A Comprehensive Review on Liposome's

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Abstract- *Drug delivery technology has advanced significantly in the medical field since the discovery of liposomes. The idea behind drug distribution is to make drugs more effective while minimizing their side effects. Liposomes are spherical vesicles made of an aqueous core and one (or more) phospholipid bilayer shells. Liposomes have been used in a wide range of nanomedicine and biomedical applications, including nanocarriers for drug delivery, due to their excellent biocompatibility, variable chemical composition, ease of preparation, and wide range of structural features. The background and development of liposomes are briefly discussed in this review paper, with an emphasis on preparation techniques and drug loading. In addition, methods for evaluating the size, entrapment efficiency, zeta potential, surface charge, lamellarity, and in-vitro drug release of liposomes. Liposomoes' stability was also discussed. Lastly, this review aims to investigate the various therapeutic applications of liposomes as a drug delivery system.*

Keywords- Liposomes, Nanocarriers, Entrapment Efficiency, Lamellarity, Drug Delivery System

I. INTRODUCTION

Dr. Alec D. Bangham, a British hematologist, and colleagues at the Babraham Institute made the initial discovery of liposomes in the 1960s. The first study on the discovery was published in 1964.[1]The small spherical vesicles known as liposomes are made up of an interior aqueous compartment that is enclosed by one or more concentric lipidic bilayers. Liposomes membrane is composed of natural and/or synthetic lipids which are relatively biocompatible, biodegradable and non-immunogenic substance. Liposomes are utilised as carriers for both water and lipophilic soluble compounds due to their special bilayer structure features.[2]

Liposomes have been studied in several pharmaceutical studies as potential drug delivery methods, and this field of study is still highly active today.[3] Liposomes are spherical, closed structures made of curved lipid bilayers that allow some of the surrounding solvent to be contained within their interior. A liposome can range in size from 20 nm to several micrometers and can be made up of one or more concentric or nonconcentric membranes, each with a thickness of around 4 nm.[4]The biocompatibility and biodegradability of liposomes are two of their appealing biological characteristics. They have the potential to improve the performance of the encapsulant by enhancing drug solubility and stability, delivering encapsulated drugs to specific target areas, and enabling sustained drug release.[2,5]

Advantages of Liposomes[6]

- Liposomes are biocompatible, completely biodegradable, non-toxic and non -immunogenic in nature.
- Allows for site-specific or targeted drug delivery.
- Increased effectiveness and therapeutic index.
- A greater level of stability through encapsulation.

Disadvantages of Liposomes[6]

- Cost of production is expensive.
- Stability issues brought on by phospholipid oxidation and hydrolysis.
- Liposomal components may cause allergic responses.

Classification

Five different types of liposomes can be distinguished based on their composition and mechanism of intracellular delivery: conventional liposomes, cationic liposomes, pH-sensitive liposomes, long-circulating liposomes and immunoliposomes.

However, vesicle size is a crucial factor in regulating the circulation half-life of liposomes, and both size and the number of bilayers affect the degree of drug encapsulation within liposomes. Thus, liposomes were typically classified on the basis of their size and number of bilayers into (i) Small unilamellar vesicles (SUV): 20-100 nm; (ii) Large unilamellar vesicles (LUV): > 100 nm; (iii) Giant unilamellar vesicles (GUV): > 1000 nm; (iv) Oligolamellar vesicle (OLV): 100-500 nm and (v) Multilamellar vesicles (MLV): > 500 nm.[2,7]

Structural Components of Liposomes

1) Phospholipids

Phospholipids are the primary building components of biological membranes. The majority of liposomes are made

of glycerophospholipids, amphiphilic lipids that are derived from glycerol molecules.[8]There are two types of glycerophospholipids: natural and synthetic, which are both responsible for the formation of liposomes. Phosphatidylcholine and phosphatidylethanolamine, which are common phosphatides in both plants and animals, are the most naturalphospholipids utilized to make liposomes.[9,10] Phospholipids have great capacity to form stable bilayers in an aqueous environment is a result of their amphipathic nature. Liposomes can consist of one, two, or more lipid bilayers and can combine two or more phospholipids. Liposomes can develop positive, negative, or neutral charges depending on the head of the phospholipids.

2) **Cholesterol**

Cholesterol is a crucial component of naturally occurring membranes, and its incorporation into phospholipid bilayers considerably changes the properties of these membranes. Although cholesterol doesn't really form bilayers on its own, it can be included in phospholipid membranes in significant levels. It boosts the encapsulation of hydrophobic drugs only if the drug input is smaller than that of the liposome's encapsulation capacity, but it improves the retention of hydrophilic drugs by stiffening a bilayer and reducing permeability.[11,12]

Loading of Drugs by Liposomes

Due to their capacity to load drugs with various features, liposomes are regarded as a good drug delivery method, as was previously indicated. The choice of an appropriate technique for drug encapsulation into liposomes depends on a number of variables, including, drug/lipid ratio, drug leakage and retention, sterility, production and scale-up facility, cost effectiveness, and liposome stability.[2,13,14]Passive and active techniques are the two ways used to encapsulate drugs into liposomes.

Passive loading

In order for the passive entrapment approaches to work, liposomes must be able to catch a specific amount of aqueous solution, including any dissolved solutes, during vesicle formation.[14,15,16]The encapsulation effectiveness following passive encapsulation is inversely correlated with the aqueous volume enclosed by the vesicles, which in turn depends on the phospholipid concentration of the dispersion and the lamellarity of the vesicles. Both encapsulation characteristics will be more influenced by the concentration and choice of phospholipids than by morphological factors, similar to the case with less water-soluble drugs that interact with the bilayer.[17]During this procedure, hydrophobic agents will be found in the bilayer (lipidic phase) of the liposome whereas hydrophilic molecules will be contained inside the aqueous phase of the liposome.

Active loading

The basic idea behind the active trapping method is to combine "empty" liposomes with a concentrated drug solution, then wait for the drug to diffuse evenly through incubation.[18] The fact that vesicle bilayers are sufficiently permeable to allow drugs to diffuse into the liposomes within a fair amount of time gives this procedure considerable benefits. To reach equilibrium between the interior of the vesicles and the surrounding medium, the drug passes through the lipid bilayers into the vesicles while following the gradient of concentration.[13,19]Because the active component is not yet present while the liposomes are being prepared, active loading has certain benefits in that it may reduce the need for handling-related safety precautions.[20]

Liposomes Preparation Method

1) Thin film hydration

The first described production method for liposome technology was the thin film hydration method, also referred to as the Bangham method.[21] In this simple approach, lipids are initially dissolved in an organic solvent, commonly chloroform, ether or methanol, and dried down to produce a thin lipid film using a rotary evaporator at reduced pressure. Aqueous solvent is used to hydrate the obtained thin lipid film, which results in the formation of liposomes.

This technique is simple to use, but it produces a population of MLVs that are heterogeneous in terms of size and shape. Consequently, liposome size reduction procedures, such as sonication forSUVs creation or extrusion through polycarbonate filters generating LUVs were useful to produce smaller and more evenly sized population of vesicles.[22,23]

2) Solvent injection techniques

In the solvent injection methods, the lipid is first dissolved into an organic phase (ethanol or ether), then the lipid solution is injected into aqueous media to form liposomes.[24]The main application of the ethanol injection technique is the finding that a narrow distribution of small liposomes can be produced by directly injecting an ethanolic lipid solution into water without extrusion or sonication.[25]

In ether injection method at 55°C to 65°C or under reduced pressure, a solution of lipids dissolved in a diethyl ether or ether-methanol mixture is progressively added to an aqueous solution of the substance to be encapsulated. Liposomes are produced as a result of the ether being removed under vacuum.An advantage of the ether injection approach compared to the ethanol injection method is the elimination of the solvent from the product, enabling the process to be run for extended durations generating a concentrated liposomal product with high entrapment efficiencies.[2]

3) Reverse phase evaporation

Organic solvent is evaporated under reduced pressure to form a lipidic layer. In a second organic phase, typically made up of diethyl ether and/or isopropyl ether, the lipids are re-dissolved, followed by the addition of an aqueous phase, resulting in the formation of an oil-in-water emulsion.[26] A homogenous emulsion is created by sonicating the material to create inverted micelles. A viscous gel is formed by the final evaporation of the organic solvent under reduced pressure, and this gel later transforms into a liposomal suspension.[27,13]The creation of a complete bilayer surrounding the remaining micelles is facilitated by the abundance of phospholipids in the environment, which leads to the formation of liposomes. Reverse phase evaporation can be used to create liposomes from a variety of lipid formulations, and these liposomes have four times the aqueous volume-to-lipid ratios of multilamellar and hand-shaken liposomes.[28,29]

4) Detergent removal

This technique comprises solubilizing the lipids with a detergent (surfactant) during the manufacture of LUVs. The non-ionic, anionic, and cationic detergents are among those that are employed. The process entails dissolving the lipids in an aqueous solution containing the detergent and the protein(s) that will be encapsulated. The critical micelle concentration (CMC) of the detergent should be high to facilitate removal. After that, dialysis or column chromatography are used to remove the detergent. The encapsulation of proteins with biomedical significance has been discovered to be compatible for this detergent removal technique.[30,31]

Size Reduction Methods

The three primary techniques—sonication, extrusion, and high-pressure homogenization represent the post-formation treatments of size reduction used most frequently in liposome formation techniques.[32]

1) Sonication

The most frequent method for prepping SUV may be sonication. Both a probe sonicator and a bath type sonicator are used to sonicate MLVs in a passive environment. The main disadvantages of this strategy are its low internal volume/encapsulation efficiency, the potential for phospholipid and chemical degradation, the removal of big molecules, metal contamination at the probe tip, and the presence of MLV in addition to SUV.[2,33]

There are two methods of sonication:

a) Probe sonication- A sonicator tip is dipped into the liposome solution when using the probe sonication method, which is typically employed for low volumes. In order to prevent local warming and deterioration of the lipidic solution due to the high energy given by the tip, the bath vessel is submerged in a water/ice bath.[34,35]

b) Bath sonication- The liposomes are arranged in a cylinder using a bath sonicator. Controlling the temperature of the lipid dispersion in this process is often simpler than it is in sonication by dispersed directly using the tip. It is possible to keep the object to be sonicated safe in a sterile container, apart from the probe, or in an inert environment.

2) Extrusion

The extrusion technique involves pushing material through membranes that have pores in them. To perform the extrusion above the phospholipids' phase-transition temperature, a heating block is placed around the extruder.[36] The liposomes undergo many extrusion cycles after being formed, passing through a membrane with predetermined pore sizes, often a polycarbonate filter, to achieve uniform size distribution.[37]

3) High pressure homogenization

In homogenization methods, liposomes can be made to pass through an opening while being subjected to high pressure in order to reduce their size, creating the idea of a high-velocity collision. Microfluidization, high-pressure homogenization, and shear force-induced homogenization procedures are only a few of the methods that fall under this category of size reduction.[38]

Characterization of Liposomes

1) Size

In terms of liposome characterisation, size is the most important characteristic. Liposomes should typically be

between 50 and 200 nm in size for drug delivery. Size-exclusion chromatography (SEC), field-flow fractionation, static or dynamic light scattering, microscopy, and other methods are available for measuring submicrometer liposome size and size distribution. The morphology of liposome preparations can be seen by employing a variety of electron microscopy (EM) techniques, including transmission EM using negative staining, freeze fracture TEM, and cryo EM. These techniques can also reveal particles of different sizes.[2]

2) Entrapment efficiency

The liposome preparations are a mixture of encapsulated and un-encapsulated drug fractions. Separating the encapsulated drug (inside the carrier) from the free drug is the first step in determining the encapsulation efficiency. The stiffness of the bilayer membrane affects the effectiveness of liposome encapsulation. The majority of the reported experimental methods to determine liposomal encapsulation efficiency call for the separation of free (unencapsulated) drug from liposome encapsulated drug using column chromatography, size exclusion chromatography, equilibrium dialysis, ultracentrifugation, and ultrafilteration. This is done before the entrapped material is quantified using analytical methods like UV/VIS spectroscopy and HPLC.[13]

3) Zeta potential

In order to address the electrostatic effects in charged nanocarriers, the zeta potential measurement is a useful tool. It is controlled by the type and distribution of the liposomes' surface charges and is reliant on the headgroup charges of the lipids. The biodistribution, pharmacokinetics, cellular affinity, and drug-internalization processes of the liposomes are all substantially influenced by the zeta potential, which is a significant determinant.[36]All of the particles in suspension will have a strong tendency to oppose one another and exhibit no tendency to aggregate if they all have a strong negative or positive zeta potential. Low zeta potential values, on the other hand, mean that there won't be any force to stop the particles from flocculating.

Laser doppler electrophoresis and Zetasizer measure the zeta potential by applying an electric field across the dispersion of liposomes.[19,39]

4) Surface charge

It is crucial to understand the surface charge on the vesicle surface because the charge on the liposome surface has a significant impact on the *in-vivo* distribution. To determine the surface charge of the vesicle, two techniques can be used: zeta potential testing and free-flow electrophoresis. Zeta potential measurements can be used to estimate the charge density of liposomal surfaces and the affinities of different ions for binding to the lipid vesicles.[13] By calculating the mobility of the liposomal dispersion in an appropriate buffer, the surface charge may be estimated (determined using Helmholtz–Smolochowski equation).[40]

5) Lamellarity

Lamellarity is another feature that can affect future liposomal applications because to its impact on the entrapment efficiency and drug release profile. The most common technique, cryo-TEM, provides useful data on liposome lamellarity, including the thickness of their bilayers and the distance between them. Using ^{31}P-nuclear magnetic resonance (NMR), it is possible to ascertain the lamellarity of a liposome preparation.[13]Other methods for determining the liposomes' lamellarity include SAXS and trapped volume determination.[10]

6) *In-vitro* release

The dialysis tube diffusion technique can be used to conduct in vitro drug release. After screening several membranes, the dialysis bag membrane should be chosen; there should be no drug adsorption and the membrane should be freely permeable to the active ingredient.[2]A specified molecular weight is removed from the liposomal sample before it is hermetically sealed inside the dialysis bag. The tubing membrane system is placed in a buffered saline solution with a pH of 7.4. To simulate an in vivo environment, the entire system is maintained at 37°C and is constantly stirred. According to the sink conditions in the receptor compartment, the kinetic experiments are conducted. The drug is evaluated by HPLC, spectrophotometer, or any other practical method in samples of the dialysate that are obtained at various time intervals. So that the receptor compartment's volume doesn't change, the sample volume is changed out for new dissolution media. To determine the release profile of the drug from the liposome suspension, each kinetic experiment is carried out in triplicate, with the average data being obtained.[41,42]

Liposomes Stability

The stability of the developed formulation is a key factor for developing liposomal drug products. The liposomes' stability during all stages of production, storage, and delivery controls the drug's therapeutic action. A well-designed stability study covers the assessment of the product's physical, chemical, and biological properties as well as the assurance of

the product's integrity during the storage duration. Thus, a stability protocol is necessary to examine the physical and chemical integrity of the drug product while it is being stored.[43] Liposome stability can be divided into physical, chemical and colloidal stability.

Physical stability - relies on the rigidity of the bilayer and the lipid mixture's inherent curvature. More stable membranes would be those with greater rigidity and curvatures close to their natural curvature.[44]

Chemical stability -refers to a liposome's capacity to maintain its level of encapsulation efficiency in the face of changes in solution chemistry, including those caused by variations in pH, the electrolyte composition, the presence of oxidizing agents, and the presence of surface active chemicals.

Colloidal stability - highlighted by the liposomes' capacity to keep their size under different storage conditions.

Liposomes Applications

1) Liposomes as drug carriers

The following benefits of using liposomes as drug carriers include: (1) Increasing the solubility of hydrophobic drugs; (2) Increasing the stability of drugs in vivo; (3) Extending the time it takes for therapeutic agents to release; (4) Reducing the uptake of drugs by normal tissues and, to some extent, reducing the side effects of therapeutic agents; and (5) Increasing drug sensitivity to disease site, fixed-point drug release, and cell phagocytosis through functional alteration of liposomes.[45]

2) Liposome as vaccine adjuvant

An established immune adjuvant that improves both cell-mediated and non-cell-mediated immunity is liposomes. After being injected intramuscularly, liposomal immune adjuvants slowly and passively release encapsulated antigen into the localized lymph node. Liposomes are targeted with the help of phosphotidyl serine in order to accumulate within lymphoid cells. Bacteria, soluble antigen, and deoxyribonucleic acid cytokinesis can all be immunized with liposomes to create a liposomal vaccine.[46,47]

3) Liposomes as sustained release drug delivery

Drugs that need a prolonged plasma concentration at therapeutic levels to obtain the highest level of therapeutic efficacy can be released slowly over time using liposomes. For prolonged release and optimized drug release rate in vivo, drugs like cytosine arabinoside can be encapsulated in liposomes.[48]

4) Liposomes in cosmetics

As liposomes' lipid makeup gives them structural similarities to human skin, they are used in the areas of dermatology and cosmetics. On the basis of several research, the trans-epidermal and trans-follicular pathways are being investigated for the purpose of targeting bioactive compounds that are encased in liposomes.[49]

5) Liposomes in cancer therapy

The body's non--specific distribution of cytotoxic drugs causes the death of both healthy and cancerous cells, leading to a number of toxic side effects. Anti-cancer drugs are delivered by liposomes with greater effectiveness and less toxicity. Doxil is a PEGylated Liposomal Doxorubicin formulation for the treatment of Kaposi's Sarcoma in AIDS patients. Doxil, the first drug that was approved by the FDA.[50]

6) Liposomes in diagnosis

By encapsulating numerous markers, liposomes can also serve as diagnostic tools. These tools aid in imaging different human organs, cells, and tissues using scanning instruments. PEGylated liposomes, Stealth pH-sensitive liposomes, and paramagnetic thermosensitive liposomes are among the liposomes frequently utilized for diagnostics.[51]

II. CONCLUSION

Liposomes have drawn a lot of attention as a drug delivery method for a variety of drugs. As a promising delivery system for both systemic and locally acting medicines utilized in therapeutic applications, liposomes have long attracted significant interest in the pharmaceutical industry. The efficacy of encapsulation and entrapment is determined by the liposome's size, shape, and lamellarity, all of which are significantly influenced by the preparation method. The characteristics of liposomes can be evaluated using a variety of methods. However, some of them take a lot of time and have expensive operation costs. The liposomal formulation's effectiveness depends on its capacity to transport the drug molecule to the target site over an extended period of time while at the same time minimizing its toxic effects. The use of liposomal delivery systems can revolutionize conventional therapy for the treatment of a variety of fatal diseases. In the upcoming years, the development of liposomes as a drug delivery system will continue to be a highest concern with a greater chance of integration into therapy.

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