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Review Article

Perspectives On Liposomes: Recent Developments, Clinical Uses, And Prospects

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ABSTRACT

Liposomes are widely recognized as a significant nanoscale drug delivery method with appealing characteristics, including an easy-to-prepare bilayer structure that assembles the cellular membrane and high biocompatibility. Over the past few decades, a great deal of work has gone into developing liposome-based drug delivery systems. Numerous drug candidates have been investigated for their potential to reduce toxicity and prolong the duration of therapeutic effect by encapsulating them in liposomes. A growing number of liposomal-based therapeutics, with a variety of uses in antiviral, anticancer, and antibacterial treatments, have been approved by the FDA and are also undergoing clinical trials. Liposomes are a promising new drug delivery system. They are known for their sophisticated technology in delivering active molecules to the site of action, and several of their formulations are currently being used in clinical settings. The field of liposome technology has advanced from studying conventional vesicles to studying "second-generation liposomes," which produce long-circulating liposomes by adjusting the vesicle's size, charge, and lipid composition. This paper focuses on strengths, limitations regarding industrial applicability, and regulatory requirements concerning liposomal drug formulations based on FDA documents.

INTRODUCTION

Liposomes are microscopic artificial bilayered vesicles in which an aqueous volume is entirely surrounded by a membranous lipid bilayer composed of natural or synthetic phospholipids. They have hydrophilic and hydrophobic compartments that can hold a range of drug candidates. It is obvious that liposomes can be

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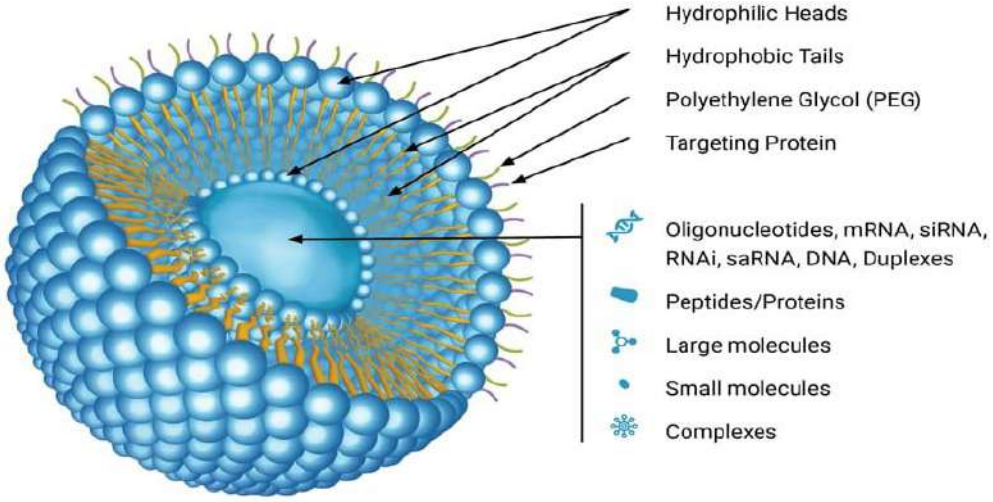
used to encapsulate gases such as nitric oxide to treat pulmonary hypertension.[1] The properties of liposomes vary significantly depending on their lipid composition, surface charge and preparation method. Furthermore, the rigidity, fluidity and charge of the bilayer determined by the choice of components. For example, unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine) give much more permeable and less stable bilayers, whereas the saturated phospholipids with long acyl chains (dipalmitoyl phosphatidylcholine) form a rigid, rather impermeable bilayer structure.[2] It has been showed that phospholipids effectively form closed structures when they are hydrated in aqueous solutions. Depending on the nature of drugs, vesicles with one or more phospholipid bilayer membranes can transport aqueous or lipid drugs. Lipids exhibit amphipathic behaviour in aqueous media, meaning that their hydrophobic sections are confiscated into spherical bilayers entropically. This process is influenced by the thermodynamic phase properties and self-assembling features of lipids.[2] In view of the fact, liposome exhibit magnificent properties, such as protecting the encapsulated substances from physiological degradation, extending the half-life of the drug, controlling the release of drug molecules, and excellent biocompatibility and safety.[7] By using passive or active targeting, liposomes can deliver their payload to the diseased site selectively, reducing systemic side effects, increasing the maximum tolerated dose, and enhancing therapeutic benefits.[3]



Liposome properties can be controlled through the type of lipids used in their preparation. Porphyrinphospholipids were employed in a recent study to create liposomes that can release their contents when exposed to near-infrared light. To create a temperature-triggered liposome, which uses temperature as an external stimulus, fatty acid elastin-like polypeptide was employed. Clinically temperature-sensitive liposomes offer benefits like increased drug accumulation because of their in vivo stability, expanded intravenous drug administration, and enhanced liposome-based drug release. [1] The main aim of these article is to understand and update the research in liposomal drug delivery system.

CLASSIFICATION OF LIPOSOMES

Liposomes can range in size from tiny vesicles (0.025 μm) to large ones (2.5 μm). Furthermore, the membranes on liposomes can be single or bilayer. The amount of drug encapsulated in the liposome is influenced by the size and number of bilayers, and vesicle size is an acute parameter in

determining the circulation half-life of liposomes. Liposomes can be classified into multilamellar vesicles (MLV), oligolamellar vesicles and unilamellar vesicles (ULV). OLVs and MLVs have 2–5 and >5 concentric lipid bilayers and shows anionic like structures respectively. Unilamellar vesicles again classified into two categories: large unilamellar vesicles (LUV) and small unilamellar vesicles. Classically, several unilamellar vesicles will combine to form a multilamellar structure of concentric phospholipid spheres separated by layers of water.[2]

MECHANISM OF LIPOSOMES FORMATION

Phospholipids have been shown to form closed structures on their own when hydrated in aqueous media. Phospholipids thermodynamic phase properties and self-assembling traits elicit the entropically driven sequestration of hydrophobic regions into spherical bilayers because they are amphipathic (both hydrophilic and hydrophobic) in nature. Put differently, there are interactions between lipid molecules and water molecules that are not favourable. As phospholipid molecules self-assemble into bilayered sheets, the solvent's negative interaction with the long hydrocarbon fatty chains is reduced, resulting in a state of reduced energy and nearly maximum stability. Soaps, detergents, and polar lipids (lecithins, kephalins) are well-known examples of amphiphiles. Bilayer sheets also begin folding or curling on themselves to create closed, sealed bilayered vesicles that surround a central aqueous core in order to reach a fully stable state.[6] By taking into account the critical micelle concentration (CMC) of phosphatidylcholine in water, this phenomenon can be quantitatively explained. The concentration of the lipid in water, known as the CMC, is typically measured in moles per liter and indicates the point at which the lipid starts to form micelles or bilayer structures instead of staying in solution as monomers. Smith and Tenford measured the CMC of dipalmitoyl phosphatidylcholine and discovered that it was 4.6x10-10 M in water. This value is consistent with what was found for comparable amphiphiles. This is obviously a very small value, demonstrating the molecule's strong preference for a hydrophobic environment, like the core of a micelle or bilayer.[6]

METHOD OF PREPARATION

There are mainly four basic stages for preparing liposomes

1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analysing the final product.[2]

Basically, there are two techniques for the preparation of liposomes

1. Passive loading techniques
2. Active loading technique

Passive loading techniques include three different methods:

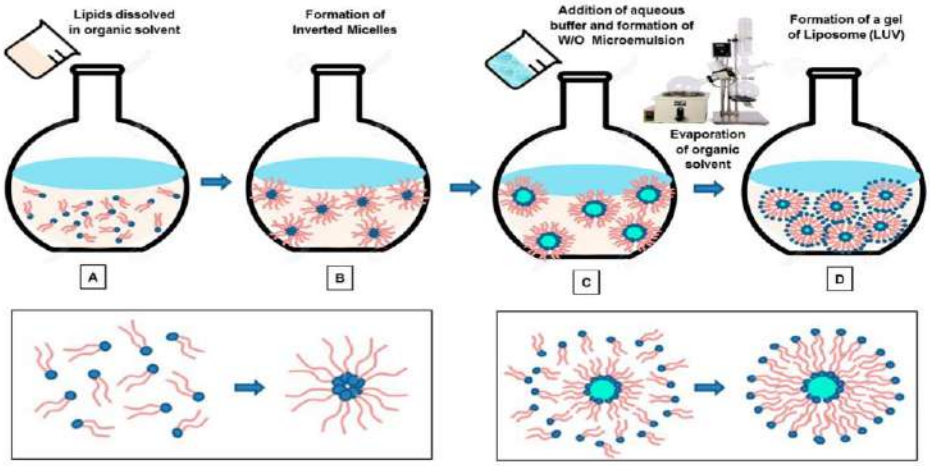
1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method.

1.Mechanical dispersion method

A. Thin film hydration method (BANGHAM METHOD)

Using a round-bottom flask, all lipids and the hydrophobic medication are dissolved in an appropriate organic solvent in this method.[8] A thin film layer was then produced by the organic solvent gradually evaporating under lower pressure. After that, an aqueous buffer solution is used to hydrate the resulting thin film at a temperature higher than the used lipid's transition temperature (Tm). A hydrophilic medication or drugs to be inserted into the liposomes' aqueous

core may be present in the hydration solution. The efficiency of drug encapsulation is determined by the rate of hydration. The higher the encapsulation efficiency, the slower the rate of hydration.[8] The control of liposome resizing, lamellarity types, and particle distributions can be achieved through two methods: using bath or probe sonicators, or extrusion through polycarbonate membranes with specific pore sizes. Compared to sonication, the extrusion method provides more stable liposomes with higher encapsulation efficiency. In addition to producing SUVs liposomes, sonication can hydrolyze or break down medications and/or lipids that are encapsulated. Liposome suspensions may be susceptible to metal contamination through probe sonication. [4]



B) Sonication

The technique that is probably most frequently used to prepare SUVs is sonication. Here, MLVs are sonicated in a passive atmosphere using a probe sonicator or a bath-style sonicator. The primary drawbacks of this technique are its extremely low internal volume and encapsulation efficacy, potential phospholipid and compound degradation, removal of large molecules, metal contamination from the probe tip, and presence of MLV in addition to SUV. They are mainly two types: Probe sonicator and bath type sonicator

a. Probe sonication:

A sonicator's tip is inserted straight into the liposome dispersion. This method has a very high energy input for lipid dispersion. The local heat produced by the energy coupling at the tip necessitates submerging the vessel in a water/ice bath. Up to one hour of sonication can deesterify more than five percent of the lipids. Additionally, titanium will slough off and contaminate the solution when using the probe sonicator.

b. Bath sonication:

A bath sonicator is filled with a cylinder containing the liposome dispersion. Compared to sonication by dispersing directly using the tip, controlling the temperature of the lipid dispersion is typically easier with this method. In contrast to probe units, the material being sonicated can be shielded in a sterile vessel or in an inert atmosphere.[2]

c. French pressure cell:

MLV is extruded through a tiny aperture in a French pressure cell. The proteins in the French press vesicle method don't appear to be very pretentious while they're being sonicated, which is an important aspect of the process. It's interesting to note that French press vesicles, which are created by sonication or detergent removal, seem to recall entrapped solutes much

longer than SUVs do. The technique calls for handling unstable materials with care. The approach is superior to the sonication method in a number of ways. As a result, the liposomes resemble sonicated SUVs in size. The method's shortcomings are that it is challenging to achieve the high temperature and that the working volumes are relatively small—the maximum being 50 mL.[2]

2. Solvent dispersion method

A. Ether injection (Solvent vaporization)

At 55°C to 65°C, or under lower pressures, a lipid solution dissolved in diethyl ether or an ether-methanol mixture is progressively injected into an aqueous solution of the material to be encapsulated. The ether is subsequently removed under vacuum, which results in the formation of liposomes. The technique's primary drawbacks are the population's heterogeneity (ranging from 70 to 200 nm) and the compounds exposure to organic solvents at high temperatures during encapsulation. [2]

B. Ethanol injection

A massive excess of buffer is rapidly injected with an ethanol lipid solution. Immediately, the MLVs are formed. The method's drawbacks include a heterogeneous population (30–110 nm), very diluted liposomes, difficulty removing all of the ethanol because it forms an azeotrope with water, and a high likelihood of the various biologically active macromolecules inactivating in the presence of even small amounts of ethanol. [2]

C. Reverse-phase evaporation method

The reverse-phase evaporation method is done by forming a water-in-oil emulsion and it is usually used as an alternative of thin-film hydration method. Firstly, the aqueous buffer containing the hydrophilic drug are mixed with the organic solvent in which lipids are dissolved. By using rotary evaporator, the organic solvent can be evaporated under a reduced pressure which leading to the formation of lipid vesicles dispersed in the aqueous solution. The average size and polydispersity of the preformed vesicles can be reduced by extrusion. The main disadvantage is therapeutic peptides may be denatured due to organic solvents and to sonication conditions. [4]

3.DETERGENT REMOVAL METHOD

Using a round-bottom flask and an appropriate organic solvent, lipids and a high critical micelle concentration (CMC) surfactant were dissolved in this method. After the solvent was gently evaporated, a thin film was obtained at the flask's bottom. The lipid film was then hydrated in an aqueous solution containing the drug molecules to produce a mixed micelles solution. Afterwards, the surfactant is eliminated using dilution, size-exclusion chromatography, adsorption onto hydrophobic beads, or dialysis. Following solution concentration, a LUV liposome vesicle will be created. The majority of hydrophilic medications separate from the liposomes during the detergent removal step, which is a major flaw in this technique.[4]

RECENT APPROACHES IN LIPOSOME PRODUCTION

Many research groups are used technique such as electroformation and hydration and extrusion methods for different applications. Formation of lipid layer on an electrode is involves in the electroformation and hydration methods. Later in presence of an aqueous solution, an electric field is applied to strip off the lipids for self-assembly into vesicles. Major drawback of this method is electric field may degrade proteins sensitive to electric field. Another extrusion method involve prepared vesicle solution is passing through a polycarbonate membrane to control the size and lamellarity of the vesicles.[1] Bulk methods produce vesicles which are not uniform both in

their lamellarity and size due to poorly controlled mechanical and chemical conditions during vesicle formation. The novel production approaches overcome this limitation by controlling of both size and lamellarity of the vesicles formed and also the reproducibility of these novel microfluidic methods are more than the conventional bulk methods. The microfluidic systems have an ability to remove the organic phase from the final vesicles unlike in bulk methods where there is a high possibility of the organic layer being entrapped in the lipid bilayer. The disadvantages of these methods in comparison to the bulk methods will be its low volume of the manufacturing process and some of the methods are cumbersome to set it up. These microfluidic techniques are typically reliable, although they only use extremely little amounts of liquids.[1]

1.Liposomes on chips

Microfluidic technologies provide a high degree of control over the process and the manufacture and overcome problems of reproducibility. Microfluidics control the volume of fluids in a geometrically constrained volume, microliter or picolitre amounts which is in sub millimetre lengths with a low Reynolds number. It can decrease the cost of the reagents and thereby increase throughput and analytical performance. Mechanical and physical characteristics of the membrane could also be altered by the presence of residual solvents in the bilayer. The lamellarity of the membrane, or the quantity of bilayers, is another important feature. The size and size distribution of the prepared liposomes are also influenced by the manufacturing processes. The vesicle population must be monodisperse for the majority of applications. Size distribution affects membrane curvature, stability, encapsulation efficiency, and transport rates across the membrane. Variability in these parameters results from any variation in size.[9] The method's primary benefit lies in its capacity to generate monodisperse vesicles. Apart from the size and composition of the membrane, other parameters that affect the stability of the vesicles are temperature, pH, salinity, and osmolarity. Vesicle instability may result in lysis, aggregation, coalescence, or budding. When formed by the emulsion transfer process, unilamellar vesicles can remain stable for over 26 days, as reported by Tan et al. A greater degree of process control is required to prepare durable vesicles, and microfluidic systems can help with that. With the use of microfluid systems, variables like vesicle size, temperature, osmolarity, pH, salinity, and fluid mechanical forces can all be precisely controlled.[1] Another aspect to take into account as contrasting various microfluidic technologies is their usability. The simplicity of use often determines what is used, as microfluidic tools can be complex and laborious to set up and operate. In the preparation of liposomes, bulk techniques such as double emulsion templating, pulsed jetting, transient membrane ejection, ice droplet hydration, droplet emulsion transfer, and hydrodynamic focusing can be employed as microfluidic approaches. A microfluidic technique with superior encapsulation efficiency using monodisperse unilamellar liposomes was reported, along with a hydrodynamic pinch off mechanism.[1]

2.Flow focusing

This method, as shown by Jahn et al., has an aqueous solution on either side and a central stream of solution with phospholipids in alcohol. The alcohol diffuses into the aqueous layer when the three flows combine to form a microchannel, diluting it beyond a critical concentration where the lipids self-assemble to form liposomes. Depending on the flow rates, the monodisperse

vesicles created by this method range in diameter from 50 to 150 nm. Microfluidic tweezing, which is analogues to flow focusing and was described by S. Lin et al., is a technique used to create membrane tubes that are suitable for the creation of vesicles from tubes. This procedure produces polydisperse vesicles. This method can be used in a continuous process to prepare vesicles. It permits the creation of aqueous and organic solutions that are stocked and linked to a microfluidic apparatus to enable the continuous synthesis of vesicles. Jahn et al. do not address encapsulation efficiency much, but it should be noted that since the formation of vesicles depends on the diffusive process from the organic layer into the aqueous layer, some material may escape into the surrounding environment prior to the formation of vesicles. Additionally, alcohol may become trapped in the liposomes created using this method by partitioning into the membrane and causing problems with stability.[1]

3.Pulsed jetting

This is a neat trick that works similarly to blowing bubbles out of a loop of soap. A planar lipid membrane is exposed to aqueous solution injected into tiny jets via a micro-nozzle. They are carried farther by the aqueous solution's momentum, which pinches the lipid membrane to create a vesicle. Funakoshi et al. provided the initial description of it with this approach, the encapsulation efficiency is excellent. One constraint is the encapsulation of large molecules, such proteins. Their ability to tolerate the shear force is unknown. The remaining solvent from the phospholipid solution in the membrane is another significant issue with this method. Kirchner et al. used Raman spectroscopy to find that the decane used in the membrane formation is present in the final vesicles at thickness of upto tens nanometres. The other two drawbacks of this methods are that it requires a lot of work to set up and is extremely sensitive to the materials and operating conditions. Accurately placing the micronozzle or micropipette is very difficult. Every time the instrument was used in this bilayer formation step, the manual pipetting micronozzle had to be adjusted. The viscosity, temperature and composition of the membrane are among the crucial parameters that indicate how the fluid jet deforms the membrane. It may frequently be necessary to replace the solutions each time the device is used. [1]

4.Double emulsion template

Utilizing a combination of organic solvent, including toluene and chloroform, the oil phase of lipid stabilized water in oil water emulsion is evaporated in this process. The external and internal oil-water phases combine to form a lipid bilayer, which eventually forms a liposome, when the oil phase is removed. Shum et al. provided the first illustration of the high throughput technique. Using this technique, monodisperse vesicles with high encapsulation efficiencies are produced.[1] Tan et al. employed a procedure, but they produced the lipid stabilized water-in-oil emulsion using microfluidic device and oleic acid, which they then transferred to an aqueous solution with water and ethanol. The phospholipids are forced to self-assembled into a lipid bilayer by the oleic acid, resulting in the formation of unilamellar and monodisperse vesicles. The vesicles formed by this method last for over 26 days. Later on, the entire procedure was carried out in a microfluidic device by the same group. Moreover, it is more biocompatible than the earlier techniques for double emulsion because ethanol is used to extract oleic acid.[1]

5.Droplet emulsion transfer

This technique was demonstrated by Pautot et al. on a macroscale. Phospholipids stabilized a water-

in-oil emulsion and moved the droplets into an aqueous medium. As the droplets traverse the interface between the oil and aqueous phases, they collect a second lipid layer. This technique results in unilamellar bilayered vesicles. The droplet emulsion method was utilized by Norieaux et al. to prepare vesicles encapsulated for gene expression. Vortexing was used to carry out the emulsification process, producing non-monodisperse vesicles. A microfluidic apparatus was used to greatly enhance the emulsification process and generate enhance the emulsification process and create a droplet emulsion. After that, this was moved into a prefabricated bulk oil-water interface. By employing a widely recognized method for microfluidic droplet formation, polydispersity problems were resolved. Despite employing various implementations, the emulsion transfer method was still unable to completely eradicate oil matter residues, even though it solves a number of other manufacturing challenges for liposomes.[1]

6.Hydrodynamic focusing

A clinically useful nanoscale vesicular system is produced by this hydrodynamic focusing technique. It is not strictly possible to classify the previously discussed techniques as microfluid systems. Diffusion-dominated mass transfer and a typical low Reynolds number microfluidic system make up microfluidic hydrodynamic focusing (MHF). For MHF, microfluid devices with a cross flow geometry or a 3D angular coaxial geometry were employed. The device's central channel usually passes through an alcohol solution that contains lipids, which is coaxially flowed through an aqueous phase made of buffers or water. In the case of 3D annular coaxial chips, the lipid solution is hydrodynamically focused into narrow sheets with a circular cross-section or a cross-flow geometry. The focused stream's size can be managed by adjusting variables like the total flow rate (TFR) and volumetric flow rate ratio (FRR). he monodispersed liposomes generated by this MHF technique could have their size and other characteristics adjusted by FRR or TFR. Compared to conventional bulk-phase preparation methods, Jahn et al. conjectured that a micrometer length scale of the sample stream allows for controllable and reproducible chemical and mechanical conditions across the stream width. M. Guimarães Sá Correia et al. examined the effects of varying FFR and TFR on liposome size and found that lower FFR and TFR led to larger particle sizes. Particles formed at 20 ml min−1 in their study were smaller than those formed at 6 ml min−1 [74]. This system makes it simple to scale up to an industrial level and can be used to produce batches that are relevant to clinical practice.[1]

CLINICAL APPLICATIONS OF LIPOSOMES

Several types of liposomal formulations were successfully implemented in clinical fields as antitumor, anti-fungal therapies, analgesics. In the USA, Doxil® was the first clinical anticancer liposome medication to be approved (1995). By inventing the pH gradient active loading and using PEGylation for stealth liposomes, it paved the way for numerous other liposomal formulations to enter the clinical application fields. When circulation half-life is not the main objective, conventional liposomes without PEGylation may be appealing. The primary purpose of DepoFoamTM is to release drugs gradually, ensuring a steady supply of medication for extended period of time.

1.Liposomes for cancer treatment

Doxil®, also known as Caelyx®, was introduced by Sequus Pharmaceuticals in 1995.Doxil was created in polyethylene glycol with the goal of treating Kaposi’s sarcoma. Another FDA approved PEGylated liposomal formulation

encasing DOX is called LipoDox®, which Sun Pharma produced in 2012. Under the generic name Daunoxome®, daunorubicin was the second anthracycline antineoplastic medication loaded in liposomes to treat acute myeloid leukemia (AML). Non- PEGylated liposomes containing DOX, known as Myocet®, have been shown to have a shorter circulation half-life and fewer adverse cardiac effects. Enclosed in the DepoFoamTM multivesicular enclosure, Depocyt® consists of Citarabine, a cell-cycle cytotoxic drug, allowing for a sustained two-week release. For the treatment of osteosarcoma, a novel liposome formulation known as Mepact® has received international approval. Under the brand name Marqibo®, vincristine is also integrated into sphingomyelin/cholesterol-based liposomes. With a longer circulation time and no surface modification, this approved formula led to a higher accumulation in the target tissues where vincristine is released gradually. Another PEGylated liposome with irinotecan that has a long-acting antitumor effect is called Onivyde®. Furthermore, Vyxeos®, also referred to as CPX-351, is made up of a 5:1 mixture of cytarabine and daunorubicin encapsulated in a liposome. This formulation improved efficacy while reducing side effects.[4]

2.Liposomes for fungal treatment

Fungisome® and Ambisome® are two of the main anti-fungal liposome formulations that have been approved. With many advantages over the free drug, they encapsulate the antifungal medication amphotericin B. These saline-stabilized Amphotericin B liposomes have a greater bioavailability, reduced toxicity, and fewer side effects.[4]

3.Photodynamic therapy

The only liposomal medication delivery agent authorized for treating age-related macular degeneration is Visudyne®, which works by preventing the development of new blood vessels in the eye.[4]

4.Pain management

Using DepoFoamTM Technology, the morphine formulation DepoDurTM produces a sustained release formula that extends the clinical effect time. Additionally, Exparel® releases Bupivacaine gradually for long-lasting pain relief via the use of DepoFoamTM technology.[4]

5.Intracellular drug delivery

Liposomal drug delivery systems enable more effective drug delivery to the cytosol, where the drug's receptors are found. Normally, cells absorb N-(phosphonacetyl)-L-aspartate (PALA) very poorly. Compared to free drug, these medications exhibited increased activity against ovarian tumor cell lines when encapsulated within liposomes.[5]

6.Sustained release drug delivery

Drugs that need a prolonged plasma concentration at therapeutic levels to achieve the best therapeutic efficacy can be released continuously with the help of liposomes. Liposomes can be used to encapsulate medications such as cytosine arabinoside for optimal sustained release.[5]

7.Intraperitoneal administration

Treatment for intraperitoneal (I.P.) tumors involves injecting the medication into the I.P. cavity. However, the quick removal of the medications from the I.P. cavity reduces the amount of medication present at the site of disease. On the other hand, liposomal encapsulated medications can deliver the maximum fraction of the drug to the target site for an extended period of time and have a lower clearance rate than free medication.[5]

8. Liposomal drugs for Alzheimer's disease

The greatest obstacle facing Alzheimer's disease treatment is getting active ingredients past the blood-brain barrier. Lowering the level of amyloid

β (Aβ) in peripheral blood has been one treatment approach for Alzheimer's disease. By performing this, the buildup of Aβ in the brain's small arteries and capillaries is stopped, preventing the development of senile plaques. The impact of liposomes containing cardiolipin (cardiolipin liposomes, CL-LIP) and phosphatidic acid (phosphatidic acid liposomes, PA-LIP) on the amount of β-amyloid in plasma, blood, and the brain was investigated. It has been discovered that structures with PA or CL can alter brain metabolism directly or indirectly by affecting the distribution of Aβ. It was possible to lower the levels of β-amyloid in peripheral blood using both kinds of liposomes. This was linked to the quick interaction between phosphatidic acid and Aβ before liver and spleen macrophages removed it. Amyloid β was bound by both released cardiolipin and phosphatidic acid. Peripheral blood replaced the brain at the resulting junction. The observed therapeutic outcome serves as a crucial illustration of the application of liposomes in Alzheimer's disease treatment The BBB keeps the majority of toxins and drug molecules out of the body. Nonetheless, unique configurations found in the blood-brain barrier can improve the transport of certain substances, such as glucose, which are essential for normal brain function. These substances use a receptor-mediated mechanism to cross the BBB. The effective administration of the medication into the brain can be achieved by utilizing this feature. [1] The lipid bilayer of liposomes containing cholesterol and soybean phospholipid, loaded with coumarin 6, was altered to include glucose through the incorporation of different PEG-glucose conjugate chain lengths. The findings indicate that the brain had higher concentrations of developed liposomes containing a medium-chain PEG than peripheral organs. Conversely, liposomes made with short-chain PEG exhibit greater accumulation in the organs outside of the brain. Because the PEGchain in this instance was too short to expose glucose, it was not present on the liposome's surface. As a result, the liposomes were unable to pass through the BBB using the glucose transporter. Longer chain PEG is somewhat flexible, which causes PEG to fold on the surface of liposomes and lessens the liposomes' capacity to interact with glucose receptors and, as a result, pass through the blood-brain barrier. This demonstrated that selecting the right receptor is crucial, but so is exposing it to the drug carrier's surface.[1] Modified liposomes have been used successfully in several other attempts to target the BBB. One is G-Technology®, a well-known, FDA-approved, patented technology that has been shown to improve brain targeting. It involves glutathione and PEGylation of liposomes, which pass through the BBB through a sodium-dependent transporter.[1]

7.Liposomal drug for Parkinson's disease

A neurodegenerative condition called Parkinson's disease (PD) affects 1-2 persons per 1000 worldwide. Loss of dopaminergic neurons (DA) in the midbrain's substantia nigra (SN) is the primary cause of Parkinson's disease (PD). It has long been thought that oxidative stress causes unstable free radicals to form, which in turn causes nerve cell death in Parkinson's disease (PD). Parkinson's disease can be treated with a variety of therapeutic approaches, however their efficacy is limited. The distribution of drugs across the blood-brain barrier to the intended brain tissue and the side effects of prolonged administration rank among these challenges as the most difficult to overcome. For diagnosis and treatment, numerous drug delivery systems, including liposomes, dendrimers, niosomes, and other nanoparticles, are being thoroughly studied.[1] Using charged liposomes to deliver dopamine HCl is one method of treating

Parkinson's disease. The benefits of this strategy include the drug's protection against deterioration in an animal model and the efficient passive delivery of the cargo to the brain. Using liposomal tyrosinase delivery to the tumor directly, another strategy makes use of tyrosinase's capacity to raise dopamine levels in brain tissue by supplying lysine. Glutathione-containing liposomes have also been developed to treat Parkinson's disease. This strategy aimed to protect the mesencephalic neuronal cells by keeping their glutathione levels at the appropriate level. Recently, liposomes modified with chlorotoxin have been used to encapsulate L-DOPA, a traditional anti-Parkinson's medication. In an animal model, the targeting moiety of stealth liposomes was chlorotoxin, which effectively delivered cargo.[1]

FUTURE PERSPECTIVES

The percentage of liposomal publications that use liposomes as drug carriers rises with time: 50% in 2000, 70% in 2010, and 74% in 2020. Despite the fact that the field of nanomedicine was developed later than the application of liposomes, the number of publications in this field has increased exponentially over time. With 3024 publications about liposome medicine in 2020, the extremely low percentages (7%) of medicine/drug nanoliposomes in total nanomedicine/drug observed may be erroneous data. Up until February 18, 2016, the FDA reported that over 500 applications for liposomes had been received.[10] Of these applications, 3% were NDAs, 1% were ANDAs, and 96% were INDs. About 100 submissions were made for combination therapy, which involved using liposomes in addition to another therapeutic.[3] Many liposomal products will soon be moved from the laboratory bench to the pilot plant and market, according to data gathered from the pharmaceutical industry and laboratory level. Many smart liposomal systems, including stimuli-sensitive liposomes (like ThermoDox) and active targeting liposomes (like anti-EGFR immunoliposomes, phase II; MBP-426, phase II) are being developed in laboratories or are undergoing clinical trials.[11] It is possible to use the microenvironment at the intended disease site to cause the liposome carrier to release the medication. Temperature, pH, light, electromagnetic fields, enzymes, and hypoxia are examples of internal or external stimuli that are commonly studied as an "on-off" switch for drug release.[3] The second Phase III clinical trial for ThermoDox, the most rapidly developed thermosensitive liposomes, failed to produce the desired results when combined with radiofrequency ablation for the treatment of hepatocellular carcinoma. But failure merely indicates that the liposomal product failed in a particular clinical design; these astute strategies will offer liposomes numerous new chances to improve therapeutic efficacy and lessen side effects.[3]

CONCLUSION

Liposomes have proven to be an effective drug delivery method for treating a variety of illnesses, from cancer to pain management. The water-insoluble, poorly bioavailable, and extremely toxic drug's pharmacokinetic and pharmacodynamic qualities were improved by the biocompatible, biodegradable, and low immunogenicity liposome formulation. Although there are currently a large number of liposome-based FDA-approved medicines on the market and more in active development, liposome-based therapeutics still have unmet clinical needs. Obstacles to production encompass a range of factors such as batch reproducibility, minimal entrapment in certain drug candidates, efficacious sterilization techniques, shelf stability, and, above all, clinical use scale-up. For the industry, producing

liposomes with multiple functions remains a challenge. Currently, over 500 liposomal formulations are undergoing various stages of clinical investigation, and several liposome formulations have been approved for use in treating various diseases. However, the chemical and physical stability of liposomes presents significant challenges. Consequently, the development of liposomes with high stability is imperative as it greatly influences their clinical application. Therefore, approximate estimation of the optimal liposomal formulation in their constituents and 3-D structure morphology may be made possible by in silico simulation and computational investigations.

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