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Liposomes A Novel Drug Carrier

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Abstract

Liposomes are spherical vesicles consisting of one or more phospholipid bilayers, which are under extensive investigation as drug carriers for improving the delivery of bioactive agents and many different compounds in biological, pharmaceutical, and medical and nutritional research. The majority of those clinically approved have diameters of 50–300 nm. Among several talented new drug delivery systems, liposomes characterize an advanced technology to deliver active molecules to the site of action and reduce undesirable side effects improving its in vitro and in vivo activity, as well as reducing the toxicity of the drug and enhancing the efficacy of the encapsulated drug. The present review will briefly explain the characteristics, advantages, scalable techniques based on the type of produced liposomes and potential applications of liposomes in food, cosmetics, gen genetic engineering, immunology, cancer therapy, infection, and also the diagnosis.

Keywords: Liposomes, immunology, nutritional, toxicity.

Introduction

Liposomes were first discovered in 1961 by British hematologist Alec Douglas Bangham at the Babraham Institute in Cambridge, United Kingdom. He published his research in 1964. These were discovered while testing AD Bangham and RW Horne's new electron microscopes with dry phospholipids and Gram-negative stains of the organization. [1] They found that self formed "pocket like" arrangements were termed "multilayered smectic mesophases" or "Banghasomes" by AD Bangham. His close friend, Gerald Weissman, suggested that double-

layered phospholipid vesicles called liposomes would be more useful. [2] They found that phospholipid hydration leads to the formation of bilayer phospholipid vesicles whose structure resembles that of the cell membrane. Thereafter, it became an important part of extensive research on drug delivery by scientists due to its biocompatibility and ability to encapsulate hydrophilic and lipophilic drugs.

In 1974, Gregoriadis et al. The use of liposomes in chemotherapy is recommended, and liposomes are considered a good candidate due to their safety, size control, and ease of operation. [3] Research on polyethylene glycol long-term liposomes began in 1990. [4] Since PEG-protein conjugation increases the half-life of proteins, researchers began conjugating PEG to liposomes to extend their half-life. [5] The development of long-lasting PEG liposomes is more effective in drug delivery, especially in cancer treatment. Kim et al. Studies have shown that PEG liposomes have better efficacy, safety, and stability in vivo compared to traditional delivery products. [6] PEG may help it escape from the reticulo endothelial system and reduce its distribution to other organs of the body. Therefore reduce the toxicity of cytotoxic drugs. Liposomes are popular for their contributions to various industries such as drug delivery, cosmetics, and biological processes. [7] Liposome is of Greek origin: “Lipos” means “fat” and “Somas” means “body”. Liposomes were first described in 1964 by AD Bangham and colleagues. His close colleague, Gerald Weissman, coined the term “liposome”, meaning “small vesicles containing one or more lipid layers.” Liposomes are colloidal particles formed by hydration of phospholipids with water, leading to the formation of liposomes with diameters in the range of 0.01-0.5 µm. The production of liposomes has become one of the most important new drug delivery methods and has been extensively studied by scientists due to their biocompatibility and biodegradability. Liposomes have gained widespread interest as drug delivery vehicles, and liposome research is increasing due to their ability to act as biological agents, making them versatile in many areas of research.[8] They have one or more aqueous cores embedded in phospholipid bilayers composed of natural or synthetic phospholipids. Liposomes are made from natural phospholipids that are non-toxic, non-immunogenic and biologically inert. Both hydrophilic and lipophilic substances can be carried in them. Drug targeting can also be achieved by modifying the surface to make it more localized to the diseased tissue. Due to their biphasic nature, liposomes can serve as carriers for both hydrophilic and lipophilic drugs. Highly hydrophilic drugs ($\log P < -0.3$) are found in the aqueous space, while lipophilic drugs ($\log P > 5$) are found in the lipid bilayer of liposomes. For example, drugs with an average partition coefficient of 1.7 ($\log P < 4$) cause problems in the transport of drugs because they are in equilibrium between the lipid and aqueous layers and are associated with the critical phase of leakage during storage. [10] Naturally, phospholipids exist in two layers (bilayers), where the hydrophilic polar heads are attracted to water inside and outside the membrane, while the lipophilic hydrocarbon tails are attracted to each other to form a bilayer. Format. Two layers. Keep away from water sources. The hydrocarbon tails of one layer meet the hydrocarbon tails of the other layer, forming a double layer. When the phospholipid bilayer breaks down, it forms spheres that are smaller than normal cells; these can be single-layer or double-layer spheres. One layer of the spheres is micelles, and the two layers are liposomes. Liposomes are made from naturally derived

phospholipids, such as egg phosphatidylethanolamine, or pure surfactant components, Such as DOPE(dioleoylphosphatidyl ethanolamine

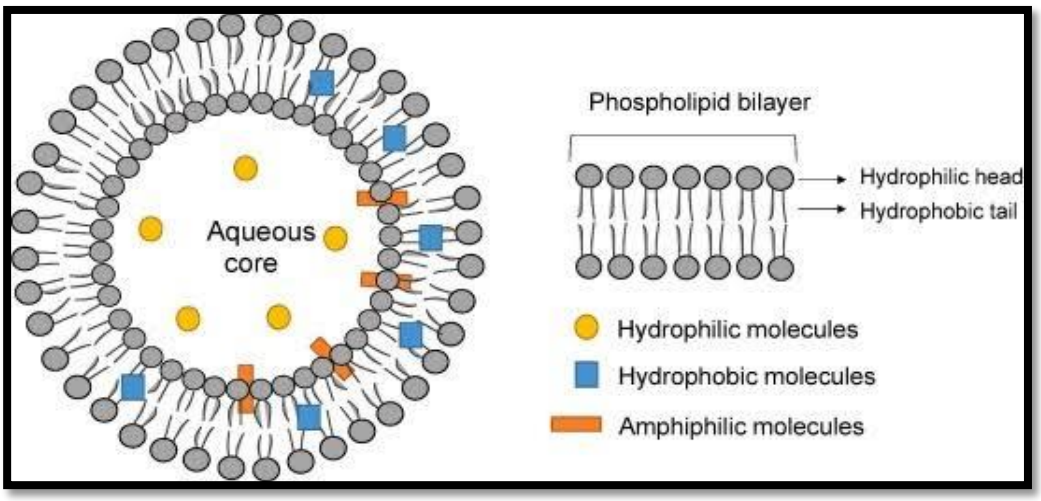

Fig.no.1. Structure of liposomes

The structural components are:

1) Phospholipids

Phospholipids are the main components of liposomes. The most commonly used phospholipid in liposomal for mulations is phosphatidylcholine (PC8). Phosphatidylcholine is an amphiphilic molecule consisting of:

• A hydrophilic polar head group, phosphocholine

• A glycerol bridge

• A pair of hydrophobic molecules acyl hydrocarbon chain The chemical structure of naturally occurring sim p hosphatidylcholine contains a glycerol link . for two saturated or unsaturated acyl chains. The stability of liposo me membranes depends on the volume of hydrocarbon chains of lipid molecules9. The properties of fatty acids in lipid molecules (such as the number of double bonds in the chain) determine bilayer properties such as flexibi lity and phase behavior. Phospholipids are abundant in nature and contain choline, which can be use d to prepare liposoms

Examples of phospholipids are

• Phosphatidyl choline (Lecithin) PC

• Phosphatidyl ethanolamine(Cephalin)-PE

• Phosphatidyl serine (PS)

• Phosphatidyl Glycerol (PG)

2) Cholesterol

Cholesterol is another important component of liposomes. It is a widely used sterol. The addition of sterols modulates the stability and hardness properties. It does not create two layers by itself. It is incorporated into phospholipids at a very high level, with molar ratios of cholesterol to phosphatidylcholine as high as 1:1 or 2:1. The presence of cholesterol in the lipid bilayer increases its stability, leading to high solubility and processing of the membrane. Cholesterol reduces the permeability of water-soluble molecules and increases the fluidity and stability of biological organisms. Cholesterol blocks interactions and weakens liposomes.

Attractive biological properties of liposomes:

- Liposomes are biocompatible.
- Liposomes can capture water-soluble (hydrophilic) drugs in their internal water and water-insoluble (hydrophobic) drugs in the membrane.
- Liposome-incorporated drug resistance resulting from inactivation. Affected by external factors; but does not cause side effects.
- Liposomes have the unique opportunity to deliver drugs into cells, even within individual cell compartments.
- Easily change the size, value and location of liposomes by adding new components Add the lipid mixture to the lipid mixture before preparing the liposome and/or by changing the preparation method.

Advantages of liposomes:

1) Provides controlled drug release

2) Biodegradable, biocompatible, flexible

3) Nonionic

4) Ability to carry water-soluble and fat-soluble drugs

5) Drugs stabilize oxidation

6) Improves protein stability

7) Control of hydration

8) Provides prolonged release

9) Target drug delivery or a specific location to distribute drugs

10) Improve the weight of the environment of embedded drugs

11) Change the pharmacokinetics and pharmacodynamics of drugs

12) Can be controlled by many methods

13) Can combine microscopic and Macromolecules

14) Reservoir as drug

15) Improve therapeutic index of drug

16) Treatment to be avoided locations

17) can adjust dose distribution

Disadvantages of liposomes

1. Production cost is high.

2. Leakage and fusion of encapsulated drugs/molecules.

3. Sometimes phospholipids undergo reactions similar to oxidation and hydrolysis.

4. Short half-life.

5. Low resolution.

6. There are several fixed locations.

Other problems related to liposomes are as following:

1. **Sterilization:**

Sterilization of liposomes is a complex process. Because it is not resistant to heating and some kind of electricity. Using birth control pills may affect safety. The only sterile method is a membrane filter that can filter out liposomes <0.2 μm in size. This method cannot filter bacteria

2. **Short self-life and stability:**

The stability of liposome formulations is difficult to achieve due to chemical and physical degradation. They are chemically affected by oxidation and hydrolysis and can cause the body to fuse to form large vesicles. It can be prevented by adding antioxidants such as tocopherol and adding. cholesterol to prevent fusion.

3. **Encapsulation effect**:

The amount of drug encapsulated by liposomes is generally low, and drug leakage sometimes occurs.

4. **Removal from circulation by the reticulo endothelial system (RES):**

The main disadvantage of liposomes as drug carriers is their rapid absorption by phagocytes of the mononuclear phagocytic system (MPS). Larger liposomes are cleared from the circulation more quickly than smaller liposomes. PEGylation can extend the lifespan of liposomes.

MECHANISM ACTION OF LIPOSOMES

1. Endocytosis – carried out by phagocytes (e.g. neutrophils) on reticuloendothelial cells.

2. Adsorption – Occurs through electrostatic force on the cell or interaction with the cell material.

3. Fusion – occurs as a result of the release of the liposome bilayer into the plasma and the continuous release of the liposome contents into the cytoplasm.

4. Lipid exchange – Liposome contents are not affected during the transfer of liposome lipids to the cell membrane.

CLASSIFICATION OF LIPOSOMES

The liposomes may be classified based on

1. **Structure**
2. **Method of preparation**
3. **Composition**

1.Classification Based on StructureVesicle Types with their Size and Number of Lipid Layers

1.Multilamellar liposomes

Multilamellar vesicles (MLVs) are liposomes containing many concentric lipid bilayers, 0.1–0.5 μm in size. MLV has onion patterns. Its main advantages are that it is easy to build and has a solid structure. The main disadvantage of these liposomes is the limited space for loading compounds. Because many internal domains are surrounded by multiple lipid bilayers, the volume available for cargo is limited, and the size of these liposomes also limits their injection.

2. Monolayer liposomes

Monolayer vesicles consist of double-layered phospholipid spheres surrounded by a liquid. Monolayer vesicles can be subdivided into small single-layer vesicles (SUVs) of 0.02–0.05 μm in size. These vesicles cannot be removed from the blood due to their small size. Therefore, they have a higher chance of entering tissues and

exerting therapeutic effects, and large monolayer vesicles (LUVs) have a size greater than 0.06 microns, leaving plenty of room for the compounds to be transported.

3. **Multivesicular liposomes**

Vesicles consist of many nonconcentric vesicles encapsulated in two layers, called multivesicular vesicles (MVV). These can be various liposomes ranging in size from 2 to 40 microns.

4. **Oligolamellar liposomes**

Compared to multilayer liposomes, oligolamellar liposomes have fewer layers. Their sizes vary between 0.1 and 10 microns.

5. **Giant liposomes (GL)**

It is the largest liposome with a size of 10-1000 Um. This GL can be used for different diagnosis and treatment. They can be SUV or LUV

2. Based on Method of Preparation Different Preparation Methods and the Vesicles Formed By these Methods

A**) Multilayer liposomes (MLV)**

(i**) Lipid hydration method**

This is the most commonly used method to prepare MLV. The process will dry the lipid solution, thus forming a film at the bottom of the round-bottomed container, and then moisten the film by adding an aqueous buffer and vortexing the dispersion for a period of time. The hydration step is performed at a temperature above the gel-liquid crystal transition temperature Tc of the lipid or above the Tc of the component with the highest melting point in the lipid mixture. Depending on its solubility, the compound to be encapsulated is added to an aqueous buffer or a lipid-containing organic solvent. MLV is easy to prepare by this method, and many products can be encapsulated in liposomes. The disadvantage of this method is small volume, low encapsulation efficiency and uneven size.

MLV with high encapsulation performance can be encapsulated in weak organic solvents (petroleum ether, diethyl ether). Emulsify contents by vigorous vortexing or sonication. Organic solvents are removed by passing nitrogen gas through the mixture. MLV was formed in the aqueous phase immediately after removal of the organic solvent. The main disadvantage of this method is that the product to be encapsulated is exposed to organic solvents and ultrasonic treatments.

3. **Based on Composition Different Liposome with their Compositions**

Conventional liposomes:

Composed of neutral or negatively charged phospholipids and cholesterol. Subject to coated pit endocytosis, contents ultimately delivered to Lysosomes if they do not fuse with the endosomes, useful for E.E.S targeting; rapid and saturable uptake by R.E.S; short circulation half life, dose dependent pharmacokinetics

Cationic liposomes:

Consist of cationic lipids. Fusion with the cell or endosomal membrane; suitable for transporting negatively cha rged macromolecules (DNA, RNA); easy to build, structurally unstable; It is toxic in high doses and is generally limited to cosmetics.

pH sensitive liposomes :

Phospholipids consist of phospholipids such as ethanolamine and dioleyl phospholipid ethanolamine. The Lined Pit undergoes endocytosis at low pH, fuses with the cellular or endosomal membrane, and releases its contents into the cytoplasm; It is suitable for intracellular transport of weak bases and large molecules. Biodistribution and pharmacokinetics are similar to liposomes.

Long circulating or stealth liposomes:

Made from moderate heat transfer lipids, cholesterol, and 5-10% PEG-DSPE. Hydrophilic surface coating, less cold, hence less RES absorption, long half-life (40 hours); dose-related pharmacokineticsMade from moderate heat transfer lipids, cholesterol, and 5-10% PEG-DSPE. Hydrophilic surface coating, less cold, hence less RES absorption, long half-life (40 hours); dose-related pharmacokinetics

Immuno liposomes:

Known or latent liposomes with antibodies or known sequences. Receptor mediated endocytosis, cell-specific binding (target); The contents can be released outside the cell near the target tissue, and the drug will di ffuse across the plasma membrane to produce its effect.

METHOD OF PREPARATION

Methods for preparing liposomes include soluble lipids in organic solvents, drying the lipids from the organic so lution, dispersing the lipid in aqueous media, purifying the resulting liposome,

and analyzing the final product. All liposome preparations included

Four steps:

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

Techniques used for the preparation of liposomes are Described below;

1.Hand Shaking method:

In this method, lipids are dissolved in organic solvent (usually ethanol) in a round-bottom flask and shaken regularly in a cyclic manner. When the organic solvent evaporates, it forms a lipid film on the RBF, which is then purified and washed. Water and shake constantly to form liposomes. This method can be used to prepare MLV liposomes. Nowadays, the rotary evaporator is used for lipid film formation and hydration as it is more reliable than the manual method.

1.sonicationmethod :

It is the most used method to prepare MLV and SUV prepared by handshake method and field evaporator metho d. Two types of sonication methods are used in the preparation of SUVs.

A). Probe sonication method: In this method, the tip of the titanium probe is directly dispersed into the liposome dispersion for SUV generation. In this way, the input power is high and therefore heat is produced. Liposome dispersions were stored in an ice chamber to maintain temperature. The main disadvantage of this method is that titanium particles behave like mud in the solution and contaminate the solution.

B) Ultrasonic bath: In this method, the liposome dispersion in the container is placed on the ultrasonic bath. This method for SUV production is easier than probe sonication as the temperature can be easily controlled. Sterilized liposomes can be obtained without titanium particles.

2.French Press Method:

In this method, unstable MLV is passed and converted into SUV and LUV to the small size of the device. Liposomes produced by this method are more reliable as they have better stability than liposomes prepared by ultrasound. The disadvantage of this method is the small working volume of up to 50 ml and the difficult to control temperature.

3. freezing and thawing liposomes:

Here, SUVs produced by ultrasonic process are slowly and continuously freeze-thawed and LUVs are produced by accumulation of SUVs during the time-thawing process. In this way, the encapsulation rate is increased by 20%-30%.

4.Solvent dispersion method:

A)Ether injection (solvent evaporation):

In this method, lipids dissolved in ether or ether-methanol mixture are slowly injected into the drug at a temperature of 20°C, containing: drug. . in aqueous environment. 50 to 65 °c or decompression. Removal of ether under vacuum results in the formation of liposomes. The main disadvantage of this process is the formation of a

heterogeneous liposome population (70-200 nm) during the encapsulation process and the liposomes being exposed to high temperature, which will affect the liposome stability.

b)Ethanol Injection: MLV formation as a result of injecting lipids and ethanol in opposite directions. Its disadvantage is the formation of a heterogeneous liposome population (30-110 nm). It Is also difficult to remove ethanol from the drug, thus increasing the deactivation time of bioactive macromolecules.

C)Reverse Phase Evaporation Method:

This method results in a reaction in the history of liposomes. The ratio of water to lipid used in this method is high; approximately four times higher than holding method, or MLVs. This method is created by reverse micelles in which an aqueous medium is sonicated. The aqueous medium contains water-soluble molecules for the encapsulated, lipids and organic phase. Slow removal of the organic solvent results in the formation of a gel-like consistency. Most importantly, the gel-like structure falls into liposomes.

5.Detergent removal method (removal of unencapsulated drugs)

A) Dialysis:

In this method, detergent is used to make lipids at critical micelle concentration (CMC). When removed by dialysis, a dialysis model is used using products such as LipoPrep (Diachema AG, Switzerland). [27]

B) Detergents (cholates, alkyl glycosides, Triton – 2 beads for detergent removal (SERVA Electrophoresis Gmb H, Heidelberg, Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA)

C) Gel permeation chromatography:

Sephadex G-50, Sephadex G-1 00 (Sigma-Aldrich, MO, USA), Sepharose 2B-6B and Sephacryl S200-S1000 (General Electric Company, Tehran, Iran) can be used as column packing for gel filtration. Liposomes cannot enter this volume, making it easier to obtain liposomes. The physical and chemical properties of liposomes have a direct impact on their in vivo and in vitro properties. The properties of liposomes should be determined by analyzes such as GLC, TLC and HPTLC immediately after liposome formation. Size, number of lamellae, internal morphology, charge and bilayer fluidity play a direct role in in vivo properties. Sterilization of liposomes is difficult because they are heat sensitive. [28] Therefore, it must be prepared under sterile conditions. Various methods for determining size, number of lamellae, value, and bilayer fluidity are listed in the table.

Use of liposomes

1. Therapeutic value of liposomes as drug carriers, especially antibiotics, antibiotics and antibiotics.

2. As anti-cancer and cytotoxic drugs such as cytarabine and alkylating agents.

3. When used as a vaccine adjuvant, i.e. IM, they secrete antigens slowly and accumulate in the lymph nodes.

4. In ophthalmic drug delivery systems, iodouridine is used to treat acute keratitis.

5. Sustainability allows topical or localized application of liposomes. Examples include biological proteins or peptides such as vasopressin.

6. Site-specific target: In some cases, liposomes with ligands attached to their surface can bind to target cells ("key and lock" mechanism). Exantineos, anti-inflammatory and anti-inflammatory.

7. Chelating agents increase the transfer of hydrophilic charged molecules such as antibiotics, plasmids and genes into cells.

8. Chelation therapy in heavy metal poisoning.

9. Liposomes as protein carriers in immunology

10. Continuous or controlled delivery

11. Tumor diagnostic imaging Intracellular drug delivery

12. Site-specific targeting

13. Enzyme replacement

14. Membrane research< 15 .Oral drug delivery

16. Gene therapy

17. Formulation aids

18. Cosmetics

LIMITATIONS OF LIPOSOMES

1. Stability
2. Sterilization
3. Encapsulation efficiency
4. Active targeting
5. Gene therapy
6. Lysosomal degradation

MARKETED PREPRATION OF LIPOSOME

Liposome (Doxil ™) Doxorubicin = Kaposi sarcoma

Liposome (EVACT) = breast cancer

Liposome (DaunoXome) Daunosome = Advanced Kaposi' sarcoma,small cell lung cancer, leukaemia & solid tumour.

Liposome (VincaXome) Vincristine = Solid tumour

Conclusion

Liposomes are the most widely used exploratory nanocarriers for targeted drug delivery. Liposomes are spherical lipid vesicles (usually particle size 50-500 nm) consisting of one or more lipid bilayers formed by emulsifying natural or synthetic lipids in an aqueous medium. Many drug molecules have good pharmacological effects, but are used only because of their toxicity. These drugs can be used by reducing their toxicity and improving their pharmacological effects. Liposome formulation is a suitable method to achieve the therapeutic effect of this drug. The composition of the liposome makes it safer because it is inert and similar to cell membranes, making it an interesting area of research for scientists. Liposomes are effective carriers for cancer drugs and are becoming increasingly popular in chemotherapy. Researchers are developing liposome technology to improve the clinical and pharmacokinetic properties of powerful drugs while reducing their toxicity.

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