INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 5, May 2026 | ISSN: 2456-4184 | IJNRD.ORG

A COMPREHENSIVE REVIEW ON LIPOSOMAL DRUG DELIVERY SYSTEM

Komal Rahevar [1], Dixit Patanvadiya *, Mukesh Patel[1], DB Meshram[1]
[1]M. pharm Ph.D, M.pharm, PH.D. Professor,[1]M. pharm, PH.D. principle,
Pioneer Pharmacy College, Ajwa-Nimeta Road, Vadodara, Gujarat, India -390019

ABSTRACT

Liposomes are spherical vesicular drug delivery systems that consist of phospholipid bilayer(s) enclosing an aqueous core. They exhibit a unique amphiphilic nature that allows for the ability to contain both hydrophilic and lipophilic drugs, which increases the solubility, stability, bioavailability, and therapeutic effect of both free and encapsulated drugs, while also reducing systemic toxicity. Liposomes can be classified according to their structure, method of preparation, composition and therapeutic applications. Liposomes are prepared by various methods like thin-film hydration, reverse-phase evaporation, solvent injection, detergent removal, heating method or supercritical fluid methods. Mechanism of drug release from liposomes includes thermosensitive release, pH-sensitive release, enzyme-mediated degradation, diffusion, endocytosis, and adsorption, and fusion. Liposomal formulations must be evaluated based on characterization parameters. Liposomes have been found to have lots of applications in cancer chemotherapy, ophthalmic drug delivery, vaccine delivery, gene therapy, and targeted therapeutics. Future prospects are in the direction of personalized medicine, smart programmable liposomes, target delivery to the brain, gene editing applications and large-scale industrial production. In conclusion, liposomes remain a vital tool in contemporary pharmaceutical research, and serve as a promising platform for the development of innovative drug delivery systems.

Keywords

Liposomes, Liposomal Drug Delivery System, Nanocarriers, Targeted Drug Delivery, Controlled Drug Release.

➢ INTRODUCTION

The aqueous solubility and permeability issues in more than 40% of marketed drugs and drug discovery pipelines is a recent concern.[1] With the help of the computerized combinatorial chemistry, new drug entities have been discovered by the potential therapeutic action on the target cell. Such low solubilities and permeability can result in low bioavailability.[2]

The anti-cancer or chemotherapeutic agents are very toxic to the cancer cell and are equally toxic to the normal cells. Therefore, a specific formulation of a drug substance is required which is capable of specifically recognizing the site of the disease being treated without harming the normal cell. So far, formulation scientists have tried various methods, such as nanoparticles, microparticles and liposomes, to deliver a drug directly to the targeted disease site.[3]

Bingham discovered liposomes for the first time in the 1960's and are one of the most widespread drug delivery systems.[4]

The liposome is a spherical-shaped vesicle that consists of one or more phospholipid bilayers. In particular, the liposome is a drug or target molecule carrier. 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 give a short overview of the liposome products available. Also, we talked about the formation, classification and characterization of liposomes.

➢ CLASSIFICATION OF LIPOSOMES [6-8]

The Liposomes classification is based on-

- ✓ Structure
- ✓ Preparation Process
- ✓ Composition and its Application
- ✓ Conventional liposome
- ✓ Liposome specialty

✓ Based on Structure

Vesicle type	Abbreviation	Diameter Size	No. of Lipid Layers
Unilamellar vesicle	UV	All size ranges	One
Small Unilamellar vesicle	SUV	20-100 nm	One
Medium Unilamellar vesicle	MUV	More than 100 nm	One
Large Unilamellar vesicle	LUV	More than 100 nm	One
Giant Unilamellar vesicle	GUV	More than 1.0 µm	One
Oligolamellar vesicle	OLV	0.1-1.0 µm	Approx. 0.5
Multilamellar vesicle	MLV	More than 0.5 µm	5-25
Multi vesicular vesicle	MV	More than 1.0 µm	Multi compartmental structure

✓ Based on Method of Preparation

Preparation Method	Vesicle Type
Single or reverse phase evaporation Lamellar vesicle	REV
Multi lamellar vesicles formed by the method of reverse phase evaporation	MLV-REV
Stable pluri lamellar vesicle	SPLV
Frozen and thawed multi lamellar vesicle	FATMLV
Vesicle prepared by extrusion technique	VET
Dehydration-Rehydration method	DRV

✓ Based on Composition and Application

Type of Liposome	Abbreviation	Composition
Conventional	CL	Neutral or negatively charge phospholipids and cholesterol
Fusogenic	RSVE	Reconstituted sendai virus envelops
pH sensitive	-	Phospholipids like DOPE or PER with either OA or ChEM
Cationic	-	Cationic lipid with DOPE
Long circulatory	LCL	Neutral high temp, Cholesterol and 5-10% PEG,
Immuno	IL	CL/LCL with monoclonal antibody

✓ Based upon Conventional Liposome
- o Normalize Mixtures of Natural Lecithin (PC)
- o Glycolipid-loaded liposome
- o Synthetic Phospholipids with the same natural Phospholipids chain

✓ Based upon Specialty Liposome
- o Carbohydrate coated
- o Bipolar fatty acid
- o Lipoprotein coated

- Methyl/ Methylene x- linked
- Multiple encapsulated
- Antibody directed

There are several pathways in and outside the body by which liposomes can operate, which are as follows: - [9]

- Liposome binds to the plasma membrane and seems to fuse with them, allowing the substance to be released into the cell.

- The liposomes are taken up in the case of phagocyte cells, organelles called lysosomes function on the phospholipid walls and the active pharmaceutical ingredients are released.

➢ THE METHOD OF PREPRATION OF LIPOSOME

There are several different ways to make liposomes. The process of liposome manufacture and the phospholipids type critically affects the final liposomes characteristics. [10]

Liposome's fabrication procedures can be classified into:

✓ The method of thin film hydration (Bangham method)

In this technique all lipids and the hydrophobic drug are dissolved in appropriate organic solvent in a round bottom flask. After that, the organic solvent was slowly evaporated under reduced pressure to form a thin film layer. The hydration solution may contain a hydrophilic drug to be loaded into the liposomes aqueous core. The slower the rate of hydration, encapsulation efficiency is higher as long as the rate of hydration determines the efficiency of drug encapsulation. Liposomes can be resized using the extrusion process through a specific polycarbonate membranes pore size, or bath or probe sonicator process. Lamellarity types and particles distributions can be controlled using both. Stable liposomes with high EE are achieved by the extrusion method compared with sonication. The sonication typically yields SUVs liposomes and can destroy or hydrolyze encapsulated drugs and/or lipids. Liposomes suspensions can be subject to potential metal contamination when the probe sonication is used.[11]

✓ Reverse-phase evaporation method

A water-in-oil emulsion that is prepared by the reverse phase evaporation method is the alternative to the thin-film hydration. First, the lipids are dissolved in an organic solvent which is then directly mixed with an aqueous buffer containing the hydrophilic drug. The organic solvent then evaporated under a reduced pressure rotary evaporator leading to form lipid vesicles dispersed in the aqueous solution. The average size and polydispersity of the preformed vesicles can be reduced by extrusion. [10]

This approach can be used for therapeutic peptides with a high molecular mass of molecules, but organic solvents can denature therapeutic peptides and sonication conditions can also.[12]

✓ Solvent injection methods

The various injection methods were grouped by the type of organic solvent used. An organic solvent which dissolved the lipids and the hydrophobic active agents was injected quickly into an aqueous phase. Direct solvent evaporation during mixing process can be done using diethyl ether; injection into a 10-20-fold aqueous solution is required for ethanol; use a rotary evaporator, dialysis or filtration to evaporate ethanol under vacuum. This method mostly prepared liposomal formulations with higher polydispersity indexes (PDI). In addition, continuous exposure to high temperature and organic solvent might reduce drug and lipids stability.[13]

✓ Detergent removal method

The lipid and a high critical micelle concentration (CMC) surfactant were dissolved in an appropriate organic solvent in a round bottom flask in this method. A thin film was obtained at the bottom of the flask after solvent gentle evaporation. The lipid film was then hydrated in an aqueous solution containing the drug molecules to get a mixed micelles solution. The surfactant is then removed by dialysis, size-exclusion chromatography,

adsorption onto hydrophobic beads or dilution. Finally, the liposomes vesicle (LUVs) will be prepared after solution concentration. One of the major disadvantages of this approach is that during the detergent removal step, most hydrophilic drugs are removed from the liposomes.[14]

✓ Heating method

Mozafari developed a heating technique for the production of liposomes, which included the hydration of a phospholipid in an aqueous solution containing 3 vol% glycerol followed by an increase in temperature to 60 or 120°C. Glycerol is utilized since it is a water soluble and physiologically acceptable chemical with the ability to act as an isotonising agent and increase the stability of lipid vesicles due to preventing coagulation and sedimentation. No degradation of lipid was reported for liposomes fabricated by the heating method and no need for sterilization as high temperature was used in this technique. For heat sensitive materials like DNA, a drug was added to the solution at various stages: at the beginning; when the temperature reached above the transition temperature of the lipids; at ambient temperature after the preparation of the liposomes.[15]

✓ pH jumping method

The pH jumping method is another process to make liposomes without using solvents. In this method, the aqueous solution of phosphatidic acid and phosphatidylcholine are exposed to almost four-fold increase in pH over short time to break down MLVs into SUVs. The percentage of SUVs vs LUVs produced is determined by the ratio of phosphatidic acid: phosphatidyl choline.[16]

✓ Supercritical fluidic method

Beyond certain temperatures and pressures that are called the critical values, non-condensable fluids are very dense fluids which are called supercritical fluids. As the line between the liquid and gas phase disappears, supercritical fluids have many particular characteristics compared with conventional fluids. Of these properties, solvents with special properties have been of special interest to researchers. Interestingly, supercritical carbon dioxide (scCO2) is a very good organic solvent alternative. Although it is low cost, it is noxious, but not flammable. In addition, it has a relatively low critical temperature and pressure (31 C and 73.8 bar) with the dissolution properties analogous to those of nonpolar solvents.[17]

➢ STRUCTURE AND MECHANISM OF DRUG DELIVERY FROM LIPOSOMES

Liposomes are tiny spherical vessels, containing one or more phospholipid bilayers surrounding an aqueous compartment. They are generated by dispersion of amphiphilic phospholipids in an aqueous medium; the amphiphilic phospholipids themselves will spontaneously assemble into bilayer vesicles through hydrophobic and hydrophilic interactions. Like biological cell membranes, liposomes are very biocompatible, and well suited for drug delivery applications.[18]

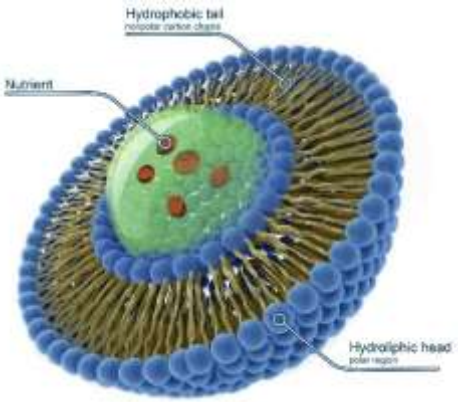

Figure 1. Structure of liposomes

The basic structure of liposomes is composed of polar hydrophilic heads that face the aqueous environment, and hydrocarbon tails that are oriented towards each other inside the liposome to create a bilayer membrane. This configuration maximizes the stability of the vesicular structure by minimizing the free energy of the system. Hydrophilic drugs are present in the aqueous internal compartment, while the hydrophobic drugs are contained in the phospholipid bilayer membrane. The physicochemical properties of amphiphilic drugs can cause them to partition between the two compartments.[19]

✓ MECHANISM OF DRUG DELIVERY FROM LIPOSOMES

The release of drugs from liposomes is a complicated process that depends on the liposome composition, membrane fluidity, liposome size, surface charge, route of administration, physiological environment, and on interactions of liposomes with biological membranes. Controlled and targeted release of the encapsulated drug at the site of action is a major factor to consider in terms of the therapeutic effectiveness of Liposomal formulations.[20]

Drug release from liposomes is usually accomplished by several mechanisms such as adsorption, fusion, lipid exchange, endocytosis, diffusion and degradation of vesicles. Such mechanisms may be present alone or together depending on the type of liposome and biological environment.[21]

✓ Fusion with the cellular membrane.

The cellular membrane fusion is one of the most significant mechanisms of liposomal drug release. In such a case, the liposome phospholipid bilayer fuses directly with the plasma membrane of the target cell, the contents of the liposome moving into the cytoplasm. Fusion takes place due to the similarity of the membrane properties of liposomes to that of the membrane of the living cells.[22]

Fusion-mediated delivery is especially beneficial for the delivery of macromolecules into the cell, like proteins, peptides and nucleic acids. Lipid composition, surface charge, membrane fluidity and the presence of fusogenic lipids (e.g., dioleoyl phosphatidylethanolamine, DOPE) all influence the efficiency of membrane fusion.[23]

✓ Endocytosis and Phagocytosis

After ingestion by cells, either by endocytosis or phagocytosis, liposomes are also able to deliver drugs. In this process, liposome enters the cells into the endosomes or phagosomes. Then lysosomal enzymes break down the phospholipid bilayer resulting in the release of drugs into the cell.[24] Reticuloendothelial system (RES) phagocytic cells, especially in the liver and spleen, actively take up conventional liposomes. Useful for targeting intracellular infections and macrophage-associated diseases like tuberculosis and leishmaniasis.[25]

✓ Adsorption on Cell Surface

Liposomes can bind to cells by electrostatic or hydrophobic interactions in some instances. The drug diffuses slowly from the liposomal membrane into the target tissues after adsorption, but does not completely enter the vesicles.[26] Liposomes with positive charge have higher adsorption and drug transfer efficiency with the negatively charged membranes of the cells.[27]

✓ Lipid Exchange Mechanism

Lipid exchange between liposomal membranes and biological membranes and plasma lipoproteins is also a route of drug release. In circulation the phospholipids of liposomes can exchange with plasma components leading to destabilization of the liposome and drug release.[28] This phenomenon is particularly significant in the long-circulating liposomes where the progressive transfer of lipids ensures a long-lasting drug release.[29]

✓ Diffusion-Controlled Release

Drugs with a hydrophilic core embedded in an aqueous shell can slowly release into the external environment via the phospholipid bilayer. The rate of diffusion is affected by the permeability of the membrane, the presence of cholesterol within the membrane, the lipid packing, and temperature.[30] The more rigid the membrane with saturated phospholipids and cholesterol, the slower the diffusion of drugs and the longer they remain in the membrane. On the other hand, unsaturated phospholipids make the membranes more fluid and promote drug leakage.[31]

✓ Enzyme-Mediated Degradation

Enzymes such as phospholipases, which are found in biological fluids, can break down phospholipids found in liposomal membranes. The enzymatic degradation destabilizes the membrane and induces the release of the drugs that are entrapped.[32]

Enzyme-sensitive liposomes have been specifically formulated to release the drugs selectively at pathological sites where the concentration of enzymes is increased, like in a tumor or in an inflamed tissue.[33]

✓ pH-Triggered Drug Release

pH-sensitive liposomes should develop a release of drugs in acid conditions, such as those present in tumor tissues, inflammatory sites, or endosomes in the cell interior. The destabilization of the lipid bilayer is seen under acidic conditions with rapid drug release.[34]

✓ Thermosensitive Drug Release

Thermosensitive liposomes are able to deliver drugs when temperature is increased. Such liposomes are made with lipids having phase transition temperatures just higher than the physiological temperature. When heated, the permeability of the membrane will be dramatically increased, which will lead to a rapid release of the drug.[35]

✓ Electroporation

In an advanced liposomal system, drug release can be triggered by external stimuli like ultrasound, magnetic fields or light irradiation. These stimuli disrupt or alter the permeability of the cell's membrane which causes controlled release.[36]

➢ CHARACTERIZATION OF LIPOSOMES

✓ Determination of size distribution and lamellarity.

The standard liposome size is different for different processing techniques and different phospholipid content. The size and size distribution is evaluated by several different techniques such as Scanning Electron Microscopy (SEM), negative-stain TEM, optical microscopy and freeze-fracture TEM.[37] On the other hand, molecular weight of the compound is estimated by hydrodynamic methods, such as by ultracentrifugation, field-flow fractionation, gel-exclusion chromatography and analytical centrifugation.[38] These methods also allow for the comparison of liposomes in terms of size distribution, elution characteristics and uniformity. These methods can be used to assess the mean diameter of liposomes that are less than 1 µm. The lamellarity of liposomes (the number of lipid bilayers) can be obtained using the methodologies of cryo-electron microscopy, 31P Nuclear Magnetic Resonance (NMR) and Small-Angle X Ray Scattering (SAXS), while liposome lamellarity can be used to provide details of the size, uniformity and lamellarity of liposomes. Lamellarity can be described as the total number of lipid bilayers visible adjacent to a lipid vesicle.[39]

✓ Zeta Potential

The surface charge characteristics of microspheres are measured and characterized using zeta potential. When the zeta potential is high, it means the dispersion stability is high and the liposomal solution does not aggregate. Those spheres with a zeta potential < (+/-) 30 mV are considered to have suspension instability. The zeta potential of the liposomes can be measured using a zeta sizer which is placed at the opposite end of the cell with the particle dispersion between the electrodes. Oppositely charged particles are attracted to the electrode of the opposite charge. The particles produce dispersed light, which is dependent on the speed of the particles as they pass through an electric field with a known intensity in the interference pattern of two laser beams.[40]

✓ Entrapment Efficiency

The proportion of the liquid phase and the amount of water-soluble medication captured during liposome production is known as encapsulation efficiency. The formula for it should be % entrapment/mg of lipid. Increasing the effective ness of encapsulation will increase the medication's absorption rate. A number of methods exist for the measurement of entrapment rate such as solid-phase extraction, size exclusion chromatography, mini-column centrifugation, hold low-fiber centrifugal ultrafiltration, centrifugal ultrafiltration, and protamine clumping.

$$E\ (\%) = [(Total\ drug - Unencapsulated\ drug) / Total\ drug] * 100$$ [41]

Liposomes with low to moderate Encapsulation Efficiencies (EE) (usually 10-30%, for hydrophilic drugs) are often prepared using the traditional techniques. These methods are sensitive to different factors, including hydration conditions, lipid content and mechanical processing (e.g. sonication) and consequently have

inconsistent performance from batch to batch, and are difficult to scale up, often further reducing EE.[42] In contrast, the microfluidic preparation techniques, especially Microfluidic Hydrodynamic Focusing (MHF), provide much higher and reproducible EE for hydrophilic and even higher for lipophilic drugs, as the processes of rapid mixing and precise liposome self-assembly happen under tunable flow conditions. [43] Moreover, because no post processing steps, like extrusion, are required in micro fluidics to obtain the desired form, the encapsulated content remains preserved, and easy scaling up by parallelization without jeopardizing EE makes it a better method for today's liposomal drug development.[44]

✓ Stability Studies

Liposomes are both chemically, physically and biologically stable; this is taken into account when deciding the length of time these can be expected to survive during the stabilization tests. If liposomes are physically stable, they can be observed to change color by the naked eye and using TEM and AFM. The stability of chemicals can be assessed by Thio barbituric Acid (TBA) testing, TLC, HPLC and HPTLC methods as well as by drug oxidation, hydrolysis and destruction. [45] Investigating liposome stability is vital to the successful use and longevity of any medicinal application. The recent studies have been directed to enhance liposome stability by various approaches. This can be done by modifying liposomes with glycolipids that have strong hydro gen bonding with liposome head groups.[46] The interaction enhances the development of microstructural domains and reorganization of the bilayer structure and thus increases the phase transition temperature, the membrane packing and the membrane thickness, which was examined in separate studies using mixed phospholipids (DMPC-DOPC and DPPC-DOPC). The liposomes were subjected to accelerated aging conditions, and physical stability was determined by dynamic and static light scattering, while chemical stability was determined by HPLC. The results showed that lipid content was a significant factor that affected the stability of liposomes. In addition, the storage stability of liposomes has been investigated and it has been found that the liposomes stored at -70 °C were stable and homogeneous for at least 9 months, while the liposomes stored at 4 °C showed a progressive increase in particle size over time. Pharmacokinetic and pharmacodynamic properties improve so significantly by encapsulating the drugs in liposomal or lipid drug delivery system that the drugs can be adopted into regular use.[47]

➢ **Advantages of Liposome [48]**

✓ Provides selective passive targeting to tumor tissue (liposomal doxorubicin).
✓ Liposome are increased efficacy and therapeutic index of drug (Actinomycin-D). Encapsulation provides 2x the stability of Liposome.
✓ Liposomes are biocompatible, completely biodegradable, non-toxic, flexible and nonimmunogenic for systemic and non-systemic administrations.
✓ Liposome are reduction in toxicity of the encapsulated agent (Amphotericin B, Taxol).
✓ Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
✓ Site avoidance effect.
✓ Flexibility in the coupling with site specific ligands for active targeting.

➢ **Disadvantages of Liposome [48]**

✓ High production cost.
✓ Leaks and in-encapsulated fusion of drug / molecules.
✓ Sometimes phospholipid undergoes the reaction of oxidation and hydrolysis.
✓ Short half-life.
✓ Low solubility.
✓ Fewer stables.

➢ **APPLICATIONS OF LIPOSOMES**

✓ Ophthalmic Disorders

Ocular Conditions include treatment with various externally applied medications, including creams, lotions, solutions and suspensions for corneal inflammation, dry eyes, and rejection of retinal transplants. These supplements are absorbed in the eye in lower amounts due to the presence of several barriers in the eye. To address this challenge, compositions of lipids are used. A liposome suspension and a spray which delivers the

drug into the conjunctival sac are being developed for the treatment of dry eyes.[49] The most popular solution for eyes infected with gram-positive and gram-negative germs is ciprofloxacin/ciprocin. In rabbits, the area under the curve for the lipid-based formulations of ciprofloxacin is greater than that for the droplets, which leads to longer residence time, higher bioavailability in the retina and lower doses.[50]

✓ In Cancer Chemotherapy

Malignant cells exhibit different characteristics and activity from normal cells and cancerous cells can invade more easily. The high permeability of the carcinoma allows for easy infiltration of the different cancer cells with macromolecules and mi cromolecules. Al too, the tumor tissue is ideal for targeted drug delivery because it has specific genetic markers (integrins and aminopeptidase) expressed by the malignant cells. There are numerous medications that are manufactured as liposomes, such as methotrexate, paclitaxel and docetaxel.[51] There are two ways in which the chemotherapy medicines are transported into the can cerous site: the lysozyme enzyme-mediated polymer breakdown and the transport of the pH (7.4 blood pH vs the acidic pH of the malignant cells). When umbelliprenin and doxorubicin, a medication for breast cancer, are loaded into lipids, the liposomes' consistency in size and spread at the desired location are improved, and their toxicity to the tested human breast cancer cell lines in increased.[52]

✓ In Vaccines

Liposomes can be used in the formulation of vaccines by external modification with different chemical and/or biological substances, like peptide antigens or viral complexes in order to increase immunogenicity and biological activity. For instance, the membrane-proximal exterior region of HIV virions, which has minimal immunogenicity and boosts immune responses, is called the membrane-proximal exterior region.[53] Liposomes can encapsulate hydrophilic and hydrophobic antigens as vaccines, enhancing their immunogenicity and stability. They are able to be targeted for specific immune responses because of their size, charge, and lipid content. Cationic liposomes also have a strong binding affinity to Antigen-Presenting Cells (APCs) which improves antigen uptake and presentation for robust T cell-mediated immunity. In recent years, a series of multifunctional liposomal vaccines have been developed to enhance antigen cross-presentation by MHC-I pathways by targeting specific cell compartments (such as the endoplasmic reticulum), and to generate humoral and cellular immune responses.[54] Liposomal formulations have helped COVID-19 mRNA vaccines to be successful by preventing the degradation of mRNA and by enhancing its uptake by host cells. Liposomes are also employed in licensed vaccines for hepatitis A and influenza, thus proving their therapeutic potential. As research continues, liposomal vaccine delivery technologies have promise of further enhancing the effectiveness of vaccinations and pathogen immunity.[55]

✓ In Gene Delivery

The most popular application of liposomes containing cationic molecules is as genome transporters. A commonly used cationic lipid particle for gene transfer is Lipofectamine 2000. The treatment of the malignancy is based on the use of turmeric and STAT3 siRNA liposomes (prepared by the Bangham process). Liposomes inhibit the development of B16F10 carcinoma cells, in contrast to releasing curcumin and STAT3 siRNA. Furthermore, liposomes are used to deliver the CRISPR or Cas9 gene to treat a variety of cancers and genetic diseases.[56] Liposomes have emerged as an important biocompatible and versatile non-viral carrier system to introduce nucleic acids into the cells of interest. In recent years, efforts have focused on increasing the efficiency and level of accuracy of gene delivery with liposomes. The incorporation of diosgenin in liposomal vehicles mediates changes in the endocytic pathway that lead to increased uptake of the nucleic acids and CRISPR/Cas9-mediated gene editing in cells.[57] Additionally, liposomes have also been successfully used to deliver CRISPR genome editing technology, which may provide a way to make precise and effective genetic changes in cells and tissues. The enhancements in these areas reflect the potential for liposomes in more advanced aspects of gene therapy, particularly in delivering more complex genetic constructs, like CRISPR/Cas9, with greater specificity and fewer off-target effects.[58]

➢ MARKETED FORMULATIONS

There are a number of liposomal formulations successfully commercialized for the treatment of cancer, fungal infections, pain management, ophthalmic diseases and vaccine delivery. Among the first and most successful liposome formulations, Doxil is a PEGylated liposomal doxorubicin approved in 1995 for ovarian cancer and Kaposi's sarcoma [59]. Lipo-Dox, another similar formulation, was approved in 1998 for treating breast and

ovarian cancers [60]. The conventional liposomal daunorubicin preparation DaunoXome was approved in 1996 for the treatment of Kaposi's sarcoma. [61]

Sphingomyelin liposomal vincristine sulfate (Marqibo) was the first agent with the liposomal format to receive approval in 2012 for the treatment of acute lymphoblastic leukemia (ALL) among hematological malignancies.[62] Vyxeos, a dual drug liposomal carrier with daunorubicin and cytarabine, was approved for AML in 2017, similarly. [63]

Liposomal systems have similarly proven to be very effective in antifungal therapy. AmBisome, a small unilamellar liposomal formulation of amphotericin B, approved in 1997, is remarkably used to treat systemic fungal infections, due to its less nephrotoxicity. In 1995 another lipid-based amphotericin B product called Abelcet was approved for invasive fungal infections. [60,64]

Visudyne has been approved in 2000 for ophthalmic and photodynamic therapy (PDT) applications used to treat macular degeneration (MDG). [65] Liposomal formulations are also widely used in pain management. A multivesicular liposomal injection of morphine sulfate called DepoDur was approved in 2004 for the treatment of postoperative pain. Similarly, the 2011-approved Exparel delivers long lasting postoperative pain relief via a multivesicular liposomal delivery system.[66]

Lipid nanoparticles have been of global importance more recently in the context of the COVID-19 pandemic, when they were utilized to deliver vaccines. Lipid nanoparticle delivery and prevention of COVID-19 using mRNA has been demonstrated by Comirnaty (tozinameran) approved in 2020, and Spikevax (elasomeran) approved in 2021. [67,68]

Other marketed liposomal anticancer drugs are Myocet (2000) approved for the treatment of metastatic breast cancer; multilamellar liposomal preparation Mepact (2009) approved for the treatment of osteosarcoma. All of these commercial products are representative of the clinical efficacy and therapeutic potential of liposomal drug delivery systems in different disease indications. [59-68]

➢ RECENT ADVANCES

Liposomal drug delivery systems have made a significant transformation to the field of nanomedicine and targeted delivery with recent advances. New liposomal technologies have been developed to enhance the stability of the drug, selectively target certain tissues, control the release of the drug, increase the therapeutic activity of the drug and increase patient adherence. The developments of advanced liposomal systems are further accelerated by the integration of nanotechnology, molecular biology, surface engineering and artificial intelligence.[69]

✓ PEGylated (Stealth) Liposomes:

Coated with polyethylene glycol (PEG) to decrease the opsonization and increase the circulation in the systemic circulation. Demonstrate anti-cancer activity (such as Doxil), with advantages such as better pharmacokinetics and longer duration of action in the blood. Repeat challenges are associated with rapid blood clearance. [69,70]

✓ Ligand-Targeted Liposomes:

Utilize ligands such as antibodies, peptides, folic acid for active targeting to increase drug delivery to diseased cells and reduce off-target effects. In cancer treatment, it has been noted that liposomes targeting folic acid and transferrin have enhanced targeting efficiency.[71]

✓ Stimuli-Responsive Liposomes:

Drugs can be released in response to a stimulus (pH, temperature, enzymes), which helps in achieving therapeutic precision and minimizing side effects. Thermosensitive liposomes for hyperthermia; pH-sensitive liposomes for the delivery of drugs to tumor environments; and enzyme-sensitive liposomes for the release of drugs in diseased tissues.[69]

✓ Cationic Liposomes for Gene Delivery:

Transport non-viral vectors for gene therapy: Delivery of nucleic acids (mRNA vaccines, siRNA etc.). They're demonstrating their effectiveness in delivering mRNA vaccines - such as those for COVID-19 - by innovating their capabilities. [69,74]

✓ Multifunctional Liposomes:

Therapeutic and diagnostic properties wrapped together into a single system, including imaging agents with therapeutic agents. Simultaneous diagnosis and treatment based on magnetic liposomes, which can be steered using MRI. [70,76]

✓ In Vaccine Delivery:

liposomes can be employed as carriers and adjuvants to enhance immune responses. Increased in prominence during the COVID-19 pandemic, due to its ability to increase antigen stability and presentation. Use in a number of vaccines such as infectious diseases and cancer immunotherapies. [69,74]

✓ Quality by Design (QbD) and AI Based Optimization:

Apply QbD concepts to improve critical quality attributes of liposomes using AI optimization approach. Leverages AI and machine learning in formulation optimization and predictive models to aid pharmaceutical development of liposomes.[73]

✓ Advanced Routes of Administration:

Going beyond the traditional parenteral route to oral, pulmonary, ocular, transdermal, intranasal and brain-directed administration. Intravenous liposomes are promising for the nose-to-brain route, pulmonary liposomes for respiratory diseases and ocular liposomes to increase the time of corneal drug residence. [69,78]

➢ FUTURE PERSPECTIVES

The potential for liposomal drug delivery systems is immense, as ongoing advancements in nanotechnology, biotechnology, precision medicine, and pharmaceutical engineering hold the promise of further revolutionizing the field. The future liposomal formulations will be more intelligent, personalized and able to overcome the current therapeutic limitations. [69]

✓ Personalized and Precision Medicine

In the future, liposomal systems will be tailored for each patient, based on his or her genetic makeup and disease markers as well as his or her physical features. Liposomal formulations can be tailored to match the specific needs of each patient, potentially enhancing the effectiveness of treatment and reducing its side effects. Liposomes, which are targeted to specific receptors, will be more selectively effective in treating cancer, neurological conditions and autoimmune disorders. Companion diagnostics and biomarkers could further revolutionize personalized treatment. [70,72]

✓ AI Computer Modelling

In the future, liposomal formulation will be developed with the help of artificial intelligence. Formulation stability, drug loading efficiency, pharmacokinetics and therapeutic performance can be predicted using machine learning algorithms. Computational modelling and simulation techniques will aid the researchers in optimizing the composition of liposomes, speed up the drug development process, and also minimize experimental costs and failure rates. [73]

✓ Advanced Gene and RNA Delivery

Liposomes are expected to be one of the most popular platforms for gene editing and nucleic acid therapeutics. Targeting efficient delivery of mRNA/siRNA, DNA, CRISPR-Cas systems, and antisense oligonucleotides will be done in future studies. The recent success of lipid nanoparticle-based COVID-19 vaccines has driven the global interest in the use of RNA therapeutics for the treatment of genetic disorders, infectious diseases, and cancer. [69,74]

✓ Developing Smart and Programmable Liposomes.

The future liposomes could have programmable and self-regulating characteristics that react exactly to the signals of the various diseases. These smart systems can let out drugs just at the site of the disease, based on the stimuli, e.g. enzymes, pH, temperature, or magnetic field. Another potential application of programmable liposomes is the ability to control the release of drugs over time and space, potentially improving therapeutic efficacy and minimizing side effects. [69]

✓ Brain and Mitochondrial Targeting (BMT) liposomes

There is strong interest in research to overcome biological barriers like the blood–brain barrier and intracellular organelle membranes in the future. Liposomes targeting other organs of the brain and mitochondria are novel approaches to the treatment of neurodegenerative diseases and therapy-resistant cancers. The systems could enhance the results of treatment for disorders like Alzheimer's disease, Parkinson's disease, glioblastoma and mitochondrial diseases. [78]

✓ Combination Therapy

New liposomal systems can be designed to carry more than one drug, gene, imaging agent, as well as immunotherapeutic agents in the same carrier. Multifunctional systems will enable combination therapy and in-situ monitoring of diseases. Liposomes loaded with theragnostic agents are likely to have a major impact in precision oncology and individual treatment planning. [69,73]

➢ CONCLUSION

In the field of drug delivery, liposomes have truly become revolutionaries, providing a biocompatible, biodegradable, and versatile method of drug delivery which can enhance the therapeutic activity of a variety of drugs. They can carry both hydrophilic and hydrophobic substances, release drugs in a controlled and targeted manner, and lessen the toxicity of the drug, which are of great importance to modern pharmaceutical applications. Developments in formulation technologies and surface modification techniques have greatly improved the stability, circulation time and targeting efficiency of liposomal systems. The liposomes have found great application in cancer chemotherapy, in the therapy of the eye, in the formulation of vaccines, in the delivery of genes and in the treatment of infectious diseases. The clinical importance of liposomes and their therapeutic reliability is reflected by the approval and commercialization of a number of liposomal formulations. Moreover, recent advances in PEGylation and ligand targeted systems, stimuli responsive systems and formulation design using artificial intelligence have created new opportunities for precision medicine and nanotherapeutics. These are anticipated to be the direction of future research, including personalized liposomal drugs, smart responsive systems, RNA/gene delivery, brain targeting, and scalable manufacturing technologies. While there are some challenges to address, like high production costs, stability problems and complex production processes, continuous progress is anticipated in nanotechnology and pharmaceutical engineering to overcome these limitations. Hence liposomes continue to be one of the most promising and evolving drug delivery systems, offering a vast potential for future drug and biomedicine applications.

➢ REFERENCES

1. Moinuddin SM, et al. Facile formation of co-amorphous atenolol and hydrochlorothiazide mixtures via cryogenic-milling: enhanced physical stability, dissolution and pharmacokinetic profile. Int J Pharm. 2017;532(1):393-400.

2. Lombardino JG, Lowe JA. The role of the medicinal chemist in drug discovery then and now. Nat Rev Drug Discov. 2004;3(10):853-862.

3. Kalepu S, et al. Liposomal drug delivery system: a comprehensive review. Int J Drug Dev Res. 2013;5(4):62-75.

4. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. Front Pharmacol. 2015;6:286.

5. Mishra H, et al. A comprehensive review on liposomes: a novel drug delivery system. J Drug Deliv Ther. 2018;8(6):400-404.

6. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: an updated review. Curr Drug Deliv. 2007;4:297-305.

7. Riaz M. Liposomes preparation methods. Pak J Pharm Sci. 1996;9:65-77.

8. Gregoriadis G, Florence AT. Liposomes in drug delivery. Drugs. 1993;45:15-28.

9. Dunnick JK, Rooke JD, Aragon S, Kriss JP. Alteration of mammalian cells by interaction with artificial lipid vesicles. Cancer Res. 1976;36:2385-2389.

10. Bhupendra P, Narendra K, Suman S, Amit R. Liposome: method of preparation, advantages, evaluation and its application. J Appl Pharm Res. 2015;3:1-8.

11. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. Pharmaceutics. 2017;9:12.

12. Shi NQ, Qi XR. Preparation of drug liposomes by reverse-phase evaporation. In: Lu WL, Qi XR, editors. Liposome-Based Drug Delivery Systems. Berlin: Springer; 2017. p. 1-10.

13. Szoka F Jr, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proc Natl Acad Sci U S A. 1978;75:4194-4198.

14. Enoch HG, Strittmatter P. Formation and properties of 1000-A-diameter, single bilayer phospholipid vesicles. Proc Natl Acad Sci U S A. 1979;76:145-149.

15. Mozafari MR. Liposomes: an overview of manufacturing techniques. Cell Mol Biol Lett. 2005;10(4):711-719.

16. Hauser H, Gains N. Spontaneous vesiculation of phospholipids: a simple and quick method of forming unilamellar vesicles. Proc Natl Acad Sci U S A. 1982;79:1683-1687.

17. Lesoin L, Boutin O, Crampon C, et al. CO2/water/surfactant ternary systems and liposome formation using supercritical CO2: a review. Colloids Surf A Physicochem Eng Asp. 2011;377:1-14.

18. Bangham AD, Horne RW. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J Mol Biol. 1964;8:660-668.

19. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, et al. Liposome: classification, preparation and applications. Nanoscale Res Lett. 2013;8:102.

20. Pattni BS, Chupin VV, Torchilin VP. New developments in liposomal drug delivery. Chem Rev. 2015;115(19):10938-10966.

21. Immordino ML, Dosio F, Cattel L. Stealth liposomes. Int J Nanomedicine. 2006;1(3):297-315.

22. Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2012;64:302-315.

23. Gabizon A, Catane R, Uziely B, et al. PEG-coated liposomes. Cancer Res. 1994;54:987-992.

24. Gregoriadis G, Florence AT. Liposomes in drug delivery. Drugs. 1993;45:15-28.

25. Barenholz Y. Doxil—the first FDA-approved nano-drug. J Control Release. 2012;160:117-134.

26. Mozafari MR. Nanoliposomes: preparation and analysis. Methods Mol Biol. 2010;605:29-50.

27. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomedicine. 2015;10:975-999.

28. Allen TM. Long-circulating liposomes. Trends Pharmacol Sci. 1994;15:215-220.

29. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use. Pharmaceutics. 2017;9(2):12.

30. Sharma US, Sharma A. Liposomes in cancer treatment and diagnosis. Int J Pharm. 1997;154:123-140.

31. Peer D, Karp JM, Hong S, et al. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2:751-760.

32. Cattel L, Ceruti M, Dosio F. From conventional to stealth liposomes. J Chemother. 2004;16:94-97.

33. Hua S, Wu SY. Lipid-based nanocarriers for targeted therapy. Front Pharmacol. 2013;4:143.

34. Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R. Thermosensitive liposomes. Science. 1978;202:1290-1293.

35. Torchilin VP. Targeted pharmaceutical nanocarriers. AAPS J. 2007;9:E128-E147.

36. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomedicine. 2015;10:975-999.

37. Aranda-Lara L, Morales-Avila E, Luna-Gutiérrez MA, Olivé Alvarez E, Isaac-Olivé K. Radiolabeled liposomes and lipoproteins as lipidic nanoparticles for imaging and therapy. Chem Phys Lipids. 2020;230:104934.

38. Hasan MM, Hasan M, Mondal JC, Al Hasan M, Talukder S, Rashid HA. Liposomes: an advance tool for novel drug delivery system. Pharma Innov J. 2017;6:304-311.

39. Bokrova J, Marova I, Matouskova P, Pavelkova R. Fabrication of novel PHB-liposome nanoparticles and study of their toxicity in vitro. J Nanopart Res. 2019;21(3):49.

40. Smith MC, Crist RM, Clogston JD, McNeil SE. Zeta potential: a case study of cationic, anionic, and neutral liposomes. Anal Bioanal Chem. 2017;409(24):5779-5787.

41. Ong S, Ming L, Lee K, Yuen K. Influence of the encapsulation efficiency and size of liposome on the oral bioavailability of griseofulvin-loaded liposomes. Pharmaceutics. 2016;8(3):25.

42. Lombardo D, Kiselev MA. Methods of liposomes preparation: formation and control factors of versatile nanocarriers for biomedical and nanomedicine application. Pharmaceutics. 2022;14(3):543.

43. Nunziata G, Borroni A, Rossi F. Advanced microfluidic strategies for core-shell nanoparticles: the next-generation of polymeric and lipid-based drug nanocarriers. Chem Eng J Adv. 2025;22:100759.

44. Hood RR, Shao C, Omiatek DM, Vreeland WN, DeVoe DL. Microfluidic synthesis of PEG- and folate-conjugated liposomes for one-step formation of targeted stealth nanocarriers. Pharm Res. 2013;30(6):1597-1607.

45. Feghhi M, Sharif Makhmalzadeh B, Farrahi F, Akmali M, Hasanvand N. Anti-microbial effect and in vivo ocular delivery of ciprofloxacin-loaded liposome through rabbit's eye. Curr Eye Res. 2020;45(10):1245-1251.

46. Yi X, Gao S, Gao X, Zhang X, Xia G, Liu Z, Shi H, Shen X. Glycolipids improve the stability of liposomes: the perspective of bilayer membrane structure. Food Chem. 2023;412:135517.

47. Jakubek ZJ, Chen S, Zaifman J, Tam YYC, Zou S. Lipid nanoparticle and liposome reference materials: assessment of size homogeneity and long-term −70 °C and 4 °C storage stability. Langmuir. 2023;39(7):2509-2519.

48. Sharma V, Mishra D, Sharma A, Srivastava B. Liposomes: present prospective and future challenges. Int J Curr Pharm Rev Res. 2010;1(2):5-16.

49. Natarajan JV, Darwitan A, Barathi VA, et al. Nanomedicine for glaucoma: liposomes provide sustained drug delivery and improved ocular bioavailability. Asian J Pharm Sci. 2021;16(2):179-197.

50. Hathout RM, Mansour S, Mortada ND, Guinedi AS. Liposomes as an ocular delivery system for ciprofloxacin: enhanced corneal penetration and improved therapeutic efficacy. Int J Pharm. 2020;587:119692.

51. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. Pharmaceutics. 2021;13(3):356.

52. Khezri K, Saeedi M, Maleki Dizaj S. Co-delivery of doxorubicin and umbelliprenin via liposomes for breast cancer therapy. J Drug Deliv Sci Technol. 2022;68:103041.

53. Alving CR, Peachman KK, Rao M, Reed SG. Liposomal vaccine adjuvants and delivery systems. Expert Opin Drug Deliv. 2021;18(6):807-820.

54. Schwendener RA. Liposomes as vaccine delivery systems: a review of the recent advances. Ther Adv Vaccines Immunother. 2022;10:25151355221087994.

55. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6:1078-1094.

56. Kulkarni JA, Cullis PR, van der Meel R. Lipid nanoparticles enabling gene therapies: from concepts to clinical utility. Nucleic Acid Ther. 2021;31(2):146-157.

57. Zhang S, Shen J, Li D, Cheng Y. Strategies in liposomal gene delivery systems for CRISPR/Cas9-mediated genome editing. Acta Pharm Sin B. 2022;12(5):1883-1903.

58. Yin H, Kanasty RL, Eltoukhy AA, et al. Non-viral vectors for gene-based therapy. Nat Rev Genet. 2021;22(4):215-234.

59. Gregoriadis G. Liposomes: A Practical Approach. Oxford: Oxford University Press; 1990.

60. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65:36-48.

61. Sercombe L, et al. Advances and challenges of liposome assisted drug delivery. Front Pharmacol. 2015;6:286.

62. Bulbake U, et al. Liposomal formulations in clinical use: an updated review. Pharmaceutics. 2017;9(2):12.
63. Pattni BS, Chupin VV, Torchilin VP. New developments in liposomal drug delivery. Chem Rev. 2015;115:10938-10966.
64. Akbarzadeh A, et al. Liposome: classification, preparation and applications. Nanoscale Res Lett. 2013;8:102.
65. Immordino ML, Dosio F, Cattel L. Stealth liposomes review. Int J Nanomedicine. 2006;1(3):297-315.
66. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomedicine. 2015;10:975-999.
67. Hou X, et al. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6:1078-1094.
68. USFDA approved liposomal and lipid nanoparticle products database (2020-2026).
69. Senjab RM, AlSawaftah N, Abuwatfa WH, Husseini GA. Advances in liposomal nanotechnology: from concept to clinics. RSC Pharm. 2024;1:928-948.
70. Gatto MS, Johnson MP, Najahi-Missaoui W. Targeted liposomal drug delivery: overview of the current applications and challenges. Life. 2024;14(6):672.
71. Fidan Y, Muçaj S, Timur SS, Gürsoy RN. Recent advances in liposome-based targeted cancer therapy. J Liposome Res. 2024;34(2):316-334.
72. Chen J, Hu S, Sun M, et al. Recent advances and clinical translation of liposomal delivery systems in cancer therapy. Eur J Pharm Sci. 2024;193:106688.