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REVIEW ARTICLE

Liposomal drug delivery: Recent developments and challenges

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ABSTRACT

The spherical vesicles known as liposomes may contain one or many phospholipid bilayers. The first liposomes were found in the 1960s. One of the many distinctive drug delivery methods is the liposome, which offers a complex way to transfer active molecules to the site of action. Clinical trials are now testing a variety of formulations. Long-lasting second-generation liposomes are created by altering the vesicle's lipid composition, size, and charge. Superficial vesicles have given way to liposome growth. Glycolipids and other substances have been used to make liposomes for the modification of outer surfaces through various types of targeting ligands and detecting agents or moiety. Now, the liposomes developed for the different market and it is flooded with cosmetics and, more crucially, medications. Three of the main applications of liposome technology include steric and environmental stabilization of loaded molecules, remote drug loading through pH and ion gradients approach, and simultaneously lipoplexes which is the complexes forms of cationic liposomes with anionic nucleic acids or proteins for the gene delivery or siRNA technology. The scope of liposome research was expanded, allowing for the production of various goods. The present review focuses on the different aspects of liposomal drug delivery concerning types, preparation, pros, and cons.

KEY WORDS: Drug delivery, Liposome, Nanocarriers, Phospholipids, Targeting, Vesicles

INTRODUCTION

Liposomes mediate drug delivery are innovators among the lipidic nanocarriers. These colloidal nanocarriers are made up of bio-compatible, non-immunogenic natural phospholipids, which can capture fat-soluble, water-soluble, amphiphilic, biphasic insoluble drugs and cytotoxic agents into their aqueous core and lipophilic drugs in lipid bilayer for the treatment of various diseases. Liposomes have increased the consideration of conventional cancer chemotherapeutics because as a drug delivery system, they can increase the amount of drug attumor sites and can decrease the amount of drug like DOX at the sites of normal tissues.

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LIPOSOME

Liposomes are tiny and spherical synthetic vesicles consisting of phospholipids and non-toxic cholesterol. Due to their size, hydrophobicity, and hydrophilicity, liposomes are preferred as attractive drug delivery systems (along with biocompatibility). The lipid composition, surface charge, size, and manufacturing technique affect liposome's behavior.[1] The chosen bilayer components regulate the bilayer's charge as well as its "rigidity" or "fluidity."

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Unsaturated phospholipids present in nature, such as egg or soybean phosphatidylcholine (PC), produce porous and fragile bilayers in contrast to saturated phospholipids, such as dipalmitoylphosphatidylcholine, which contain long acyl chains and produce a robust, essentially impenetrable bilayer structure.[2-4]

The US FDA has approved five pharmaceutical (intravenously administered) medications based on liposomes and structures that mimic liposomes in the past 5 years (DOXIL, Daunosomes, Ablett, Amphotech, and AmbiSome).[5] This serves as an example of how liposome technology may be used for more difficult medical procedures. The development of novel liposome-based medical treatments is exciting given the continued expansion in the sales of these drugs, totaling over a quarter billion dollars in 1999. Before medical products, liposome-based cosmetics (such as Niosome and Capture) were available. Liposomes are presently often used in high-end cosmetics.[6]

Some of the superior pharmacokinetic qualities of nanoparticles and liposomes include drug dispersion, longer circulation duration, targeted controlled release, higher intracellular concentration, and more excellent drug solubility and stability in the body.[7] Drug delivery methods based on nanoparticles ranging from 1 to 100 nm were used to attain these advantages. A vast surface area encourages cellular interactions and various surface property changes.[8-10]

By codelivering several drugs, NP-based treatments have allowed synergistic therapy and prevented drug resistance.[11] As CPX-351, a liposomal formulation, cytarabine, and daunorubicin are mixed in liposomes with a molecular weight ratio of 5:1 and a diameter of 100 nm.[12-14] Daunorubicin and cytarabine are combined in CPX-351.

STRUCTURAL COMPONENTS OF THE LIPOSOME

Transporting compounds with physiological activity use the spherical lipid bilayers known as liposomes, ranging in diameter from 50 to 1000 nm. In treating dermatological and anticancer medications, topical liposomes have several uses, including lowering the adverse effects of drugs when taken by themselves and increasing the duration and effectiveness of therapy. By including amino acid fragments, such as antibodies, proteins, or specific portions that target certain receptor sites, liposomes can be utilized to target particular cells.

Applications for liposomes include improved gene therapy effectiveness and DNA vaccination. Liposomes are particularly helpful in treating diseases that affect the immune system's phagocytes because they tend to gather in phagocytes, which see them as strange intruders. Liposomes are made up of both structural and non-structural components.

LIPOSOMES ARE MADE UP OF THE FOLLOWING STRUCTURAL COMPONENTS

Phospholipids

The two phospholipids that primarily contribute to the structural functions of biological membranes are sphingolipids and phosphodiglycerides. The most common phospholipid molecule is PC. PC particles create planar bilayer sheets because they cannot dissolve in water, which lessens the unfavorable interactions between the mostly liquid phase and the long hydrocarbon fatty series. Most liposomes are made of glycerol, which contains phospholipids and accounts for more than half of the lipid weight in biological membranes.

These are phosphophatidic acid derivatives. Phospholipids can be found in the following forms:

i. Phosphatidyl choline (Lecithin) – PC
ii. Phosphatidyl ethanolamine (cephalin) – PE
iii. Phosphatidyl serine (PS)
iv. Phosphatidyl inositol (PI)
v. Phosphatidyl Glycerol (PG)

Cholesterol

The hydroxyl group of cholesterol faces the aqueous surface, and its aliphatic chain runs perpendicular to the acyl chains in a bilayer structure. The molar ratio of cholesterol to PC in phospholipid membranes can rise to as high as 1:1 or even 2:1, despite cholesterol not forming a bilayer. Despite interactions between hydrophobic and specific head groups being linked to the high solubility of cholesterol in phospholipid liposomes, the organization of cholesterol in the bilayer is still unclear.[15]

CATIONIC LIPOSOME

Gene therapy approaches cannot properly transport genes into target cells due to a significant barrier. Alternative gene delivery techniques have been developed in response to the drawbacks of utilizing viral vectors, notably those related to safety concerns. Among these, cationic lipid-based systems are the most prominent (lipoplexes).

For the delivery of therapeutic genes, cationic liposome-DNA complexes (Lipoplexes) may be a helpful substitute for viral vectors. However, liposomology has several drawbacks, including insufficient loading of drugs for which pH and ion gradients do not apply, a lack of control over drug release rate, therapeutically effective active targeting, and an inability to get past biological barriers

(like the blood-brain barrier), and the requirement for more inexpensive suitable raw materials for a variety of non-medical applications (lipids).

One drawback is their inability to effectively deliver and express genes, their toxicity at high concentrations, the potential for harmful interactions with negatively charged macromolecules on serum and cell surfaces, and their limited ability to reach tissues outside the vasculature without the use of intravenous drug delivery.

In cationic lipids, a linker group connects a positively charged head group to a hydrophobic lipid anchor, each part serving a specific purpose. Cationic liposomes often contain neutrally charged and cationic lipids (colipid). When positively charged cationic lipids attach to negatively charged DNA, condensed DNA complexes are created.[16]

LIPOSOMAL DRUG DELIVERY SYSTEM FACING BIOLOGICAL STUDIES

Liposomes are dealt with by various defense systems designed to find, neutralize, and get rid of invasive molecules, much like other foreign things. These defenses include reticuloendothelial system (RES), opsonization, and immunogenicity.[17] Liposomes must overcome these difficulties to function efficiently, even though other factors, like the enhanced permeability and retention effect, may help with drug delivery.[18]

TYPES OF LIPOSOMAL DRUG DELIVERY SYSTEM

There are four different types of liposomal delivery systems, and they are-

Conventional liposomes

The initial generation was conventional liposomes [Figure 1]. They are made up of cationic, anionic, or neutral phospholipids and cholesterol and are surrounded by a lipid bilayer [Figure 1]. Liposomal administration improved the therapeutic index of encapsulated medications such as doxorubicin and amphotericin in the 1980s when research on their clinical potential began.[19-22] Traditional liposomal formulations reduced chemical toxicity *in vivo* compared to free medication by changing pharmacokinetics and biodistribution to optimize medicine delivery to diseased tissue. On the other hand, the delivery system was prone to rapid clearance from the blood, which limited its therapeutic efficiency.[23] The fast clearance was linked to plasma component opsonization and absorption by the RES fixed macrophages, especially in the liver and spleen.[22]

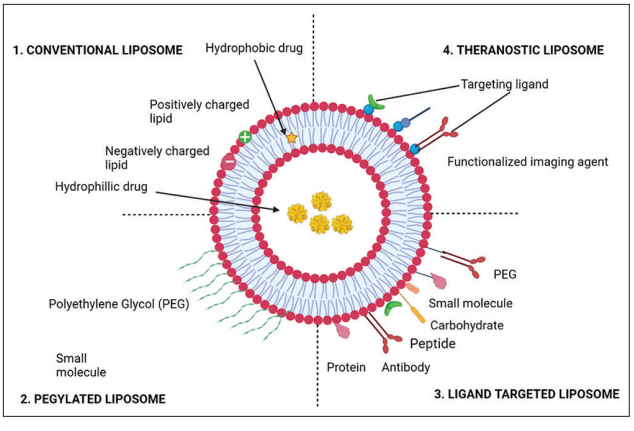

Figure 1: Graphic depicts many types of liposomal drug delivery systems.

Sterically-stabilized liposomes

Sterically stabilized liposomes have been developed to improve liposome stability and blood circulation. The hydrophilic polymer polyethylene glycol (PEG) was the best candidate for sterically stabilizing liposomes. By restricting *in vivo* opsonization with serum components and RES identification and uptake, establishing a steric barrier improves the efficacy of encapsulated medicines. Liposome not only enhances blood circulation and helps pharmaceuticals concentrate where they are needed, but it also delays the clearance of medications.[24-26] Liposome pharmacokinetics are affected by steric stabilization,[27] with reported half-lives ranging from 2 to 24 h in rodents (mice and rats) and up to 45 h in humans, depending on particle size and coating polymer characteristics.[28,29] Liposomes are encased in PEG, improving their circulation but reducing their ability to interact with their intended targets.[17,30]

Ligand–targeted liposomes

Because they selectively produce or over-express specific ligands (such as receptors or cell adhesion molecules) at the disease site, ligand-targeted liposomes offer a lot of potential for delivering drugs to specific cell types or organs *in vivo*.[17,31] Ligands include antibodies, peptides/proteins, and carbohydrates [Figure 1]. Antibodies, particularly monoclonal antibodies, are one of the most adaptable ligands to create immunoliposomes on liposome surfaces.[32,33] Because monoclonal antibodies have two binding sites on the molecule, they have a higher level of stability and binding avidity. Because lipid assemblies are usually dynamic structures, surface-coupled ligands have a lot of motional flexibility to position themselves for optimal substrate interactions.[17]

A combination of the above (all 3)

Liposomes are a versatile and adaptive technology that can boost the systemic effects of various treatments. Immunoliposomes' *in vivo* performance has been a significant hurdle to realizing their potential as effective site-specific drug carriers because of their poor pharmacokinetics and immunogenicity.[33] As a result, the future generations of liposomes will integrate the earlier design to improve liposomal targeting and drug

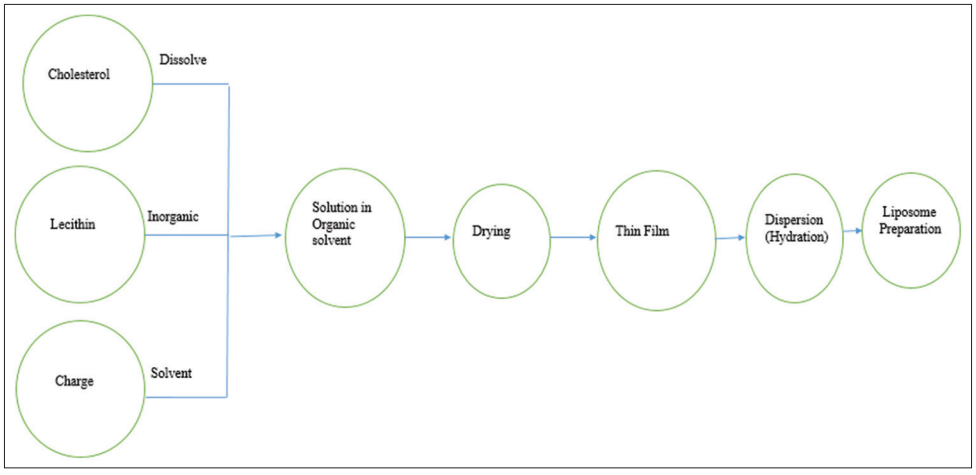

Figure 2: Method of preparation of liposomes and drug loading.

delivery even further. Immunoliposomes pharmacokinetics have been greatly enhanced by combining target-specific binding with steric stabilization of PEG (resulting in extended circulating immunoliposomes).[34]

METHOD OF PREPARATION OF LIPOSOME AND DRUG LOADING

The bulk of liposomes is created either by adding a pharmaceutical or medicinal solution at some stage during the liposome synthesis process or by encasing water-soluble (hydrophilic) components in an aqueous solution of these compounds as hydrating fluid [Table 1]. The organic solution dissolves the lipid-soluble (lipophilic) elements of the constituent lipid, which then evaporate to create a dry drug-containing lipid film that is later hydrated. These techniques include adding the entrapped agents before or during the production process (Passive loading). After the production of complete vesicles, some substances with ionizable groups and those with both lipid and water solubility can be integrated into liposomes (remote loading) [Figure 2] and various marketed liposomal preparation presented in Table 2.

Table 1 : Benefits of drug loading in liposome

Benefits	Examples
1. Enhanced Solvability of Lipophilic and amphiphilic Drugs	Minoxidil and anthracycline, respectively: hydrophilic drugs, such as anticancer agent acyclovir and doxorubicin
2. Passive targeting of the mononuclear phagocytic system cells of the immune system	Amphotericin B, Vaccines, immunomodulators
3. For the administration locally, Liposomes sustained-release system was used.	Cortisones, Doxorubicin, cytosine arabinoside
4. Area avoidance mechanism	Doxorubicin and amphotericin B
5. Area-specific targeting	Anti-infection, Anti-inflammatory and anticancer
6. Enhanced transfer of charged molecules and hydrophilic	Genes, Antibiotics, Plasmids, and chelators
7. Enhanced the penetration into the tissues	Anaesthetics, Corticosteroids, and insulin

Table 2: Market liposomal formulation

Chemical	Trade Name	Manufacturer
Doxorubicin	Doxil	Sequus Pharmaceuticals
Amphotericin B	Abelect	The liposome company
Daunorubicin	DaunoXcene	Nexstar Pharmaceuticals
Amphotericin B	ambiosome	Nexstar Pharmaceuticals
Amphotericin B	Amphotec	Sequus Pharmaceuticals

ADVANTAGES

Some of the advantages of liposomes are as follows:

- The therapeutic index of actinomycin- D is enhanced by liposomes
- Through encapsulation, stability improved through liposomes
- Liposomes are flexible, fully biodegradable, non-toxic, biocompatible, and for systemic and non-systemic administration for their non- immunogenic
- Liposomes decreased the cytotoxicity of encapsulated agents, that is, Taxol and amphotericin B
- Liposomes decreased the revelation of sensitive tissues to toxic drugs
- Site escaping effect
- Liposomes are flexible enough to couple with site-specific ligands to achieve active targeting.

DISADVANTAGES

Some of the disadvantages of liposomes are as follows:

- Less solvability
- Quick half-life

- Oxidation and hydrolysis-like reactions experienced by phospholipid
- Synthesis and association of encapsulated molecules
- Manufacturing cost is high
- Fewer stables.

CONCLUSION

Liposomes have a lengthy history in the pharmaceutical industry. The intracellular transport of antisense compounds, ribosomes, proteins/peptides, and DNA has a lot of promise with liposomes. Due to their propensity to circulate for prolonged periods, liposomes with enhanced pharmaceutical distribution to disease regions are employed more often in clinical settings. Liposomes can also help disease-causing cells locate the source of the problem. Finally, compared to free vitamins, liposomal drugs are both safer and more potent. However, liposomes have firmly cemented their place in modern distribution strategies focusing on readily available goods and medicinal applications.

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