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A Review on Liposomes: A Versatile Tool in Drug Delivery

[1*]Mohini Sunil Mali, [2*]Rohit Kailas Patil, [3]Kalpeshkumar S.Wagh, [4]Kalpesh S. More, [5]Shital R. Rajput

[1,2] *Department of Pharmaceutics, Kisan Vidya Prasarak Sanstha'S Institute Of Pharmaceutical Education Boradi, Tal- Shirpur, Dist- Dhule.*

[3,4,5.] *Department of Pharmaceutics, Kisan Vidya Prasarak Sanstha'S Institute Of Pharmaceutical Education Boradi, Tal- Shirpur, Dist- Dhule.*

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ABSTRACT:
Liposomes, dynamic lipid-based vesicles, have emerged as versatile tools in drug delivery, offering many opportunities to improve therapeutic outcomes. This comprehensive review covers various aspects of liposomes, starting with an in-depth introduction to their key role in drug delivery systems. The mechanism of liposome formation is an important basis for understanding their function, and demonstrates the self-assembly of lipids into bilayer structures. The classification of liposomes reflects their various properties, from standard applications to more specialized formulations designed for specific applications. We review lipid hydration, solvent dispersion, microfluidization, and reverse phase evaporation, providing detailed insight into the methods that shape the properties of liposomes.
The application section reveals the great potential of liposomes for drug delivery, demonstrating their ability to encapsulate a wide range of therapeutic agents. From targeted drug delivery to increased bioavailability, liposomes play an important role in optimizing therapeutic strategies. The evaluation of liposomes includes parameters such as size, stability, and drug release kinetics, an important aspect to ensure their efficacy.

KEYWORDS: Liposomes, Bioavailability, Thin film hydration, Applications

I. INTRODUCTION:

[1].Thirty-six years have passed since liposomes were first discovered.[2].Over time, liposomes have evolved from biomembrane models to drug carriers with clinical utility. The range of medical applications of liposomes extends from chemotherapy for cancer and fungal infections to vaccines and newer gene therapy. Liposomal drugs and vaccines on the market include the anticancer drugs doxorubicin and daunorubicin, as well as the antifungal drug amphotericin B (AmpB) and hepatitis A and influenza vaccines. Gene therapy is still in its infancy and the liposomal gene carrier has just entered the clinical trial phase. As the use of liposomal delivery systems expands, the number of biopharmaceutical companies delivering liposomal drugs or integrating liposomal delivery technology into their technology platforms is increasing rapidly. Due to their versatile nature, liposomes can be used for a variety of applications that require different requirements on the carrier. The liposomes themselves are assembled in an aqueous solution and components can be added or removed in a modular fashion. As a result, their properties can be customized according to the application. This review will make it clear that this is not always easy to accomplish. The first part of this review provides important information in accordance with the motto "Only by remembering the past can we learn from the present".

[3]. Liposomes are 30 nm to micrometers in size, with a phospholipid bilayer thickness of 4-5 nm . [4]. Many neoplastic agents that are highly cytotoxic to tumor cells in vitro also affect normal cells. This is because the therapeutic index (TI) is low, meaning that the dose required to produce an antitumor effect is toxic to normal cells. Such drugs must be targeted to specific sites (disease sites) to minimize their toxic effects on normal tissues. [5,6]. Various amphipathic molecules have been used to form liposomes, and the preparation method can be tailored to control their size and morphology. Drug molecules can be concentrated in the aqueous phase or attached to lipid bilayers; The exact location of the drug in the liposome will depend on the physicochemical properties and lipid composition.

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II. MECHANISM OF LIPOSOME FORMATION :

[7]. Most liposomes are made up of phospholipids, which are amphiphilic molecules (having a hydrophilic head and a hydrophobic tail). The hydrophilic part is mainly phosphoric acid bound to water-soluble molecules, while the hydrophobic part consists of two fatty acid chains with 10-24 carbon atoms and 0-6 double bonds in each chain. [8]. When these phospholipids are dispersed in the water environment, they form a lamellar sheet, with the polar head group facing the water area, the fatty acid group facing each other, and finally forming a spherical/vesicle like structure called a liposome. The polar part is in contact with the water area while shielding the non-polar part (pointing at an angle to the surface of the membrane). [9].When phospholipids are hydrated in water, sonication, shaking, heating, homogenization, etc. together with energy intake such as lipid-lipid and lipid-water molecules, hydrophilic/hydrophobic interactions lead to the formation of bipartite vesicles. reach thermodynamic equilibrium in the water phase.

CLASSIFICATION OF LIPOSOMES :

Sr. No.	Based On Lamellarity And Size	Type of liposome
1)	Small Unilamellar Vesicles (SUV); 20−100 Nm	conventional liposomes
2)	Large unilamellar vesicles (LUV); >100 nm	long-circulating liposomes
3)	giant unilamellar vesicles (GUV); >1000 nm	cationic liposomes
4)	oligolamellar vesicles (OLV); 100−1000 nm	stimuli-sensitive liposomes (pH, temperature, magnetic field)
5)	multilamellar vesicles (MLV); >500 nm	multilamellar vesicles (MLV); >500 nm

Table No. 01: Classification of Liposomes

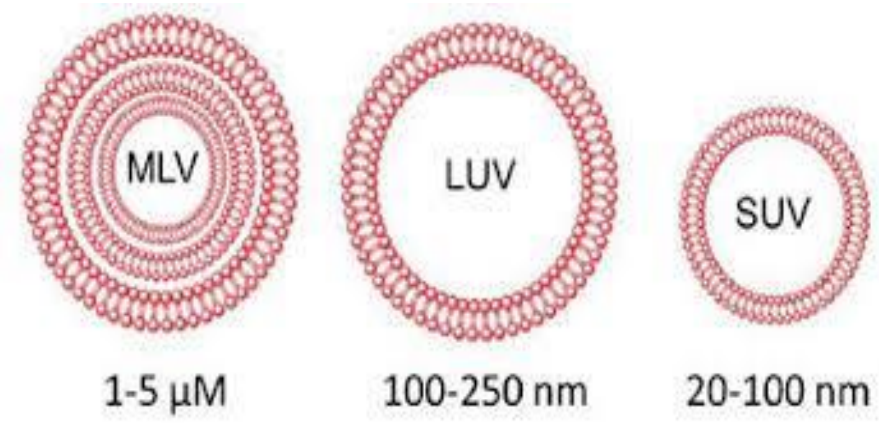

Fig No. 01: Structure of Liposomes

[10]. Liposomes can be classified in several ways depending on their size and the number and composition of their vesicles (Table 3). It is important to understand the properties of the liposomes used to choose the appropriate route of administration and also to evaluate the pharmacokinetic fate of the drug delivery system. For example, the number of vesicles has a direct effect on drug absorption, surface binding, drug release from the system, and retention characteristics.

III. METHOD OF PREPARATION OF LIPOSOMES:-

[11]. Conventional methods for preparing liposomes include dissolving lipids in organic solutions, drying lipids from organic solutions, dispersing lipids in aqueous solutions, purifying the resulting liposomes, and analyzing the final product. [12,13] Of all the methods used to prepare liposomes, the thin film hydration method is the simplest and most widely used method. MLVs are produced in this way in the range of 1-5 µm. If the drug is hydrophilic, it can enter the aqueous buffer, and if the drug is hydrophobic, it can be incorporated into the lipid film. But the weakness of this method is the encapsulation efficiency (only 5-15%) for hydrophobic drugs. By hydrating lipids in the presence of organic solvents, the encapsulation efficiency of MLV can be improved.

[14].LUVs can be prepared by solvent injection, detergent dialysis, calcium binding compounds, and phase evaporation methods. Light vehicles, MLV or

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LUV can be prepared by extrusion or sonication. All of these preparation methods include the use of organic solvents or detergents, even small amounts that can cause poisoning.

IV. GENERAL METHOD OF PREPARATION AND DRUG LOADING :

Preparation of Lipid for Hydration:

When preparing liposomes with a mixed lipid composition, the lipids must first be dissolved and mixed in an organic solvent to ensure a homogeneous lipid mixture. This process is usually carried out using chloroform or a chloroform:methanol mixture. The goal is to obtain a clear lipid solution to completely mix the lipids. Typically lipid solutions are prepared at 10-20mg lipid/ml organic solvent, but higher concentrations can be used if lipid solubility and mixing are acceptable. After the lipids are thoroughly mixed in the organic solvent (<1mL), the solvent is removed to produce a lipid film. For small amounts of organic solvents, the dryer can evaporate the flow of nitrogen or argon in the fume hood. For larger volumes, remove the organic solvent by rotary evaporation with a thin lipid film on the sides of the round-bottom flask. The lipid film was dried well to remove the remaining organic solvent by placing the vial or bottle under a vacuum pump overnight. If the use of chloroform is contraindicated, a third alternative is to dissolve the lipids in lipanol or cyclohexane. [15].The lipid solution is transferred to a container and frozen by placing the container on dry ice or rolling the container in a dry ice or alcohol (ethanol or methanol) bath. Care must be taken when using the bath procedure so that the container can withstand sudden temperature changes without breaking. After freezing, the frozen lipid cake is placed in a vacuum pump and lyophilized to dryness (1-3 days depending on thickness). The thickness of the lipid cake should not be greater than the diameter of the container used for lyophilization. Dry lipid film or cakes can be removed by vacuum pumping, the container must be tightly closed and taped, and stored frozen until ready to hydrate.

V. SOLVENT DISPERSION METHODS

Ether Injection Method

[16].A lipid solution dissolved in diethyl ether or ether/methanol mixture is injected into an aqueous solution of the material maintained at a temperature of 55-65°C or under reduced pressure. Removal of ether under vacuum results in the formation of liposomes. The main weakness of the method is the inhomogeneity of the population (70-190 nm) and the effect of the compound in organic solvents or at high temperatures.

Ethanol Injection Method

[17].An ethanol lipid solution is quickly injected into the bulk of the buffer. MLVs are generated instantly. The disadvantage of the method is that it is difficult to remove all the ethanol due to the heterogeneous population (30-110 nm), liposomes are highly soluble, form azeotropes with water, and can immobilize various biologically active macromolecules. even a small amount of ethanol.

Reverse Phase Evaporation Method An initial water in oil emulsion is formed by brief sonication of a two-phase system containing phospholipids in an organic solvent (diethyl ether or isopropyl ether or a mixture of isopropyl ether and chloroform). The organic solvent is removed under reduced pressure, resulting in a sticky gel. Liposomes are formed when residual solvent is removed by continuous rotary evaporation under reduced pressure. With this method, a high encapsulation efficiency of up to 65% can be obtained at low ionic strength, for example 0.01M NaCl. This technique has been used to encapsulate both small and large macromolecules. The main drawback of the method is the effect of the coated material on organic solvents and short-term sonication.

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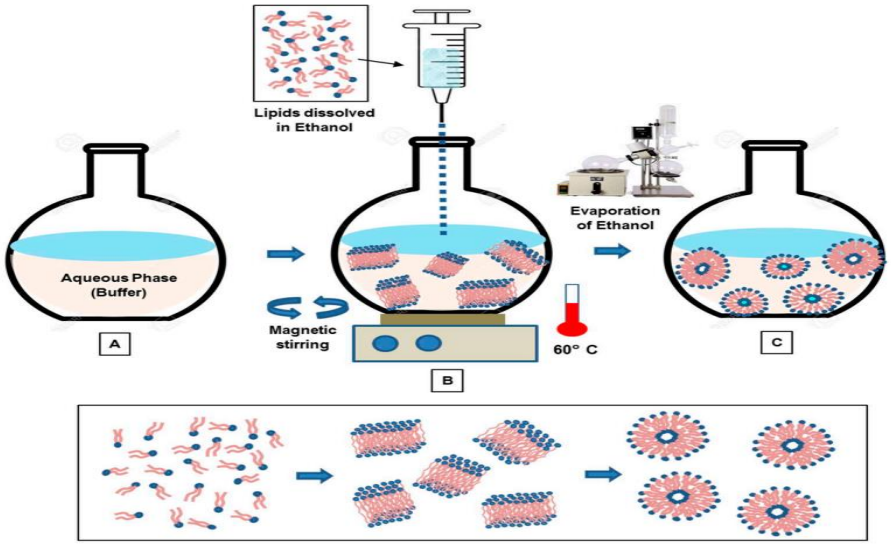

Fig No.: 02 Ethanol Injection Method

Microfluidization:

[18].A method based on microfibrillation / microemulsification / homogenization was developed to prepare liposomes. MICROFLUIDIZER is available from Microfoods Corporation, Massachusetts, USA. A pellet mill based on this technology can produce 20 gallons/minute of liposomes in the 50-200 nm size range. Up to 75% encapsulation efficiency can be obtained.

Proliposomes:

[19].In proliposomes, lipids and drugs are coated with a soluble carrier and form a free-flowing granule material, forming an isotonic liposomal suspension upon hydration. The proliposome approach can enable large-scale production of liposomes, especially those containing lipophilic drugs.

Reverse-Phase Evaporation Method

[20-22].In this method, lipids are dissolved in an organic solvent (eg a mixture of diethyl ether and chloroform (1:1 v/v) or diethyl ether/isopropyl ether or chloroform/methanol (2:1 v/v)). and vice versa support the formation of micelles by adding a certain amount of water phase (buffer) to the solution. Lipids organize themselves at the oil-water interface, forming an oil-in-water (W/O) microemulsion. A W/O microemulsion can be emulsified by mechanical methods or sonication to facilitate the formation of a homogeneous dispersion. A phosphate buffer (or lemon-Na2HPO4) is often added to the water phase to increase the efficiency of liposomes. Using a continuous rotary evaporator (at low pressure) allows the organic solvent to be removed until a sticky gel is formed. The slow removal of organic solvents favors the disruption of reverse micelles and promotes the formation of continuous liposomes (LUVs). At a certain critical point, the gel collapses, the excess phospholipids in the solution medium are distributed around the opposite micelles and form a lipid bilayer around the water droplets (residual), leading to the formation of liposomes.

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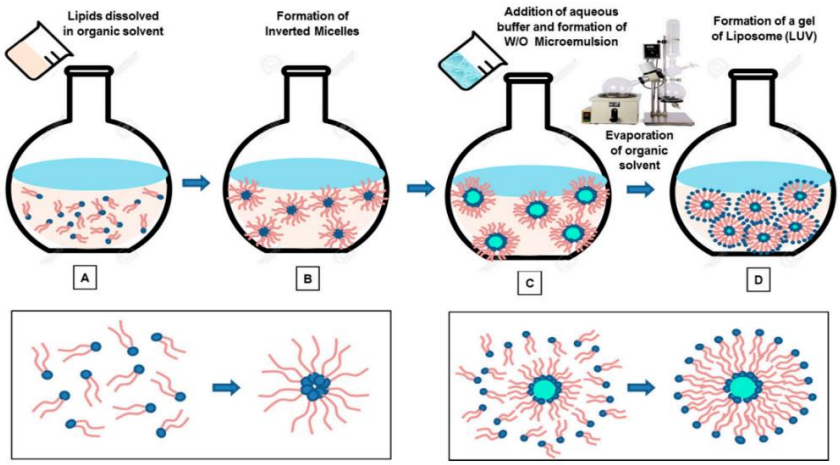

Fig No.02: Reverse-Phase Evaporation Method

VI. Applications of liposome:

[23].Liposome research has grown significantly over the past 30 years. Various types of liposomes with variable size, phospholipid composition, cholesterol composition, and surface morphology can now be designed to suit a variety of applications. [24]. Using a liposome carrier, the liver and spleen can be targeted, and tomography can easily distinguish between benign and malignant tissues. Liposomes have great utility in transdermal drug delivery systems. In plant cell therapy, the liposomal drug delivery mechanism helps to reduce toxicity and increase drug efficacy. Liposomes target their functional areas by binding a series of amino acids to specific cell receptors.

A. Liposome for Respiratory Drug Delivery System

[25].Liposomes are widely used in various types of respiratory diseases. Liposomal aerosols can be formulated to provide sustained release, avoid local irritation, reduce toxicity, and improve stability. When preparing liposomes for pulmonary delivery, composition, size, loading, drug/lipid ratio, and method of drug delivery must be considered. The liquid or dry form is inhaled during nebulization.

B. Liposome as Vaccine Adjuvant

[26-27].Liposomes are highly designed as immunoadjuvants that enhance cellular and non-cellular immunity. Liposomal immunomodulator acts by slow release of encapsulated antigen in cellular vaccine and passive accumulation in regional lymph nodes. Lymphoid accumulation of liposomes is achieved by targeting liposomes with the help of phosphotidyl serine. Liposomal vaccines can be prepared by injecting microbes, soluble antigens, and liposomal deoxyribonucleic acid cytokines.

C. Liposomes for Brain Targeting

[28-29].The biocompatible and biodegradable properties of liposomes are used in brain drug delivery systems. Small diameter (100 nm) and large diameter liposomes freely diffuse across the BBB. However, small intact vesicles coupled with brain drug transport vectors can be transported across the BBB by receptor-mediated or absorbance-mediated transcytosis. Cationic liposomes undergo absorption-mediated endocytosis into cells, whereas a similar absorption-mediated transcytosis across the BBB has not been identified. Mannose-coated liposomes reach the brain and help transport loaded drugs across the BBB. Neutropeptides, leukenkephalin and mefenkephalin, and cytosorphin usually do not cross the BBB when administered systemically. Due to the versatility of this method, the antidepressant amitriptyline usually penetrates the BBB.

D. Liposome in cancer therapy

[30-31].All cancers cause toxic effects with long-term use. The liposomal approach results in tumor targeting with less toxic drugs. Small and stable liposomes passively target a variety of tumors because they can travel longer distances. Today, many anticancer drugs are packaged in liposomes, providing enhanced targeting.
Bioavailability.

E. Liposome in Tumor Cell Therapy

[32].Antibiotics have serious side effects when taken long term. Liposomal therapy to target

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tumor cells has improved tumor therapy by minimizing side effects. Although small and stable liposomes are supposed to passively target various tumors, they can circulate for a long time and become extra vascular in the tissue with increased vascular permeability.61,62. Absorption of liposomes by macrophages in the liver and spleen has hampered the development of liposomes as drugs for 20 years. Many antibiotics have been incorporated into liposomes for the purpose of increasing bioavailability.

F. Liposome as Anti-Infective Agents

[33].Cellular pathogens such as protozoa, bacteria, and fungi live in the liver and spleen, so therapeutic agents can be applied to organs that use liposomes as a transport system to remove these pathogens. 58 Diseases such as leishmaniasis and histoplasmosis can be treated; candidiasis, erythrococcosis, aspergillosis, gerardiasis, tuberculosis and malaria by conjugating and targeting drugs with liposomal carriers. Amphotericin B, a polyene antibiotic, has been associated with significant kidney damage when used to treat systemic fungal infections. Amphotericin B binds to sterols in susceptible fungal membranes and increases membrane permeability. This substance is dangerous because of its specificity and proximity to cholesterol in mammals. The first liposome formulation of amphotericin B has recently passed all clinical trials and is now marketed for the protection of various fungal diseases including mucormycosis, aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, and cryptococcosis. Liposomal amphotericin B reduces kidney and overall toxicity by passively targeting the liver and spleen at normal doses, but kidney toxicity usually occurs at high doses due to drug saturation of liver and spleen macrophages. By coating the vesicles, o-stearoyl amylopectin, polyoxyethylene or mono-sialogangliocyte liposomes can be specifically targeted to the lungs. Encapsulation of anti-tuberculosis agents such as isoniazid and rifampicin in lung-targeted liposomes modulates toxicity and increases the effectiveness of these products.59 Different formulations of amphotericin have been approved in clinical trials and are now marketed in most European countries.

VII. EVALUATIONS OF LIPOSOMES :-

Particle size and distribution:

[34].The measurements are analyzed by an analyzer based on the theory of laser diffraction, with a minimum power of 5MW.

Trapped Volume –

[35].This is an important parameter related to liposomes. This is the amount of lipids covered by water. This can vary between 0.5 and 30 microliters / micromole.

Percentage yield of liposomes-

[36].The prepared liposomes were prepared and collected. The measured weight is divided by the total amount of drugs and substances used to prepare the liposomes.

Surface charges

[37].A method for measuring surface charge based on free-flow electrophoresis of multilayer varistors (MLVs).

• Using cellulose acetate plate immersed in pH 8.8 sodium borate buffer.
• About 5N moles of lipid sample was applied to the plate and then subjected to electrophoresis for 30 minutes.
• liposomal gels are separated based on their surface charge.

This technique can be used to determine charge heterogeneity in liposome suspensions, as well as to detect impurities such as fatty acids.

Encapsulation Efficiency (EE)

[38].The amount of drug loaded into the liposomes helps to assess the drug's behavior in biological systems. The % of drug encapsulation is determined by first subtracting the free drug fraction from the entrapped drug fraction. Encapsulated fractions are formulated to leach liposomes into aqueous solutions using appropriate detergents.

Drug Release Study

[39].500 ml of 20% ethanol was used as an eluent; 10 ml of release agent is withdrawn and placed in a dialysis bag. 5 mL of drug-containing liposomes and 5 mL of the same drug-containing ethanol solution as liposomes were dissolved in a dialysis vessel at 37 °C and stirred at 300 × g , respectively. Samples of 100 µl of fluid from the dialysis bag were collected at hours 1, 2, 4, 6, 8, 10, 12, and 24 to determine and calculate the cumulative release rate. The release curve is plotted against time (t).

FUTURE PERSPECTIVE :

Looking ahead, the future of liposomal medicine offers exciting opportunities. Advances in

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nanotechnology, surface modification techniques, and targeted delivery strategies promise to improve the accuracy and efficacy of liposomes. In addition, the combination of imaging techniques and personalized medicine approaches can contribute to the development of liposomal formulations. Overcoming challenges such as manufacturability and long-term stability will be important in translating liposomal drugs from the laboratory to widespread clinical use. Collaborative efforts between scientists, clinicians, and industry stakeholders will be instrumental in realizing the full potential of liposomes, ushering in a new era of innovation and patient-centered drug delivery.

CONCLUSION:-

In summary, liposomes are versatile tools in drug delivery and offer unique advantages in encapsulation and controlled release of therapeutic agents. Different methods of liposome preparation provide researchers with a diverse set of tools that allow them to customize according to the needs of specific drugs and patients. The broad spectrum of applications, from targeting specific tissues to improving drug stability, demonstrates the versatility of liposomal drug delivery systems. Given the complexity of liposomal formulations, it is clear that ongoing research and innovation will continue to improve and expand the potential of liposomes in the field of drug delivery.

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