NOVEL VESICULAR DRUG DELIVERY SYSTEM: A BRIEF REVIEW

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ABSTRACT: ***Drug delivery systems have become important tools for the specific delivery of a large number of drug molecules. Since their discovery in the 1960s liposomes were recognized as models to study biological membranes and as versatile DDS of both hydrophilic and lipophilic molecules. Among several talented new drug delivery systems, liposomes characterize an advanced technology to deliver active molecules to the site of action and at present, several formulations are in clinical use. Liposome has been used as a potential carrier for several diseases from cardiovascular disease to bacterial infection and also it can reduce the toxicity of highly potent drugs and simultaneously utilized to pharmacokinetics and therapeutic efficacy. Liposomes are colloidal spheres of cholesterol non-toxic surfactant, sphingolipids, glycolipids, long-chain fatty acid and even membrane proteins and drug molecules. It differs in size, composition, and charge and drug carrier loaded with a variety of molecules such as small drug molecules, proteins, nucleotides or plasmids, etc. the focus of this chapter is on the various methods of preparation, characterization of liposomes, advantages, applications, and clinically approved liposomal drugs.***

keywords: Liposomes; Characterization; Drug delivery; Stability; Drugs

I. INTRODUCTION

Artificial lipid vesicles were initially described by English hematologist Alec Bangham in 1961. (also called liposomes). It has been widely recognized and exploited as pharmaceutical delivery vehicles, chemical microreactors, and model biomembrane systems. [1]. The first description of swelling phospholipid systems was published in 1965 by a group of researchers. Within a few years, a variety of encapsulated phospholipid bilayer structures made up of single bilayers were characterized, first as 'bang comes' and then as 'liposomes'2. Liposomes are small spherical artificial vesicles made from cholesterol and non-toxic phospholipids. Liposomes are attractive drug delivery devices due to their size, hydrophobic and hydrophilic properties (along with biocompatibility). Liposome characteristics vary greatly depending on lipid composition, surface charge, size, and manufacturing process.[3]. The concept that liposomes can entrap pharmaceuticals and be employed as drug delivery devices was established by early pioneers such as Gregoriad is and Perrie. [2].

1. Liposomes are designed to have the following optimal qualities.
2. Drug loading and control of drug release rate
3. Overcoming the rapid clearance of liposomes
4. Intracellular delivery of drugs
5. Receptor-mediated endocytosis of ligand-targeted liposomes
6. Triggered release
7. Delivery of nucleic acids and DNA

Structural components of Liposome's [1]:

The main components of liposomes are:

1. Phospholipids
2. Cholesterol

Fig.1. The liposome from the inside and out.

Phospholipid

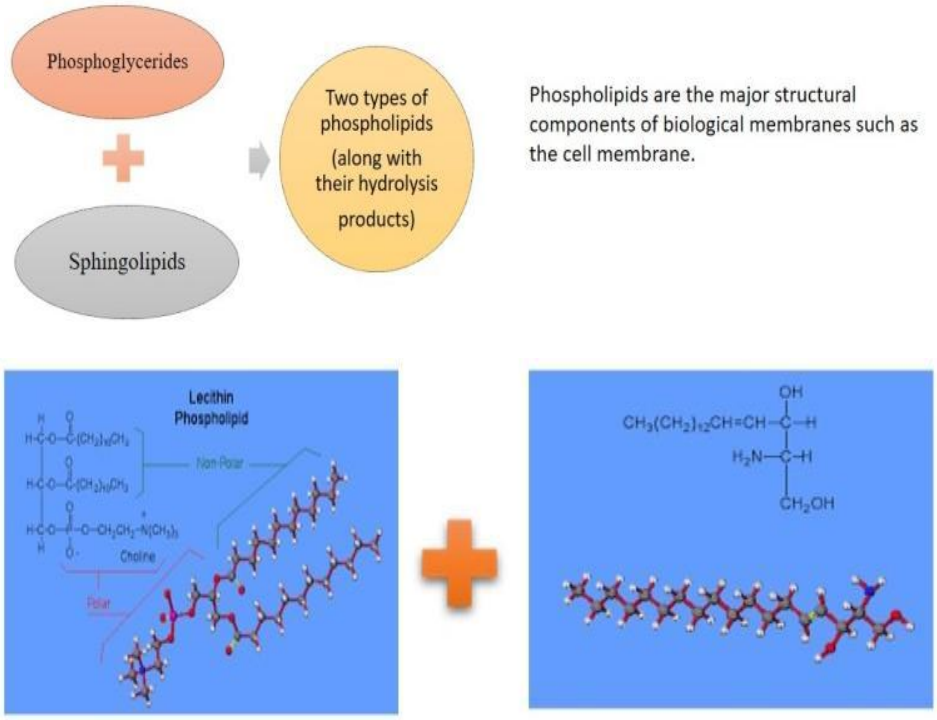


Fig. 2. Phosphoglycerides and sphingolipids have similar chemical structures.

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

Cholesterol - Cholesterol is a waxy, fat-like molecule that is necessary for our bodies to function. 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.

CLASSIFICATION OF LIPOSOMES- [1]

1. Based on structural parameters

i. MLV: Multi lamellar vesicle(0.5µm)
ii. OLV: Oligolamellar vesicle (0.1-1µm)
iii. UV: Unilamellar vesicle (All size range)
iv. SUV: Small unilamellar vesicle (30-70 nm)
v. MUV: Medium-sized unilamellar vesicle
vi. LUV: Large unilamellar vesicle (>100µm)
vii. GUV: Giant unilamellar vesicle (>1µm)

2. Based on the method of preparation

1. REV: Reverse phase evaporation vesicles
2. MLV-REV: Multi lamellar vesicle by REV
3. DRV: Dehydration- rehydration method
4. VET: Vesicle prepared by extraction method
5. SPLV: Stable unilamellar vesicles
6. FATMLV: Frozen and thawed MLV

3. Based on the composition of the application

1. Conventional liposome
2. Fusogenic liposomes
3. Ph sensitive liposomes
4. Cationic liposomes
5. Long circulatory liposome
6. Immuno liposomes

Multilamellar liposomes [4]
The multilamellar vesicle (MLV) is a liposome made up of many concentric lipidic bilayers ranging in size from 0.1 to 0.5 m in diameter. Anion structure is present in MLVs. Their key benefit is that they are simple to construct and have a solid foundation. The limited room for adding chemicals is a key drawback of these liposomes.

Unilamellar liposomes
A single phospholipid bilayer sphere encloses an aqueous solution in unilamellar vesicles. Small unilamellar vesicles (SUV) are small unilamellar vesicles with a size range of 0.02–0.05 m. Because of their small size, these vesicles are not eliminated from the bloodstream.

Multivesicular liposome
A multivesicular vesicle is made up of multiple non-concentric vesicles contained within a single bilayer (MVV). Multifunctional liposomes with sizes ranging from 2 um to 40 um can be used.

Oligolamellar liposome
In comparison to the multilamellar liposome, the oligolamellar liposome has fewer layers of lamella. Their size varies between 0.1 and 10 um.

Giant liposome (GL)
These are the largest liposomes, with sizes ranging from 10 to 1000 um. This GL can be used for a variety of medicinal and diagnostic purposes. They can be SUVs or LUVs.

II. MECHANISM OF LIPOSOME FORMATION

Phospholipids are the building blocks of liposomes (amphiphilic molecules having a hydrophilic head and hydrophobic tail). The hydrophilic part is mostly phosphoric acid coupled to a water-soluble molecule, whereas the hydrophobic part is made up of two fatty acid chains, each having 10-24 carbon atoms and 0-6 double bonds. When disseminated in an aqueous media, they align themselves so that the polar head group faces outwards into the aqueous region and the fatty acid groups face each other, forming spherical, vesicle-like structures known as liposomes. Along with the shielding of the non-polar half, the polar fraction remains in touch with the aqueous zone. When phospholipids are hydrated in water, they are subjected to energy inputs such as sonication, shaking, heating, homogenization, and so on. To achieve a thermodynamic equilibrium in the aqueous phase, hydrophilic/ hydrophobic interactions between lipid-lipid and lipid-water molecules lead to the production of bilayered vesicles. Because phospholipids make up the majority of the cell membrane, they have great biocompatibility and amphiphilic characteristics. It has self-assembly, emulsifying, and wetting properties thanks to its amphiphilicity. When phospholipids are placed into an aqueous environment, they self-assemble and produce various structures with diverse properties depending on the surroundings. Phospholipids, for example, have a natural proclivity for forming liposomes, which can be used as drug targeting molecules. They also have excellent emulsifying capabilities, which help to keep emulsions stable. This can be employed in the coating of the medicine to impart hydrophilicity to hydrophobic pharmaceuticals in addition to the wetting characteristic. These three characteristics are used in a variety of medication formulations. Phospholipids come in a variety of shapes and sizes due to differences in aliphatic chains and alcohols. Furthermore, different phospholipid sources increase the variety of phospholipids.[2]

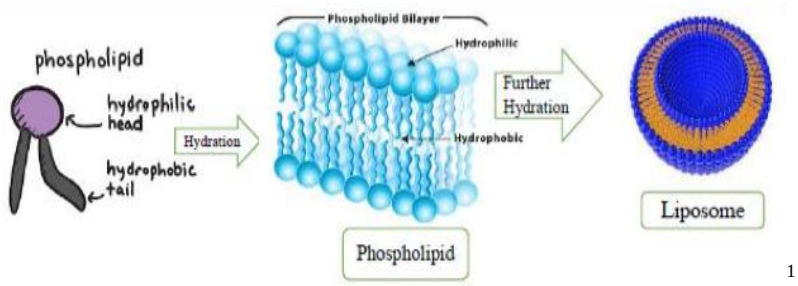


Fig. 3. Mechanism of action of liposome

The reason for bilayer formation includes:

• Folding into tight concentric vesicles reduces the unfavourable interactions between hydrophilic and hydrophobic phases.

• The creation of huge vesicles reduces the significant free energy difference that exists between the hydrophilic and hydrophobic environments. Because spherical shapes have the least amount of surface tension and are the most stable.

The fatty acid carboxyl ions have a better electrostatic connection with a repulsion at neutral pH, which keeps the liposomes stable in the lamellar phase. Fatty acid carboxyl groups are protonated at acidic pH, resulting in the development of the HII phase. This results in unstable liposomes that are easy to aggregate, fuse, and release their contents. As a result, pH-sensitive liposomes are created for various drug delivery applications.

Liposomes have a unique TC (transition temperature) at which they shift from gel to liquid crystalline. During the crystalline phase, the encapsulated medicines are liberated. Liposomes can only form if the temperature is higher than the transition temperature. The transition temperature of a pure lipid liposome is 41.4°C, however lipids from natural sources, such as lecithin, have a broad transition temperature. The Krafft point of lecithin, which is 58°C, is the upper limit of temperature for liposome synthesis, hence a temperature range of 41.4°C to 58°C is appropriate for liposome development, such as thermosensitive liposomes. The size of the liposomes' vesicles is determined by the phospholipid content.

The stabilisation of phosphatidylethanolamine into a bilayer using antibody derivatives of fatty acids such palmitic acid results in liposomes that are targeted to certain tissues. The concentration of immunoglobulin molecules at the contact point causes bilayer instability after attachment to the target's cell surface. Finally, liposomal content is made available at this location. Specific subcellular targeting is still in its infancy and is currently being researched in vitro. Polymer (Rh123)-PEG-DOPE (Rhodamine 123-Polyethylene glycol-1,2-dioleoyl-sn-glycero-3-phosphoethanol amine) contains mitochondriotropic dye rhodamine, which can be used to target mitochondria. The use of a rhodamine-123-conjugated polymer on the surface of a liposome improves mitochondrial targeting.

Advantages of Liposome[1]

1.Liposome increased efficacy and therapeutic index of the drug .

2.Liposome increases stability via encapsulated drug.

3. For systemic and non-systemic applications, liposomes are nontoxic, flexible, biocompatible, totally biodegradable, and non-immunogenic.

4.Liposome reduced the toxicity of the encapsulated agent.

5. Liposomes minimise the amount of harmful medications that reach sensitive tissue. Pharmacokinetic effects have improved (reduced elimination increased circulation lifetimes) this product is suitable for controlled release.

Disadvantages of Liposome[1]

1.Sometimes phospholipid underdogs oxidation and hydrolysis-like reaction.

2.Drug leakage/entrapment/drug fusion.

3.Biological activity is short / t1⁄2.

4.Low solubility and oxidation off bilayer phospholipid.

5.Rate of release and altered biodistribution.

6. low therapeutic index and dose effectiveness.

7. Repeated IV administration problems.

General methods of preparation[5]

There are four main processes to preparing liposomes or manufacturing liposomes in any method:

1. Drying down lipids from an organic solvent.
2. Dispersing the lipid in aqueous media.
3.Purifying the resultant liposome.
4. Analysing the final product.

Method of liposome preparation and drug loading [6]

The following methods are used for the preparation of liposomes:
1. Passive loading techniques
2. Active loading technique.

Passive loading techniques include three different methods:
1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method (Removal of non encapsulated material)

1.The following are types of mechanical dispersion methods:
1.1. Sonication.
1.2. French pressure cell: extrusion.
1.3. Freeze-thawed liposomes.
1.4. Lipid film hydration by handshaking, non-hand, shaking, or freeze-drying.
1.5. Micro-emulsification.
1.6. Membrane extrusion.
1.7. Dried reconstituted vesicles

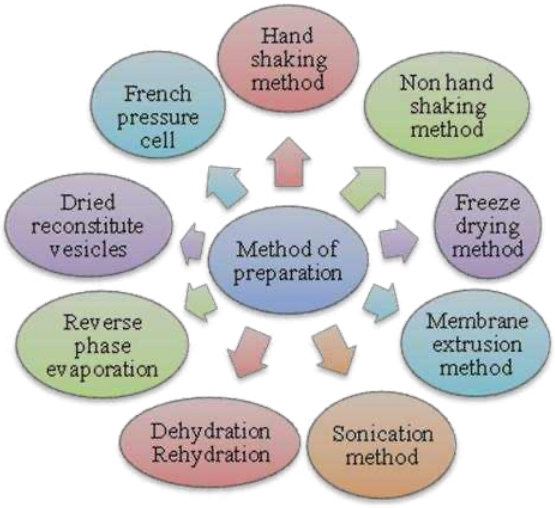


Fig. 4. Mechanical dispersion methods

2.1 SONICATION [5]

The most widely utilised procedure for preparing SUVs is sonication. Under a passive atmosphere, MLVs are sonicated with a bath-type sonicator or a probe sonicator. The main drawbacks of this approach are its low internal volume/encapsulation efficacy, the possibility of phospholipids and compounds to be encapsulated degrading, the elimination of big molecules, metal contamination from the probe tip, and the existence of MLV alongside SUV.[3]
There are two Sonication techniques:

Probe Sonication: A sonicator's tip is directly involved in liposome dispersion. In this approach, the energy input into lipid dispersion is extremely high. Because the coupling of energy at the tip causes localised heat, the vessel must be immersed in a water/ice bath. More than 5% of the lipids can be deesterified during sonication for up to 1 hour. Titanium will also peel off and pollute the solution while using the probe sonicator.

Bath Sonication: In a bath sonicator, the liposome dispersion is placed in a cylinder. With contrast to Sonication by dispersal directly utilising the tip, controlling the temperature of the lipid dispersion or scatter is usually easier in this method. The substance being sonicated can be protected in a sterile vessel or under an inert atmosphere, which is different from the probe units.

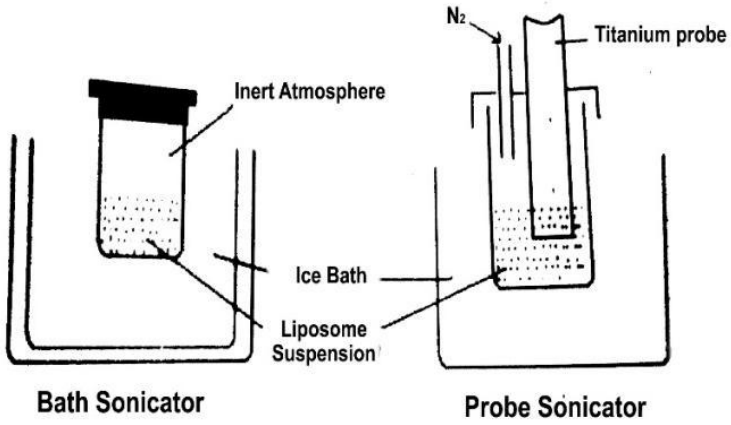


Fig. 5. Method of sonication[1]

2.2 FRENCH PRESSURE CELL: EXTRUSION

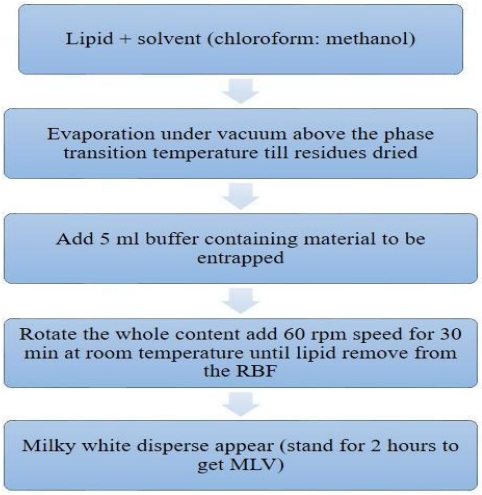
MLV is extruded through a tiny aperture in a French pressure cell. The proteins do not appear to be as arrogant during the French press vesicle method as they do during sonication, which is an essential aspect. A fascinating observation is that the entrapped solutes in the French press vesicle appear to be recalled substantially longer than those produced by sonication or detergent removal in SUVs.The method entails handling unstable materials with care. The approach has a number of advantages over sonication. Liposomes formed as a result are larger than sonicated SUVs. The method's disadvantages are that the high temperature is difficult to achieve and that the working volumes are modest (approximately 50 mL at most).

2.3 FREEZE-THAWED LIPOSOMES

Liposomes that have been frozen and thawed SUVs are quickly frozen and then slowly thawed. Sonication disperses aggregated materials to LUV in a short amount of time. The fusing of SUVs during the freezing and thawing procedures results in the formation of unilamellar vesicles. By raising the phospholipid concentration and the medium's ionic strength, this kind of synthesis is significantly suppressed. Encapsulation efficiencies ranging from 20% to 30% were achieved.

2.4: HANDSHAKING 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 the rotary evaporator and rotated at 60 rpm or below until the layer adhering to the RBF'



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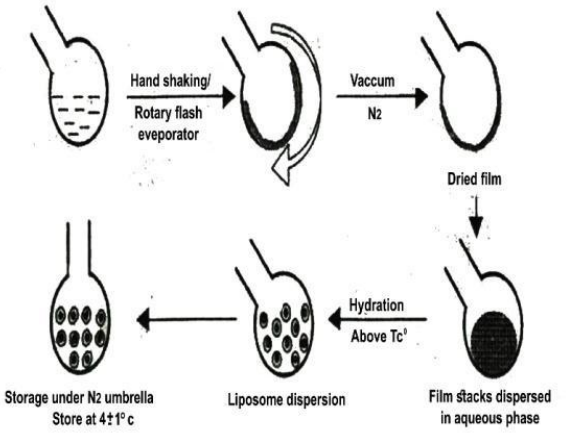

Fig. 6. Method of handshaking

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 generated when the remaining fluid is added to an iso-osmolar glucose solution.

2.5 Membrane Extrusion

During the breaking and resealing of phosphate lipid bilayers as they pass through polycarbonate membranes in this technology, vesicles' contents are swapped with dispersion medium, and less pressure is required than in the French pressure cell used to treat MLVs and LUVs. Finally, nucleation trach membranes and tortuous trach membranes are created.

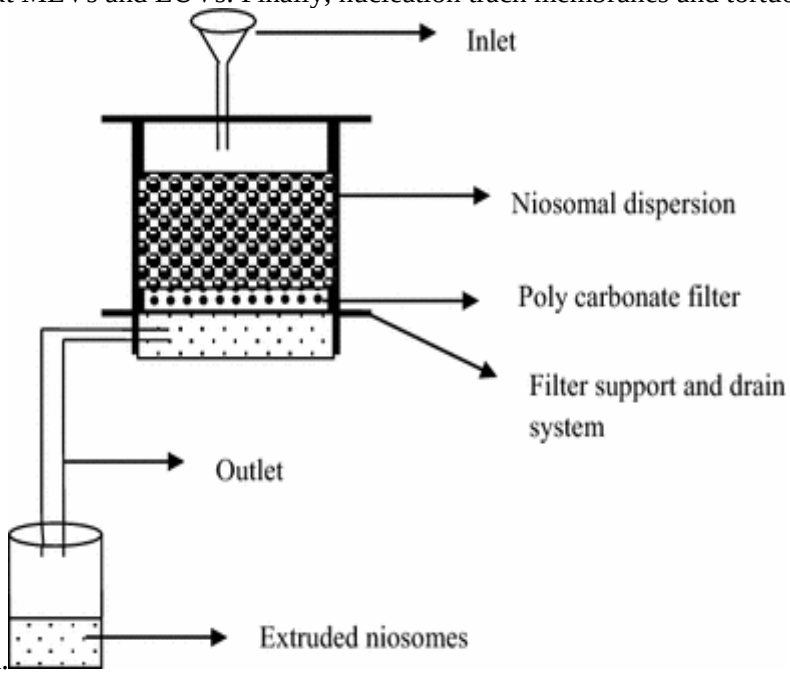

Fig. 7. Method of membrane Extrusion

2.6 Dried reconstitute vesicle :
The produced liposomes are rehydrated in an aqueous fluid containing an active component, and then the mixture is dehydrated.

III.SOLVENT DISPERSION METHOD

Ether injection (solvent vaporization): At 55°C to 65°C or under reduced pressure, a lipid solution mixed in diethyl ether or an ether-methanol mixture is progressively injected into an aqueous solution of the substance to be encapsulated. Liposomes are formed as a result of the elimination of ether under vacuum. The technique's principal drawbacks are the technique's heterogeneous population (70 to 200 nm) and the exposure of encapsulated compounds to organic solvents at high temperatures.
Ethanol injection: A lipid solution of ethanol is injected rapidly into a large amount of buffer. The MLVs are generated at the same time. The method's drawbacks include the population's heterogeneity (30 to 110 nm), the dilute nature of liposomes, the difficulty of removing all ethanol because it forms an azeotrope with water, and the high likelihood of biologically active macromolecules inactivating in the presence of even small amounts of ethanol.
Reverse phase evaporation method [7]
This method advanced liposome technology by allowing the creation of liposomes with a high aqueous space-to-lipid ratio and the ability to entrap a considerable percentage of the aqueous material offered for the first time. The formation of inverted micelles is the basis of reverse-phase evaporation. After sonicating a mixture of a buffered aqueous phase containing the water-soluble molecules to be encapsulated into the liposomes and an organic phase in which the amphiphilic molecules are solubilized, these inverted micelles are formed. The inverted micelles are converted to a viscous state and gel form as the organic solvent is slowly removed. The gel state collapses at a critical stage in the process, disrupting some of the inverted micelles. The presence of too many phospholipids in the environment causes a full bilayer to develop around the remaining micelles, resulting in the formation of liposomes. Reverse-phase evaporation liposomes can be generated from a variety of lipid formulations and have a four-fold higher aqueous volume-to-lipid ratio than hand-shaken liposomes or multilamellar liposomes. To summarise, a two-phase system comprising phospholipids in an organic solvent such as isopropyl ether or diethyl ether, or a combination of isopropyl ether and chloroform with aqueous buffer is shaped by short sonication. Under reduced pressure, the organic solvents are disengaged, resulting in the formation of a viscous gel. When leftover solvent is removed during rotational evaporation under lower pressure, liposomes are formed. In a medium with low ionic strength, such as 0.01 M NaCl, this approach can achieve high encapsulation effectiveness of up to 65 percent. Small, big, and macromolecules have all been encapsulated using this technology. The main disadvantage of the method is that the materials to be encapsulated come into contact with organic solvents and are subjected to brief durations of sonication. Breakage of DNA strands or denaturation of some proteins may occur as a result of these circumstances. Handa et al. presented a modified reverse-phase evaporation process, with the key benefit being that the liposomes had good encapsulation efficiency (about 80 percent)

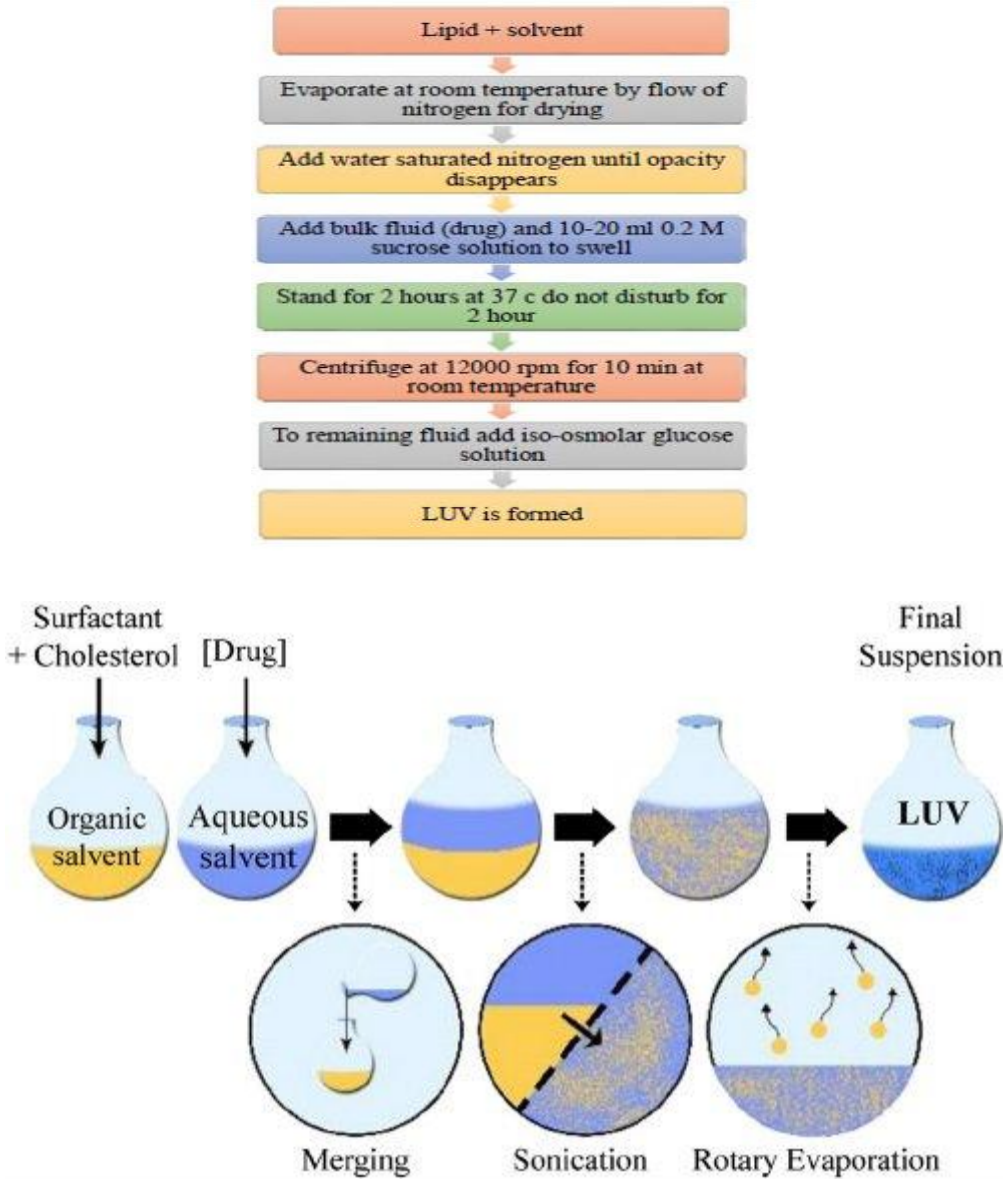

Fig.8.Method of reverse-phase evaporation method [1]

IV. METHOD FOR EFFECTIVE REMOVAL (REMOVAL OF NON- ENCAPSULATED MATERIAL)[5]

To solubilize lipids, dialysis detergents at their critical micelle concentrations (CMC) were used. As the detergent is removed, the micelles grow more phospholipid-rich and eventually unite to create LUVs. Dialysis was used to eliminate the detergents. For the removal of detergents, a commercial equipment called LipoPrep (Diachema AG, Switzerland), which is a dialysis system, is available. Dialysis can be done in huge detergent-free buffers encased in dialysis bags (equilibrium dialysis).

Removal of mixed micelles with a detergent (cholate, alkylglycoside, Triton X-100) (absorption)

Shaking a mixed micelle solution with beaded organic polystyrene adsorbers such XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Bio-beads SM2 achieves detergent absorption (Bio-Rad Laboratories, Inc., Hercules, USA). Detergent adsorbers have the advantage of being able to eliminate detergents with a low CMC that aren't completely depleted.

Gel-permeation chromatography

The detergent is depleted using size special chromatography in this procedure. Gel filtering can be done with Sephadex G-50, Sephadex G-l 00 (Sigma-Aldrich, MO, USA), Sepharose 2B-6B, and Sephacryl S200-S1000 (General Electric Company, Tehran, Iran). Liposomes are unable to pass through the pores of the beads in a column. They percolate through the crevices between the beads. Liposomes and detergent monomers can be separated very well at low flow rates.

Dilution :

The micellar size and polydispersity essentially rise when an aqueous mixed micellar solution of detergent and phospholipids is diluted with buffer, and as the system is diluted beyond the mixed micellar phase boundary, a spontaneous transition from poly-dispersed micelles to vesicles occurs.

Stealth liposomes and conventional liposomes

Liposomes are similar to biomembranes, however they are still foreign bodies. After interaction with plasma proteins, the mononuclear phagocytic system (MPS) recognises liposomes. Liposomes are removed from the bloodstream as a result. Synthetic phospholipids, particles coated with amphipathic polyethylene glycol, covering liposomes with chitin derivatives, freeze-drying, polymerization, and micro-encapsulation of gangliosides are used to overcome these stability issues. Stealth liposomes are sphere-shaped vesicles with a phospholipid bilayer membrane that are used to deliver medications or genetic material into cells. A liposome can be made up of natural phospholipids with mixed lipid chains coated or stabilised by PEG and colloidal polymers. In novel medication delivery and controlled release, stealth liposomes are obtained and developed. The successful doxorubicin-loaded liposome product Doxil (Janssen Biotech, Inc., Horsham, USA) or Caelyx (Schering- Plough Corporation, Kenilworth, USA) for the treatment of solid tumours was developed using this stealth principle.

Drug loading in liposomes

Drug loading can be accomplished passively (i.e., the drug is encapsulated during liposome creation) or actively (i.e., the drug is encapsulated during liposome formation) (i.e., after liposome formation). Hydrophobic medicines, such as amphotericin B taxol or annamycin, can be directly incorporated into liposomes during vesicle formation, and drug-lipid interactions control the degree of uptake and retention. The ability of liposomes to capture an aqueous buffer containing a dissolved drug during vesicle formation is required for passive encapsulation of water-soluble medicines. The trapped volume circumscribed in the liposomes and medication solubility restrict the trapping efficacy (usually 30 percent).

Freeze-protectant for liposomes

Before being delivered to the target place, natural extracts are frequently damaged because to oxidation and other chemical processes. Freeze-drying has long been a regular method in the manufacturing of pharmaceuticals. The vast majority of these items are made from simple aqueous solutions that have been lyophilized. Although traditionally, water is the only solvent that must be removed from a solution using the freeze-drying method, many pharmaceutical products are still created utilising a process that involves freeze-drying from organic co-solvent systems. Freeze-drying (lyophilization) is the process of removing water from frozen items at extremely low pressures. Pharmaceutical equipment companies sell freeze-driers in a variety of sizes, from small laboratory models to huge industrial systems.

Evaluation of Liposome[1]

Physical, chemical, and biological parameters are the three types of characterization parameters that can be used to evaluate a product.

Physical Characterization

Characterization Parameter	Analytical Method/ Instrument
Vesicle shape and surface morphology	Transmission electron microscopy, freeze-fracture electron microscopy
Surface charge	Free-flow electrophoresis
Mean vesicle size and size distribution	Photon correlation spectroscopy, laser light scattering, gel permeation, and gel exclusion
Lamellarity	Small-angle X-ray scattering, 31 P-NMR, Freeze fracture electron microscopy
Electrical surface potential and surface pH	Zeta potential measurement
Phase behavior	Freeze fracture electron microscopy, Differential scanning calorimetry

Percent of free drug/ percent capture	Minicolumn centrifugation, ion-exchange chromatography

Chemical Characterization:

Characterization parameter	Analytical method/ instrument
Phospholipid concentration	Lipid phosphorous content using ballet assay, HPLC
Cholesterol concentration	Cholesterol oxidized assay and HPLC
Drug concentration	Appropriate methods are given in monograph for individual drug
Phospholipid peroxidation	UV absorbance TBA iodometric and GLC
Phospholipid hydrolysis	HPLC and TLC and fatty acid concentration
Phospholipid auto-oxidation	HPLC and TLC
Anti-oxidant degradation	HPLC and TLC
pH	pH meter

Biological Characterization:

Parameters	Analytical method/instrument
Sterility	Aerobic or Anaerobic Cultures
Pyrogenicity	Limulus Amebocyte Lysate (LAL) test
Animal toxicity	Monitoring survival rates, histology, and pathology

Liposomal Drug Delivery Systems Based on Synthetic Polymers [8]

Carbopol-Based Liposomal DDS: Carbopol hydrogel formulation is a synthetic type of hydrogel, which is a polyacrylic acid derivative. Carbopol 980, Carbopol 974NF resin, and Carbopol 940 have been widely used as pharmaceutical carriers due to their outstanding properties such as bio-adhesivity, biocompatibility, and low toxicity . Carbopol hydrogel formulation is a polyacrylic acid derivative that is a synthetic type of hydrogel. Due to its remarkable features like as bio-adhesivity, biocompatibility, and low toxicity, Carbopol 980, Carbopol 974NF resin, and Carbopol 940 have been widely used as pharmaceutical carriers. Because the functional carboxylic acid groups (–COOH) can generate hydrogen bridges to interpenetrate the mucus barrier, carbopol can swell quickly in water and stick to the intestinal mucus. Furthermore, due to the presence of carboxylic groups in its structure, carbopol might block the function of the most important enzymes in the gastrointestinal system. In recent investigations, Hosny demonstrated that drug-loaded liposomes could be incorporated into the Carbopol hydrogel-based system, which served as a temporary depot. They did the research in vitro to improve low viscosity and poor long-term release, both of which are linked to liposome setbacks. The findings suggested that the degree of encapsulation and lengthening of the drug release rate of either pharmaceuticals or loaded liposomes in temporary Carbopol depots is heavily influenced by vesicle features like charge and stiffness. These investigations found that a loaded liposome incorporated with a Carbopol-based system was an effective medication delivery strategy for ophthalmic and vaginal illnesses.

Polyvinyl Alcohol-Based Liposomal Drug Delivery Systems.

With a molecular mass of 80 kilodaltons, polyvinyl alcohol (PVA) is a water-soluble, extremely hydrophilic synthetic polymer (KDa). PVA is a versatile material that can be used in a variety of applications, including industrial, commercial, medicinal, and food items. Furthermore, due to several appealing qualities like as low toxicity, good film-forming, biodegradability, emulsifying capacity, biocompatibility, and adhesive capabilities, PVA has attracted a lot of interest in pharmaceutical applications. Chemical cross-linking agents including citric acid derivative, glutaraldehyde, and formaldehyde, as well as physical cross-linking procedures like UV photo-cross-linking, freezing-thawing, and radiation, have been used to make PVA-based hydrogels or scaffolds. The impact of PVA-based polymers on the release rate of pre-encapsulated drug-loaded liposomes have been studied in a number of ways. PVA was thought to increase liposome viscosity, making them more stable and less permeable, resulting in a prolonged release liposomal delivery mechanism in these combination systems. Photo cross-linking affects the success of calcein-loaded liposomes placed inside a temporary depot, according to a recent study by Litvinchuk and colleagues. Liposome stability, viscosity, and long-term drug release are only a few of them. Ciprofloxacin, a synthetic chemotherapeutic antibiotic, was one of the medications successfully integrated into liposome and PVA-based delivery systems, according to reports.

STABILITY OF LIPOSOMES[2]

The stability of the liposomes, which includes manufacture, storage, and administration, determines the therapeutic efficacy of the drug molecule. During the development and storage of an active molecule, a stable dosage form ensures the physical stability and chemical integrity of the active molecule. The examination of its physical, chemical, and microbiological properties, as well as the assurance of the product's integrity throughout storage, are all part of the stability research with designing.

Physical Stability: [5]

When phospholipids are hydrated in water, they form liposomes, which are bilayered vesicles. The vesicles that result from this process are of various sizes. The vesicles tend to coalesce and grow in size during storage to achieve a thermodynamically favourable condition. Drug leakage from the vesicles can occur during storage due to vesicle fusion and breaking, compromising the liposomal drug product's physical stability. As a result, vesicle form, size, and size distribution are crucial criteria to consider when assessing physical stability.

Chemical stability : [2]

Phospholipids are chemically unsaturated fatty acids that are susceptible to oxidation and hydrolysis, which might affect the drug's stability. pH, ionic strength, solvent system, and buffered species all have a role in liposomal formulation maintenance. Antioxidants such as -tocopherol or butylated hydroxyl toluene (BHT), manufacturing the product in an inert environment (presence of nitrogen or Argon), or adding EDTA to eliminate trace heavy metals can all help to avoid oxidative degradation of liposomes. The production of lysophosphatidylcholine is caused by the hydrolysis of the ester link at the C-4 position of the glycerol moiety of phospholipids (lysoPC). The permeability of the liposomal contents will be improved as a result of this. As a result, controlling the lysoPC limit within the medication product of lysosomes is critical.

THERAPEUTIC APPLICATIONS OF LIPOSOME: [9,2]

Any DDS tries to beneficially alter the drug's pharmacokinetics and distribution. Because of liposomes' ability to carry a wide variety of substances, including antimicrobial agents, cancer drugs, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials, as well as their structural versatility and the innocuous nature of their compound, applications of liposome-based formulations and products are extremely broad. The following are some of the most important therapeutic applications of liposomes in drug delivery:

Drug targeting

For site-specific drug delivery systems, liposomes can be combined with opsonins and ligands (e.g., antibodies, sugar residues, apoproteins, or hormones, which are tagged on the lipid vesicles). The ligand binds to certain receptor sites, causing the lipid vesicles to congregate at those locations.

Cancer therapy

The pharmacokinetics and pharmacodynamics of related medications can be improved by liposome-based chemotherapeutics used in the treatment of cancers such as breast cancer. Liposomes can direct a medicine to its targeted location of action in the body, boosting therapeutic efficacy. Anthracyclines are anti-cancer medications that impede the growth of dividing target cells by intercalating into their DNA, killing mostly fast dividing cells.

Transdermal drug delivery

Transdermal DDSs have a number of advantages over other delivery techniques, such as injectable and oral. The stratum corneum limits the passage of macromolecules and hydrophilic medicines, which is the fundamental flaw in the transdermal delivery technique. The stratum corneum's intercellular lipids play a crucial function in building the skin's permeability barrier.

Intracellular drug delivery

LDDS can help increase the transport of prospective medications to the cytosol (where drug receptors are located). Normally, N-(phosphonacetyl)-L-aspartate (PALA) is poorly absorbed by cells. When these medicines were encapsulated within liposomes, they had more activity against ovarian carcinoma cell lines than when they were free.

Sustained release drug delivery

Liposomes enable sustained release of target medicines, which is required for optimal therapeutic efficacy, which requires a prolonged plasma concentration at therapeutic levels. In vivo, drugs like cytosine Arabinoside can be encapsulated in liposomes for prolonged release and a better drug release rate.

Site-avoidance delivery

Anti-cancer medications have a limited therapeutic index, which causes cytotoxicity in normal tissues (TI). In such cases, the TI can be enhanced by encapsulating the medications in liposomes, which reduces drug distribution to normal cells. For example, doxorubicin has a serious side effect of cardiac toxicity, but when synthesised into liposomes, the toxicity was lowered but the therapeutic activity remained same.

Site-specific targeting

Site-specific targeting can deliver a bigger fraction of the medicine to the desired (diseased) site while decreasing the drug's exposure to normal tissues. Long-circulating immunoliposomes can detect and bind to target cells with increased specificity after systemic injection. When muramyl peptide derivatives were formed as liposomes and delivered systemically to patients with recurrent osteosarcoma, there was an increase in tumoricidal activity of monocytes.

Treatment of HIV infection

Several novel medications, such as antiretroviral nucleotide, have been developed in recent years for the treatment of HIV patients. Liposomes can be used to deliver antiviral oligonucleotides and other antiviral medicines. Concentric lipid bilayers, which can be produced to protect molecules and target medications to specific areas, are thus prospective anti-HIV nanocarriers.

Immunology

Liposomes aggregate quickly in macrophages, and this property can be utilised in macrophage vaccination and activation. Antigens contained in liposomes are used in immunology to generate antibodies, trigger passive and active immunisation, and for a variety of other purposes. Allison and Gregoriadis reported the first use of liposomal as an immune adjuvant. Liposomes are being used as immunological adjuvants in a variety of applications, including hepatitis B-derived polypeptides, influenza virus subunit antigens, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates. In experimental animals, liposome-based vaccinations have shown to be effective against viral, bacterial, parasite, and tumour infections.

Antibiotic therapy

Antibiotics are more effective with liposomes for two reasons: For starters, they encapsulate hydrophilic antibiotics like vancomycin and triclosan, and their lipid composition facilitates antibiotic penetration into microbe cells. As a result, the drug's effective dose and toxicity are reduced. Second, they prevent the enclosed drug from being degraded by enzymes. Penicillins and cephalosporins, for example, are protected from breakdown by the beta-lactamase enzyme, which is produced by some microbes.

Genetic engineering

Liposomes can link to target cells in a variety of ways, allowing for intracellular delivery of therapeutic molecules that would not be able to penetrate the cellular interior in their "free" state (i.e., non-encapsulated) due to unfavourable physicochemical properties. This feature of liposomes is utilised to deliver genetic material, such as DNA fragments, to certain microorganism cells in order to code for specific peptides.

Diagnosis

Liposomes are used in diagnostic X-ray and nuclear magnetic resonance imaging as well as therapeutic imaging modalities. Liposomes encapsulate contrast ants and are used in diagnostic X-ray and nuclear magnetic resonance imaging.

Cosmetics

Liposomes are utilised in dermatology and cosmetics because of their capacity to enclose a wide range of biological elements and deliver them to epidermal cells. Because the moisture content of the skin is so important in cosmetic applications, cosmetic care is concerned with restoring the skin's moisture balance. Liposomes are quickly hydrated and can help to alleviate dry skin, which is a contributing factor to skin ageing. Anti-inflammatory drugs, immunostimulants, and enhancers of molecular and cellular detoxification within liposomes could also help to prevent age spots, dark circles, wrinkles, and other skin problems.

Food and farming industry

Liposomes have been used in the food industry to develop new flavours, control flavour release, improve food colour, and modify the texture of food components because they can entrap unstable compounds such as antimicrobials, antioxidants, flavours, and bioactive elements and protect them from a variety of environmental and chemical changes such as enzymatic chemical changes, temperature and ionic strength variations, and releasability. According to studies, adding proteases to the cheese combination reduces the cost and time it takes to make cheese. Additionally, liposome-entrapped proteinases decrease the firmness of cheddar cheeses while increasing their elasticity and improving their flavour, while liposome-entrapped lipase increases the cohesiveness and elasticity of cheddar cheese while decreasing the firmness.

LIST OF CLINICALLY- APPROVED LIPOSOMAL DRUGS

Name	Trade Name	Company	Indication
Liposomal Amphotericin B	Abelcet	Enzon	Fungal Infection
Liposomal Amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Deposit	Pacira (Formerlyskyepharma)	Malignant lymphomatous meningitis
Liposomal Daunorubicin	DaunoXome	Gilead sciences	HIV- related Kaposi's Sarcoma
Liposoma Doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy
Vincristine	On TCS	--	Non-Hodkin's lymphoma
Lurtotecan	NX211	--	Ovarian Cancer
Nystatin	Nolan	--	Topical antifungal agent
Liposome-PEG Doxorubicin	Doxil/Caelyx	Ortho Biotech,Schering-Plough	HIV-related Kaposis's sarcoma,metastatic breast cancer,metastatic ovarian cancer
Liposomal Vaccine	Epaxal	Berna Biotech	Hepatisis A
Liposomal Vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal Morphine	Depo Dur	Skyepharma,Endo	Postsurgical analgesia
Liposomal Verteporfion	Visudyne	QLT,Novartis	Age-related macular degeneration,pathologic myopia,ocular histoplasmosis
All-trans retinonic acid	Altragen	--	Acute promyelocytic leukaemia; non-Hodgkin's lymphoma;renalcell carcinoma;kaposi's sarcoma
Platinum compounds	Platar	--	Solid tumors
Annamycin	--	--	Doxorubicin-resistant tumors
E1A gene	--	--	Various tumors

DNA plasmid encoding HLA-B7 and α2 macroglobulin	Allovectin-7	--	Metastatic melanoma

V.CONCLUSION

The analysis found that liposomes are one of the few unique drug delivery methods that could be useful in managing and targeting medication distribution. Orally, parenterally, and topically, as well as in cosmetics and hair technology, they are utilised in sustained-release formulations. Liposomes have the potential to improve the targeted administration of a wide range of medications, including antimicrobials, cancer treatments, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic material. Liposomes are showing promise as an intracellular delivery mechanism for antisense compounds, ribosomes, proteins/peptides, and DNA, among other things. Finally, when compared to free complements, liposomal medicines have lower toxicity and higher efficacy. However, we can claim that liposomes have established their place in the modern delivery system based on pharmaceutical uses and available items.

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