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Liposomes as a Novel Drug Delivery System

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***Abstract*: A flexible and promising drug delivery method are liposomes. Liposomes provide several advantages over conventional drug delivery systems, such as site-targeting, controlled or prolonged release, protection of medications from clearance and degradation, increased therapeutic effects, and less harmful side effects. consequences Liposomes offer numerous advantages and applications as efficient drug carriers in pre-clinical and clinical research. Furthermore, problems with liposomal stabilization, effective targeting strategies, and some of their shortcomings were covered. The ability to alter the drug biodistribution of numerous medications has been made possible by the development of liposomes, which has enhanced the medicinal qualities of such substances. To sum up, the purpose of this research is to examine the liposomes that are presently available on the market and are employed for a variety of medicinal purposes.**

***Keywords*: liposomes, novel delivery, phospholipids, application in drug delivery.**

1. Introduction

Paul Ehrlich in 1906 initiated the period of development for targeted delivery when he visualized a medicine delivery medium that would target medicine directly to diseased cells, what he called as magic pellets, liposomes are globular shaped small vesicles that can be produced from cholesterols, non-toxic surfactants, sphingolipids, glycolipids, long-chain adipose acids and indeed membrane proteins. Phospholipids spontaneously form an unrestricted structure when dissolved in water with internal waterless terrain bounded by phospholipids bilayer membranes; this makes the transport of medicine to be easy. The development of targeted delivery technology began in 1906 when Paul Ehrlich featured a drug administration system that Liposomes are globular- shaped, small vesicles that can be created from cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long- chain adipose acids, and indeed membrane proteins. He appertained to them as" magic pellets" because they would deliver medicines directly to damaged cells. When phospholipids are dissolved in water, they spontaneously form a unrestricted structure with an interior waterless terrain that's framed by bilayer membranes of phospholipids. This facilitates medicine delivery. The hydrophobic drug is stored in the liposome's hydrophobic regions, whereas the hydrophilic medicine has been stored in the liposome's center [1]. this vesicular system is called liposome [2] Liposomes are a type of colloidal vesicle according of one or further lipid bilayers boxed in waterless spaces**.** colorful medicines, including antibiotics, antifungals, anticancer agents, proteins, hormones, peptides, and others, are reprised in liposomes. Due to their metabolism, multitudinous medicines only take extremely bitsy quantities of time to reach a remedial position. Liposomes are used as an implicit vehicle for delivery of drug and remedial position archiving [3] The phospholipid membrane of liposomes is 4-5 nm thick, and the liposome size varies i.e. 30 nm to micrometer scale. Monolayer and bilayer forms are appertained to as micelles and liposomes, independently. Because of their unique parcels, liposomes are used in the distribution of medicines. A number of papers concentrate on natural operations, and new developments in liposomal methodology [4].

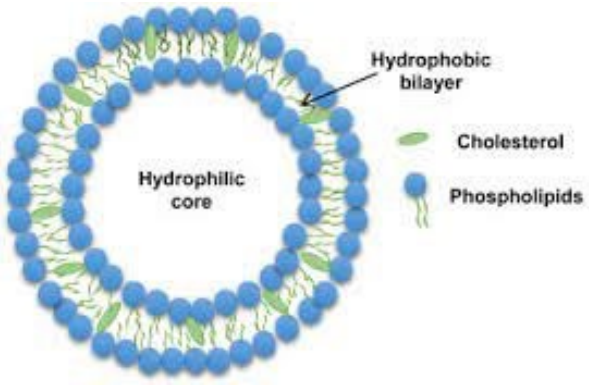

Fig. 1. Structure of Liposome [45]

2. Components of Liposome

1) Phospholipids: The main elements of structure of liposomes are phospholipids. The most common phospholipids in liposomal the Phosphatidylcholine preparation Figure 2. An amphipathic molecule known phosphotidylcholine is made with phosphocholine, a hydrophilic polar head group. A pair of hydrophobic acyl hydrocarbon chains are connected by a glycerol. The composition of spontaneously occurring A glycerol moiety linked to two acyl chains—which may be saturated or unsaturated—makes up phosphatidylcholine. This arrangement of the lipid molecules' hydrocarbon chains determines how stable the liposome membrane is [5]. Examples of phospholipids are,

- Phosphotidyl choline (Lecithin) PC
- Phosphotidyl serine (PS)
- Phosphotidyl Glycerol (PG)
- Phosphotidyl ethanolamine (Cephalin) PE

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Every lipid has a temperature at which it becomes less fluid. Another name for this temperature is the transition temperature (TC). The TC is located directly according to the acyl chain's length; the longer the chain, the higher the TC and more rigid the membrane. The TC is essential because it influences the membrane's stability, aggregation, permeability, and response to fusing with other liposomes. further affecting how the liposomes respond when biological systems are observed [6].

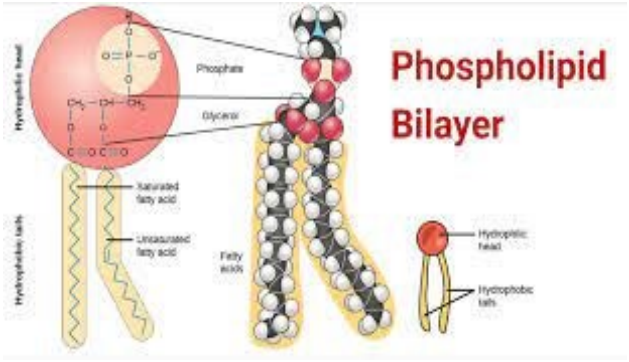

Fig. 2. Phospholipids [46]

2) Cholesterol: Another essential liposome structural element is cholesterol. It is a sterol that is often utilized. The formation of sterols influences the extends the time that blood is in circulation in the bloodstream 9 as a function of flexibility and stability [6].

It doesn't create a bilayer structure on its own. It gets absorbed at very high concentrations into phospholipids, producing molar ratios of 1:1 or 2:1 between cholesterol and phosphotidyl choline. The lipid bilayer becomes more stable and forms a highly organized, rigid membrane structure when cholesterol is present [7].

Cholesterol increases the cellular membrane's fluidity and rigidity while decreasing the permeability of molecules that are soluble in water. Cholesterol prevented the liposomes from interacting and becoming unstable [8].

Advantages:

Due to its amphipathic nature, it can bind both water-soluble and insoluble drugs [9], [10].

- It provides targeted delivery of medications.
- improved effectiveness of medications and therapeutic index
- Non-ionic
- Liposomes are helpful in reducing the quantity of toxic drug exposure to delicate tissues.
- The effect of site avoidance
- Enhance the stability of proteins
- Direct drug-cell interaction
- Biodegradability of liposomes
- Biocompatible

Disadvantages:

- Poor solubility
- Less stable
- It is possible for the encapsulated drug to leak or fuse.
- High production costs
- Phospholipids may get oxidized.
- Liposomal components may cause allergic reactions in particular individuals [11].

3. Methods of Preparation

1. Passive loading technique.
2. Active loading technique.

A. Mechanical dispersion dispersion Method

This method encloses an average percentage of the overall volume—between 5 and 10%—of aqueous volume for swelling. Consequently, a significant amount of the water-soluble chemical declines during swelling; whereas, the lipid-soluble compound can be fully encapsulated. As long as their concentration is not higher than that of the membrane's structural element, that is [12]

- *Lipid hydration by hand shaking*

Step (1) - First, a lipid mixture including various phospholipids and charge components in chloroform was produced. methanol (2:1) solvent combination (v/v). After that, insert a ground glass neck into a flask with a circular bottom. This flask is fixed to a 60 rpm rotating evaporator. At roughly 30 degrees Celsius, or the lipid's transition temperature, the organic solvent evaporates. By closing the tip, the evaporator is sealed away from the vacuum source. After adding nitrogen to the evaporator, the cylinder's pressure is continued to rise until there is no longer any difference between the interior and outside of the flask. Take the flask out of the evaporator and place it on a lyophilizer to get clear of any extra solvents [13], [14].

Step (2) - Hydration of lipid layer

The flask is taken out of the lyophilizer, rinsed with nitrogen, and then 5 milliliters of saline phosphate buffer are added. Once again, the flask is attached to the evaporator and given a dinitrogen (N2) flush. At room temperature and pressure, the evaporator rotates at the same speed (for rpm values less than 60). After 30 minutes or until all of the lipid has been extracted from the flask wall and a uniform, milky suspension has been produced, the flask is stopped rotating. To achieve MLVs (multilamellar vesicles), the suspension is let to stand for two hours at room temperature or at a temperature greater than the lipid's transition temperature [13].

- *Sonication*

Sound waves are applied in the process of "sonication" to mix up particles in solution. One can utilize this disruption to combine solutions, dissolve a solid more quickly into a liquid, and extract dissolved gas from a liquid [15]. The process of converting MLVs into small unit lambellar vesicles (SUVs) is called sonication. The ultrasonic to turn MLVs into SUVs, radiation is offered. Two techniques are employed:

- *Probe sonication method*
- *Sonication in the bath (13)*

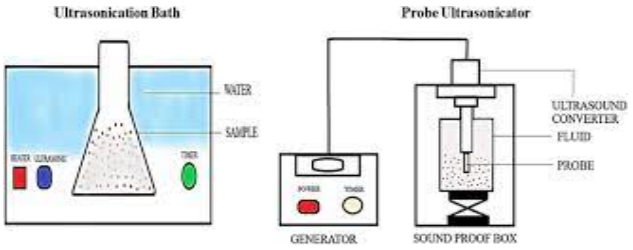

Fig. 3. Sonication apparatus [47]

- *Probe sonication method*

For high energy in small volume applications (such as high lipid content or viscous aqueous phase), the probe sonicator is employed [16]. This method involves submerging the sonicator tip straight into the liposome dispersion, which is very high. Local overheating is caused by energy dissipation at the tip. The vessel needs to be submerged in an ice bath after that. Over the course of the sonication, over 5% of the lipids may be de-esterified for up to an hour. Additionally, titanium will slough off and contaminate the solution when using the probe sonicator [17]. One drawback of the probe sonicator is that it might contaminate preparations by introducing metal particles from the probe tip, which can lead to the formation of SUVs. They undergo ultra-centrifugation purification [18]. The most popular equipment for preparing SUVs is bath sonication [16]. It is vital to look at how probe-sonication, which is frequently utilized to homogenize liposome formulations, affects the drug entrapment efficiency (EE) of liposomes [19].

- *Bath sonication method*

For a high volume of diluted lipids, the bath sonicator is utilized [15]. An immersion sonicator is used to disperse liposomes in a tube. regulating the lipid dispersion's temperature. Using the tip to sonicate the dispersion directly is a simpler way. The material is sonicated and then placed in a sterile container in an inert environment. The liposomes' lipid bilayer can then combine with other bilayers to release the contents of the liposomes. Lipid bilayers can be delivered via liposomes that have been created in a DNA or medication solution [17].

- *French pressure method*

The high-pressure mechanism is a basis of this technique. Using this technique, homogenous unilamellar liposomes of intermediate size (between 30 and 80 nm) may be prepared in volumes of 1 to 40 ml [20]. When it comes to stability, this liposome improves on sonicated liposomes. The pressure cell's initial high cost is one of this method's limitations. This approach produces liposomes with fewer defects than sonicated liposomes [13].

B. Solvent dispersion method

The lipid and other components of the liposome membrane may dissolve in another solution using these methods. The resultant solution is mixed with the aqueous phase. There is material to be entrapped in this aqueous phase [18]. This solvent dispersion method uses the reverse phase evaporation, ethanol injection, and ether injection techniques [21].

- *Ether injection method* [22], [23], [24]

Lipid solutions are dissolved in ether, diethyl ether, or a combination of methanol and ether for injection. These combinations are gradually injected at 55–65°C or low pressure into the material to be encapsulated's aqueous solution. Subsequently, ether is extracted using a vacuum, which causes liposome production.

- *Ethanol injection method (20)*

This is a simple approach. In this technique where a lipid's ethanol solution is easily injected to an excessive amount of salt using a little needle. The resolution of Ethanol is diluted with phospholipid and water. molecules. They are uniformly distributed. via the medium. This process produces a significant amount of SUVs (around 25 nm) diameter).

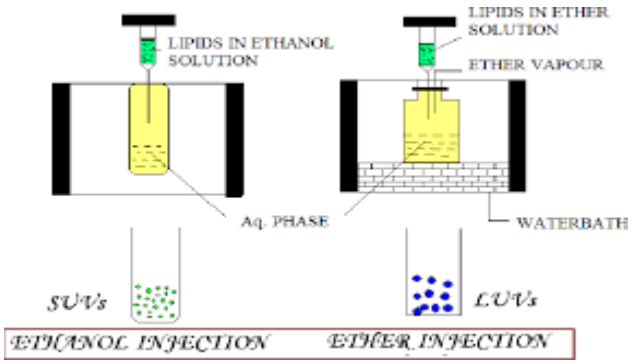

Fig. 4. Ethanol and Ether injection methods [48]

- *Reverse phase evaporation method*

water-based buffer and (diethyl ether). This lipid mixture is put into a flask with a circular bottom. Through rotary evaporation, the organic solvent is being removed under pressure. Lipids are redissolved in the organic phase and the system is purified with nitrogen. The best solvents to use are diethyl ether and isopropyl ether when the lipids have been redissolved and the emulsion has been obtained. The solvents are then removed by evaporating a semi-solid gel under reduced pressure [22], at a temperature of 20 to 25°C and a rotation speed of about 200 rpm. An aqueous solution emerges together with a thick gel. To eliminate solvent remnants, add more water or buffer and let the suspension evaporate for a further 15 minutes at 20°C. After diaphragming the mixture, centrifuge or run it through a 4B column [25]. Resulting liposomes are called reverse phase evaporation vesicle' (REV).

C. Detergent removal method

- *Dialysis*

Lipids are solubilized by the detergent at their critical Michelle concentration (CMC). The phospholipid micelles separate from the detergent and finally come together to form LUVs. Dialysis is one method for removing the detergent [26], [27], [28]. The primary advantage of the detergent dialysis approach is the formation of uniformly sized liposome populations. The main drawbacks of this approach are the potential for detergent residue to be retained within the liposome [29].

- *Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption)*

XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg,

Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA) are two examples of beaded organic polystyrene absorbers that are used to achieve detergent absorption through shaking a mixed micelle solution. Detergent can be removed at very low CMC thanks to detergent absorbers [26].

- *Dilution*

The dilution of an aqueous detergent and phospholipid mixed micelle solution with buffer. Micellar and polydispersity sizes are essentially increasing [26].

4. Purification of Liposomes

Centrifugation, gel filtration, chromatography, and dialysis are typically used to purify liposomes. The most popular chromatographic separation agent is Sephadex-50. A hollow fiber dialysis cartridge may be used in the dialysis procedure. On the other hand, SUVs in regular saline can be isolated using the centrifugation method by centrifuging at 200000g for 10–20 hours. Centrifugation at 100,000g for less than an hour is used to separate MLVs [30].

Mechanism of action of liposomes:

Liposome performs their action by four different medium. They're as follows:

1. Endoytosis: This is performed by reticuloendothelial system phagocytic cells, such as neutrophils [31].

2. Adsorption: It happens to the cell surface as a result of interactions with components of the cell surface or general electrostatic forces [32].

3. Fusion: It occur when the liposomal bilayer inserts itself into the plasma membrane, releasing liposomal content into the cytoplasm continuously [33].

4. Lipid exchange: Liposomal lipids are transferred to the cellular membrane in this manner without the liposomal contents being associated [34].

Applications:

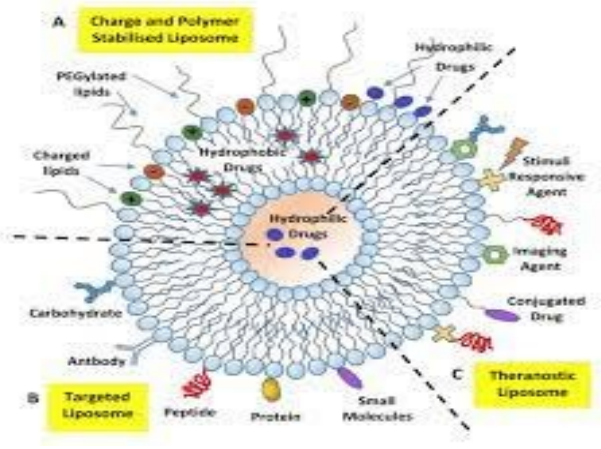

Fig. 5. Application [49]

- Liposomes as delivery systems for drugs or proteins.
- Liposomes in antiviral (anti-HIV) and antibacterial (lung therapies) treatments.
- In the treatment of tumors.
- In gene therapy.
- In Immunology.
- Liposomes as synthetic blood substitutes.
- Liposomes as carriers of radiopharmaceuticals and radio diagnostic
- Liposomes in dermatology and cosmetics [35].

Clinical Applications

Cancer therapy:

Drugs that are taken in conjunction with liposome-based chemotherapeutics to treat cancer, including breast cancer, can have better pharmacokinetic and pharmacodynamic effects. A drug's therapeutic efficacy can be increased by using liposomes to direct the medication to the desired place of action in the body. Anthracyclines are medications that, by penetrating into DNA, stop specific anti-cancer therapies from proliferating and killing cells, primarily those that divide quickly. This kind of medicine is extremely harmful since these cells are found in blood cells, gastrointestinal mucosa, hair, and cancers. Anti-cancer medications can accumulate at the tumor site thanks to the encapsulation of cytotoxic chemicals within liposomes. In addition, the phospholipid bilayer limits the amount of drug that is exposed to sensitive healthy tissue and stops the body from breaking down the drug's encapsulated active form before it reaches tumor tissue. Consequently, reduces the toxicity of treatments for cancer [36].

Antimicrobial Therapy:

Compared liposome-encapsulated rifabutin to free rifabutin, there was a notable increase in activity against Mycobacterium avium infection [37]. Furthermore, rifampin's antitubercular action significantly improved when it was contained in egg phosphatidylcholine liposomes. When the drug-loaded liposomes' surface was grafted with the tetrapeptide tuftsin, a macrophage activator, there was an additional rise in activity. In reducing the load of lung bacilli in infected mice, rifampin administered twice weekly for two weeks in tuftsin-bearing liposomes was at least 2,000 times more effective than the free medication [38]. When treating Mycobacterium avium intracellular infections (MAI), liposome-encapsulated clarithromycin may be more effective than the free version. Moreover, combining the medication with ethambutol may increase its efficacy even more [39]. Additionally, when the liposomal gentamicin preparation TLC G-65 was tested both alone and in combination with rifapentine, clarithromycin, clofazimine, and ethambutol in the beige mouse model of disseminated Mycobacterium avium infection, the results indicated that the combination of rifapentine and TLC G-65 was more active than either agent alone. When combined with TLC G-65, clarithromycin had equal activity to either drug used alone. Ethambutol enhanced TLC G-65's action with regard to the liver, while clofazimine enhanced it with regard to the spleen [40].

Therapeutic Applications

1. Occular Application

Three extremely effective systems guard the eye: (a) an epithelium layer that acts as a strong barrier against penetration; (b) tear flow; and (c) the blinking reflex. The quick washout of medications from the corneal surface and the poor penetration of pharmaceuticals into the deeper layers of the coenea and

aqueous humor are caused by all three mechanisms. It was first documented in 1981 that liposomes encapsulating idoxuridine improved the effectiveness of herpes simplex-infected ocular ulcers in rabbits [41]. Lee (1985) found that the physiochemical features of the medicines and lipid mixture used might either enhance or impede drug delivery by ocular distribution through the use of liposome carriers. Corneal adhesion was assessed using ganglioside-containing liposomes and wheat germ agglutinin, a lectin with a strong affinity for both ganglioside and the cornea [42].

2. Pulmonary Application

The use of pulmonary delivery of liposomes has been investigated as a target-selective substitute for systemic administration of antibiotics used to treat pulmonary infections as well as antiasthamatic and antiallergic drugs. Liposomes are effective medicines delivery vehicles for the lungs because of their ability to solubilize weakly water-soluble compounds, making them more suitable for aerolization. Due to its biodegradability, extended lung residency periods are possible without running the risk of allergic reactions or other negative some effects. Lipohave the unique ability to target One of the special drug delivery methods that helped create effective medications is liposome technology. This technology may be used to target and regulate the administration of pharmaceuticals and enhance their therapeutic effects. Both lipophilic and hydrophilic drugs can be readily incorporated into liposomes. The ability of the liposomal formulation to transfer the molecules to the intended place over an extended period of time while reducing the side effects of the drug is what makes it successful. It is anticipated that the medications will eventually diffuse out of the phospholipid bilayers in which they are contained. Cut your writing time by more than half macrophages that are either immune-impaired or diseased. Research on liposome aerosol toxicity has been done methodically [43]. Discovered that after continuous exposure of alveolar macrophages to liposomes, there was no impairment of phagocytic activity or vitality. showed increased enzyme activity and sustained tissue protection after pulmonary liposome instillation in combination with catalase and superoxide dismutase, albeit the exact mechanism responsible for the observed protection was still unknown [44].

5. Conclusion

One of the special drug delivery methods that helped create effective medications is liposome technology. This technology may be used to target and regulate the administration of pharmaceuticals and enhance their therapeutic effects. Both lipophilic and hydrophilic drugs can be readily incorporated into liposomes. The ability of the liposomal formulation to transfer the molecules to the intended place over an extended period of time while reducing the side effects of the drug is what makes it successful. It is anticipated that the medications will eventually diffuse out of the phospholipid bilayers in which they are contained. Many factors, such as drug quantity, the ratio of drug to lipid, capsule efficacy, and in vivo drug release, must be taken into account while developing liposomal drug therapy delivery techniques. Liposomes are administered orally, parenterally, and topically. They are also utilized in sustained release formulations, hair and cosmetic technologies, diagnosis, and as effective gene delivery vehicles for a number of licensed medications. These days, liposomes are employed as adaptable drug delivery vehicles. The liposomal approach is a useful tool for improving the pharmacokinetics and therapeutic efficacy of certain extremely powerful medications, all the while reducing their toxicity.

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