

Liposomal Drug Delivery System - A Concise Review

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Abstract

Liposomes are microscopic self-assembling unilamellar or multilamellar vesicles made up of phospholipid bilayer. Both the hydrophilic and hydrophobic drugs can be attached to the lipid bilayer of liposomes and can show their efficacy in the target cell of the human body. After discovering the liposome by Bangham, et al. and his colleagues, this drug delivery system gained much popularity in every aspect of the pharmaceutical dosage form. Recently, the liposomal drug delivery system has been commercially manufactured and applied in a variety of ailments, including black fungal infection of post-COVID 19, cancer, analgesics, vaccines, and photodynamic therapy, etc. This review tersely described the liposomal formation, classification, characterization, and the overview of marketed drugs.

Keywords: Liposome; Phospholipids; Black Fungus; COVID 19

Introduction

Recently, more than 40% of marketed drugs and drug discovery pipelines 70 to 90% are suffering poor aqueous solubility and permeability problems [1,2]. The computerized combinatorial chemistry has led to discovering new drug entities by potential therapeutic action on the target cell. These poor solubilities and permeability can lead to low bioavailability [3,4]. The anticancer or chemotherapeutic agents are highly cytotoxic to the malignant cell, equally damaging the normal cells. For this reason, drug substances need a specific formulation that can specifically bind with the target disease site without damaging the normal cell. At present, formulation scientists have attempted several techniques, including nanoparticles, microparticles, and liposomes, for the targeted drug delivery to the specific disease site.

The liposome is a spherical-shaped vesicle that consists of one or more phospholipid bilayers. Notably, the liposome is a carrier for drugs or targeted molecules. Interestingly, liposome formulation can be encapsulated by both hydrophilic and lipophilic drugs,

i.e., biological classification system (BCS) class i, ii, iii, and iv drugs, and applied to the disease site of the body. This system is made of colloidal size with a range of 0.01 to 5.0 μm in diameter [5].

In this review, we provide a concise picture of the liposome-based products on the market. In addition, we mentioned liposomal formation, classification, and characterization.

Formation of liposome

A liposome is a potential carrier of the hydrophilic and lipophilic drug substance. Figure 1 represents the liposome of spherical-shaped phospholipid bilayers. The hydrophobic drug substance is loaded on the hydrophobic part, and the hydrophilic drug substance is loaded on the hydrophilic portion of the liposome (Figure 1).

Commercial liposomal drug delivery

Currently, several pharmaceutical agents, including vaccine, antiviral, anticancer drugs, proteins, and macromolecules, are en-



Figure 1: Liposomal drug delivery.

capsulated commercially in liposomal form [6] (Table 1). Recently liposomal injection amphotericin B was successfully applied in post-COVID 19 infected black fungus [7-9]. Liposomal amphotericin B injection is very effective against black fungal disease. The black fungus infects the lungs, stomach, intestine, skin, sinuses, and brain; however, this disease is rare, and thousands of infected cases were reported during the second wave of COVID 19 in India and a few reported cases in Bangladesh [8,10].

| | | | | |
|------------------|-------------|------|------------------------------|--|
| Verteporfin | Visudyne® | 2000 | Valeant Canada LP | Age-related macular degeneration, pathologic myopia, and ocular Histoplasmosis |
| Cytarabine | DepoCyt® | 1999 | Pacira (formerly SkyePharma) | Neoplastic meningitis and lymphomatous meningitis |
| Cisplatin | Lipoplatin® | 2007 | Regulon, Inc | Epithelial malignancies |
| Morphine sulfate | DepoDur® | 2004 | SkyePharma, Endo | Postoperative pain following major surgery |

Table 1: List of marketed drugs.

Besides post-COVID 19 treatment, liposomal drug delivery is also applied in cancer therapy, different types of fungal disease, analgesics, viral vaccines, and photodynamic therapy [6]. The liposomal dosage form is also involved in pulmonary arterial hypertension and lung disease. Furthermore, several researchers are working on the liposomal drug delivery systems to develop dry powder inhaler (DPI), organ-on-chip or nanochip, and invasive treatment.

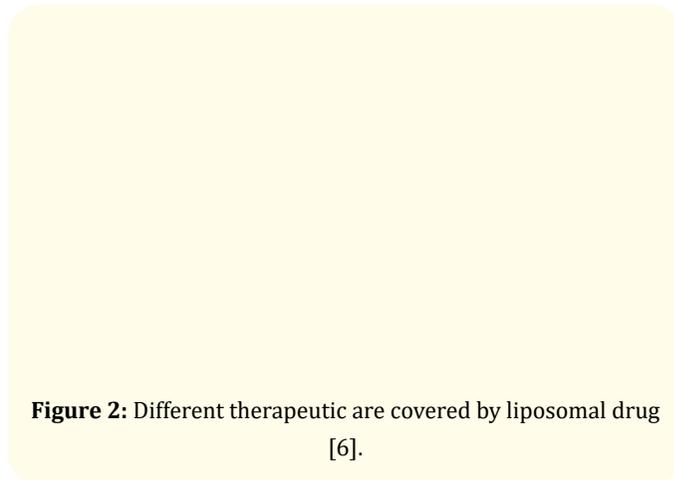


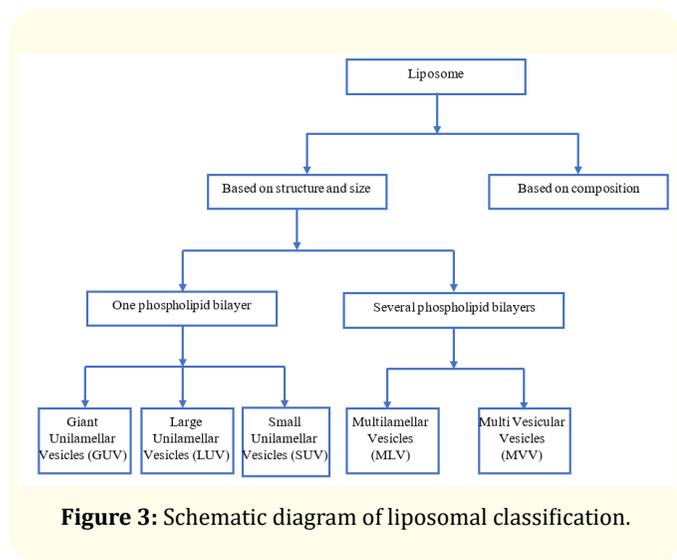
Figure 2: Different therapeutic are covered by liposomal drug [6].

| Drug Name | Trade Name | Year | Manufacturer | Indications |
|----------------|-------------|------|-----------------------------|--|
| Amphotericin B | Abelcet® | 1995 | Enzon | Fungal infection |
| | Amphotec® | 1996 | Ben Venue Laboratories, Inc | |
| | Ambisome™ | 1997 | Gilead Sciences | |
| Daunorubicin | DaounoXome™ | - | Gilead Sciences | Kaposi's sarcoma |
| Doxorubicin | Doxil™ | 1995 | Ortho Biotech | Refractory Kaposi's sarcoma, recurrent breast cancer, and ovarian cancer |
| | Caelyx™ | 1995 | Schering-Plough | |
| | Myocet® | 2000 | Zeneus | |
| | Lipo-Dox® | - | TTY BIOPHARM | |

Classification of liposome

Liposome classification is based on the size, the number of phospholipid bilayers, composition, and drug delivery mechanism

[11,12]. However, based on the size and number of the phospholipid bilayers, the liposomes are divided into two classes named one phospholipid and several phospholipids. Both categories can further be subdivided into several groups. Moreover, liposomes are divided into several groups depending on the composition, including conventional liposomes, fusogenic liposomes, pH-sensitive liposomes, cationic liposomes, long-circulating liposomes, and immune liposomes [12].



Preparation of liposomes

In 1961, the lipid-based vesicles were reported by Bangham., *et al.* and his coworker [13]. After that, plenty of liposome preparation has been utilized, including lipid hydration, ethanol injection, freeze-drying, reverse phase evaporation, etc. In the conventional methods, the lipid is initially dissolved in an organic solvent and then dried by a rotary solvent evaporation technique. The lipids are dispersed in an aqueous solution, and then the resulting liposomes are purified (Table 2). Liposome forms spontaneously when lipids are dispersed in an aqueous medium. The thin-film hydration methods are simple and widely used in lab-scale and semi-production scale operations. The liposome fabrication involves the three most important steps: vesicle formation, size reduction, and purification (Table 2).

Liposome characterization

Liposome behavior in both physical and biological systems is influenced by various parameters such as size, shape, lamellarity,

| Steps | Process | Types of Liposomes |
|------------------------|---|--|
| Vesicle Formation | Lipid hydration followed by vortex or manual stirring | Multilamellar vesicles (MLV) |
| | Reverse-phase evaporation | MLV, Large unilamellar vesicles (LUV) |
| | Organic solvent injection | MLV, LUV, Small unilamellar vesicles (SUV) |
| | Freeze-thawing | MLV, LUV |
| | pH gradient | LUV, SUV |
| | Dehydration-rehydration | MLV |
| | Detergent dialysis | MLV, LUV |
| Vesicle size-reduction | Extrusion through polycarbonate membranes | LUV, SUV |
| | High-pressure homogenization | LUV, SUV |
| | Microfluidization | Mainly SUV |
| | Sonication | Mainly SUV |
| Purification | Centrifugation | - |
| | Dialysis | - |
| | Column chromatography separation | - |
| | Ultrafiltration | - |

Table 2: Methods of liposome preparation [14-16].

entrapment volume, etc. Thus, liposome in-vivo behavior depends on these factors too (Table 3) [17].

| Characterization Parameters | Instrumentations |
|---|-------------------------------------|
| Chemical Characterization | |
| Drug Concentration by Assay | HPLC, UV |
| Phospholipid Concentration by Barlett/Stewart assay | HPLC |
| Cholesterol concentration | HPLC |
| Lipid Peroxidation | UV absorbance, TBA, iodometric, GLC |
| Lipid hydrolysis, Cholesterol auto-oxidation, ant-oxidant degradation | HPLC, TLC, |

| | |
|-------------------------------------|--|
| pH | pH meter |
| Osmolarity | osmometer |
| Physical Characterization | |
| Vesicle size and surface morphology | Transmission electron microscopy (TEM), Freeze-fracture electron microscopy |
| Size distribution | Dynamic light scattering (DLS), Zetasizer, TEM, Polymerase chain reaction (PCR), Gel permeation, Exclusion |
| Surface charge | Free-flow electrophoresis |
| Electric surface potential and pH | Zeta potential measurement, pH probes |
| Lamellarity | SAXS, ³¹ NMR, Freeze fracture EM |
| Phase behavior | Freeze fracture electronic microscope, Differential scanning calorimetry (DSC) |
| % Entrapment Efficiency | Minicolumn centrifugation, Gel exclusion, Ion exchange, Protamine aggregation, Radiolabeling |
| Drug release | Diffusion |
| Biological Characterization | |
| Sterility | Aerobic or anaerobic cultures |
| Pyrogenicity | Limulus amoebocyte lysate (LAL) test |
| Animal toxicity | Monitoring survival rates, Histopathology |

Table 3: Liposome Characterization [17].

Conclusion

Liposomal drug delivery is gaining popularity due to its contribution to the pharmaceutical drug delivery and cosmetics arena. In the pharmaceutical drug delivery sector, liposomes successfully footprinted in the commercial market in 1995 by introducing Doxil®. After that, the liposomal drug delivery system never looked back, and numerous researches are ongoing in both the academic and pharmaceutical industries. From this review, readers can get concise information on marketed liposomal drugs, preparation, and characterization.

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