

Liposome: A Drug Delivery System

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Abstract

Liposomes are microscopic, spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core. Since their discovery in the 1960s, they have emerged as one of the most successful and versatile platforms for drug delivery. Their unique structure allows them to encapsulate both hydrophilic (water-soluble) and lipophilic (fatsoluble) drugs, protecting them from degradation, improving their solubility, and modifying their pharmacokinetic profile. Liposomal formulations can reduce the systemic toxicity of potent drugs, extend their circulation time, and enable targeted delivery to specific tissues, such as tumors, via passive or active mechanisms. This review explores the fundamental structure of liposomes, their advantages and disadvantages, key manufacturing challenges, and their successful translation into clinically approved products. We also discuss recent advancements and future perspectives, including the development of "smart" liposomes and their expanding role in gene therapy and vaccines.

Keywords:- Liposomes, Drug delivery system, Phospholipid bilayer, Encapsulation, Hydrophilic drugs, Lipophilic drugs, Targeted delivery, Controlled release, Pharmacokinetics, Nanocarriers, Clinical applications, Smart liposomes, Gene therapy, Vaccines.

Introduction

The Greek words 'Lipos' which means fat and 'Soma' that means body, was combined to form spherical concentric vesicles called liposomes. Liposomes are round sac phospholipid molecules. It encloses a water droplet especially as form artificially to carry drug into tissue membrane. Liposome is a nanoparticle (size-100nm).¹ Liposome were first described by Bangham in 1961, it turned into an accidental discovery in which he scattered the phosphatidyl choline molecule in water, for the duration of this he located that the molecule was forming a closed bilayer shape having an aqueous segment which were entrapped by means of a lipid bilayer.² Liposomes are useful because they act as carriers for a variety of drugs and have potential therapeutic or other properties. Various carriers such as nanoparticles, microparticles, polysaccharides, lectins, and liposomes can be used to target drug to a specific sites. Liposomal drug delivery is gaining interest due to its contribution to various areas like drug delivery, cosmetics, and biological membrane structure.³

This unique composition makes liposomes ideal drug delivery vehicles because they can encapsulate both:

Hydrophilic drugs (water-soluble) in the central aqueous core.

Hydrophobic drugs (lipid-soluble) within the lipid bilayer itself.⁴

Structure Of Liposome:-

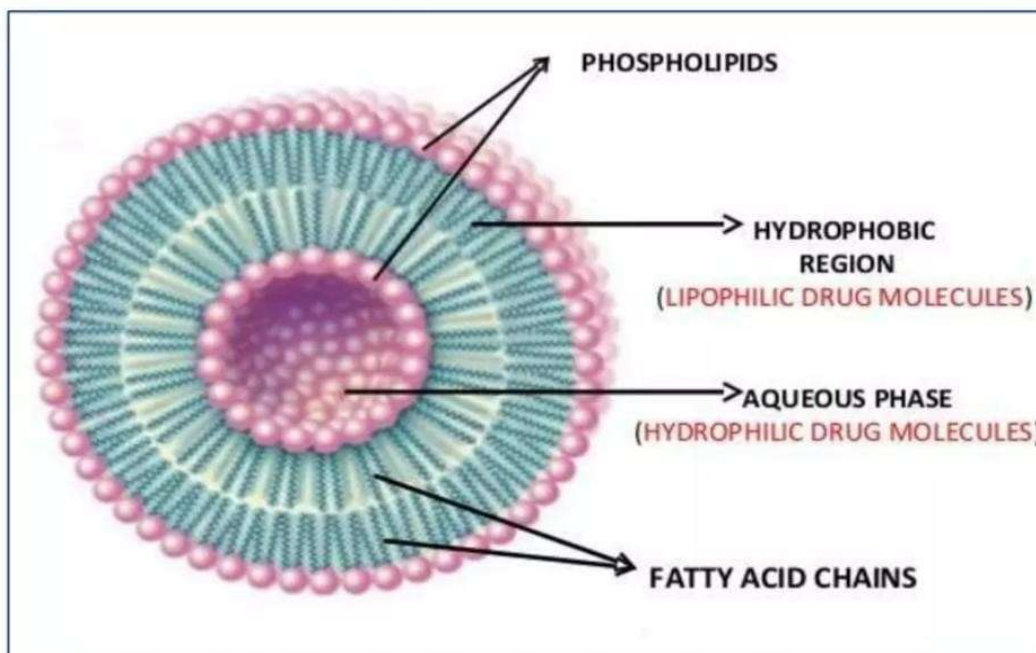


Fig 1: Structure Of Liposome

The structure of a Liposome — a spherical vesicle composed of one or more phospholipid bilayers surrounding an aqueous core.

Main Components:-

1. Phospholipids:

Form the bilayer membrane of the liposome.

Each molecule has:

A hydrophilic (polar) head facing outward.

A hydrophobic (non-polar) tail facing inward.

2. Hydrophobic Region:

The lipid bilayer where lipophilic (fat-soluble) drugs are incorporated.

These drugs embed between the fatty acid chains.

3. Aqueous Phase (Core):-

interior that traps hydrophilic (water-soluble) drugs.

water-filled

4. Fatty Acid Chains:-

The hydrophobic tails of the phospholipids; they form the interior of the bilayer membrane.

Function in Drug Delivery:

Hydrophilic drugs → trapped inside the aqueous core.

Lipophilic drugs → integrated within the lipid bilayer.

Liposomes protect drugs from degradation, enhance bioavailability, and allow targeted delivery to specific tissues.⁴⁻⁵

Advantages of Liposomes:-

1. Targeted Drug Delivery:- Liposomes can encapsulate drugs and deliver them to specific target tissues or cells, allowing for targeted therapy. This minimizes the exposure of healthy tissues to the drug, reducing side effects.

2. **Improved Bioavailability:-** Liposomes can encapsulate poorly water-soluble drugs, improving their solubility and bioavailability, which can be a critical factor in drug effectiveness.
3. **Sustained Release:-** Liposomes can release drugs gradually over time, leading to sustained therapeutic effects and reducing the need for frequent dosing.
4. **Protection of Sensitive Compounds:** Liposomes can protect sensitive drugs or bioactive compounds from degradation due to environmental factors, such as enzymes, pH changes, or oxidation.
5. **Versatility:** They can be tailored in terms of size, composition, and surface modifications to optimize their performance for specific drugs or therapeutic applications.
6. **Reduced Toxicity:** Liposomal drug delivery can reduce the toxicity of certain drugs by minimizing their exposure to healthy tissues while targeting diseased cell.
7. **enhanced Cellular Uptake:** Liposomes can improve the cellular uptake of drugs or therapeutic agents, making them more effective in treating diseases.
8. **Cosmetic Applications:** Liposomes are used in cosmetics to enhance the penetration of active ingredients into the skin, improving their efficacy.
9. **Food Technology:** In the food industry, liposomes are used to encapsulate and protect flavors, vitamins, and nutrients, enhancing the quality and shelf life of food products.
10. **Biocompatibility:** Liposomes are generally well-tolerated by the body, making them suitable for various medical and cosmetic applications.
11. **Research Tools:** Liposomes are valuable tools in biomedical research for delivering biomolecules, dyes, or other compounds to cells for experimental purposes.
12. **Diagnostic Applications:** Liposomes are used in diagnostic assays for drug screening, disease detection, and other diagnostic purposes.
13. **Immunogenicity:** Liposomes can enhance the immunogenicity of vaccines, resulting in a stronger and more specific immune response.
14. **Customization:** Researchers can customize liposomes for specific applications by modifying their properties, such as size, charge, and surface functionality.^{1,7,8,9}

Disadvantages of Liposomes:

1. **Storage Stability:** Liposomes can be prone to instability during storage, leading to aggregation, leakage of encapsulated substances, or changes in size and structure.
2. **Scalability:** Scaling up the production of liposomes can be challenging and costly, may limit their widespread use in large-scale pharmaceutical manufacturing.
3. **Uniformity:** Achieving uniformity in liposome size and composition can be difficult, affecting their performance and reproducibility.
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5. **Immunogenicity:** Some liposome formulations may trigger an immune response, potentially causing adverse reactions in the body.
6. **Limited Drug Loading:** Liposomes have a finite capacity for drug loading, which can be a limitation when trying to deliver high doses of certain drugs.
7. **Complexity:** The development of liposomal formulations requires expertise and can be a complex process, which may limit their accessibility to researchers and manufacturer
8. **Expense:** Producing liposomal formulations can be costly, which may lead to higher drug prices for liposome-based therapies.
9. **Compatibility Issues:** Some drugs may not be suitable for encapsulation in liposomes due to compatibility issues, limiting the range of drugs that can benefit from liposomal delivery.

10. Clinical Translation: Despite promising results in preclinical studies, not all liposome-based therapies have successfully transitioned to clinical use, highlighting challenges in translating laboratory findings to real-world applications.

11. Interaction with Biological Systems: Liposomes may interact with proteins or cells in ways that affect their stability, drug release, or performance.

12. Biodegradability: Depending on their composition, liposomes may not be readily biodegradable, which can raise environmental concerns.

13. Niche Applications: Liposomes may not be suitable for all drug delivery needs, and alternative delivery systems may be preferred in certain cases.^{10,11,12}

Classification Of Liposomes:-

Liposomes are divided into different types depending on their size, number of layers (bilayers), composition, and method of preparation.

Classification of Liposomes Based on Composition:-

1. Conventional Liposomes:-

These represent the first generation of liposomes and are composed of natural or synthetic phospholipids with or without cholesterol.

Composition: Phosphatidylcholine, phosphatidylethanolamine, sphingomyelin ± cholesterol.

Function: Cholesterol helps modulate bilayer fluidity and stability.

Application: General drug delivery, diagnostic imaging.¹³

2. pH-Sensitive Liposomes:-

These liposomes contain pH-responsive lipids that destabilize and release their drug payload in acidic environments (e.g., tumor tissues or endosomes).

Composition: Phosphatidylethanolamine combined with acidic lipids (like oleic acid).

Function: They remain stable at physiological pH but release drugs at lower pH.

Application: Targeted cancer therapy and delivery to intracellular compartments.¹⁴

3. Cationic Liposomes:-

These liposomes carry a positive surface charge that allows electrostatic interaction with negatively charged biomolecules such as DNA or RNA.

Composition: Cationic lipids like DOTAP (dioleoyltrimethylammonium propane) or DOTMA.

Function: Facilitate gene transfection and nucleic acid delivery.

Application: Gene therapy, vaccine delivery.¹⁵

4. Immunoliposomes:-

These are antibody-targeted liposomes where antibodies or antibody fragments are covalently attached to the liposome surface to achieve active targeting of specific cells or tissues.

Composition: Conventional or PEGylated liposomes conjugated with monoclonal antibodies, antibody fragments (Fab, scFv), or ligands.

Application: Tumor-targeted drug delivery, site-specific cancer chemotherapy, and delivery of enzymes or diagnostic agents.

Function: The attached antibodies recognize and bind to target cell receptors or antigens, facilitating receptor-mediated endocytosis and site-specific drug delivery.⁶

5. Long Circulating Liposomes (LCLs) / Stealth Liposomes:-

Also known as stealth liposomes, these are modified liposomes designed to evade detection and clearance by the body's immune system, thereby prolonging their circulation time.

Composition: Liposomes modified with hydrophilic polymers such as polyethylene glycol (PEG), typically DSPE -PEG2000, along with cholesterol and phospholipids.

Function: PEG forms a steric barrier on the liposome surface, preventing opsonization and uptake by the reticuloendothelial system (RES).¹⁶

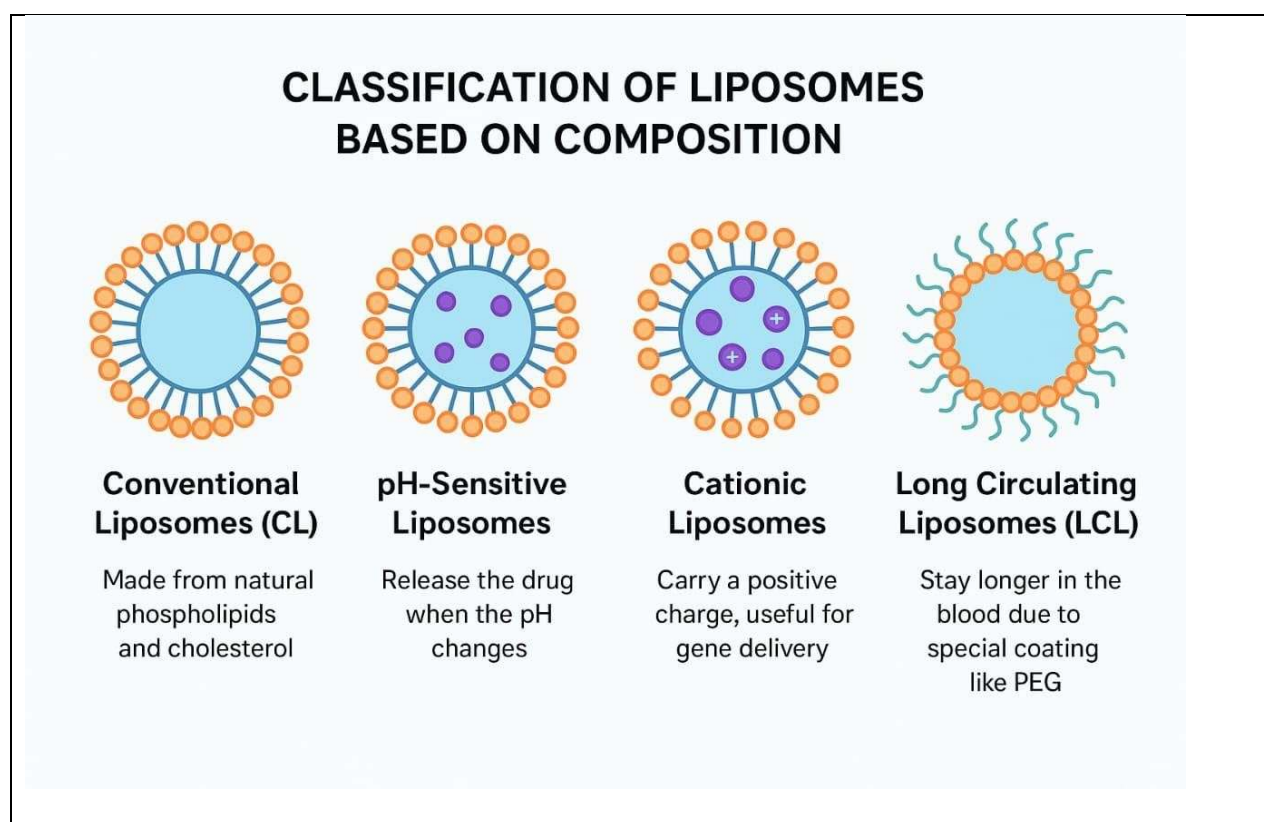


Fig 2. Classification Of.Liposomes Based On Composition

Classification of Liposomes Based on Size and Number of Bilayers:-

1. Multilamellar Vesicles (MLV):-

Structure: Have many concentric lipid bilayers (like an onion).

Size: Large — about 0.5 to 5 μm in diameter.

Content: Contain several aqueous (water) layers between lipid membranes.

Advantage: Can carry both hydrophilic (water-loving) and lipophilic (fat-loving) drugs.

Disadvantage: Uneven size and less efficient drug release.

2. Large Unilamellar Vesicles (LUV):-

Structure: Have a single lipid bilayer surrounding a large aqueous core.

Size: About 100–1000 nm.

Advantage: High drug-loading capacity and better control over release.

Use: Suitable for delivering large molecules like proteins or genes.

3. Small Unilamellar Vesicles (SUV):-

Structure: Contain only one lipid bilayer and a small inner aqueous space.

Size: Very small — about 20–100 nm.

Advantage: Good for targeting and quick circulation in the body.

Disadvantage: Less space to carry drug.^{17,18}

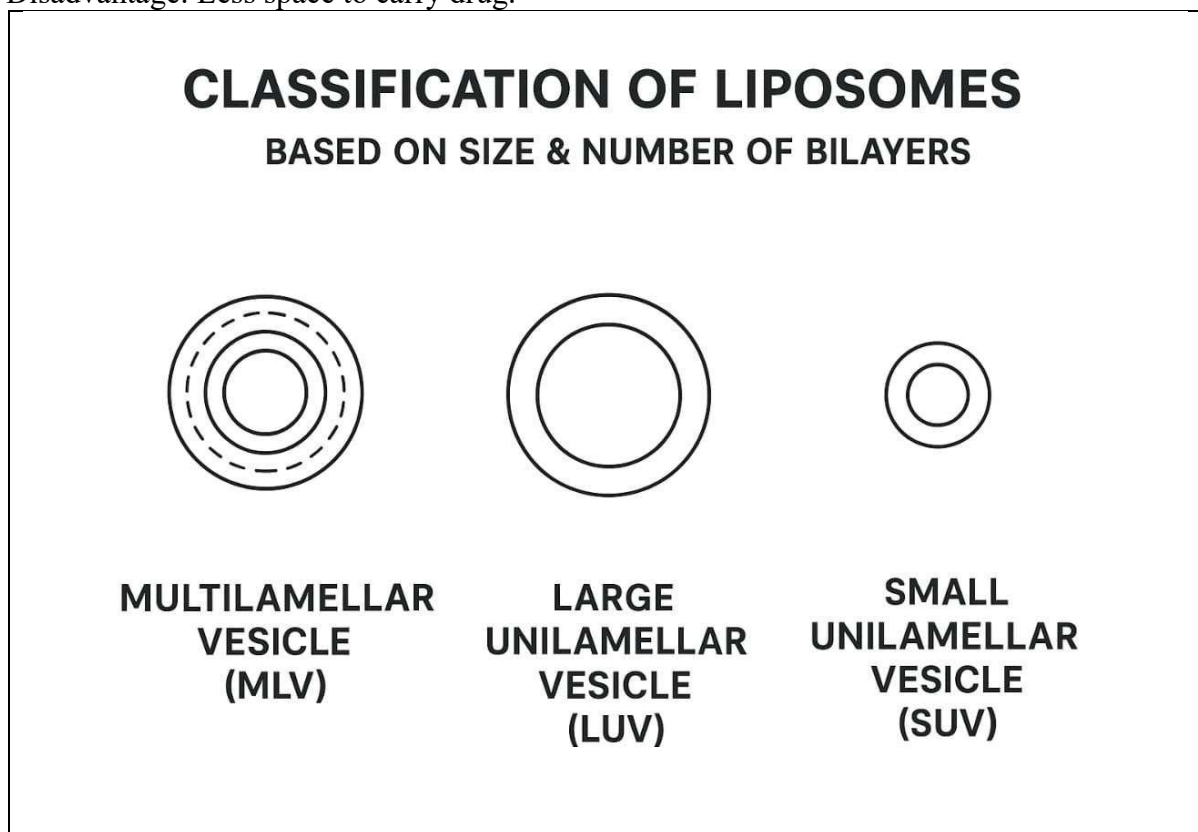


Fig 3. Classification of Liposomes Based on Size And Number of Bilayers

Methods of Liposome Preparation:-

The method used to prepare liposomes depends on several factors such as the type of drug, desired liposome size, number of lipid layers, and the purpose of the formulation (for example, drug delivery, diagnostic use, etc.).

Important factors affecting the preparation:-

The chemical nature of the drug and lipids.

- 1.
- 2.

- The type of solvent or medium used.
required drug concentration and toxicity.
4. The stability and size of liposomes needed for the formulation.
5. Ease of large-scale production.

3. The

Main Conventional Methods of Liposome Preparation:- Reverse Phase Evaporation Method

1.

Principle: Lipids are dissolved in organic solvents like diethyl ether or chloroform, then mixed with an aqueous buffer to form a water-in-oil (W/O) emulsion.

Process: Lipids are dissolved in an organic solvent.

Aqueous buffer (containing the drug) is added and sonicated to form a W/O emulsion.

The organic solvent is slowly removed under reduced pressure using a rotary evaporator.

Liposomes form as the solvent evaporates.

Advantages: High encapsulation efficiency for hydrophilic drugs.

Disadvantages: Use of organic solvents may leave residues.

2. Solvent Dispersion Method

Principle: Lipids are first dissolved in an organic solvent, then injected into an aqueous solution.

Process: The organic solvent disperses in water, forming small lipid vesicles.

Example: Ether injection or ethanol injection techniques.

Advantages: Simple and easy to perform.

Disadvantages: Liposomes may be unstable or too small.

3. Detergent Removal Method

Principle: Lipids are solubilized with detergents to form micelles. Detergents are then slowly removed to form liposomes.

Process: Lipids + detergent → micelles.

Detergent is removed (by dialysis, gel filtration, or adsorption).

Liposomes form spontaneously.

Advantages: Produces small unilamellar vesicles (SUVs).

Disadvantages: Time-consuming due to detergent removal.

4. Thin Film Hydration Method (Bangham Method)

Principle: Lipids are dissolved in organic solvents and dried to form a thin film, which is then hydrated with an aqueous solution.

Process: Lipids are dissolved in chloroform or methanol.

Solvent is evaporated to form a thin film on the flask wall.

Hydration with aqueous buffer leads to swelling and formation of liposomes.

The size can be reduced by sonication or extrusion.

Advantages: Simple and widely used.

Disadvantages: Produces multilamellar vesicles (MLVs) with broad size distribution.

4,6,19

Liposome Stability:

The steadiness of liposomes is vital in deciding the helpful impact of drugs. Steadiness can be separated into two categories:

A. Physical steadiness: It is the capacity of liposome to preserve their shape and properties over time. The rack life of liposomes can be influenced by different physical

marvels such as combination, accumulation, shape and measure changes. The most issue that emerges is the spillage of chemical compounds. Shape and estimate ought to be considered as basic characteristics in security safeguards. To guarantee soundness within the body, the wealth of super saturation in phospholipids ought to be decreased. The item ought to be put away at 4 degrees Celsius to anticipate solidifying and secure from light.

B. Chemical Steadiness: Phospholipids are inclined to hydrolysis due to their unsaturated greasy corrosive composition, which can influence the soundness of the treatment. Cancer prevention agents such as butylated hydroxyl anisole (BHA) can be utilized to avoid oxidative debasement of liposomes.

Liposomes are broadly utilized in quality treatment within the treatment of infections.^{20,21}

Mechanism of Action of Liposomes:-

Liposomes are small spherical vesicles made of phospholipid bilayers, very similar to the cell membrane. Because of this structure, they can carry drugs inside them and release those drugs at the right place in the body.

Their mechanism of action mainly involves 5 steps:-

1. Encapsulation of Drug

Liposomes can hold drugs in two places:

Inside the water core → for water-soluble (hydrophilic) drugs

Inside the lipid bilayer → for fat-soluble (lipophilic) drugs

This protects the drug from degradation by enzymes or acidic pH.

2. Surface Modification (Targeting)

Liposomes can be modified for better action:

PEGylation (adding PEG) → makes them long-circulating (stealth liposomes).

Ligand targeting (antibodies, sugars, peptides) → helps liposomes attach to specific cells like tumor cells

This improves drug delivery to the required site.

3. Distribution in the Body

After injection (usually IV), liposomes travel in the blood.

Because of their lipid nature, they:

Avoid rapid clearance

Reduce toxicity (especially for anticancer drugs)

Tumor tissues have leaky blood vessels, so liposomes can enter them more easily (EPR effect — Enhanced Permeation and Retention).

4. Interaction with Cells

Liposomes deliver drugs to cells through multiple mechanisms:

A. Adsorption

Liposomes stick to the cell surface through:

Electrostatic interactions

Hydrophobic interactions

This allows drug transfer.

B. Fusion with Cell Membrane

Liposome bilayer merges with the cell membrane → drug directly enters the cell.

C. Endocytosis/Phagocytosis

Cells take in the liposome via vesicle formation.

Inside the cell, the liposome breaks down and releases the drug.

5. Drug Release

Liposomes release drug by:

Breaking of lipid bilayer inside the cell

pH change (tumor tissues are acidic)

Fusion with membrane

Enzymatic degradation

This allows controlled and targeted delivery, reducing side effects. ^{22,23}

Basic Components of Liposomes

Liposomes or lipid vesicles are colloidal particles having phospholipid molecules as an important constituent in the enclosed lipid bilayer or lipid drug sheet-disk complexes. Most of the liposomes which are intended to be used for human beings contain phosphatidylcholine, with a fatty acyl chain of different lengths and varying in the degree of saturation as a major membrane building block.

Phospholipids

The general chemical structure of the phospholipids shows a glycerol backbone. At position 3 of the glycerol molecule, the hydroxyl is esterified to phosphoric acid. The hydroxyl groups at positions 1 and 2 of the glycerol are usually esterified with long chain fatty acids. The lipid nature of the phospholipids can be attributed to these long chain fatty acids. The phosphate moiety along with the attached hydroxyl group which represents the head group of phospholipid. The most common phosphatides in case of animals and plants are phosphatidylethanolamine and phosphatidylcholine which are also called as lecithin. These two components contribute the major structural part of most biological membranes. The main component of liposomes are glycerophospholipids, which are amphiphilic (both hydrophilic and hydrophobic) lipids made up of a glycerol molecule which is bound to the phosphate group and two fatty acid chains that may be saturated or unsaturated in nature. The final properties of liposomes are affected by structure and the characteristics of phospholipids.

The phosphate group can be also bonded to another organic molecule. According to these organic groups, the natural phospholipids are categorized as phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylglycerol (PG) and phosphatidylserine (PS). Glycerophospholipids which are responsible for the formation of liposomes can be categorized in two different forms i.e. natural and synthetic. Mostly the natural phospholipids which are used to design liposomes, are phosphatidylcholine (PC) and phosphatidylethanolamine (PE), that are abundant phosphatides in plants and animals.

Steroids

Cholesterol has a steroid backbone and its derivative is involved in the preparation of liposomes. This derivative is used in the formulation of liposomes to improve their bilayer characteristics, to improve the stability of bilayer membrane in the presence of biological fluids like blood and plasma. And also it reduces the permeability of water soluble molecules through the membrane.

The cholesterol molecule oriented itself in between the phospholipid molecule with its hydroxyl group phasing towards the water phase and the tricyclic ring sandwiched between the first few carbons of the fatty acyl chains into the hydrocarbon core of bilayer.

^{25,26,27}

Factors affecting drug release from liposomes

Liposomes are the most successful nanoparticle delivery systems developed to target drugs to the site of action. There has been tremendous development in the field of liposomal drug delivery which has led to various clinically approved formulations that are efficacious, biocompatible and possess improved pharmacokinetics. The drugs loaded in liposomes become bioavailable only when they are released. Therefore, to have optimum therapeutic activity, modifying/controlling the release rate of drug from liposomes is very essential. There are different methods described in literature for improving and optimising rate of drug release from liposomes. Drug release from liposomes is affected by the following factors:

1. Cholesterol content of the liposomes
2. Nature of encapsulated drug
3. Membrane composition of liposomes
4. Application of external stimuli conditions

Cholesterol content used in the formation of liposomes:

Liposomes made of phospholipids and cholesterol have demonstrated a decrease in bilayer permeability as the amount of cholesterol increases. The addition of sphingomyelin or cholesterol to liposomes gives the bilayer rigidity and enhances drug retention in liposomes. A study of the impact of cholesterol content on liposome stability and in vitro release has been discussed. The study outlines the potential benefits of cholesterol as a stabilizing agent that helps to give strength to the bilayer, thereby lowering its permeability to electrolyte and non-electrolyte solutes. The study involved loading hydrophilic drug (atenolol) and hydrophobic drug (quinine) into the liposomes. Liposomes were prepared in five different lipid: cholesterol ratios using the thin-film hydration method. Particle size, (%) encapsulation efficiency, and in vitro drug release patterns were assessed for each formulation. According to the results, formulations with high cholesterol levels (up to 50%) had subpar drug release and encapsulation profiles. The optimal encapsulation and medication release profile was demonstrated by the optimized formulation with a 30% cholesterol content. Therefore, achieving high encapsulation and drug loading values during the formulation of drug-loaded liposomes is facilitated by optimizing the cholesterol to lipid ratio. According to studies, cholesterol makes the core part of the membrane bilayer more hydrophobic, which may encourage the incorporation of hydrophobic molecules. Drug encapsulation and loading efficiency are reduced as a result of competition between cholesterol and the hydrophobic drug, both of which prefer to fit into the bilayer. The significance of regulating cholesterol content in assessing the impact of various lipids for figuring out the in vitro release kinetics of liposomes was discussed in another study. The study's objective was to assess the ideal lipid for liposome formulation and the amount of cholesterol needed to enhance the liposomes' overall release kinetics. To mimic medication encapsulation and release, liposomes were created using the sonication method using ¹⁴C radiolabeled inulin as a marker. According to the results, 21% cholesterol was chosen in order to maximize the liposomes' stability and release profile.

Nature of encapsulated drug:-

Another important factor affecting drug release from liposomes is seen in choosing drugs whose physical characteristics favor retention of drug in liposomes. Liposomes possess the ability to entrap both hydrophilic and hydrophobic drug due to their unique structural organization. There are several drugs that have been successfully delivered through liposomes and have been approved by the FDA for clinical applications. Some of the key examples include doxorubicin, vincristine, paclitaxel, bupivacaine, amphotericin B and irinotecan. The physicochemical characteristics of drug of choice and the biocompatibility of lipids are the two main considerations in development of a stable and

efficacious liposome system. A study describing the transcutaneous permeation of three drugs: amphotericin B, imiquimod and indole encapsulated by liposomes effectively explained the comparison of the penetration ability of the three drugs through their encapsulation into ultra-flexible liposomes. Among the drugs encapsulated in liposomes for this study, amphotericin B and imiquimod had poor water solubility whereas indole was water soluble. The study stated that formation and encapsulation of the three drugs into ultra-flexible liposomes increased the overall pharmacokinetics of the drugs with the three drugs showing efficient skin penetration. An effective strategy in designing liposomal drug delivery is selection of drugs that can be loaded to retain inside the liposome and selectively release at the site of action to achieve site specific drug delivery

Membrane composition of liposomes:-

Membrane composition of liposomes plays a major role in the release of drug from liposomes. Since liposomes can encapsulate both hydrophilic and hydrophobic drugs in their structure it is important to study the composition of liposomes during formulation for effective drug release. A study describing the improved liposomal drug retention was conducted by adding dihydro sphingomyelin (DHSM) in the lipid component during the formulation of liposomes. Vincristine-loaded liposomes were prepared by replacing egg sphingomyelin with DHSM in sphingomyelin: cholesterol (55:45 mol/mol) which resulted in a substantial increase in drug encapsulation and showed sustained drug release. Additionally, there was a three-fold increase in drug release half-life compared to liposomes without DHSM. Studies have also suggested that the formation of molecular complexes within the liposomes has resulted in improved retention of drugs in liposomes. Formation of molecular complexes can help in modulating the release of drug from liposome and could also help in preventing leakage of drug from vesicles. The design of liposomal co-encapsulation of oleanolic acid and doxorubicin for evaluation of antitumor efficacy utilized three different lipid compositions in formulation of liposomes. Liposomes for this study were prepared by ethanolic injection method and composed of the different lipid ratios as predicted by the statistical design. Results showed that the highest encapsulation efficiency and sustained drug release was achieved by controlling the cholesterol content in the formulation.

Application of external stimuli

Studies have shown that in order to obtain controlled release, there are several stimuli-based strategies that allow rapid release of drug at the tumour site. The use of local stimuli strategies for improving drug release from liposomes has been extensively studied. This strategy utilizes the small changes occurring in the tumour microenvironment such as change in pH, difference in temperature or the overexpression of some proteolytic enzymes for improving the rate of drug release. Formulation of thermosensitive liposomes is an effective strategy in controlling the release of drugs from the nano-lipid vesicles. Thermosensitive liposomes have shown tremendous potential when administered with local hyperthermia. There are various studies that have reported the benefits of drug targeting with thermosensitive liposomes. Temperature triggered drug delivery of thermosensitive liposomes using pre post hyperthermia mechanism has shown promising results. A study describing the formulation of lysolipid containing thermosensitive liposomes in combination with local hyperthermia was used to deliver cytotoxic proteins thereby explaining the mechanism of triggered drug release. Liposomes were prepared by thin film hydration and extrusion technique. Liposomes were prepared with different compositions of lipids. The selected formulation (86:10:4 % mol DPPC: MSPC: DSPE-PEG2000) showed efficient drug release with mild hyperthermia and was thereby considered a promising local tumour delivery strategy for cytotoxic proteins. A study describing the release of doxorubicin based on mild hyperthermia-mediated release from thermosensitive liposomes was explored and studied. Briefly, the study consisted of preparation of thermosensitive liposomes for evaluating the release profile of doxorubicin. Results showed that the injected thermosensitive liposomes loaded with doxorubicin released the drug efficiently with

mild hyperthermia at 43 °C and was monitored real time with fibred confocal fluorescence microscopy. Decrease in pH in cellular lysosomes has been successful in improving the rate of drug release in pH sensitive doxorubicin loaded liposomes. The formulation of pH sensitive liposomes was achieved by encapsulating a precursor that had the ability to generate gas bubbles in situ in acidic pH. The bubble generation in acidic pH led to the rapid release of doxorubicin thereby showing antitumor effect at the targeted site. A study involving a novel acid-labile PEGB-Hz-DPPE conjugate in developing dual pH-responsive strategy was part of the preparation of dual pH-sensitive liposomes with enhanced tumour targeted drug delivery. The effectiveness of the study was tested against pancreatic cancer cells. Results showed that as the pH in lysosomes reduced there was efficient release of doxorubicin whose effectiveness increased with the use of ultrasound waves that substantially reduced the viability of cancer cells. Thereby the study concluded by emphasising the potential of pH triggered drug release in liposomes. Thus, there are various techniques/modifications that can be done to improve and control the rate of drug release from liposomes. ²⁸

Liposomes Drug Delivery System in Clinical Use

Clinically Approved Liposomal Drugs (With Use & Benefits)

These are real, FDA-approved liposomal medicines used in hospitals.

1. Liposomal Doxorubicin (Doxil / Caelyx)

Used for: Breast cancer

Ovarian cancer

Kaposi's sarcoma

Benefits: Lower heart toxicity

Higher drug concentration in tumors

Fewer side effects compared to plain doxorubicin

2. Liposomal Amphotericin B (AmBisome)

Used for: Fungal infections

Mucormycosis

Benefits: Significantly reduced kidney toxicity

Better patient tolerability

High efficiency in severe infections

3. Liposomal Vincristine (Marqibo)

Used for: Acute lymphoblastic leukemia (ALL)

Benefits: Longer circulation time

More drug reaches cancer cells

Improved therapeutic effect

4. Liposomal Irinotecan (Onivyde)

Used for: Metastatic pancreatic cancer

Benefits: Better penetration into tumors

Increased survival rate

Sustained drug release

5. Liposomal Cytarabine (DepoCyte)

Used for: Lymphomatous meningitis

Benefits: Long-acting (drug released over weeks)

Only one dose needed every 2 weeks

6. Lipid Nanoparticles (LNPs) in mRNA Vaccines

LNPs are advanced liposomes used to deliver mRNA safely into cells.

Examples: Moderna mRNA COVID-19 vaccine

Benefits: Protects fragile mRNA

Helps mRNA enter cells for immune response

Safe and effective delivery to the body.^{5,22}

Therapeutic Applications Of Liposomes

When a conventional dosage form fails to provide a desired therapeutic effect, then new drug delivery systems are developed. Liposomes are among such systems which provide a superior therapeutic efficacy and safety in comparison to existing formulations. Some of the major therapeutic applications of liposomes in drug delivery include:

Site-avoidance delivery

The cytotoxicity of anti-cancer drugs to normal tissues can be attributed to their narrow therapeutic index (TI). Under such circumstances, the TI can be improved by minimizing the delivery of drug to normal cells by encapsulating in liposomes. Free doxorubicin has a severe side effect of cardiac toxicity, but when formulated as liposomes, the toxicity was reduced without any change in the therapeutic activity.

Site specific targeting

Delivery of larger fraction of drug to the desired (diseased) site, by reducing the drug's exposure to normal tissues can be achieved by site specific targeting. Encapsulating the drug in liposomes can be used for both active and passive targeting of drugs in order to achieve a safer and efficacious therapy. On systemic administration, long circulating immunoliposomes are able to recognize and bind to target cells with greater specificity [85,86]. In patients with recurrent osteosarcoma, there was an enhanced tumoricidal activity of monocytes, when muramyl peptide derivatives were formulated as liposomes and administered systemically.

Intracellular drug delivery

Increased delivery of potent drugs to the cytosol (in which drug's receptors are present), can be accomplished using liposomal drug delivery system. N-(phosphonacetyl)-L-aspartate (PALA) is normally poorly taken up into cells. Such drugs when encapsulated within liposomes, showed greater activity against ovarian tumor cell lines in comparison to free drug.

Sustained release drug delivery

Liposomes can be used to provide a sustained release of drugs, which require a prolonged plasma concentration at therapeutic levels to achieve the optimum therapeutic efficacy. Drugs like cytosine Arabinoside can be encapsulated in liposomes for sustained release and optimized drug release rate in vivo.

Intraperitoneal administration

Tumors that develop in the intra-peritoneal (i.p.) cavity can be treated by administering the drug to i.p. cavity. But the rapid clearance of the drugs from the i.p. cavity results in minimized concentration of drug at the diseased site. However, liposomal encapsulated drugs have lower clearance rate, when compared to free drug and can provide maximum fraction of drug in a prolonged manner to the target site.

Immunological adjuvants in vaccines

Immune response can be enhanced by delivering antigens encapsulated within liposomes. Depending on the lipophilicity of antigens, the liposome can accommodate antigens in

the aqueous cavity or incorporate within the bilayers [3]. In order to enhance the immune response to diphtheria toxoid, liposomes were first used as immunological adjuvants .

Conclusion

Liposomes are one of the most useful and advanced drug delivery systems in modern medicine. Because they are made of phospholipids, they can easily merge with cell membranes and deliver drugs directly to the target site. This property helps medicines enter cells more easily, improves the drug's overall effectiveness, reduces unwanted side effects, and allows controlled or sustained release of medicines over time. Liposomes are also biocompatible, biodegradable, and safe for the body, which makes them suitable for delivering a wide range of drugs, including antibiotics, anticancer drugs, antifungal agents, vaccines, proteins, peptides, and even genetic material like DNA or RNA.

Another important advantage of liposomes is that they can protect sensitive drugs from being destroyed by enzymes or harsh conditions in the body. They can also be modified by adding surface coatings or targeting molecules that help them reach specific tissues, such as tumor cells or infected areas. This targeted delivery lowers the dose needed, reduces toxicity to healthy tissues, and enhances the therapeutic outcome. Liposomes are also helpful in improving the stability and solubility of drugs that are poorly soluble in water, making them more effective for treatment.

Overall, liposome drug delivery systems have strengthened treatment outcomes and opened new possibilities for safe, targeted, and efficient therapy. Their ability to improve drug absorption, protect the drug, reduce side effects, and deliver medicines exactly where they are needed makes them highly valuable in modern healthcare. They continue to grow in clinical use and research, proving their importance in the future of pharmaceutical technology. With ongoing advancements in nanotechnology, liposomes are expected to play a major role in personalized medicine, cancer therapy, and advanced vaccine development.

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