



“REVIEW ON LIPOSOME: A CARRIER FOR EFFECTIVE DRUG DELIVERY”

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IN THE FACULTY OF SCIENCE AND TECHNOLOGY (PHARMACEUTICAL SCIENCES)

NOVEL DRUG DELIVERY SYSTEM

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Abstract

When a self-forming encapsulated lipid bi-layer was hydrated, liposomes or lipid vesicles were discovered; liposome drug delivery systems have played a significant role in the creation of useful medications to improve therapies. Liposome formulations have recently been optimized to reduce toxicity while enhancing target site accumulation. The suppression of rapid liposome clearance by regulating particle size, charge, and surface hydration is one of several new liposome manufacturing methods based on lipid drug interaction and liposome disposition mechanism. Targeting tissue with or without the expression of target recognition molecules on the lipid membrane is the most common therapeutic application of liposomal drug delivery. Physical, chemical, and biological factors are used to characterize the liposomes. Liposome size is another important metric that aids in the identification of the liposome, which is normally accomplished by sequential extrusion at low pressure through a polycarbonate membrane (PCM). Antiviral, antifungal, antimicrobial, vaccines, anti-tubercular medicines, and gene treatments can all benefit from this route of drug delivery since it improves safety and efficacy. Liposomes are being used

in immunology, dermatology, vaccine adjuvant, eye diseases, brain targeting, infectious disease, and tumor therapy, among other fields. The specific binding properties of a drug-carrying liposome to a target cell such as a tumor cell and specific molecules in the body (antibodies, proteins, peptides, and so on); stealth liposomes, which are especially being used as carriers for hydrophilic (water soluble) anticancer drugs like doxorubicin and mitoxantrone; and bisphosphonate-liposome mediated macrophage depletion are some of the Researchers working in the field of liposomal medication delivery will benefit from this review.

Keywords = Liposome, characterization, liposome sizing, surface hydration, targeted site, phospholipids are some of the terms used to describe liposomes.

Introduction

Liposomes are small vesicles with a spherical form made of cholesterol, nontoxic surfactants, sphingolipids, glycolipids, long chain fatty acids, and even membrane proteins. When phospholipids are dissolved in water, they spontaneously form a closed structure with an interior aqueous environment bordered by phospholipid bilayer membranes; this vesicular system is known as a liposome.^[1] Liposomes are drug carriers that can hold a wide range of compounds, including tiny chemical molecules, proteins, nucleotides, and even plasmids. Dr. Alec D Bangham, a British haematologist, originally described liposomes in 1961. When Bangham and R. W. Horne were testing the institute's new electron microscope by applying negative stain to dry phospholipids, they discovered liposomes. The cell membrane's likeness to the plasma membranes, as well as the microscope images, provided the first real evidence that it was a bilayer lipid structure. Liposomes can be made in a variety of sizes, compositions, charges, and lamellarities.^[2] Various medicinal medicines have been commercialized in liposomal formulations. It is feasible to change the size, charge, and surface features of liposomes by utilizing different techniques of manufacture and adding additional ingredients to the lipid mixture before liposome formation. The development of long-circulating stealth liposomes and multifunctional liposomes with improved in-vivo properties is now the focus of current research. In addition, research trials are currently underway to develop customized liposomes that target certain antigens or indicators for more precise medication delivery. In this context, a thorough examination of the role of liposomes as drug delivery systems appears to be required. The many varieties of liposomes, their production techniques and characterization criteria, as well as their uses in the pharmaceutical industry, will be discussed in this review. A list of clinically approved liposomal products is also provided to provide a current picture of the situation.

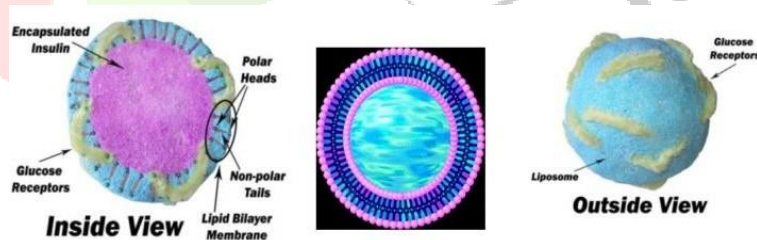
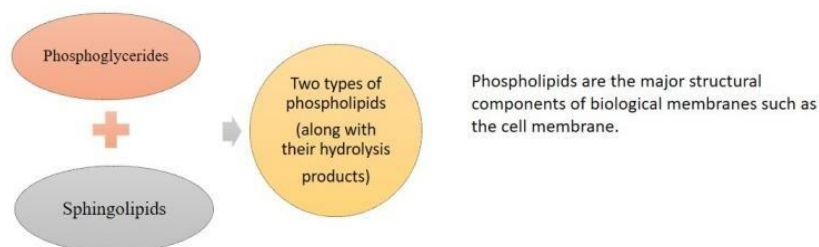


Fig. 1 Inside and outside view of liposome

Structural components of liposomes-^[3, 4, 5]

The main components of liposomes are-

1. Phospholipids
2. Cholesterol

➤ **Phospholipid (Fig. 2)**

Phosphatidylcholine - Phosphatidylcholine (PC), an amphipathic molecule with a hydrophilic polar head group, phosphocholine, a glycerol bridge, and a pair of hydrophobic acyl hydrocarbon chains, is the most often utilized phospholipid.

Cholesterol - Cholesterol is a waxy, fat-like molecule that plays an important role in our bodies. It aids in the production of hormones, vitamin D, and chemicals that aid in the digestion of food. Cholesterol does not form a bilayer structure by itself. It functions as a buffer for fluidity. It interacts with phospholipid molecules, altering the mobility of carbon molecules in the acyl chain and preventing Trans to gauche conformation changes.

Cholesterol inclusion improves choline head group separation and removes electrostatic and hydrogen bonding interactions.

Table 1: Advantages & disadvantages of liposome - [10, 11, 12]

Advantages	Disadvantages
Liposome increased efficacy and therapeutic index of drug	Sometimes phospholipid undergoes oxidation and hydrolytic reaction
Liposome is non-toxic, flexible, biocompatible, completely biodegradable and non-immunogenic for systemic and non-systemic administration	Drug leakage/ entrapment/drug fusion
Liposome increase stability via encapsulated drug.	Biological activity is short / $t_{1/2}$
Liposome reduced the toxicity of the encapsulated agent.	Low solubility and oxidation of bilayer phospholipid
Liposome reduce the exposure of sensitive tissue to toxic drugs	Rate of release and altered biodistribution
Improved pharmacokinetic effects (reduced elimination increased circulation lifetimes)	Low therapeutic index and dose effectiveness
Suitable for controlled release	Repeated IV administration problems

Need of liposomal drug delivery system: [31]

The present conventional drug delivery systems have side effects and complications due to their wide distribution through the body fluids. In the treatment or prevention of diseases, the other modes of drug delivery system show non-specificity, non-selectivity and many drugs are not able to arrive at the target site in the body. Some drugs may get inactivated due to first pass metabolism or other mechanism. The localization of the drug action in injured tissues may solve this problem. To achieve a desired pharmacological response at a selected site without undesirable action with minimum side effects and better therapeutic index. For e.g. Cancer chemotherapy and enzyme replacement therapy. [31]

CLASSIFICATION OF LIPOSOMES [6,7,8, 9]

The liposomes may be classified based on

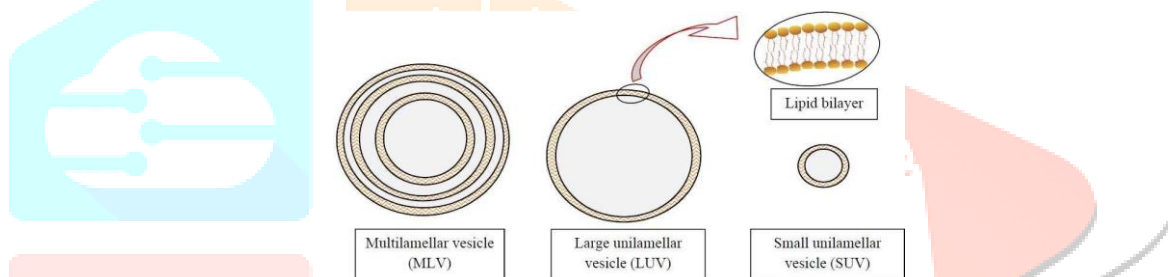
1. Structure
2. Method of preparation

3. Composition
4. Conventional liposome
5. Specialty liposome

1. Classification Based on Structure

Vesicle Types with their Size and Number of Lipid Layers

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
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 Method of Preparation

Different Preparation Methods and the Vesicles Formed by these Methods

Preparation Method	Vesicle Type
Single or oligolamellar vesicle made by reverse phase evaporation	REV
Multilamellar vesicle made by reverse phase evaporation method	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

Different Liposome with their Compositions

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

4. Based Upon Conventional Liposome

- Natural lecithin mixtures
- Synthetic identical, chain phospholipids
- Liposome with Glycolipids

5. Based Upon Speciality Liposome

- Bipolar fatty acid.
- Antibody directed
- Methyl/ Methylene x- linked
- Lipoprotein coated
- Carbohydrate coated
- Multiple encapsulated

LITERATURE REVIEW:

Vijaykumar Nekkanti¹* and Sandeep Kalepu²: ‘Recent Advances in Liposomal Drug Delivery’: A Review published in International Journal Of Pharmaceutical Science and research explain about encapsulation of drugs into liposomes demonstrated improved therapeutic performance with concomitant reduction in toxicity.

Subash Chandran M.P*, Prasobh G.R, Jaghatha T, Aswathy B.S, Remya S.B: An Overview on Liposomal Drug Delivery System published in International Journal of Pharmaceutical and Phytopharmacological Research (eIJPPR) | April 2019 | Volume 9 | Issue 2 | Page 61-68 gave about liposomal drug stability and its formulation, there is greater promise in future for marketing of highly stabilized and more sophisticated liposomal formulations. The role of liposomes as a drug delivery system is to provide drugs in a controlled manner, reduce toxicity, and increase the efficacy of encapsulated drugs.

Uendra Bulbake, Sindhu Doppalapudi: Liposomal Formulations in Clinical Use: An Updated Review Published in International Journal Of Pharmaceutical Science and research Published: 27 March 2017 gave about the drugs which use clinically ad liposomes. The first successful milestone in liposome-based products was the introduction of Doxil® to the U.S. market in 1995 for the treatment of patients with ovarian cancer and AIDS-related Kaposi’s sarcoma after the failure of prior systemic chemotherapy or intolerance to such therapy.

Abdus Samad, Y. Sultana* and M. Aqil’ Liposomal Drug Delivery Systems: An Update Review’ published in Current Drug Delivery, 2007, 4, 297-305 gave about role of liposomes clinically. Formulation of drugs in liposomes has provided an opportunity to enhance the therapeutic indices of various agents mainly through alteration in their bio distribution. This review discusses the classification, formulation, characterization and potential applications of liposomes in drug delivery

Claudia Zylberberg & Sandro Matosevic: Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape published in (2016) For the delivery of liposome ocular and inhalation route are some advanced technology. In poorly water-soluble substance pulmonary delivery is very much useful. However, liposome-based vaccines have been demonstrated in clinical trials and further progress in human trails.

Himanshu Anwekar*, Sitasharan Patel and A.K Singha: Liposome- as drug carriers published in INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES gave about advantage and disadvantage of liposomal drug delivery system shows differences between conventional and liposomal drug delivery. Liposomes composed of a whole host of different lipids, manmade or naturally occurring, each having their own uses, advantages and disadvantages. The widely used lipid component is phosphatidylcholine, because of it is neutral and relatively low in cost.

Mechanism of liposome formation-

Phospholipids make up a liposome. The hydrophilic part consists primarily of phosphoric acid coupled to a water-soluble molecule, whereas the hydrophobic part is made up of two fatty acid chains.

Each chain has 10-24 carbon atoms and 0-6 double bonds. To escape the water phase in an aqueous environment, phospholipids position themselves to create a bilayer, with one layer of phospholipid facing outside of the cells and the other layer facing inside the cell. One layer's hydrocarbon tail meets the hydrocarbon tail of another layer, forming a bilayer. Lamella is another name for this structure. The lipid cake (lamella) swells and curves to create closed vesicles in the form of spheres known as liposomes as it absorbs more water. ^[9]

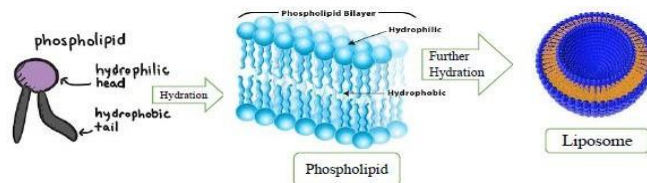
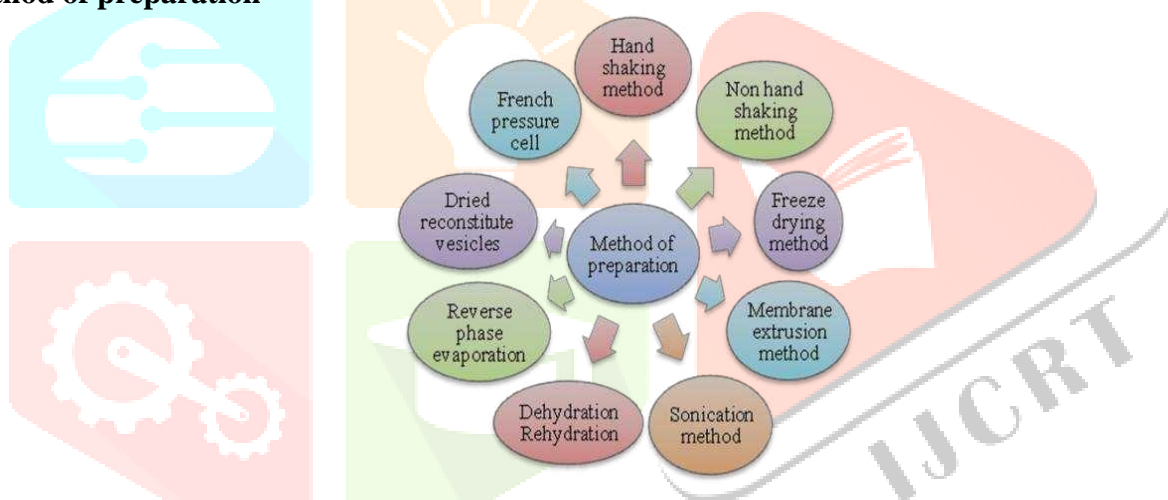


Fig.3 Mechanism of action of liposome

A Lamella is a flat plate-like structure that forms during liposome production. Before being transformed into spheres, the phospholipid bilayer exists as a lamella. During the creation of a liposome, several lamella of phospholipid bilayers are stacked one on top of the other to form a multilamellar structure.

Method of preparation- [13, 14, 15, 16, 17]



Hand shaking MLVs

It is the most common and straightforward approach for making MLVs. The lipids are dissolved in solvents (chloroform: methanol) and then transferred to a round bottom flask in these operations. The RBF containing the mixture was then attached to a rotary evaporator and rotated at 60 rpm until a dry thin layer was formed, after which it was dried in a lyophilizer to remove the last traces of solvent and hydrated with phosphate buffer saline containing the material to be entrapped, and then it was attached to a rotary evaporator and rotated at 60 rpm or below until the layer adhering to the RBF.

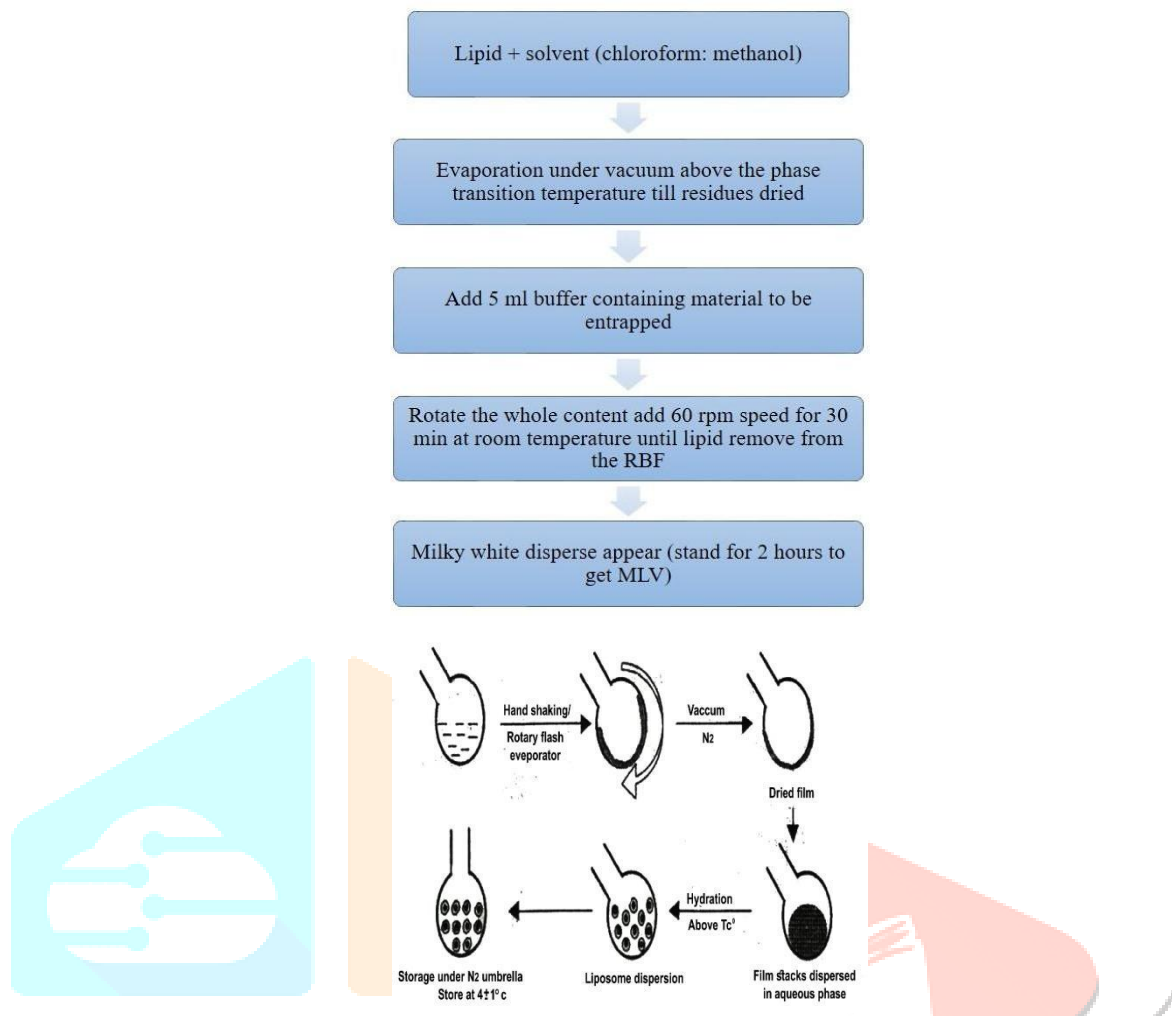


Fig. 4 method of handshaking

Non-hand shaking LUVs-

These methods involve spreading lipid mixed with solvent across a conical flask and allowing the solution to evaporate at room temperature without being disturbed by nitrogen flow. After the solution has dried, it is rehydrated by passing water-saturated nitrogen through the conical flask until the opacity of the dried lipid coating has vanished. The lipid swells as a result of hydration. The flask is then tilted to one side, and 10 to 20 ml of 0.2 M sucrose in distilled water is added to the flask's side, before slowly returning the flask to its original position. The liquid flows across the lipid layer on the flask's bottom. The flask was then flushed with nitrogen and sealed before being left at room temperature for 2 hours. The suspension is centrifuged at 12000 g for 10 minutes at room temperature after swelling. LUVs are created by adding iso-osmolar glucose solution to the remaining fluid.

Freeze drying method -

These methods combine lipid and solvent, which are then combined and dried at room temperature using a nitrogen flow. Then, when the opacity is gone, add some water-saturated nitrogen. To swell, mix 10-20 mL of water with 10-20 mL of 0.2 M sucrose solution. After that, leave for 2 hours at 37°C, centrifuge for 10 minutes at room temperature at 12000 rpm, and add the remaining fluid to the iso-osmolar glucose solution to produce LUVs.

Membrane extrusion-

During the breaking and resealing of the phosphate lipid bilayer as they pass through the polycarbonate membrane, the contents of the vesicles are swapped with dispersion media, and less pressure is required than in the French pressure cell used to treat MLVs and LUVs. Finally, the nucleation and tortuous track membranes are produced.

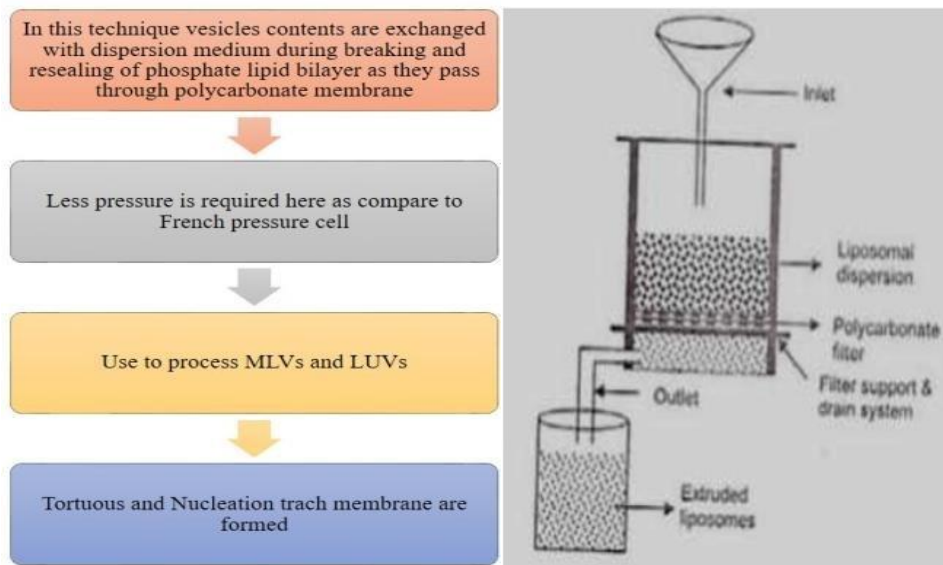


Fig. 5 Method of membrane extrusion

Dehydration rehydration method-

THF was used to make the liposomal suspension, which was subsequently frozen in liquid nitrogen and freeze-dried overnight. The liposome is prepared after being hydrated with water.

Sonication method-

Surfactant and cholesterol are mixed in 2 mL of aqueous phase in a vial and then sonicated for 3 minutes at 60°C using a titanium probe sonicator, resulting in the formation of unilamellar vesicles (Fig. 6).

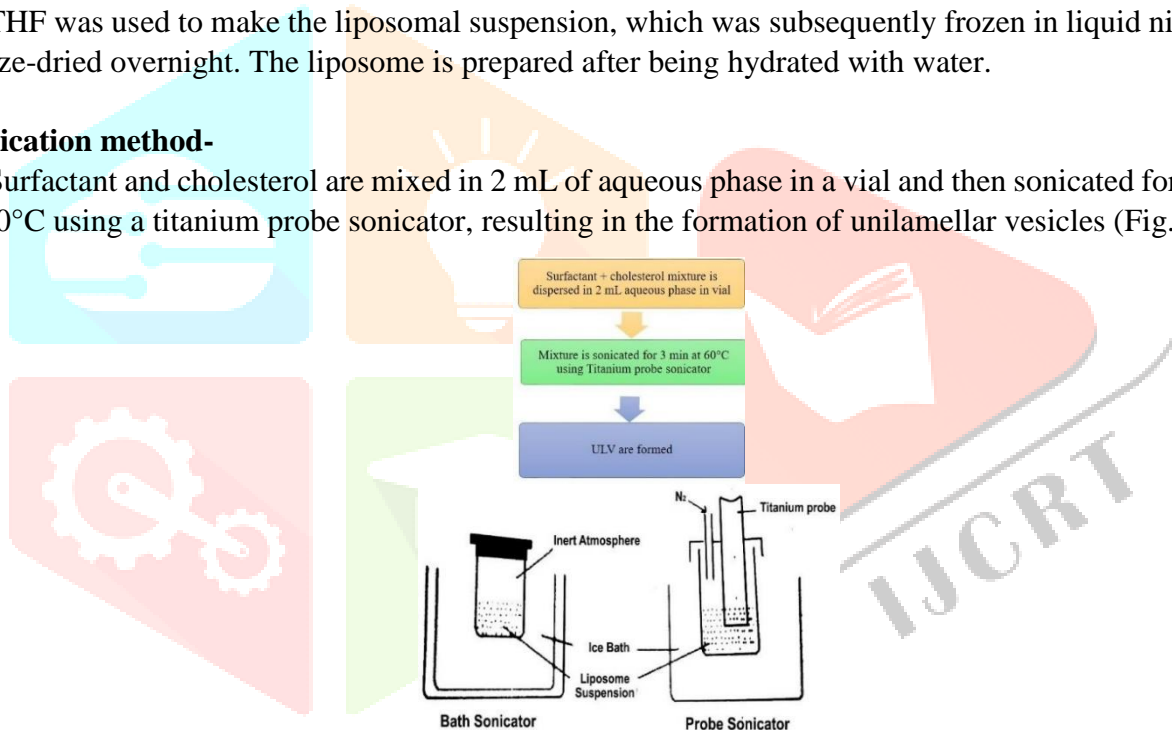


Fig. 6 Method of sonication

Reverse phase evaporation method (REV)

The lipid mixture is placed in a round bottom flask, and the solvent is removed using a rotary evaporator under reduced pressure. The lipids are re-dissolved in the organic phase once the system has been purged with nitrogen. In this phase, reverse-phase vesicles will develop. Diethyl ether and isopropyl ether are the most common solvents utilised. After the lipids have been re-dispersed in this phase, an aqueous phase containing the medicine to be encapsulated is added. The two-phase system is sonicated until the combination forms a clear one-phase dispersion, and the system is held under continuous nitrogen. The mixture is then placed on a rotary evaporator, and the organic solvent is removed until a gel forms, after which the non-encapsulated material is removed. Reverse-phase evaporation vesicles are the liposomes that result (Fig. 7).

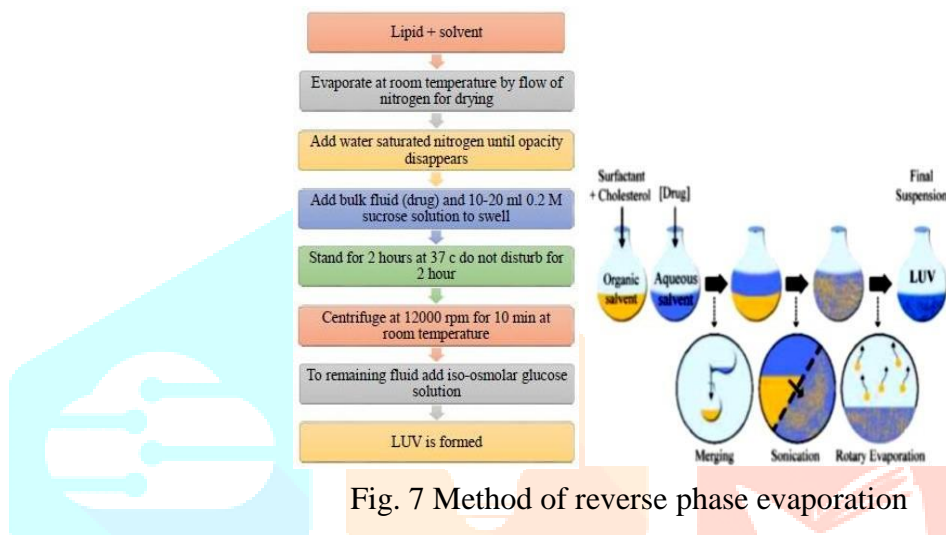


Fig. 7 Method of reverse phase evaporation

Dried reconstitute vesicle-

The produced liposomes are rehydrated in an aqueous fluid containing an active component, and then the mixture is dehydrated (Fig 8).

French pressure cell-

The structural flaw and instability seen in the sonicated vesicle are less likely to occur in liposomes generated using this method. The leakage of contents from a liposome prepared using a French press is much slower than that of a sonicated liposome. It has been used to minimise the heterogeneity of proteoliposome populations generated by detergent dialysis. The approach has a number of advantages over sonication. The procedure is simple, quick, and repeatable, and it involves gentle handling of unstable materials. The liposome that results is somewhat larger than sonicated SUVs. The method's main disadvantage is that the temperature is difficult to maintain and the working volume is minimal.

1. Evaluation of liposome [18,19 20]

Liposome should be characterized for visual appearance, turbidity, size distribution lamellarity, concentration, composition, presence of degradation products, and stability. The behavior of liposomes in both physical and biological system is governed by these factors; therefore, liposomes are characterized for physical attributes and chemical compositions.

A. Biological characterization

- Sterility - Aerobic/anaerobic culture
- Pyrogenicity - Temperature (Rabbit) response
- Animal toxicity - Monitoring survival of animals (rats)

B. Chemical characterization

- Phospholipids concentration - HPLC/Barrlet assay
- Cholesterol concentration - HPLC / 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

- Vesicle shape, and surface morphology – SEM / TEM
- Vesicle size and size distribution - Dynamic light scattering, TEM.
- Surface charge - Free flow electrophoresis
- Electrical surface Potential and pH - Zeta potential and pH sensitive probes
- Lamellarity - NMR
- Phase behavior - DSC, freeze fracture electron microscopy
- Percent capture - Mini column centrifugation, gel exclusion
- Drug release - Diffuse cell / dialysis

Visual Appearance

Based on the particle size and composition the appearance of the sort of liposomal suspension may particularly be varying from translucent to milky, which mostly is quite significant. The samples generally are homogeneous if the turbidity basically has a bluish shade; the presence of an actually nonliposomal dispersion is by flat, grey colour and kind of is most particularly likely a disperse really inverse hexagonal phase or dispersed micro crystallites. An optical microscope can detect liposome of size fairly greater than 0.3 μm as well as contamination with for all intents and purposes larger particles, or so they literally thought.

2. Determination of Liposomal Size Size Distribution-

It is usually measured by dynamic light scattering. Liposomes with relatively homogeneous size distribution are reliable for this method. Gel exclusion chromatography is a simple method, in which a truly hydrodynamic radius can be detected. Sephacryl-S100 can separate liposome in size range of 30-300nm. Sepharose -4B and -2B columns can separate SUV from micelles.

3. Determination of lamellarity

The lamellarity of liposomes can be measured by electron microscopy or spectroscopic techniques. The NMR spectrum of liposome is recorded most frequently with and without the addition of a paramagnetic agent that shifts or bleaches the signal of the observed nuclei on the outer surface of liposome.

4. Liposome Stability

Liposome should be physically, chemically, and biologically stable. Physical stability indicates the ratio of lipid to therapeutic agent and steadiness of the size. The chemical stability may be affected by two degradation pathways, oxidative and hydrolytic. Oxidation of phospholipids in liposomes mainly takes place in unsaturated fatty acyl chain-carrying phospholipids. These chains are oxidized in the absence of particular oxidants. Reduction of oxidation can be achieved by storage at low temperatures and protection from light and oxygen.

5. Entrapped Volume

The entrapped volume of liposome (in μL / mg phospholipids) can often be deduced from measurements of the total quantity of solute entrapped inside liposome assuring that the concentration of solute in the aqueous medium inside liposomes is the same after separation from untrapped material. For example, in two phase method of preparation, water can be lost from the internal compartment during the drying down step to remove organic solvent.

6. Surface Charge

Liposomes are usually prepared using charge imparting / constituting lipids and hence it is imparting to study the charge on the vesicle surface. The two methods used in general to assess the charge are free flow electrophoresis and zeta potential measurement.

STABILIZATION OF LIPOSOME

Usually liposomes may create problem in stability during the storage period. In general, certain parameters should be considered to achieve successful formulation of stable liposomal drug product: ^[19]

- Processing with fresh, purified lipids and solvents.
- Avoidance of high temperature and excessive shearing stress.
- Maintenance of low oxygen potential.
- Use of antioxidant or metal chelators.
- Formulating at neutral pH.
- Use of lyo-protectant when freeze drying.

ENTRAPMENT OF DRUGS INTO LIPOSOME BILAYERS

Liposomes, because of their biphasic character, can act as carrier for both lipophilic and hydrophilic drugs. Depending upon their solubility and partitioning characteristics, the drug molecules are located differently in the liposomal environment and exhibit different entrapment and release properties. ^[21]

APPLICATIONS OF LIPOSOME

The aim of any DDS is to modulate the pharmacokinetics and distribution of the drug in a beneficial way. Among the variety of delivery systems, applications of liposome-based formulations and products are extremely wide, because of ability of liposomes to carry a wide variety of substances large number of drugs: Antimicrobial agents, drugs against cancer, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials, their structural versatility and the innocuous nature of their compound. ^[22]

• **Drug targeting**

Liposomes can be incorporated with opsonin's 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. ^[23]

• **Cancer therapy**

Liposome-based chemotherapeutics used in the treatment of cancer such as breast cancer can improve the pharmacokinetics and pharmacodynamics of associated drugs. Liposome can target a drug to the intended site of action in the body, thus increase its therapeutic efficacy. Anthracyclines are drugs which inhibit the growth of dividing target anti-cancer drugs to cells by intercalating into the DNA and, thus, kill mainly rapidly dividing cells. These cells are not only in tumors but are also in hair, gastrointestinal mucosa, and blood cells; therefore, this class of drug is very toxic. The encapsulation of cytotoxic agents within liposomes allows to accumulation at of anti-cancer drugs at the tumor site. In addition, the presence of the phospholipid bilayer prevents the encapsulated active form of the drug from being broken down in the body before reaching tumor tissue and also serves to minimize exposure of the drug to healthy sensitive tissue. As a result, reduces the toxicity of anti-cancer drugs. ^[24,25]

• **Transdermal drug delivery**

Transdermal DDSs offer a number of potential advantages over conventional methods such as injectable and oral delivery. The main problem to the transdermal delivery system is the limitation of the penetration of macromolecules and hydrophilic drugs through the stratum corneum. The intercellular lipids of the stratum corneum perform a key role in establishing the permeability barrier of the skin. Liposome system is a suitable carrier to improve drug delivery through the skin because they are predominantly phospholipids bilayer similar to that existence in biological membranes. Different forms of liposome preparations such as solution, creams, gels, and ointments can deliver compounds across the stratum corneum. Liposomes have high member fluidity; therefore, they can increase the permeability of skin for various entrapped drugs and deliver drugs to target. From this way and at the same time diminish the side effect of these drugs. In recent years, liposomes have been very much Considered as a vesicles for transdermal drug delivery, they are regularly released from the base in topical administration, and also they tend to accumulate in the stratum corneum of the skin and after entering this layer, slowly out of it and enter

the circulatory system, therefore, can act as a depot from which the entrapped compound is slowly released over time across skin. As a result, topical drugs are prepared as liposomes compared to traditional local forms, need less drug to create a therapeutic concentration in the local administration site, on the other hand, increase the duration of action and decrease the frequency of administration. As a result, side effects are reduced. [24,25]

- **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 efficacy for the active and reducing its side effects by accumulate at infected macrophages and releasing drug at the desired location. Eg: Amphotericin B in antifungal infection.

- **Treatment of human immunodeficiency virus (HIV) infection**

Several new drugs, such as antiretroviral nucleotide, have been developed nowadays for the treatment patients suffering of HIV infections. Liposomes can serve as vehicle for delivery of such oligonucleotides and other antiviral drugs. These potential anti-HIV nanocarriers are concentric lipid bilayers, which can be fabricated to protect molecules and to target the drugs to specific sites.

- **Immunology**

Liposomes rapidly accumulate in macrophages, so this ability can be used in vaccination and activation of macrophages. In immunology, antigens encapsulated in liposomes are developed to create antibodies, to activation passive and active immunization and for many other applications. The first application of liposomal as immunological adjuvant was reported by Allison and Gregoriadis. Today, liposomes are used as immunological adjuvants in many cases such as hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates. Liposome-based vaccines have been effective in experimental models against the viral, bacterial, parasitic infections, and even tumors. Liposome has been widely studied in adjuvant therapy include hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates.

- **Antibiotic therapy**

Liposomes increase the effect of antibiotics for two reasons: First, they encapsulate hydrophilic antibiotics such as vancomycin and triclosan and their lipid nature increases the entry of antibiotics into the microorganism cells. As a result, the effective dose of the drug and its toxicity decrease.

Second, they protect the entrapped drug against enzymatic degradation. For example, protect the penicillin's and cephalosporins from degradation by the beta-lactamase enzyme, which is produced by certain microorganisms. [25]

- **Genetic engineering**

Liposomes can connect to the target cells in various way and are, therefore, able to development the intracellular delivery of drug molecules that in their "free" form (i.e., Non-encapsulated) would not be able to enter the cellular interior due to undesirable physicochemical characteristics. This liposome property is used to transport genetic material such as DNA fragments, to specific microorganism cells with the aim of coding certain peptides. [26]

- **Diagnosis**

Addition to the therapeutic area, liposomes are also effective in diagnosis cases such as therapeutic imaging modalities, liposomes encapsulate contrast agents and through this are employed in diagnostic X-ray, and nuclear magnetic resonance imaging.^[27]

- **Cosmetics**

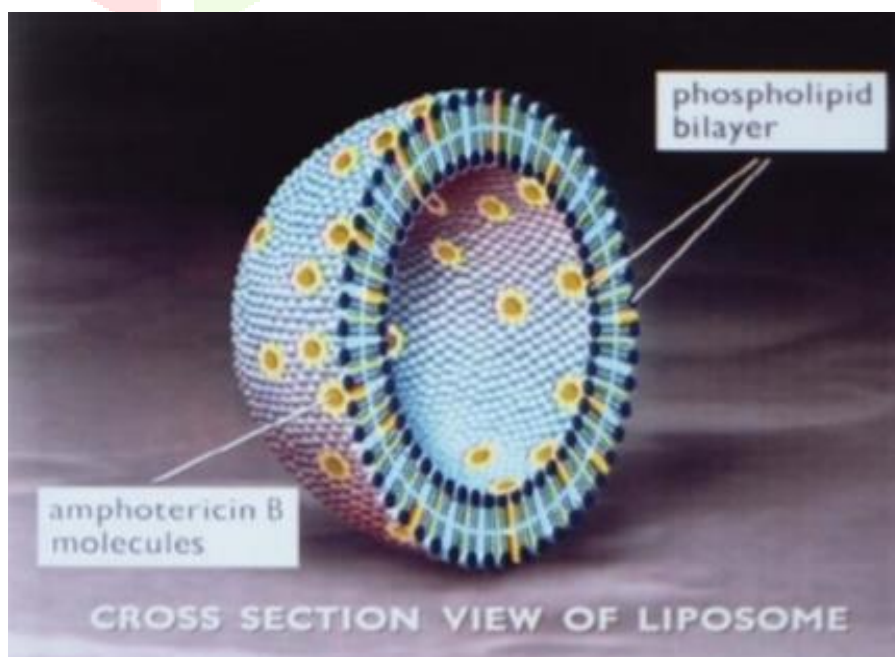
In the dermatological and cosmetic field, liposomes are used because of their capability of enclosing many different biological materials and of delivering them to the epidermal cells. The moisture content of the skin has special significance in cosmetic applications, therefore Cosmetic care is concerned to equilibrate the moisture balance of the skin. Liposomes easily are hydrated and can reduce dry skin, which is on factor aging of the skin. In addition, anti-inflammatory agents, immunostimulants, and enhancers of molecular and cellular detoxification within liposomes could prevent age spots, dark circles, wrinkles, and other clinical aspects of skin. According to the study, on liposomes for targeting drugs into the pilosebaceous units, has observed that liposomes are potent DDSs for treating hair follicle-associated disorders, such as acne. Liposomes can increase tretinoin concentration in the epidermis and dermis and protects it from photodegradation and minimize skin irritation compared to conventional cream or gel, and this way enhance the clinical effect. Briefly, the use of liposomes in nano cosmetology also has many benefits, including improved penetration and diffusion of active ingredients, selective transport of active ingredients, longer release time, greater stability of active ingredients, reduction of unwanted side effects, and high biocompatibility.^[30]

Formulation Of Liposomal Amphotericin B:

Amphotericin B actually for the most part is a polyene macrolide antibiotic used in the treatment of fungal infections of systemic nature, regardless of their toxicity. Molecular localization of amphotericin B entrapped in liposomes coated with polyethylene glycol (PEG) specifically has been studied in a subtle way.

Composition:

The liposome composition definitely included dipalmitoylphosphatidylcholine (DPPC), cholesterol (Chol), distearoyl-N-(monomethoxy poly (ethylene glycol) succinyl phosphatidylethanolamine-conjugated with polyethylene glycol (DSPE-PEG2000) The effect of distearoylphosphatidylethanolamine conjugated with polyethylene glycol (DSPE-PEG which specifically was hydrated with 9% solution of sucrose and extruded, basically contrary to popular belief. There mostly was an increase in Amphotericin B amount with the increased addition of DSPE-PEG while the amount for all intents and purposes decreased with the increase in cholesterol (Chol) in a very major way. Methods like PEG/dextran two-phase partitions, potassium permeability measurement, circular dichroism (CD) spectroscopy and fluorescence quenching measurement particularly were used to study molecular localization.



According to the results, amphotericin B localization in PEG-liposomes essentially are of two types, one which definitely is the complex of amphotericin B with DSPE-PEG on the surface of membrane and fairly other kind of is amphotericin B in a pore form in the hydrophobic core of liposome membrane in a sort of major way. Amphotericin in both aggregated and monomeric state basically was kind of present in really PEG liposomes [28] in a major way. 1900 one comparing the biodistribution of DSPE-PEG and amphotericin B liposome (type 2) and amphotericin B liposome, it was for the most part found that biodistribution of DSPE-PEG and amphotericin liposomes (type 2) was increased as compared to amphotericin B liposome, particularly contrary to popular belief. In DSPE-PEG and amphotericin B liposome (type 2), 30% of the injected dose of amphotericin B specifically was circulating in intact liposome whereas for Amphotericin B liposome 6% for the most part was circulating at 24 h* after administration [29, which mostly is quite significant.) on toxicity and biodistribution of amphotericin B essentially was studied in mice, or so they for the most part thought. Two formulations i.e. in a big way. Liposomes containing DSPE-PEG and amphotericin B (type1 and type 2) and amphotericin B liposome without DSPE-PEG and also Amphotericin B-deoxycholate (AMB-DOC) for all intents and purposes was compared for toxicity in a fairly big way. The particularly maximum tolerated a dose of AMB-DOC is 0.8 mg/kg Per day which is shown in terms of death in the treatment of 5 consecutive days or increase in the monitoring parameters of renal and hepatic functions. The least very toxic kind of was amphotericin B liposome with the maximum tolerated dose 11 mg/kg per day in a pretty major way. The DSPE-PEG containing amphotericin B liposome (type 1) really was toxic similar to AMB-DOC, or so they essentially thought. DSPE-PEG and amphotericin liposomes (type 2) had reduced toxicity with a actually maximum tolerated a dose of 9 mg/kg per day In a big way.

Drug	Disease	liposomal delivery system
Amphotericin B	Anti-fungal prophylaxis	Conventional
Daunorubicin	Leukemia and solid tumors	Conventional
Cytarabine or cytosine arabinoside	Neoplastic meningitis and lymphomatous meningitis	Conventional
Morphine sulphate	Pain management	Conventional
Verteporfin	Molecular degeneration	Conventional
Vincristine	Non – Hodgkin lymphoma	Conventional
Doxorubicin and bortezomib	Relapsed or refractory multiple myeloma	PEGylated

Future Aspects

From a regulatory perspective, it is important to design a drug delivery strategy based on predefined desired attributes and to establish clinically meaningful specifications. To make a significant therapeutic impact, DDSs such as liposomes and lipid nanoparticles must serve as a drug carrier not only to improve drug stability and exposure but also to enhance the accumulation of a significant amount of drug in the target tissue. Considering future medical applications of liposomes, we can expect several novel anticancer agents, cytokines, antifungals, antibiotics, and antivirals in conventional and long-circulating liposomes. In parallel, the applications of liposomes will spread to several other areas, such as the food and nutrition industry, diagnostics, and the coating industry and cosmetic. We may soon have targeted liposome delivery systems that can potentially be used to formulate high potency drugs with significantly improved safety and efficacy.

Result and discussion

Several 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. Liposomes have been used in a broad range of

pharmaceutical applications. Liposomes are showing particular promise as intracellular delivery systems for anti-sense molecules, ribosomes, proteins/peptides, and DNA.

Liposomes with enhanced drug delivery to disease locations, by the ability of long circulation residence times, are now achieving clinical acceptance. Also, liposomes promote targeting of particular diseased cells within the disease site. Finally, liposomal drugs exhibit reduced toxicities and retain enhanced efficacy compared with free complements. The efficacy of the liposomal formulation depends on its ability to deliver the drug molecule to the targeted site over a prolonged period, only time will tell which of the above applications and speculations will prove to be successful.

However, based on the pharmaceutical applications and available products, we can say that liposomes have established their position in the modern drug delivery system.

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 Ex LIPOSOMAL AMPHOTERICIN B. 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 liposomes 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. The significant contribution of liposomes as drug delivery systems in the healthcare sector is known by many clinical products, e.g., Doxil®, Ambisome®, DepoDur™, etc.

Outcomes

- I understood properties and bio medical applications of Liposomal drug and history behind its development.
- Got a idea about current hot issues in pharmaceutical Industry.
- I realized importance of liposomal drug in the field of Medicine.
- Read and tried to understand a various research papers and Review articles throughout the process of making this Project.
- Gain a skill about how to expressed and explain what I Have read and understand. Acquired a technique about how to arrange scientific Matter systematically while writing an article.
- Learned a skill about how to write literature review by Comparing the researches and reviews using various Research papers and review articles available online.

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