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LIPOSOMAL DRUG DELIVERY SYSTEMS: FUNDAMENTALS, ADVANCES AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Liposomes are phospholipid vesicles that have proven to be promising drug delivery systems, capable of carrying both hydrophilic and hydrophobic therapeutic agents. They have been used in a diverse array of pharmaceutical applications because of their biocompatibility, biodegradability, and ability to enhance drug solubility, stability, bioavailability, and therapeutic effects. New developments in liposomal technology, such as PEGylated liposomes, actively targeted liposomes, and stimulus-responsive liposomes, have greatly improved circulation time, site-specific delivery, and controlled drug release. With these developments, liposomes are being used in cancer treatment, vaccine delivery, fungal treatment, pain therapy, eye delivery, and transdermal drug delivery. Although they offer benefits, they also face challenges, including stability, drug leakage, manufacturing complexity, and production scale. This review summarizes liposome classification, preparation techniques, characterization methods, recent developments, clinical applications, challenges, and prospects, emphasizing the growing importance of liposomal systems in the drug delivery field.

KEYWORDS: Liposomes, Drug delivery systems, PEGylated liposomes, Targeted drug delivery, Controlled drug release.

INTRODUCTION

Nanocarriers are spherical vesicles with one or more lipid bilayers surrounding the aqueous core, called liposomes. Because of their amphiphilic characteristics, they can carry a broad range of therapeutic agents, including peptides, nucleic acids, hydrophilic macromolecules, and small hydrophobic drugs. This unique feature makes liposomes particularly attractive as vehicles for enhancing drug solubility, stability, and delivery to specific sites. Liposomes have been widely used as a basic technology due to their versatility, biomimetic design, similarity to cellular membranes, and good biocompatibility.[1] A liposome is a vesicular structure that is made up of a bilayer of phospholipids. The phospholipids have a hydrophilic polar head and a lipophilic (hydrocarbon) tail.[2] Biocompatible, low toxicity, biodegradable, and both hydrophobic and hydrophilic, liposomes are a safe and effective vehicle for encapsulating a wide variety of drugs.[3] They were first described in the 1960s, when Alec Bangham studied cell membranes and the role of phospholipids in blood coagulation.[4,5] There is a high level of customizability for liposomes in terms of their size, composition, lamellarity, and surface charge, depending on the use. This has been the subject of extensive research in liposome technology, with the development of more functional liposomal formulations, such as PEGylated liposomes, ligand-targeted liposomes, and stimuli-responsive liposomes.[6] The advanced liposomal systems are being widely investigated for cancer therapy, transdermal delivery, vaccine delivery, and gene therapy applications.[7] In recent years, the improvements in targeted delivery, therapeutic efficacy, and clinical applications of liposomal drug delivery systems have led to further enhancements in modern pharmaceutical research.

CLASSIFICATION OF LIPOSOMES[7-11]

Liposomes are commonly classified by size and the number of phospholipid bilayers (lamellarity), as these characteristics influence drug-loading capacity, stability, and biological performance. Based on these criteria, liposomes are divided into unilamellar, oligolamellar, multilamellar, and multivesicular vesicles, with further subdivision according to vesicle size. Table 1 presents the classification.

Table 1: Classification of Liposomes.

Liposome Classification	Size Range	Characteristics
Small Unilamellar Vesicles (SUVs)	30–100 nm	Small vesicles composed of a single phospholipid bilayer.
Large Unilamellar Vesicles (LUVs)	>100 nm	Single-bilayer vesicles with a relatively large aqueous core.
Giant Unilamellar Vesicles (GUVs)	>1000 nm	Large single-bilayer vesicles are commonly used as model membrane systems.
Oligolamellar Vesicles (OLVs)	100–1000 nm	Composed of approximately 2–5 concentric phospholipid bilayers.
Multilamellar Vesicles (MLVs)	>500 nm	Consists of multiple concentric phospholipid bilayers separated by aqueous layers.
Multivesicular Vesicles (MVVs)	>1 μm	Contain several non-concentric vesicles enclosed within a larger vesicle.

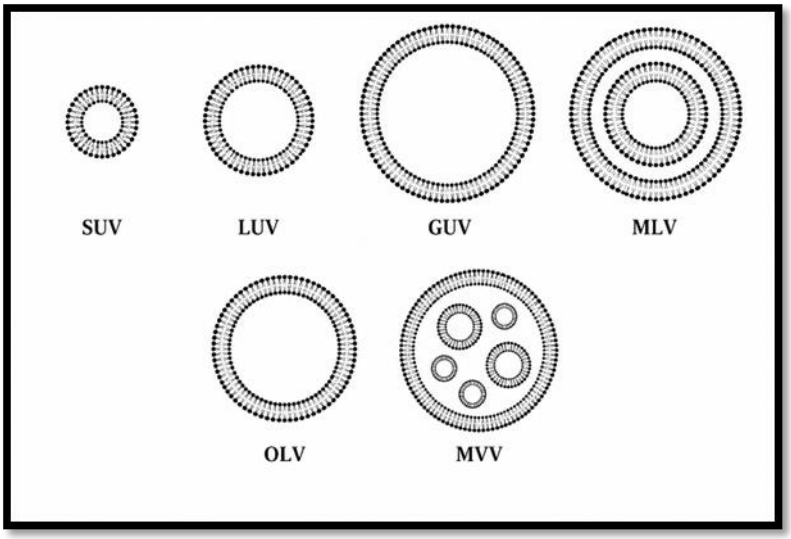

Figure 1: Schematic Representation of Different Types of Liposomes.

PREPARATION METHODS OF LIPOSOMES

Various methods have been developed to prepare liposomes with desired physicochemical characteristics and drug encapsulation efficiency. Conventional techniques such as thin-film hydration, reverse-phase evaporation, solvent injection, and detergent removal remain widely employed for liposome production. In recent years, advanced approaches, including microfluidic and supercritical fluid methods, have gained attention due to improved reproducibility, scalability, and control over liposome characteristics. Table 2 summarizes common methods used for liposome preparation.

Table 2: Methods for Preparation of Liposomes.

	Conventional methods			
Method	**Description**	**Advantages**	**Limitations**	**References**
Thin-Film Hydration (Bangham Method)	Lipids and amphiphilic molecules are dissolved in an organic solvent and placed in a round-bottom flask. The organic solvent is then evaporated using a rotary evaporator in a vacuum, creating a thin lipid film on the flask wall. Then, hydration of the thin film is performed by adding an aqueous solution containing the drug to be encapsulated, which is subjected to sonication in a sonication bath. Thus, the formation of MLVs occurs and can be extruded to produce unilamellar liposomes of desired diameter.	-Easy to prepare -Extensively utilized	-Heterogeneous MLV formation - Low encapsulation efficiency for water-soluble drugs -Poor repeatability -Unsuitable for mass production -Time-consuming	[12, 13-17]
Reverse-Phase Evaporation Method	Lipids and amphiphilic molecules are dissolved in an organic solvent and mixed with an aqueous buffer solution with the water-soluble drug to be encapsulated. Inverted micelles are formed with sonication of the mixture. Then the organic solvent is removed by rotary evaporation under low pressure, which results in the formation of viscous micelles. Some break down at a critical concentration to result in liposomes, which are surrounded by a bilayer.	-Easy to prepare -Extensively utilized -Appropriate for encapsulating large molecules like proteins and nucleic acids	-Organic solvent removal is challenging. -Possible sonication-induced denaturation of peptides	[12,14,16,18]
Solvent Injection (Ethanol/Ether)	This method may be done using several organic solvents. Both the phospholipids and the drug are dissolved in ethanol and are added to a high stirring speed water phase that is filtered or evaporated using a rotary evaporator to obtain liposomes. Diethyl ether is a second organic solvent that can be used to dissolve lipids and other amphiphilic molecules, and is a low-boiling solvent. The solution is then injected into an aqueous solution with a higher boiling point than the ether, allowing it to evaporate and form liposomes, mostly LUVs.	Ideal for the preparation of large formulation volumes	-Elevated polydispersity index -Presence of MLVs -Low encapsulation efficiency - Decreased stability resulting from organic solvents and elevated temperatures	[12,14,15,16,19]
Detergent Removal	Detergents having high critical micelles concentration (CMC) and	-Produces LUVs with	-Hydrophilic drugs detached	[12,15,16,19]

Method	lipids are dissolved in an organic solvent. Solvent is evaporated under low pressure to form a thin film lipid layer in the round bottom flask followed by hydration with an aqueous solution. The detergent is finally removed by dialysis, dilution, size-extrusion chromatography or adsorption on hydrophobic beads.	uniform size and high capacity -Easily prepared	from liposomes during detergent removal -Low liposome concentration in the final solution	
	Advanced methods			
Microfluidic Method	It is a versatile technique that enables control of microfluidics within microchannels, typically ranging between 5 and 500 µm in cross-sectional dimension. The lipids are dissolved in an organic solvent and the organic solution is then injected into the microchannels, moving in the opposite direction to the aqueous solution within the microchannels. Liposomes are created when the organic solvent and the aqueous solution are continuously mixed.	- Appropriate liposome polydispersity, morphology, average size, and lamellarity	- Elevated manufacturing expenses of the micro-circuits	[12,14,15,20,21]
Supercritical fluid method	The lipids are dissolved by a supercritical fluid such as scCO2. It is non-condensable, non-toxic, non-flammable and has a low critical temperature and pressure. The aqueous phase is continuously supplied from a liquid pump to a certain cell, which contains the supercritical lipid solution, so that the phase change of the dissolved phospholipids can occur. Once all CO2 is removed, liposomes will form because of the sudden decrease in pressure during depressurizing.	-Increased encapsulation effectiveness -Appropriate for medications with poor solubility -Controlled liposome size	-Elevated expenses despite scCO2 being inexpensive -Minimal yield	[12,15,22,23]

CHARACTERIZATION OF LIPOSOMES

Characterizing liposomes is an essential step in formulation development to ensure quality, stability, and therapeutic performance. Various physicochemical parameters, including particle size, size distribution, morphology, encapsulation efficiency, lamellarity, surface charge, and in vitro drug release, are routinely evaluated using different analytical techniques. Table 3 summarizes the commonly used characterization parameters and their corresponding analytical techniques.

Table 3: Characterization Parameters and Analytical Techniques Used for Liposomes.

Evaluation parameter	Analytical technique	References
Particle Size and Polydispersity Index (PDI)	Measuring the mean hydrodynamic radius (Rh) and the broadness of the vesicles size distribution -**Dynamic Light Scattering (DLS)**: In this case, the diameter and the polydispersity index of a diluted liposome sample are measured. The principle is the modification of the intensity of the scattered light from liposome vesicles upon application of a light source, e.g., laser beam. -**Transmission Electron Microscopy (TEM)**: Electron beam is passed through the liposomes with high acceleration (100-1000 keV) to examine the size of liposomes. There are several types of TEMs, such as cryo-TEM (which can be used to see the liposomes without staining them) and freeze-fracture TEM (which can be used to see internal and external structures of liposomes). -**Scanning Electron Microscopy (SEM)**: A high energy focused electron beam (20 keV) is used to evaluate the size of liposomes.	[24-26]
Shape and morphology	The shape and morphology of liposomes are examined by using the following techniques: **TEM, SEM, and Atomic Force Microscopy (AFM).** -**AFM**: High-resolution 3D image of liposomes taken by the scanning probe microscope technique. A sharp-tip cantilever moves up and down on a sample (liposomes) due to the features of the sample. The interaction and forces between the tip and the surface are then measured by an optical sensor. It creates an in-depth image indicating the modifications on the surface of liposomes and identifies ligands.	[27,28]
Encapsulation Efficiency (EE)	-EE is the ratio of the drug that can be successfully encapsulated in liposome vesicles to the total amount of drug used initially. -The process includes the preparation of the liposomes and separation of the encapsulated drug from the free, unencapsulated drug. This separation is done by centrifugation, ultrafiltration or dialysis. Separate the liposomes and quantify the amount of drug with analytical techniques, e.g., **spectrophotometry** or **chromatography**. The encapsulation efficiency is then presented as a percentage, which is determined by dividing the encapsulated amount of the drug by the total amount of the drug and multiplying by 100.	[15,29]
Release profile	-The amount of drug that is released from liposomes is the release profile. -The first step involves the preparation of liposomes in a buffer solution containing the drug. The liposomes are then exposed to a trigger. Samples are removed from the solution, and the released amount of the drug is measured	[27,30]

	by the **UV-vis spectrophotometry, High-performance liquid chromatography (HPLC) and Liquid chromatography-mass spectrometry (LC-MS)** methods. Data obtained are presented as a cumulative percentage of drug release versus time, and thus give a detailed profile of the release kinetics and mechanism. This profile is key for understanding how liposomal formulations will behave in biological systems and maximize their therapeutic efficacy.	
Surface charge (zeta potential)	-Measures the electrical charge on the liposome surface, which plays a significant role in the colloidal stability. -The surface charge of liposomes can be determined using DLS and Electrophoretic mobility to assess their stability. -**Electrophoretic mobility**: The sample is subjected to an electric field, and the velocity of the particles is measured as they move to the electrode of the opposite charge. The velocity is proportional to the size of the zeta potential.	[12,24]
Phase transition temperature behavior	Determine changes in the properties of the lipid bilayer in response to temperature changes. -**X-ray Diffraction (XRD)**: A liposome sample is placed in a glass capillary, and X-rays are directed at it, which interact with the electrons inside the liposomes. The X-rays diffract upon hitting the electrons, forming a diffraction pattern that changes with the gel-to-liquid phase transition, or vice versa. -**Differential Scanning Calorimetry (DSC)**: The temperature of a liposome sample is raised and the liposomes change from gel to liquid as the temperature increases. This occurs at a melting temperature (Tm), which depends on the lipid content of the vesicles. The liposomes could also be subjected to a decrease in temperature, where the heat is released, and they shift from liquid to gel phase.	[30-33]
Lamellarity	-Number of lipid bilayers -TEM, SEM, XRD, and Phosphorous-31 Nuclear Magnetic Resonance (^{31}P-NMR).	[12,32,33]

RECENT ADVANCES IN LIPOSOMAL DRUG DELIVERY SYSTEMS

Recent efforts have been directed towards the development of liposomal drug delivery systems that address the drawbacks of the traditional liposomes, like quick clearance, poor target specificity and uncontrolled drug release. Surface-modified, actively targeted, and stimuli-responsive liposomes have dramatically enhanced circulation time, biological stability, drug accumulation at diseased sites, and therapeutic efficacy. These advanced liposomal systems have broadened the applications of liposomes in drug delivery and play a major role in designing future drug delivery systems.

PEGylated (Stealth) Liposomes

The second generation of liposomes was stealth liposomes, introduced in the 1970s. They can be modified on their surface with hydrophilic polymers (PEG, polysaccharide, or glycoprotein) for improved pharmacokinetics and localization at the target site. This is done by coating the liposome surface with a steric barrier, minimizing opsonization, which marks liposomes for elimination by the mononuclear phagocytic system.[34,35] Additionally, they have enhanced biological stability and reduced leakage of the encapsulated drug.[34] Stealth liposomes have been shown to be effective for chemotherapy and gene therapy.[36]

Actively Targeted Liposomes

Third-generation liposomes are actively targeted liposomes mainly used in chemotherapy. In general, liposomes accumulate at tumor sites via the EPR effect, which allows tumors to have leaky blood vessels and increased permeability that take up more oxygen and nutrients for tumor growth. Also, tumors have poor venous return and lymphatic drainage, which allows liposomes to accumulate even more.[37] This accumulation of liposomes in tumors is known as the EPR effect. However, the drawback of passive targeting is that it does not discriminate between cancerous and healthy cells.[12] Hence, actively targeted liposomes can be created to destroy cancerous cells via receptor–ligand interactions. This is accomplished by attaching some kinds of ligands, referred to as recognition moieties, to the surface of liposomes. These ligands are specific to angiogenic endothelial cells or tumor cells, bind to the receptors they overexpress, and promote tumor targeting.[38] Antibodies, nucleic acids, carbohydrates, vitamins, and simple peptides are some examples of recognition moieties.[12] Moreover, Maruyama et al. created PEGylated immunoliposomes that carry antibodies targeting endothelial cells of the lungs in 1999. They found that these liposomes were highly targetable and also were able to escape the RES.[39] Moreover, in another study, Moghimipour et al. synthesized folate-conjugated liposomes containing 5-fluorouracil (5FU). The in vitro study of colon carcinoma (CT-26) cells showed that these liposomes have greater cellular uptake and more tumor inhibition than the free drug. Additionally, Zhang et al. prepared an integrin β3-specific ligand (B3int)-modified liposome containing DOX. Prostate cancer, including PC-3 and DU-145 cell lines, was used to perform in vitro cellular uptake studies. The results showed higher uptake of the prepared liposomes in PC-3 cells, with a 3-fold increase in cellular DOX uptake compared to that in DU-145 cells.[40]

Stimuli-Responsive Liposomes

Stimuli-responsive liposomes are liposomes that release their contents either when exposed to external (exogenous) stimuli or in response to internal (endogenous) stimuli at the target site. These internal stimuli may be a change in pH, specific enzymatic activity, or redox reactions. The external stimuli, however, may be light, heat, ultrasound, or magnetic fields.[41]

1. pH-Responsive Liposomes

These liposomes are stable at neutral pH and unstable at acidic pH; they are present in some pathological locations in the body. The pH shift leads to protonation of the functional groups of the liposome, resulting in the instability of the liposome and the release of the drug.[41]

Vila-Caballer et al. created liposomes that bear the pH-sensitive polymer stearoyl–PEG–polySDM. These liposomes are used to carry bovine serum albumin (BSA) to the bladder epithelium. It demonstrated that the mouse bladder carcinoma cells, designated as MB49, were more effective at taking up BSA at an acidic pH (6.5) than at a neutral pH (7.4). Furthermore, control liposomes were shown to lack bladder epithelium delivery ability at pH 6.5 and 7.4. On the other hand, the pH-responsive liposomes were able to efficiently deliver BSA to MB49 cells at pH 6.5, which could be useful for the targeted treatment of bladder cancer.[40,42]

2. Redox-responsive liposomes

The pathogenic sites of the body contain more glutathione (GSH) which acts as a reducing agent that can donate a hydrogen atom to the liposomes. The structure of these liposomes contains disulfide bonds, which get cleaved when they receive a hydrogen atom, thus releasing the drug at the targeted site.[43,44]

Wang et al. synthesized redox-responsive liposomes using a disulfide-derivative paclitaxel-ss lysophosphatidylcholine prodrug (PTX-ss-PC). In vitro cytotoxicity assays on lung and breast cancer cells revealed that these PTX-ss-PC liposomes are promising for inhibiting GSH-mediated tumor growth.[40,45]

3. Enzyme-responsive liposomes

These liposomes take advantage of the fact that certain enzymes are over-expressed in diseased cells. In general, they are based on the principle that the release of the drug is caused

on the cleavage of amides or esters by proteases or esterases, which modify the lipid bilayer of the liposome to release the drug at the desired location.[46]

Pourhassan et al. have manufactured secretory phospholipase A2 (sPLA2) sensitive liposomes containing oxaliplatin (L-OHP). The in vivo therapeutic efficiency of these liposomes was assessed in nude mice with squamous carcinoma FaDu (sPLA2-deficient) and colorectal adenocarcinoma Colo205 (sPLA2-expressing). They found that the drug efficacy was not increased with the use of sPLA2-sensitive liposomes (compared to low or non-sensitive liposomes) and that the mice did not survive any longer. The liver localization of these sPLA2-sensitive liposomes, on the other hand, generated a risk of hepatotoxicity and liver failure because of their high sensitivity and repeated administration for a proper therapeutic window. Moreover, reducing their toxicity comes at the expense of lowering their sensitivity, which causes them to lack an active sPLA2-controlled release mechanism, thus behaving similarly to conventional pegylated liposomes.[47]

4. Light-sensitive liposomes

Photoreactive groups become attached to the phospholipid bilayer during the synthesis. Upon activation by a light source, these liposomes lose their stability and release their contents at the target site.[48,49]

Chen et al. formulated a NIR-triggered bubble-producing thermosensitive liposome (BTSL) containing the photothermal agent (PTA) Cypate, the drug DOX, and NH4HCO3. The in vitro release study showed that the amount of DOX released from BTSL increased compared to (NH4)2SO4 liposomes after NIR irradiation at 42 °C. Furthermore, the results indicated that the system significantly enhanced the accumulation of DOX in the tumor, which resulted in improved inhibition of tumor growth and reduced side effects of DOX in vivo.[50]

5. Thermosensitive liposomes

These liposomes become hyperthermic (HT) under mild heat, causing the lipid bilayer to change from a gel to a liquid-crystalline state. This change increases the permeability of the bilayer and hence the release of the drug. Depending on the lipid bilayer composition, the required temperature to achieve HT can be set, usually in the 40–43 °C range. Moreover, magnetic field-sensitive liposomes are considered a type of thermosensitive liposome. The liposomes include a paramagnetic agent such as iron oxide, and an AMF is applied to induce magnetic hyperthermia that results in drug release at the target site.[51-53]

Derieppe et al. tracked the uptake of doxorubicin from TSL in subcutaneous rat R1 rhabdomyosarcoma xenografts. A water bath with a temperature of 43 °C and fibered confocal fluorescence microscopy (FCFM) were used for the setup. The leg bearing the tumor was placed in the water bath, with the liposomes being injected directly into the bloodstream. The results of FCFM reflected an increase in fluorescent signal, thus reflecting doxorubicin accumulation at the targeted site in tumor cells.[54]

6. Ultrasound-sensitive liposomes

High-intensity focused ultrasound is used to induce drug release from liposomes, which releases the drug by several phenomena:[55]

1. Cavitation: Gas bubbles are created and burst rapidly close to the liposomes, disrupting their structure and releasing the contents.
2. Acoustic streaming: The radiation forces from the US waves push the liposomes out of the way and cause some destabilization of the liposomes, leading to drug release.
3. Microbubble nucleation: This may also occur due to cavitation. It includes the growth of microbubbles in the liposomes, resulting in drug release upon US treatment.
4. Hyperthermia: The US energy is converted to thermal energy and releases the drug in the local hot area

Deng et al. synthesized iRGD-conjugated low temperature-sensitive liposomes loaded with DOX (iRGD–LTSL–DOX) to explore their effect with high-intensity focused ultrasound (HIFU) in targeting mammary carcinoma cells (4T1), human breast adenocarcinoma (MCF-7), and human umbilical vein endothelial (HUVEC) cells. The in vivo results indicated that DOX was released from intravascular liposomes and infiltrated into the tumor when HIFU was applied.[16,40]

CLINICAL USES OF LIPOSOMES

Cancer treatment

Cancer is the second most common cause of death after heart disease, with a deep impact on public health.[3] The use of nanocarriers in the field of chemotherapy is being actively explored, particularly liposomes which are approved by the FDA, and which are able to trap anticancer drugs in order to deliver them at the cancer cells with reduced toxicity for healthy cells.[13] They can also be used for active targeting by conjugating to ligands for specific sites, as discussed above, but they can also be used for passive targeting via the EPR effect. They also increase the circulation time and decrease the tendency to elimination of the

encapsulated drug, which is beneficial to the pharmacokinetic effect of the drug.[56] Several anticancer agents based on liposomes have been approved, such as Doxil®[57], DaunoXome®, Myocet®, Marqibo®, Onivyde®[58], LipoDox®[59], and Vyxeos®[60]. Other new formulations, like ThermoDox® and targeted liposomes loaded with oxaliplatin, are currently being investigated in clinical trials.[61]

Fungal Infections

Amphotericin B can be encapsulated in liposomes, which greatly diminishes the toxicity of the free drug, and this formulation is used extensively to treat systemic fungal infections. Liposomes are more attracted to sites of fungal infection due to their affinity for ergosterol in fungal cell membranes.[62] AmBisome® was also licensed for systemic fungal infections in 1997 and is used in the treatment of aspergillosis, candidiasis, histoplasmosis, and leishmaniasis.[57,63] Other approved formulations include Abelcet® and Amphotec®.[64,65]

Pain Management

Multivesicular liposomes are useful for a long release of analgesics, because of their special internal structure and high drug-loading capacity. DepoDur® is a liposomal form of morphine (DepoFoam® technology approved) that can be used for postoperative pain management.[66] Exparel® is a liposomal formulation of bupivacaine approved by the FDA for up to 72 hours of sustained analgesia after a single injection.[67] Furthermore, a clinical study in phase IV is being conducted to compare the effectiveness of Exparel® with the standard 25% bupivacaine in reducing pain medication use.[68]

Vaccination

1. Cancer Vaccines

Liposomes are used as antigen carriers that transport tumor-associated antigens to antigen-presenting cells (APCs) and stimulate immune responses against cancer cells.[69] They enhance antigen stability and effective transportation to immune cells.[70] The liposomal cancer vaccine PDS0101 is being evaluated in the clinic for HPV-associated cancers.[71]

2. Hepatitis A Vaccines

Virosomes are liposome-based antigen delivering and immune stimulating carriers.[62] Epaxal® is currently the first hepatitis A vaccine based on the virosome technology developed by Crucell Berna Biotech and launched in Europe in 1993. The HAV was inactivated in formaldehyde and coupled with the virosome surface for the delivery of the HAV antigen to

immunocompetent cells. The clinical trials on adults showed that more than 95% of the people had anti-HAV titers for up to 20 years after a second booster vaccine.[5,72]

3. Influenza Vaccines

Virosomal liposomes can promote antigen presentation and activate the immune system.[73] Inflexal® V contains influenza hemagglutinin in virosomes, which results in increased immune responses.[5,74] Virosomes promote interactions with antigen-presenting cells and enhance vaccine effectiveness.[75]

4. COVID-19 Vaccines

Liposomal systems based on lipids have been developed to protect and deliver mRNA inside host cells.[76,77] Vaccines from Pfizer-BioNTech and Moderna use this technology to trigger immune reactions to SARS-CoV-2. The clinical data on Pfizer/BioNTech's vaccine, Comirnaty®, showed it was highly effective against coronavirus and had a 2-dose regimen efficacy of 95% in individuals aged 16 years and older (ClinicalTrials.gov study: NCT 04368728[78]). Moreover, Moderna showed an efficacy of 94.1% in the prevention of COVID-19 and has been granted emergency use authorization by the FDA and other global agencies (ClinicalTrials. gov study: NCT04470427[79]).[63]

Other Drug Delivery Applications

The advantage of using liposomes for drug delivery to the brain is that they are biocompatible, biodegradable, and can enhance drug penetration across biological barriers. Several products have been evaluated in the treatment of glioblastoma and cryptococcal meningitis.[80,81]

Liposomes are used in transdermal drug delivery, providing controlled release and improved absorption of drugs such as corticosteroids, antibiotics, and methotrexate in the skin. Liposomal formulation of methotrexate has been seen to give better skin permeation and therapeutic efficacy in psoriasis.[82,83]

In ophthalmic drug delivery systems, liposomes increase corneal permeability, extend drug residence time, and improve therapeutic effectiveness, all while reducing ocular discomfort. The use of liposomes in glaucoma and dry eye disease has been studied, providing encouraging clinical results.[84]

CHALLENGES AND FUTURE PERSPECTIVES OF LIPOSOMAL DRUG DELIVERY SYSTEMS

Liposomes are being extensively studied and applied as a means to deliver drugs. Although liposomes have numerous advantages, including reduced toxicity, increased circulation time, and enhanced pharmacokinetic properties of the encapsulated drug, liposomes have also encountered some drawbacks and challenges that have prevented their clinical translation from bench to bedside. The phospholipid bilayer of liposomes is similar to that of cells, but it may sometimes undergo oxidation reactions and hydrolysis, which are two main causes of chemical instability. Hydrolysis occurs when the ester bonds joining the lipid components are broken.[85] These release free fatty acids, which, on hydrolysis, will reduce the pH of the surrounding medium and generate harmful substances to the human body. Vitamins C and E, antioxidants, can be used in liposome formulations to block oxidation, as well as flavonoids. Slow hydrolysis can be achieved by the addition of cholesterol, and the freeze-drying method can be used to prepare and preserve liposomes. The possibility of aggregation can be minimized by proper selection of lipids and optimization of the attachment of moieties to the surface of liposomes in the stable range in order to synthesize the liposomes.[14] The physical stability of liposomes strongly relies on the type of lipids used in their preparation, the size distribution, and the storage conditions. Any defects in the liposome's structure lead to the leakage of the encapsulated drug and liposome aggregation during storage. The use of saturated phospholipids, such as hydrogenated phosphatidylcholine (HPC), therefore, will increase the physical stability of the lipid membrane compared to unsaturated phospholipids. Further, the freeze-dried method of preservation of the liposomes might ensure good and permanent physical stability.[72] Although numerous PEGylated liposomes have been developed and have significant advantages, such as escaping the immune system, numerous studies have been devoted to their significant complications. In reality, PEGylated liposomes encounter problems in their ability to interact with the target cells due to steric hindrance (due to the PEG chain). So, uptake of liposomes by cells, which is usually by endocytosis, might be restricted. Furthermore, repeated administration of PEGylated liposomes results in the generation of antibodies because of a phenomenon called accelerated blood clearance (ABC), which affects the circulation time of liposomes in the body.[85,86]

Furthermore, for a synergistic effect and to defeat multi-drug resistance, co-delivery approaches can be employed where two or more drugs are included in one liposome. Finally, the current liposome production processes are highly complex and inefficient, making large-

scale production difficult. The most widely used technique is the ethanol injection technique, followed by the extrusion process, which is a multi-stage process and requires energy, time, and expertise, which makes large-scale production difficult. Microfluidics and nanoprecipitation are strategies that show promise by offering the potential for avoiding solvent removal and extrusion, simplifying the process, and improving scale-up efficiency for liposome production.[87]

Future studies should also include the development of combinations of liposomes and personalized medicine to create personalized drug delivery vehicles based on disease state and genomic data of the patient.[88]

CONCLUSION

Liposomes have become versatile and effective drug delivery systems due to their biocompatibility, biodegradability, and ability to encapsulate a wide range of therapeutic agents. Advances in liposomal technology have led to the development of PEGylated, actively targeted, and stimuli-responsive liposomes, which have significantly improved circulation time, targeting efficiency, controlled drug release, and therapeutic outcomes. These improvements have expanded the applications of liposomes in various fields, including cancer therapy, vaccine delivery, and other pharmaceutical applications. Despite challenges related to stability, drug leakage, manufacturing complexity, and large-scale production, ongoing research continues to address these limitations. The integration of advanced targeting strategies, multifunctional formulations, and personalized medicine approaches is expected further to enhance the potential of liposomal drug delivery systems. Overall, recent advances in liposomal technology continue to strengthen their potential as effective, safe, and targeted methods for delivering drugs.

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