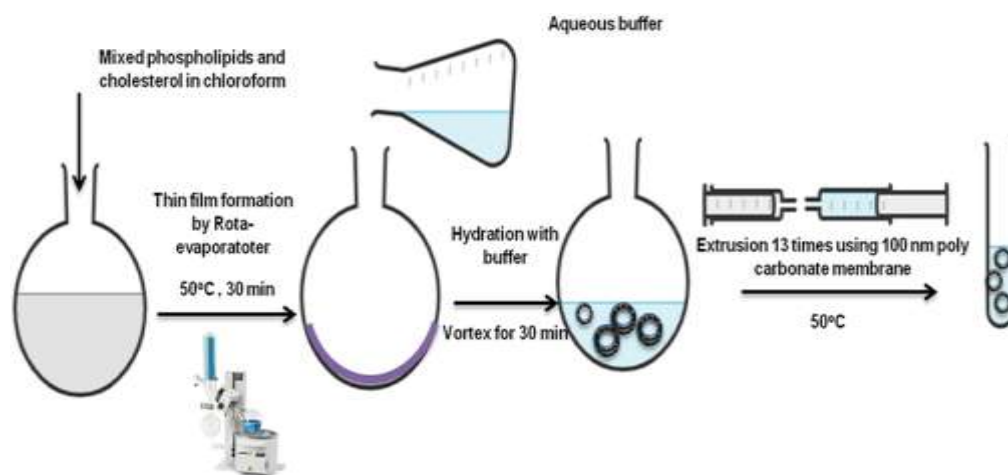


Fig.4.Liposomes preparation via thin-film hydration extrusion technique ^[29]

2. Method of forming double emulsions:

This method, also referred to as DepoFoamplatformTM, has been utilized by three parties. DepoCyte, DepoDur, and Expel are used in the producing of MVLs for commercial purposes. Entirely typical production process consists of four consecutive steps: creating emulsion of water dispersed in oil, creation of emulsion with water droplets in oil within water, solvent extraction using vacuum pressing and microfiltration for the process. The elimination of the unbound medication, levels of substance, and substitution of outside solution.^[30,31] In the course of during the manufacturing process, it is essential to ensure aseptic conditions as Multivitamin Liquids (MVLs) are involved. Sterile batches cannot be produced with micro particle sizes using 0.22 m filtration.^[32]

In the second place within the emulsion, the effectiveness of encapsulation decreases while the solvent being removed because some. The MVLs collapse, causing the drug to leak from internal aqueous phase. Furthermore, the increased temperature enhances movement and reorganization of lipid bilayers, leading to fusion of lipids leading to collapse of watery compartments.

3. Injection Method for Solvents:

This method involves dissolving lipid substance and lipophilic substances. Mixed in a

aqueous-soluble organic solvent, then organic layer is added to huge amount of liquid buffer, result form the natural formation of small single-layered liposomes. Two different solution streams are incorporated using alternative methods, utilizing a Y-connector and membrane contactors in tube setup like ShirasuPorous. The Glass membrane setup, along with crossflow introduction tool, is created to improve the mixing of organic and aqueous phases on a microscale. Please paraphrase the following text without changing the language or word count. The fast spread of solvent in water, aided by turbulence at the interface, leads to fast form of smaller and consistent liposomes. Optimizing preparation parameters can lead to achieving production with particle sizes ranging from 80 nanometers .

Reducing particle size does not require energy input, for example, sonication and extrusion. Organic solvents can separate by evaporation and dialysis for concentrating liposome suspensions. Different kind of preparation factors, including flowing rate and water solution temperatures, lipid concentration, and stirring speed, can affect particle characteristics. Combining a Y-connector and an in-line mixer results in the formation of nanosized amikacin liposomes.^[33,34]

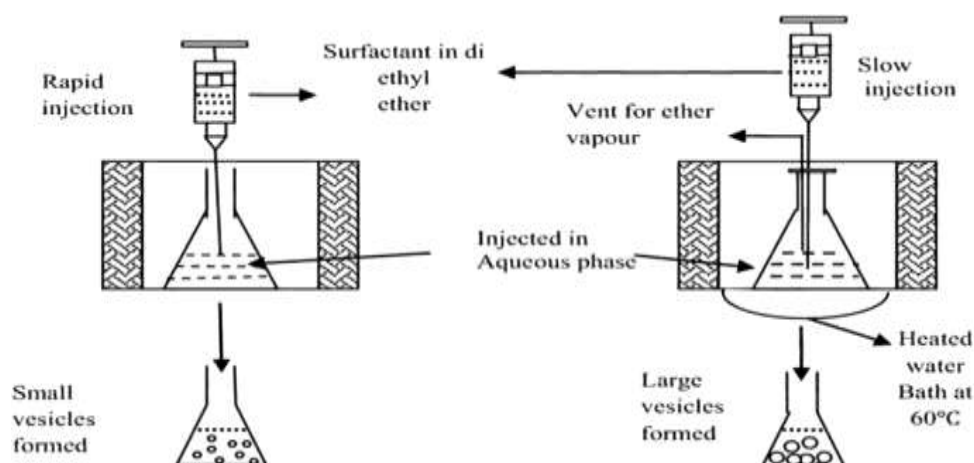


Fig.5. Preparation method used in ether and ethanol injection^[35]

4.Detergent Solubilization Method (Removal of non- encapsulated material):

In this method involve using an intermediary detergent when adding the phospholipids to the aqueous phase. The intermediary detergent helps to bring the phospholipids in dose with aqueous phase, but still protect the hydrophilic part of phospholipid. These intermediaries are often soluble in both aqueous and organic solution. This method then creates micelles. The detergent can be removed by following methods:

- a. Dialysis
- b. Detergent Absorption

5.Size Reducing of liposomes:

Following are methods of liposomes size reducing process which are also useful for the preparation method liposomes :

- a. Sonication-Bath and Probe sonicator

- b. French Pressure cell extrusion
- c. Membrane Extrusion

The Marketed Liposomal Products

A search of the FDA and EMA approved medication databases identified 14 authorized liposomal products, as summarized in Table 1. This enlist excludes generic formulations, lipid complexes such as Abelcet and liposomal products approved at the national level within European countries. Notably, Doxil was first liposomal medication approved by FDA in 1995. Currently 44% products were approved before 2000, while 58% received authorization before 2010. The primary focus of these products is cancer treatment, though other applications include infection management, vaccination, and photodynamic therapy. Administration routes vary and include intravenous infusion, oral and intramuscular injection product.

Table 1. Liposomal products approved by FDA and EMA.

Product Name	API	Approved Year/Area	Dosage Form	Adm. Route	Indication
DoxilCaelyx	Doxorubicin hydrochloride (DOX·HCl)	1995,US 1996, EU	Suspension	IV	Ovarian cancer, Kaposi's sarcoma.
DaunoXome	Daunorubicin	1996,US	Suspension	IV	Kaposi's sarcoma
AmBisome	Amphotericin B (AmpB)	1997,US	Lyo	IV	Fungal infection
DepoCyt DepoCyte	Cytarabine	1999,US 2001, EU	Suspension	IT	Lymphomatous meningitis
Myocet	DOX·HCl	2000, EU	3 vials	IV	Breast cancer

Product Name	API	Approved Year/Area	Dosage Form	Adm. Route	Indication
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
Arikayce	Amikacin sulfate	2018,US 2020, EU	Suspension	Oral inhalation	Lung disease

In this enlist includes only liposomal forms that received approval from FDA and EMA, omitting generics (e.g. doxorubicin hydrochloride) and lipid complexes product which are authorized

by nationally in Europe. Acronyms: intravenous drip, intramuscular shot, freeze-drying, muramyl tripeptide phosphatidyl ethanolamine.

Characterization of Liposomes:^[36]

CHEMICAL CHARACTERIZATION

ANALYTICAL METHODS

Chemical Characterization

Concentration

Phospholipid
Cholesterol

Barlett assay,HPLC
Cholesterol oxidase assay,HPLC

Phospholipid

Peroxidation
Hydrolysis

UV absorbance,TBA,iodometric, GLC
HPLC, TLC, Fatty Acid Conc.

Cholesterolautooxidation

Antioxidant degradation

pH

Osmolarity

Physical Characterization

Vesicle

Size& Surface morphology

TEM, Freezed fracture electron microscopy

Surface charge

Size distibution

Free flow electrophoresis
DLC,Zetasizer,TEM,PCR,gel permeation,exclusion

Lamellaritty

Phase behavior

Drug release

Biological

Characterization

Sterility

Pyrogenicity

Aerobic or anaerobic cutures

LAL test

Application of Liposomes:^[37]

Liposomes are the perfect vehicle for the distribution and delivery of drugs due to their biocompatibility and ability to carry a variety of substances in the required concentrations in body. A few of their applications are listed below:

1. **Targeted drug delivery to sitespecific:** Liposomal serve like appropriate transports for delivering drugs to specific sites. To create a targeted drug delivery, associated with ligands, including antibodies, sugar residues which has been attached to the lipid carrier, thereby it is minimizing drug toxicity.
2. **Carcinogenic therapeutics treatment:** Liposome-centered cancer treatments employed that address breast cancer with targeted precision. It improves pharmacokinetics and pharmacodynamics of the related medication and targets to its desired location, boosting its therapeutics effectiveness.
3. **Transdermal deliver product:** The primary challenge in transdermal drug administration like uptake macromolecules across stratum corneum, skin's outermost layer. Liposomes with molecular configuration similar to lipid membranes, also demonstrate significant permeable. As a result, these act as matched vehicles for delivering medications that penetrate through skin.
4. **Treatment of parasitic disorders:** It act as excellent vehicle for transporting medications to combat parasitic infections, particularly those affecting monocytes/macrophages, such as leishmania.
5. **HIV (human immunodeficiency virus) infection treatment:** Liposomes are capable of encapsulating nano carriers for anti-HIV treatment, such as antiretroviral nucleotides and antiviral medications, allowing targeted delivery to specific locations.
6. **Disease diagnosis:** Liposomes are utilized in therapeutic imaging techniques, including nuclear magnetic resonance imaging.
7. **Cosmetics:** It has been serve an excellent vehicles which are help for transporting various dermatological marketed products to skin cells. These are also incorporated into dosage form that prevent dry skin, inhibit skin aging, it has serve a transport medium for increasing, anti-inflammatory substances, immune stimulants. These likewise stops age spots,

dark circles, and acne. Primarily, the benefits of liposomes in cosmetology enhanced absorption and distribution of the active compounds in beauty products and stability of active component.

8. **Agriculture industry:** Liposomes can encapsulate unstable substances like antimicrobials, antioxidants, and bioactive components, safeguarding them from various environmental and chemical alterations, including enzymatic reactions, ionic strength variations, and temperature fluctuations.

9. **Immune Response:** They also encapsulated antigens for both passive and active immunization, aiding in the production of antibodies and enhancing immune responses.

10. **Genetic materials delivery system:** It has been utilized as transport genetic substances like DNA segments to designated cells for the synthesis of particular proteins.

11. **Liposome for Respiratory Drug Delivery System:** Liposomes are extensively utilized in treatment of different respiratory disorders due to their new benefits over new aerosol systems. These benefits are follows:

- a) Sustained release drug
- b) Prevention of local irritation
- c) Enhanced stability in their large aqueous core

Several injectable liposomal products, such as Ambisome, Fungisome, and Myocet, are already available in the market. The benefits of liposomal delivery drug products for the lungs depends on several critical factors, including:

- a) Lipid composition
- b) Particle size
- c) Surface charge

Nowadays advancements in using liposomes used as a delivering DNA to lungs have provided deeper insights into their potential for macromolecular delivery through the inhalation techniques. This emerging information such as the development of novel lipids and advanced analytical procedure, has significant implications for creating like liposomal protein dosage form.

Liposomes for inhalation can be formulated either liquid or powder forms, with drug release taking place during the nebulize process. Dry liposomes are commonly manufactured using techniques such as spray drying. Drugs which are formulated in the form of liposome mentioned in Table 2.

Table 2. Liposomes Formulate for the Respiratory Disordered

Active Ingredients	Effects
Insulin	Facilitated pulmonary adsorption also enhanced hypoglycemic effect
Catalase	It has been also effect on pulmonary oxygen toxicity
Superoxide dusmutasing effect	Reduced toxicity to subsequent hyper oxia and improved survival
Cyclo sporins	It has been adsorbed by lung and gives sustained release effect

13. **Liposomes used in Vaccine:** Liposomes have well-discovered as immuno-adjuvants, enhancing humoral immunity (as summarized in Table no.3). They serve as vaccine adjuvants through various therapeutic mechanisms, including:

1. Acting as immunological adjuvants for vaccines.
2. Serving as components of liposomal vaccines.
3. Functioning vehicles as for immunomodulation.
4. Serving tools as in immunodiagnologies.

It has been used as immuno-adjuvants work with slowly release encapsulated antigens upon intramuscular injection and by passively accumulating in regional lymph nodes. This lymphoid targeting is facilitated by liposomes containing phosphatidylserine. Liposomal vaccines can also formulated by incorporating microbes and cytokines. These components encourage immune response through antigenic proteins.

Table 3. Some Antigen as Liposome prepared method and Application

Antigen as Liposome prepared method	Application
Rabies glyco proteins	Interleukin -2 enhancement
Cholera toxin	Increase Ab* level
Diphtheria toxoid	Superior immuno adjuvant
Hepatitis B virus Higher Ab response	Hepatitis B virus Higher Ab response
Tetanus toxoids	Increased Ab titre

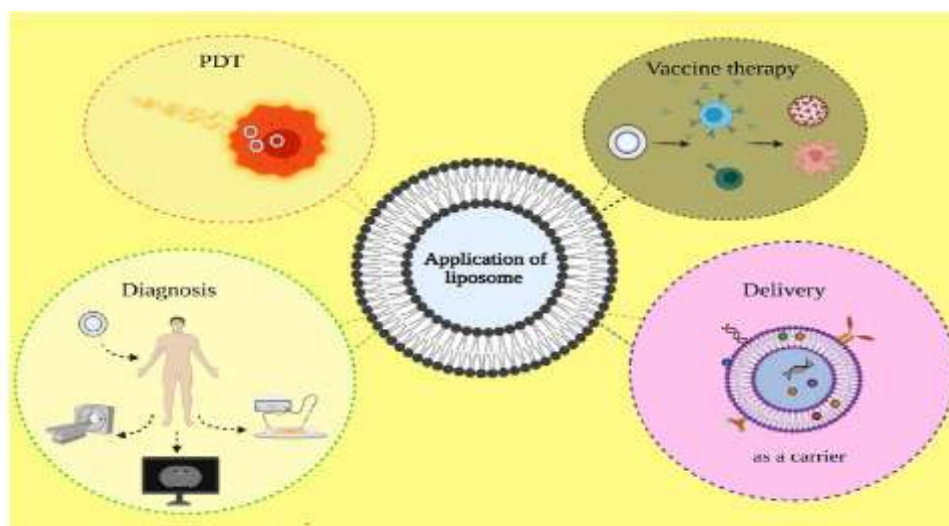


Fig.6. An example of different application area of liposomes such as photodynamic therapy, drug therapy, drug delivery, disease diagnosis, and vaccine therapy.^[24]

Liposomal Delivery: Future directions.^[38-45]

We analyzed the number of publications that included the term “liposome” in their Title, Abstract, or Keywords fields, “(liposome AND drug), or “(nano AND liposomes AND drug) within years of 1970 to 2020 in Scopus. Intriguing findings emerged. Use of immunotherapy for cancer and infectious diseases represents a compelling application of liposomal systems. Active immunotherapy depends on activating the body’s own defense systems, specifically its immune system, to identify and eliminate infected or cancerous cells. Present methods utilize liposomes along with immune stimulatory or modulatory agents such as muramyl peptides, oligonucleotides, plasmid DNA, and cytokines, particularly IL-2, in addition to antigens specific to diseases. The immune stimulators serve as signals of activation that draw immune responses towards infections or tumors. When combined with an antigen, these substances can provoke a focused immune reaction to particular disease-related antigens.

Displays a compilation of liposomal adjuvants and vaccines currently in preclinical development and clinical trials. A collection of adjuvants is available online. Another use of liposomal systems is in gene therapy strategies for cancer immuno therapy. Indeed, immuno-gene therapy is the most actively sought-after type of cancer gene therapy in ongoing clinical trials. Cancer immuno gene therapy focuses on increasing the immunogenicity of tumors by introducing genes into tumor cells that produce foreign antigens like HLA-B7 and E1A, or immune stimulatory molecules such as cytokines like IL-2 and IFN- γ , which mobilize and recruit immune effector cells. Firms conducting clinical trials that utilize this type of cancer treatment include, for instance, Vical (www.vical.com) and Targetedgenetics (www.targen.com). Synthetic oligonucleotides represent a new category of immune modulatory agents and offer significant potential for future advancements in liposome-based tumor vaccines. This can partly be ascribed to recent progress in creating methods that enable efficient encapsulation of oligonucleotides. The encapsulation of immune stimulatory oligonucleotides in liposomes can provide significant advantages. Recently developed methods enable the efficient encapsulation of oligonucleotides within liposomes. Encapsulation safeguards oligonucleotides against degradation and may increase their immune-stimulatory effectiveness (PRC, unpublished findings).

Moreover, encapsulation can alter the pattern of pro-inflammatory cytokines generated in reaction to trapped oligonucleotides. This may be attributed to the varying context in which these oligonucleotides are introduced to immune cells or to the enhanced stability of encapsulated oligonucleotides. Ultimately, antigens may be linked to the liposome surface employing the identical coupling methods used for attaching targeting ligands. This leads to the simultaneous delivery of oligonucleotides and antigen into the identical immune cell. Also the amphotericin B is a specialized lipid formulation, which is widely used as a standard treatment for number of opportunistic fungal infections. Compared to conventional amphotericin B deoxycholate (DAmB), LAmB offers a significantly increase safety profile with decrease toxicity. Which is very important for the purpose of future.

Liposomal topical drug should focus on understanding their transport through stratum corneum, interaction with skin cells, and metabolic behavior in healthy or diseased states. This studies also address their longterm stability in dermatological formulations and determine the adversity of liposome drug complex. A thorough investigation of these aspects is crucial to unlock the potential of liposomes for effective intradermal drug delivery. Nowadays the techniques for preparing liposomes, the excipients employ in various innovative formulations, and the routes of administration used to deliver it to targeted disease sites. It aims to provide an updated overview of advancements in liposomal delivery while highlighting future nanotechnological approach in the field. Recent effort in liposome research has focused on developing third generation of it and building on the success of standard liposomes (SL) in clinical trials and healthcare applications. These advanced liposomes aim to achieve site-specific targeting by attaching homing devices, such as monoclonal antibodies or receptor ligands, to their surface. At present, significant efforts are focused towards achieving specific delivery and gene expression in target organs.

Regulatory Considerations:^[51]

In the past few decades, around 100 nanomedicines have received approval from the FDA, while the EMA has approved 11 has also approved by FDA. Recently, 48 nanomedicines are undergoing clinical trials in the European Union^[46]. Recognizing that growing applications for nanodrugs and need to sharing regulatory

experiences in the scientific assessment of these products, various rules and regulation on nanomaterials and nanoproducts have been issued by the FDA, EMA, Japan's Ministry of Health, Labour and Welfare (MHLW), and the Chinese National Medical Products Administration (NMPA). These guidelines address various nanodosage products, such as liposomes, iron-

based nanosubstances and siRNA loaded nanoproducts. Notably, these all four regulatory bodies have developed guidance specifically for liposomes, likely due to their commonality as a dosage form and the greater number that have been approved for market use.

Table 4. Regulatory agent and their guidelines

Regulatory Agency	Nanomedicine Guidelines
FDA	<ul style="list-style-type: none"> Industry guidance: Assessing if a product regulated by the FDA incorporates nanotechnology and Draft Guidance on Drug Products and Biologics contain Nanomaterials. Guidelines for the industry on chemistry, manufacturing, and controls (CMC) of liposome drug.
EMA	<ul style="list-style-type: none"> Criteria for data pertaining to intravenous iron-based nano-colloidal products develop in relation to a reference drug product. Collaboration between the EMA and MHLW on the development of medicinal products utilizing block co-polymer micelles.
MHLW	<ul style="list-style-type: none"> Collaboration between EMA and MHLW for create the medicinal products utilizing block-copolymer micelles. Guidelines for creating liposome drug products and a reflection paper concerning nanotechnology-based drug products loaded with nucleic acids (siRNA).

Considering the complexity and wide range of liposomal products, it is essential to prioritize quality, safety, and effectiveness throughout every phase of life cycle of the products. In alignment with these principles, we highlight the importance of developing a thorough knowledge base to enhance our understanding of potential risks arising from manufacturing, analysis and material control on the physicochemical and biological properties of a product.^[47] Even a slight modification in lipid materials changes in the pharmacokinetics or pharmacodynamics of drug, which could result in toxic issues. FDA guidance provides detailed description of the requirements for lipid control, including the lipid source, characteristics, and stability. Sterilizing liposome products poses a significant challenge since many of these products are designed for parenteral use. Problems such as membrane blockage, compromised liposome integrity, and ineffective retention of small bacteria can arise.^[48] Consequently, identifying an effective sterilization method and validating the sterilization

process is crucial for ensuring both batch consistency and sterility in liposome products.

The recently released guideline on nonclinical pharmacokinetics of nanomedicines by the Center for Drug Evaluation, recommends or advises for in vivo measurement both the vehicles and their cargos. The in vivo behavior of various nanoparticles, including polymeric nanoparticles, nanoemulsions, and nanocrystals, has been studied through various routes of administrations, such as oral, intravenous, transdermal and nasal using ACQ probes.^[49-52] Some significant progress has been made over past five years, closer collaboration among regulatory agencies is still necessary. In the meantime, newly techniques generate for the development of conventional medicinal products have often been adapted to assure the safety, toxicity, and compatibility of nanomedicines. For regulatory perspective, the active pharmaceutical ingredient (API) of liposomes plays a pivotal role in determining the specifications to be analyzed within the regulatory framework.^[53, 54] General analysis of liposomal product submissions revealed that the most of (96%) were Investigational New

Drug applications, followed by New Drug Applications at 3%, and Abbreviated New Drug Applications making up the remaining 1%. Among these submissions, doxorubicin hydrochloride mostly used commonly drug substance incorporated into liposomes, accounting for 31%.^[55] In the past 20 years, the U.S. Food and Drug Administration has been tackled significant regulatory challenges and develop a framework to oversee nanotherapeutics. FDA's evolving advancements in this regulatory landscape offer valuable insights into addressing these challenges and guiding the development such formulations.^[56]

II. CONCLUSION

In the realm of liposomal therapy, liposomes demonstrate superior characteristics compared to conventional drug, include target site drug, sustained release as well as safeguarding drugs from degradation and elimination. It has show less adverse effects. Liposomes have gained considerable interest as drug delivery mechanisms, successfully carrying a range of pharmaceuticals across multiple applications. They demonstrate specific potential for delivering antisense molecules, ribosomes, proteins, peptides, and DNA inside cells. Liposomes are gaining clinical acceptance by delivering drugs to disease locations and showing prolonged circulation times. Also in this liposomal therapy, the modulation of drug characteristics in vivo is essential for creating an effective liposome. Recent research focuses on synovial targets, and advancements in liposomal formulations are enhancing our ability to utilize liposomes for targeted delivery. Over time, this method could increase drug product delivery and decrease complications that arise from the disease.

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