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Liposomes as Potential Delivery System for Herbal and Synthetic Drugs

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ABSTRACT

Background: Liposomes represent an appealing drug delivery system because of their better and adaptable physicochemical and biophysical features, which allow for easy manipulation to address various delivery concerns.

Purpose: The use of liposomes for drug delivery currently has been greatly impacted across many biomedical fields. They have been proven to be effective in achieving the following objectives: stabilizing medicinal compounds, eliminating obstacles to cellular and tissue absorption, and enhancing the bio distribution of drugs to target sites in vivo. This reduces systemic toxicity while facilitating the effective distribution of encapsulated compounds to target areas. Liposome-assisted drug delivery platforms have made progress in clinical translation, despite a great deal of research and a number of promising preclinical results.

Method: Recent literature has been surveyed from PUBMED, GOOGLE SCHOLAR, etc., like search engines, for summarising detailed developments in the field of liposomes for various applications, which could prove to be a novel drug delivery system.

Result and Conclusion: In this review, the focus has been on drug loading in liposomes, mechanism of transportation, method of preparation of liposomes, advancements in drug transport facilitated by liposomes, and applications of liposomes in biomedicine.

1. Introduction

Liposomes are amphiphilic compounds, meaning that one of their parts is attracted to water (hydrophilic) while the other is not attracted to it (hydrophobic). When lipids are exposed to water, the hydrophobic portions of the molecule interact unfavorably with the solvent, causing the lipids to self-assemble, frequently forming liposomes (Nsairat *et al.*, 2022). Drug administration via liposomes is appealing due to their size, hydrophobic and hydrophilic properties, and biocompatibility. Liposome characteristics are greatly influenced by the lipid composition, surface charge, size, and the manufacturing process (Liu *et al.*, 2022a).

A lipid bilayer that encircles an aqueous core and divides it from the surrounding material, resembling a membrane, makes up a liposome. They were first identified as bloated phospholipid systems by Bangham and his coworkers in 1961 (Bangham, 1983; Bangham, 2005). In the years that followed, others containing phospholipid bilayer structures were identified. These structures were first referred to as bangosomes and subsequently as liposomes, which were formed by combining the Greek words "lipo" for fat and "soma" for body. Liposomes are special in that they can compartmentalize and saturate both hydrophilic and hydrophobic molecules (Anand *et al.*, 2023). Because of this distinctive quality as well as biocompatibility and biodegradability, liposomes are highly appealing as drug delivery systems (Çağdaş *et al.*, 2014).

For a variety of chemical substances with biological activity, liposomes constitute flexible and sophisticated nano-delivery methods (Nsairat *et al.*, 2022). The choice of an adequate preparation procedure that results in the synthesis of liposomes with varying sizes, lamellarities, and physicochemical qualities influences the final amount of the medication that is encapsulated (Šturm & Ulrih, 2021). Drugs, both hydrophilic and hydrophobic, are trapped inside liposomes to avoid their common general toxicity, which is frequently observed in cancer medications (Eloy *et al.*, 2014). As a result, it represents a particularly efficient method that improves the therapeutic efficacy of the medicine. Targeting the tumor site either passively or actively is possible thanks to liposome modification (Kaur *et al.*, 2023).

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Four types of liposomal distribution systems are distinguished: ligand-targeted liposomes, sterically stabilized liposomes, regular liposomes, and a combination. The first generation of liposomes to be created were conventional liposomes. They consist of a lipid bilayer composed of neutral (phospho) lipids, cationic, anionic, or neutral (phospho) lipids, and cholesterol enclosing an aqueous volume (Sercombe *et al*., 2015). During the 1980s, clinical research on encapsulated medicines such as doxorubicin and amphotericin found that liposomal administration was effective in increasing the therapeutic index of medications. Conventional liposomal formulations improved drug delivery to diseased tissue by altering pharmacokinetics and biodistribution, which reduced chemical toxicity *in vivo* when compared to free medication. However, the therapeutic efficacy of the delivery method was limited due to its susceptibility to rapid clearance from circulation (Bulbake *et al*., 2017).

The biological obstacles that liposomal drug delivery systems must overcome:

- The body has several defense mechanisms that liposomes must overcome in order to identify, neutralize, and get rid of invasive substances, just like any other foreign particle that gets inside. The RES, immunogenicity, and opsonization are some of these defenses (Willis & Forssen, 1998). Although these challenges need to be addressed for liposomes to function at their best, other elements, like the enhanced permeability and retention (EPR) effect, can be used to improve drug delivery (Wu *et al*., 2021).
- The RES and liposome clearance: The RES is the main site of liposome accumulation after systemic injection. The RES is connected to the liver, spleen, kidney, lungs, bone marrow, and lymph nodes. The liver has the highest capacity for liposomal uptake, followed by the spleen, which can collect up to ten times as many liposomes as other RES organs. The RES's ability to sequester liposomes from the circulation is linked to microvasculature fenestrations, which have pore sizes ranging from 100 to 800 nm, which is large enough to allow the extravasation and subsequent clearance of the majority of drug-loaded liposomes (50-1000 nm in size) (Sercombe *et al*., 2015).

1.1. Opsonization and Destabilization of Vesicle

The overall biodistribution, efficacy, and toxicity of nanocarriers are determined by the degree of interaction between liposomal drug delivery systems and plasma proteins (Sercombe *et al*., 2015). It has been discovered that plasma proteins are crucial for both vesicular instability and RES-mediated liposomal clearance (Olusanya *et al*., 2018). Size, surface charge, and stability are some of the factors that influence liposome opsonization by serum proteins (Ishida *et al*., 2001a). The degree of this interaction has been shown to decrease with liposome size from 800 to 200 nm in diameter because small liposomes are unable to sustain opsonic activity (Ishida *et al*., 2001b).

1.2. The Effect of Improved Permeability and Retention (EPR)

Liposomes that did not undergo opsonization and the RES both exhibit the EPR phenomenon (Wu, 2021). The increased permeability of the vasculature supplying sick tissues (such as tumors and inflammatory disorders) is known as the EPR effect. These sites exhibit fenestrations between 300 and 4700 nm due to deregulations in angiogenesis and/or increased expression and activation of vascular permeability factors (Lugano *et al*., 2020). The liposomes can then extravasate and accumulate through passive targeting (Wang *et al*., 2021).

2. Classification of Liposomes

Emulsifying natural or synthetic lipids in an aqueous medium produces liposomes, which are spherical lipid vesicles with a diameter of 50–500 nm and a particle size of one or more lipid bilayers. Additionally, membranes of liposomes might be single or bilayer. The number of bilayers and vesicle size both have an impact on the amount of drug encapsulated in liposomes, which is a key factor in determining the circulation half-life of liposomes (Lombardo & Kiselev, 2022). Depending on the size and quantity of their bilayers, according to their lamellarity, liposomes can also be divided into two groups: (A) Multilamellar vesicles (MLVs) are made of multiple lipid bilayers and range in size from 1 to 5 m. (B) A Large Unilamellar Vesicle (LUV) has a single lipid bilayer and is 100-250 nm in size. (C) Small Unilamellar Vesicles (SUV) are made up of a single phospholipid bilayer that surrounds the aqueous phase and ranges in size from 20 to 100 nm (Pandey *et al*., 2016).

In unilamellar liposomes, on the vesicle, a single phospholipid bilayer sphere encloses the aqueous fluid. Multilamellar liposomes include vesicles that resemble onions. Many smaller unilamellar vesicles will usually form on the inside of bigger ones in a multilamellar structure of concentric phospholipid spheres separated by water layers (Jabin *et al*., 2018).

3. Drug Loading in Liposomes

Active drug loading occurs after the liposome is created, whereas passive drug loading occurs when the drug is

encapsulated during the liposome's formation. How much of hydrophobic drugs, such as annamycin or amphotericin B taxol, can be directly incorporated into liposomes during vesicle formation is determined by drug-lipid interactions (Sur *et al.*, 2014). Depending on the degree to which the drug dissolves in the liposome membrane, 100% trapping effectiveness is frequently achievable.

Passive encapsulation of water-soluble medications depends on liposomes' capacity to capture aqueous buffer containing a dissolved pharmaceutical during vesicle formation (Akbarzadeh *et al.*, 2013). The trapping efficacy, which is usually about 30%, is limited by the trapped volume defined in the liposomes as well as drug solubility. On the other hand, water-soluble medications having protonizable amine functions can be actively trapped with a trapping effectiveness that can be close to 100% by employing pH gradients (Akbarzadeh *et al.*, 2013).

4. Mechanism of Transportation

The interactions of liposomes with cells and their ultimate fate *in vivo* after injection determine both the drawbacks and advantages of liposome drug carriers (Daraee *et al.*, 2016). Studies of the contacts between liposomes and cells *in vivo* and *in vitro* have revealed that the primary interactions between liposomes and cells are either simple adsorption (by specific interactions with cell-surface components, electrostatic forces, or by non-specific weak hydrophobic) or endocytosis (by phagocytic cells of the reticuloendothelial system, such as macrophages and neutrophils) (Ishida *et al.*, 2001a).

It is extremely uncommon for liposomes to fuse with the plasma cell membrane by inserting their lipid bilayer into the plasma membrane and simultaneously releasing their contents into the cytoplasm(Abbasi *et al.*, 2023). Passive encapsulation of water-soluble medications depends on liposomes' capacity to capture aqueous buffer containing a dissolved pharmaceutical during vesicle formation (Akbarzadeh *et al.*, 2013).The trapping efficacy, which is usually about 30%, is limited by the trapped volume defined in the liposomes as well as drug solubility. On the other hand, water-soluble medications having protonizable amine functions can be actively trapped with a trapping effectiveness that can be close to 100% by employing pH gradients.

5. Methods for Liposome Preparation

Thin film, reverse evaporation, double emulsion, centrifugal, injection, calcium fusion, ammonium sulphate gradient, and other techniques are frequently employed in the lab to prepare liposomes (Figure 1). To ensure the final smooth transition to mass production, these methodologies must test the main process conditions and process phases to explain the rationality and reproducibility of the process (Lombardo & Kiselev, 2022).

The thin film hydration method is the most widely utilized technique for liposome preparation. Bangham, who discovered liposomes, was the first to publish the membrane approach (Bangham, 1983; Bangham, 2005). The first and most popular method is this one. Before adding a buffer containing water-soluble pharmaceuticals, mix the lipid and the lipid-soluble medication in a sufficient amount of chloromethane or other organic solvents. Then, use nitrogen gas or decompression rotary evaporation to remove the organic solvent, allowing the lipid to form a thin layer on the container wall.

To hydrate the lipids, leave them at room temperature for a predetermined period of time. The lipid membrane fragments absorb water and inflate when the lipids are shaken and dispersed above the phase transition temperature. Multi-cell liposomes (MLV) with particle sizes between 1 and 5 μm can be produced by the lipid membrane flexing and closing. The diameter equalization technique can be used to disperse the liposomes created by the thin film method if you wish to alter the size and other characteristics of liposomes, particularly to transform MLV into single-chamber liposomes (SUV or LUV), as MLV made by hydrating lipids is too big or highly uneven. The film approach can be separated into the following categories based on the various dispersion techniques: hand-shaken multilamellar vesicles,extrusion vesicles, dried- rehydration vesicles, sonicated vesicles, homogenization vesicles and micro fluidization vesicles (Pande, 2023).

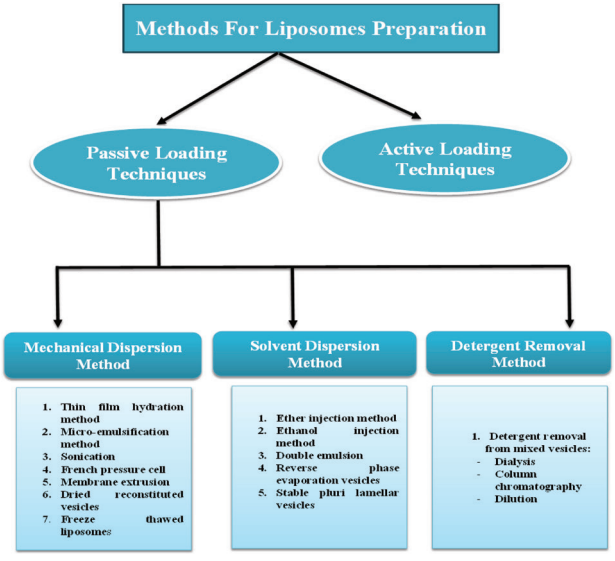

Figure 1: Methods for Liposome Preparation

5.1. Active Loading

In active loading, liposomes are initially produced with a transmembrane gradient, indicating that the aqueous phases inside and outside the liposomes differ. Following its dissolution in the external aqueous phase, an amphipathic drug may then penetrate the phospholipid bilayers and engage with a trapping agent in the core to lock the drug in place (Pauli *et al.*, 2019).

5.2. Passive Loading

The process by which liposomes are created concurrently with a drug is known as passive loading. Hydrophilic substances are distributed evenly throughout the loading. While hydrophobic medications are maintained inside the lipid bilayer with drugs that have a poorly formed water-lipid bilayer, hydrophilic substances are generally disseminated uniformly in the aqueous phase. When medications are not very soluble in water, they are first dissolved with lipids in an organic solvent, then the solvent is evaporated to create a thin film of the drug, which is then hydrated with an aqueous phase. When loading water-soluble medications, the drug-containing lipid layer is distributed throughout the aqueous phase (Pauli *et al.*, 2019).

5.2.1. Thin Film Hydration Method

The oldest, most popular, and easiest way for creating MLVs is the Thin-Film Hydration technique, also known as the Bangham method. The primary phospholipid components are dissolved in an organic solvent such as dichloromethane, chloroform, ethanol, or a chloroform-methanol mixture to ensure a homogeneous mixture. The organic solvent can be eliminated gradually through evaporation under a vacuum pump at a temperature of 45 to 60°C. Small volumes of less than 1 ml of the organic solvent may be evaporated in a fume hood using a dry nitrogen or argon stream until all traces of the organic solvent are gone, but rotary evaporation is typically employed for larger volumes. After the organic solvent has been eliminated, a uniform, dry, thin lipid coating is left behind. In the last stage, the lipid film is hydrated using a suitable aqueous medium or buffer or distilled water or phosphate saline buffer at pH 7.4 for the pharmaceutical formulation. The hydration procedure lasts for about 1 to 2 hours and is often carried out between 60 - 70 °C, which is always above the temperature at which the components shift from one phase to another. The agitation at this point might assist in separating the lamellae of the swelling lipids from the surface of the internal channel. The resulting liposome suspension is then kept overnight at 4°C to aid in complete lipid hydration. The hydration stage causes the lipid to swell and hydrate, which causes the creation of a highly heterogeneous MLV suspension in terms of size and lamellarity (Maja *et al.*, 2020).

5.2.2. Microemulsification Method

The microemulsification process creates small MLVs. This method involves introducing the lipids into the microfluidizer either as large MLVs or as a slurry of unhydrated lipids in an organic medium. A microfluidizer at a pressure of 10,000 psi pumps the fluid via a 5mm hole. Under this high pressure, the fluid moves through the microchannels, causing the two streams to meet at right angles and at higher velocities. The fluid in this state is gathered and moved through the pump and interaction chamber until the spherical vesicles are produced (Bande *et al.,* 2022).

5.2.3. Reverse Phase Evaporation Method

A rota evaporator is used to extract the solvent while lowering the pressure after the lipid mixture has been placed in a flask with a flat bottom. When nitrogen is used to purge the system, the lipids are redissolved in the organic phase. The reverse-phase vesicles will form during this stage. The solvents that are most commonly utilized are diethyl ether and isopropyl ether. The lipids in the aqueous phase are redispersed before the medicine to be encapsulated is added. The two-phase system is sonicated until the combination becomes a distinct one-phase dispersion while the system is kept under continuous nitrogen. After that, the mixture is placed on a rotary evaporator, which removes organic solvent until a gel forms before removing the non-encapsulated material (Choudhury *et al.*, 2020).

5.2.4. Sonication

Sonication is perhaps the process most commonly used to prepare SUVs. In this case, MLVs are sonicated in a passive atmosphere using a bath-type sonicator or a probe sonicator. The main disadvantages of this approach are its incredibly low internal volume/encapsulation efficacy, the possibility of phospholipid and chemical degradation, the removal of large molecules, meta contamination from the probe tip, and the presence of MLV in addition to SUV. There are two methods of sonication:

- Probe sonication: The tip of the sonicator comes into direct touch with the liposome dispersion. This method requires a significant amount of energy to disperse lipids. The energy coupling at the tip creates local heat; hence, the vessel must be immersed in a water/ice bath. Up to 1 hour of sonication can result in the desertification of more than 5% of the lipids. Additionally, while utilizing the probe sonicator, titanium will flake off and contaminate the fluid.

- Bath sonication: A cylinder containing the liposome dispersion is put into a bath sonicator. In contrast to sonication via direct dispersal utilizing the tip, this method typically makes it simpler to control the temperature of the lipid dispersion (Deshmukh *et al.*, 2016).

5.2.5. Freeze-Drying Method

These methods involve combining the solvent and lipid and then letting them evaporate and dry at room temperature. Then, until the opaqueness is eliminated, add water-saturated nitrogen. Mix 10–20 mL of a 0.2 M sucrose solution with water to cause swelling. Then, to produce LUVs, reaming fluid was added to an iso-osmolar glucose solution and centrifuged for 10 minutes at room temperature at 12,000 rpm after standing for two hours at 37°C (Choudhury *et al.,* 2020).

5.2.6. Membrane Extrusion

This method uses less pressure than French pressure cells to process MLVs and LUVs because the contents of the vesicles are exchanged with the dispersion media as they pass through polycarbonate membranes and break and reseal phosphate lipid bilayer (Choudhury *et al.,*2020).

5.2.7. French Pressure Cell Extrusion

MLV is extruded through a tiny hole in a French pressure cell. The French press vesicle approach has the advantage that the proteins do not appear to be as pompous as they do during sonication. An intriguing observation is that French press vesicles, formed by sonication or detergent removal, seem to recall encapsulated solutes subsequently longer than SUVs do (Akbarzadeh *et al.,* 2013).

5.2.8. Ether Injection

At 55°C to 65°C reduced pressure, a solution of lipids dissolved in diethyl ether or an ether-methanol mixture is progressively added to an aqueous solution of the item to be encapsulated. In the process of removing ether under vacuum, liposomes are produced (Akbarzadeh *et al*., 2013).

5.2.9. Dialysis

Lipids have been solubilized using the detergents at their critical micelle concentrations. The micelles get better and better at phospholipid as the detergent is removed, eventually combining to form LUVs. Dialysis was used to remove the detergents. For the removal of detergents, a commercial product called LipoPrep, a dialysis system variant, is available. Equilibrium dialysis bags filled with sizeable, detergent-free buffers (Hadorn *et al*., 2012).

5.2.10. Dilution

When detergent and phospholipids are added to an aqueous mixed micellar solution, the micellar size and polydispersity fundamentally increase. As the system is diluted past the mixed micellar phase boundary, a spontaneous transition from polydisperse micelles to vesicles takes place (Albarzade *et al.,* 2013).

5.2.11. Reverse Phase Evaporation Method

The reverse phase evaporation approach advanced the liposome technology. These are created by sonicating a mixture of an organic phase that solubilizes the amphiphilic molecules and a buffered aqueous phase that includes water-soluble molecules to be encapsulated into the liposomes. These inverted micelles change into a viscous condition and a gel upon removal of the organic solvent. When the gel state collapses at a crucial stage, an abundance of phospholipids in the surrounding environment contributes to the construction of a full bilayer around the remaining micelles, which leads to the formation of liposomes. This method's principal drawback is the brief durations of sonication and interaction of the materials to be encapsulated with organic solvents, which could cause DNA strand breaks or denaturation of some proteins (Divyasree *et al.,* 2022).

5.2.12. Double Emulsion

Using this technique, a primary w/o emulsion is created by first dissolving the medication in an aqueous phase and emulsifying it in an organic solvent of a polymer. A w/o/w2 double emulsion is created by further combining this main emulsion with an emulsifier that contains an aqueous solution. Microspheres are left in the aqueous continuous phase after the solvent is removed, and they are collected by centrifuging or filtering (Divyasree *et al*., 2022).

5.2.13. Stable Pluri Lamellar Vesicles (SPLVs)

Stable pluri lamellar vesicles are produced using this technique, which also includes the production of a water-in-organic phase dispersion with excessive lipid and drying under continuous bath sonication with erratic nitrogen supply. The majority of the entrapped aqueous medium is located in the compartment between adjacent lamellae; thus, SPLVs need a large aqueous core. The average level of entrapment is around 30% (Hadorn *et al*., 2012).

5.2.14. Dried Reconstituted Vesicles (DRV)

In the DRV approach, an empty SUV dispersion needs to be freeze-dried before being mixed with an aqueous fluid that contained the substance to be captured. As a result,

solid lipids in finely reduced form are hydrated, but rather than drying the lipids from an organic solution, the freeze-drying step is added to freeze and lyophilize a performed SUVs dispersion. In contrast to random matrix structure, this results in an ordered membrane structure that, when water is added, can rehydrate, fuse, and reseal to create vesicles with a high encapsulation efficiency. In order to capture the water-soluble hydrophilic components, empty SUVs are added to the dispersion and then dried together (Charumathy *et al*., 2022).

6. Applications of Liposomes in Medicine and Pharmacology

Various liposomal-based formulations have been effectively used in medical applications as anticancer, antifungal, and analgesic medicines. Doxil® was the first clinically licensed anticancer liposome medication in the United States (1995) (Bulbake *et al*., 2017). By pioneering the pH gradient active loading and the use of PEGylation for stealth liposomes, it paved the path for various other liposomal formulations to reach the clinical application areas. When circulation half-life is not a concern, conventional liposomes without PEGylation might be appealing. Depo Foam TM is primarily utilized for progressive drug release, ensuring a constant drug supply for long-term impact (He *et al*., 2019).

6.1. Liposomes in Vaccinations

Liposome formulations could protect DNA/RNA and protein payloads from biodegradation. Furthermore, their transfection efficiency could be enhanced by modifying surface charge, size, and lipid structure. Two commercial vaccines based on virosome technology are currently on the market, Epaxal® and Inflexal® V (Berna Biotech Ltd, Bern, Switzerland), a hepatitis A vaccine. Virosomes are liposomal formulations that have viral envelope proteins anchored to their lipid membrane (Felnerova *et al*., 2004).

Recently, COVID-19 mRNA-based vaccines utilized liposome protection to increase their *in vitro* and *in vivo* stability (Gregoriadis, 2021). The liposome-based mRNA anti-COVID-19 vaccine has been designed by Pfizer/BioNTech and Moderna and is already being administered worldwide. These vaccines were made to maintain the stability of liposomes in blood and to promote immune responses. Their components include distearoyl phosphatidyl choline and cholesterol, which are considered the main constituents of conventional liposomes (Ferreira *et al*., 2021). Four major ingredients were used in COVID-19 vaccines: Cationic lipids, for instance, 1,2-dioleoyl-3 (trimethylammonium) propane (DOTAP), bind to the negatively charged mRNA, pegylated lipids stabilize the particle, and phospholipids and cholesterol molecules form the required structure (Kelly *et al*., 2011). These formulas encapsulate mRNA, protect it from nucleases, and deliver it into cells, where the mRNA is released and used to generate proteins. During the COVID-19 pandemic, many liposome-based vaccines have been developed with great success. Accordingly, mRNA coding for the protein spike of the coronavirus would be encapsulated into liposomes that are designed to be stable in the circulating blood until they are taken up by phagocytic cells in the body by endocytosis. The mRNA will then be expressed as the spike protein, in turn promoting an immune response to it that will kill or inactivate the invading virus.

6.2. Marketed Clinical Liposomes

6.2.1. Cancer Treatment

Sequus Pharmaceuticals introduced Doxil®, also known as Caelyx®, in 1995. Doxil was created as a polyethylene glycol-coated doxorubicin (DOX) liposome to treat Kaposi's sarcoma. Sun Pharma created LipoDox®, an FDA-approved PEGylated liposomal formulation encapsulating DOX, in 2012. Daunorubicin, marketed as DaunoXome®, was the second anthracycline antineoplastic medication packaged in liposomes to treat acute myeloid leukemia (AML). Myocet® is a DOX-encapsulated non-PEGylated liposome with a shorter circulatory half-life and fewer cardiac adverse effects (Bulbake *et al*., 2017).

Cytarabine, a cell-cycle cytotoxic agent, is trapped in the DepoFoam™ multivesicular enclosure, allowing for a continuous two-week release (Francia *et al*., 2021). Mepact®, a novel liposome formulation, has been authorized internationally for the treatment of osteosarcoma.Under the brand name Marqibo®, vincristine is also integrated into sphingomyelin/cholesterol-based liposomes (Schiller *et al*., 2015). This authorized formula provided a longer circulation period without surface modification, resulting in greater accumulation in target tissues where vincristine is progressively released. Onivyde® is another PEGylated liposome that contains irinotecan and has a protracted anticancer action. Furthermore, Vyxeos®, also known as CPX-351, is made up of a 5:1 mixture of Cytarabine and Daunorubicin contained in a liposome. This formulation minimized side effects while increasing efficacy. Finally, paclitaxel, an anticancer medication, was integrated with Lipusu® liposomes to effectively treat gastric carcinoma with far fewer side effects. (Zhen *et al*., 2021).

6.2.2. Photodynamic Therapy

Visudyne® Visudyne®, a Novartis AG, Switzerland product, is the first light-activated medication approved for the treatment of individuals with age-related macular

degeneration (AMD) who have mostly typical subfoveal choroidal neovascularization. Visudyne® was developed to treat aberrant blood vessels in the eye caused by disorders such as wet macular degeneration (Neil, 2001). Visudyne® comprises verteporfin (VPF), a synthetic chlorine-like porphyrin with a light absorption peak at 692 nm that is used as a photodynamic treatment (PDT) photosensitizer. Photodynamic treatment may provide targeted neovascular membrane elimination while causing minimum harm to retinal and choroidal structures**.**This therapeutic approach employs low-intensity light with a wavelength within the absorption band of the injected dye to irradiate photosensitized tissues and generate local cytotoxic effects through photochemical processes. Visudyne® liposomes are unilamellar phospholipid vesicles composed of the lipids DMPC and egg phosphatidyl glycerol (EPG). The molar ratio of photosensitizer to phospholipid mixture is approximately 1:8.0, and the liposome size ranges between 150 and 300 nm (Bulbake *et al*., 2017). VPF's lipophilicity resulted in 100% integration efficiency into the liposome. Photodynamic therapy with VPF liposomes in selected patients with neovascular AMD lessened the possibility of moderate and severe vision loss (Chang & Yeh, 2012).

6.2.3. Fungal Treatment

Two major approved antifungal liposome formulations were Ambisome® and Fungisome®. They encapsulate the amphotericin B antifungal drug with many advantages compared to the free drug (Ries, 2015). These amphotericin B liposomes were stabilized in saline and have longer bioavailability and less toxicity and side effects (Rudramurthy *et al*., 2013).

6.2.4. Pain Management

DepoDur™ is a morphine formulation using DepoFoam™ Technology that resulted in a sustained release formula with prolonged clinical effect time. Exparel® also uses the DepoFoam™ technology to release Bupivacaine for sustained pain relief gradually (Zhigaltsev *et al*., 2010).

Table 1: Therapeutic application of liposomes (Nsairat *et al*., 2022).

Usage	Trade name	Active ingredient(s)	Liposome platform (Molar Ratio)	Manufacturer	Year Approved	Administration Route
Anti-Cancer	Doxil®	Doxorubicin	HSPC:Cholesterol:PEG 2000-DSPE (56:38:5)	Sequus Pharmaceuticals	1995	I.V
	DaunoXome®	Daunorubicin	DSPC:Cholesterol (2:1)	NeXstar Pharmaceuticals	1996	I.V
	Depocyt®	Cytarabine	DepoFoam™	SkyPharma Inc.	1999	Spinal
	Myocet®	Doxorubicin	Cholesterol:EPC (45:55)	Elan Pharmaceuticals	2000	I.V
	Mepact®	Mefamurtide	DOPS:POPC (3:7) Multilamellar liposome	Takeda Pharmaceutical Limited	2004	I.V
	Lipodox®	Doxorubicin	DSPC:Cholesterol:PEG 2000-DSPE (56:39:5)	Sun Pharma	2012	I.V
	Marqibo®	Vincristine	SM:Cholesterol (60:40)	Talon Therapeutics	2012	I.V
	Onivyde™	Irinotecan	DSPC:Cholesterol:MPEG-2000-DSPE (3:2:0.015)	Merrimack Pharmaceuticals	2015	I.V
	Lipusu®	Paclitaxel	NA	Luye Pharma Group	2006	I.V
	Vyxeos®	Cytarabine:Daunorubicin 5:1	DSPC:DSPG:Cholesterol (7:2:1)	Jazz Pharmaceuticals	2017	I.V
Anti-Fungal	Ambisome®	Amphotericin B	HSPC:Cholesterol:DSPG (2:1:0.8)	Astellas Pharma	1997	I.V
	Fungisome®	Amphotericin B	PC:Cholesterol (7:3)	Lifecare Innovations	2003	I.V
Photodynamic therapy	Visudyne®	Verteporphin	Verteporphin:DMPC&EPG (1:8)	Novartis AG	2000	I.V

Analgesic	DepoDur™	Morphine sulfate	DepoFoam™	SkyPharma	2004	Epidural
	Exparel®	Bupivacaine	DepoFoam™	Pacira pharmaceuticals	2011	I.V

7. Conclusion

Liposomes have been used effectively as an efficient medication delivery mechanism for a variety of ailments ranging from cancer therapy to pain management. The formation of biocompatible, biodegradable, and low immunogenicity liposomes improved the pharmacokinetics and pharmacodynamics of a water-insoluble, poorly bioavailable, and extremely toxic medication. To overcome their limitations, liposomes have experienced multiple evolutions in terms of ingredients and manufacturing techniques. Liposome physical and chemical stability are important issues. As a result, the necessity to construct liposomes with excellent stability has a substantial influence on their therapeutic application.

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Authorship Contribution

Muskan Sood: conceived, drafted, and designed the manuscript and figure; Pranab Moudgil: writing, reviewing, and editing; Anu Jindal: critically review and final approval of the version to be published. Shaveta Bhardwaj: collecting data regarding marketed clinical liposomes; Kalpna Kashyap: collecting data regarding applications of liposomes; all authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of the article.

Declaration

It is an original article and has neither been sent elsewhere nor published anywhere.

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