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A COMPREHENSIVE REVIEW ON LIPOSOMES AS NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Phospholipids organized in one or more bilayers around an aqueous core make up the majority of liposomes, which are spherical vesicular drug delivery vehicles. Because they can include both hydrophilic and lipophilic medicines, they are significant new drug delivery methods. Liposomal encapsulation can extend drug circulation, alter pharmacokinetic behavior, increase drug solubility and stability, and lessen undesired exposure to healthy tissues. For use in pharmacological and therapeutic applications, a variety of liposome varieties have been produced, including conventional, uniflagellar, multilamellar, PEGylated, targeted, and stimuli-responsive liposomes.

Liposomes are prepared using a variety of techniques, including thin-film hydration, reverse-phase evaporation, ethanol injection, and microfluidic techniques. Particle size, polydispersity index, zeta potential, morphology, encapsulation efficiency, and drug-release behaviors are significant characterisation criteria. Liposomes have been extensively studied for regulated and targeted medication administration, especially for pulmonary disorders, cancer, fungal infections, pain management, and nucleic acid delivery. Clinical use has been achieved for a number of liposomal formulations, including Doxia®, Ambi some®, Oneyda®, Vyxeos®, Marqibo®, and Arikayce®. Physical and chemical instability, drug leakage, manufacturing complexity, scale-up, and variable targeting efficiency are still issues, nevertheless. Future uses of liposomal drug delivery are anticipated to grow because to recent developments in stimuli-responsive liposomes, active targeting, microfluidic production, and RNA delivery.

KEYWORDS: Liposomes, Novel Drug Delivery System, Phospholipids, Drug Encapsulation, Targeted Drug Delivery, Controlled Release, Nanocarriers

1. INTRODUCTION

Innovative medication delivery systems have been developed to overcome certain problems with conventional dose forms. Conventional drug delivery may result in poor solubility, rapid disintegration, a short biological half-life, nonspecific distribution, insufficient bioavailability, and unwanted systemic toxicity. Nanocarrier-based drug delivery systems provide a means of modifying the pharmacokinetic and pharmacodynamic properties of pharmaceuticals [3, 4].

Liposomes are one of the most important vesicular drug delivery methods. Because they are amphiphilic, they can contain hydrophilic drugs in the aqueous core and lipophilic drugs in the lipid bilayer. They are artificial spherical vesicles having an aqueous compartment surrounded by one or more phospholipid bilayers [3,7]. Liposomes can be employed to deliver a range of therapeutic compounds due to their structural flexibility [7,14]. In 1964, Alec Bangham and colleagues published the first description of liposomes. Since then, a lot of work has been done to improve drug encapsulation, circulation time, controlled drug release, targeting ability, and physical stability [3,4].

Liposomes' pharmacological significance stems from their capacity to modify the dispersion of integrated medications. Encapsulation can lessen the amount of free drug that is exposed to healthy tissues and shield delicate medications from deterioration. Targeting behavior and circulation can be further altered by surface modification using polyethylene glycol (PEG), antibodies, peptides, proteins, or other ligands.

Numerous pharmaceutical medicines that have been approved illustrate the therapeutic success of liposomes. While AmBisome® offers a liposomal version of amphotericin B for antifungal therapy, Doxil® was created to deliver doxorubicin while altering its pharmacokinetic and toxicity profile. Liposomal applications have been extended into oncology, pain management, pulmonary infections, and other therapeutic domains by further approved formulations. [4,5,18]

As a result, liposomes serve as a crucial link between nanomedicine and pharmaceutical formulation research, with ongoing advancements leading to more accurate, stable, and patient-specific drug delivery. [3,4]

2. STRUCTURE AND COMPOSITION OF LIPOSOMES

When exposed to an aqueous environment, amphiphilic phospholipids, which make up the majority of liposomes, naturally organize into bilayer structures. [7,14]

A typical liposome contains

- Aqueous core
- Phospholipid bilayer
- Hydrophilic head groups
- Hydrophobic fatty-acid tails
- Cholesterol

- Surface-modifying components, when required [7,14]

While the hydrophobic fatty acid chains inside the membrane face one another, the hydrophilic parts of phospholipids face the aqueous environment.

Principal Elements

Phospholipids: They make up liposomes' fundamental structural membrane. Phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, and sphingomyelin are typical examples. [14]

Cholesterol: Cholesterol is frequently added to membranes to increase their stiffness and decrease excessive permeability and medication leakage. [3,14]

PEG: Polyethylene glycol can be added to the liposome surface to lengthen circulation time and slow down the mononuclear phagocyte system's quick detection and clearance. [15]

Targeting Ligands: Antibodies, peptides, folate, aptamers and other compounds can be linked to the surface for targeted drug administration. [3,11]

3. CLASSIFICATION OF LIPOSOMES

Liposomes can be categorized based on their size, quantity of lipid bilayers, and functional properties.[8]

3.1 Tiny Unilamellar Vesicles

Small unilamellar vesicles are comparatively small and have a single phospholipid bilayer.[17]

3.2 Big Unilamellar Vesicles

One lipid bilayer encircles a sizable water compartment in big unilamellar vesicles.[16]

3.3 Vesicles with many layers

Multiple concentric lipid bilayers divided by aqueous layers make up multilamellar vesicles.[14]

3.4 Liposomes with several vesicles

These can offer extended medication release and have several internal watery compartments.[12]

3.5 Stealth or PEGylated Liposomes

These liposomes are made to extend circulation time and have PEG on their surface.[11]

3.6 Liposomes that are targeted

Antibodies, peptides, proteins, or other ligands that identify certain receptors are present in targeted liposomes.[21]

3.7 Liposomes that Respond to Stimuli:

These are made to release medications in reaction to particular stimuli, such temperature, pH, enzymes, or redox conditions.[24]

4. MECHANISM OF DRUG DELIVERY

The drug-delivery mechanism of liposomes involves several stages.

4.1 Administration

A suitable method, such as intravenous, intramuscular, pulmonary, oral, topical, or ophthalmic administration, is used to administer the liposomal formulation.[17]

4.2 Distribution

Following administration, liposomes disperse throughout biological fluids and tissues in accordance with their composition, size, surface charge, and surface changes.[11]

4.3 Protection of Drug

The encapsulated medication is shielded from early destruction by the lipid bilayer, which also sometimes modifies how it interacts with plasma proteins.[18]

4.4 Target Accumulation

Through passive distribution mechanisms, liposomes may accumulate preferentially in specific organs. Surface ligands can also be used to accomplish active targeting.[22]

4.5 Cellular Interaction

Liposomes may interact with cell membranes through:

- Adsorption
- Fusion
- Endocytosis
- Lipid exchange

4.6 Intracellular Drug Release

The medicine may be released into the intracellular milieu by the liposomal carrier upon cellular uptake.[11]

The overall mechanism can therefore be represented as

Administration → Circulation → Distribution → Target interaction → Cellular uptake → Liposomal destabilization → Drug release → Pharmacological action.

5. PREPARATION METHODS

An organic phase that contains lipids is emulsified with an aqueous phase. Liposomes with comparatively high aqueous-phase encapsulation are created when the organic solvent is removed

The preparation method affects liposome size, lamellarity, encapsulation efficiency and stability.[28]

5.1 Thin-Film Hydration Method

This is one of the most commonly used laboratory methods.

Steps

1. Lipids are dissolved in an organic solvent.
2. The solvent is evaporated.
3. A thin lipid film is formed.
4. The film is hydrated using an aqueous solution.
5. Liposomes are formed.
6. Size reduction can be performed if required.

Advantages

Easy to use and extensively applicable.

Limitations

Scale-up issues and a wide variation of particle sizes could arise.[11]

5.2 Reverse-Phase Evaporation

An organic phase that contains lipids is emulsified with an aqueous phase. Liposomes with comparatively high aqueous-phase encapsulation are produced when the organic solvent is removed.[23]

5.3 Ethanol Injection

An aqueous phase is injected with ethanol-dissolved lipids. Liposomes spontaneously arise as a result of rapid mixing.[25]

5.4 Detergent Removal

Lipids are dissolved with detergents and then eliminated via filtration, dialysis, or other methods.[24]

5.5 Freeze-Thaw Method

For some medications, repeated freezing and thawing may enhance encapsulation by changing the shape of the vesicles.[25]

5.6 Microfluidic Method

Particle-size control and repeatability can be enhanced using microfluidic systems, which offer regulated mixing of lipid and aqueous phases. Additionally, they have the potential for scalable and continuous manufacture.[26]

6. CHARACTERIZATION OF LIPOSOMES

Characterization is essential to determine the quality and performance of liposomal formulations.

6.1 Particle Size

Dynamic light scattering is frequently used to measure particle size. It affects physical stability, cellular uptake, and biodistribution.[13]

6.2 Polydispersity Index

The distribution of particle sizes is described by PDI. A more homogeneous liposome population is typically indicated by a lower PDI.[14]

6.3 Zeta Potential

Zeta potential can be used to evaluate electrostatic stability and gives information about the surface charge.[15]

6.4 Morphology

Morphology can be examined using:

- Transmission electron microscopy
- Scanning electron microscopy
- Cryo-electron microscopy
- Atomic force microscopy

6.5 Encapsulation Efficiency

The percentage of medication integrated into the liposomes is known as encapsulation efficiency. Encapsulation Efficiency (%) is calculated by dividing the total amount of drug by the amount of encapsulated drug x 100.[17]

6.6 Drug Loading

The amount of drug linked to a specific amount of fat or formulation is known as drug loading.[19]

6.7 Drug Release

Diffusion cells, dialysis membranes, or other appropriate techniques are used for in-vitro release investigations. [20]

7. DRUG ENCAPSULATION AND DRUG RELEASE

7.1 Passive Drug Loading

A traditional technique called "passive drug loading" involves incorporating the medication into liposomes as the vesicles are forming. Lipophilic medications attach themselves to the phospholipid bilayer, while hydrophilic drugs are typically confined in the aqueous compartment. The drug's physicochemical characteristics, lipid composition, aqueous volume, and preparation method all affect how effective passive loading is. Certain hydrophilic medications may exhibit relatively low encapsulation efficiency, despite the method's simplicity and suitability for a wide range of pharmacological substances. The amount of drug incorporated into the liposomal system can be increased by optimizing lipid concentration, drug-to-lipid ratio, and preparation conditions.[22]

7.2 Active or Remote Drug Loading

Active loading, sometimes referred to as distant loading, entails the creation of liposomes prior to the drug's incorporation. The medicine is driven into the vesicle by a chemical gradient that is created across the liposomal membrane, such as a pH or ammonium sulfate gradient. When compared to passive loading, this method can offer significantly better drug retention and encapsulation efficiency for appropriate medications. Particularly for several anticancer medications, active loading has been crucial to the creation of therapeutically effective liposomal formulations. To achieve consistent drug loading, the technique necessitates meticulous control over the liposomes' internal and exterior constituents.[28]

7.3 Factors Affecting Drug Encapsulation

Lipid composition, cholesterol concentration, drug solubility, drug-to-lipid ratio, pH, ionic strength, vesicle size, and preparation technique are some of the formulation and processing factors that impact drug encapsulation. Due to their distinct positions inside the vesicle, hydrophilic and lipophilic medicines exhibit distinct behaviors during liposome formation. Cholesterol can have an impact on drug retention and membrane packing, and pH variations can have an impact on the drug's ionization state. Therefore, to achieve high encapsulation efficiency and good drug retention during storage, the right formulation components and manufacturing circumstances must be chosen.[24]

8. DRUG RELEASE MECHANISMS

8.1 Passive Diffusion and Membrane Permeation

The integrated drug may gradually diffuse across the phospholipid bilayer to cause drug release from liposomes. The drug's physicochemical characteristics as well as the lipid membrane's permeability and composition determine the diffusion rate. While hydrophilic medications typically stay in the aqueous compartment until membrane permeability or vesicle integrity changes, hydrophobic drugs linked to the bilayer may diffuse through the membrane. Thus, temperature, membrane fluidity, lipid composition, and cholesterol content can all affect the release rate. Reducing quick exposure to high drug concentrations and sustaining drug concentrations over time are two benefits of controlled diffusion.[16]

8.2 Membrane Destabilization and Cellular Uptake

Liposomes can release their contents when the lipid bilayer becomes destabilized by interaction with biological membranes, changes in environmental conditions or degradation of lipid components. After reaching cells, liposomes may undergo adsorption, fusion or endocytosis. Endocytosis can transport the vesicles into intracellular compartments where changes in pH or enzymatic conditions may promote drug release. Fusion with cellular membranes can also result in transfer of lipids and drug into the cell. These processes are important because the therapeutic activity of many liposomal

formulations depends not only on circulation and tissue distribution but also on efficient release of the active drug at the appropriate biological site.[21]

8.3 Stimuli-Responsive Drug Release

When exposed to particular physiological or externally applied stimuli, stimuli-responsive liposomes are made to release their pharmacological payload. Thermosensitive liposomes can release their contents when exposed to a specific temperature, whereas pH-sensitive liposomes can react to acidic surroundings. Drug release is facilitated by enzyme-responsive systems, which take advantage of variations in enzyme activity between normal and sick tissues. Other experimental systems react to magnetic, light, or redox conditions. Although the stimulus must be carefully chosen to ensure that the liposome remains stable during storage and circulation, these methods are being explored to achieve greater control over the location and timing of drug release.[9]

9.0 TARGETED AND ADVANCED LIPOSOMAL SYSTEMS

9.1 Passive Targeting

The preferential distribution or concentration of liposomes in specific tissues without the use of targeting ligands is known as passive targeting. This process is influenced by the target tissue's biological traits, circulation time, liposome size, and surface features. Because of aberrant tumor vasculature and poor lymphatic outflow, nanoparticle accumulation in tumors has historically been linked to the improved permeability and retention impact in cancer studies. However, the degree of this effect varies greatly between patients and different types of tumors. As a result, while passive targeting may not always offer adequate or reliable targeting in clinical settings, it can aid in drug accumulation.[14]

9.2 Active Targeting

Attaching particular molecules to liposome surfaces in order to identify receptors or other chemical structures found on target cells is known as active targeting. As targeted ligands, antibodies, antibody fragments, peptides, folate, transferrin, polysaccharides, and aptamers have all been studied. The liposome may exhibit enhanced cellular attachment and internalization when the ligand interacts with its matching receptor. For cancer and other illnesses involving particular biological targets, this strategy is very appealing. However, permanent ligand attachment, adequate ligand accessibility, and proper receptor expression are necessary for active targeting, and these variables can differ significantly between patients and experimental models.[26]

9.3 Targeting Ligands

The targeted target's biological properties influence the choice of targeting ligand. While smaller antibody fragments and peptides may give better accessibility and smaller size, monoclonal antibodies can offer great specificity. While transferrin-based systems can interact with transferrin receptors, folate has been studied for targeting cells that express folate receptors. Due of their capacity to

identify specific molecular targets, aptamers and carbohydrates have also been investigated. During formulation development, rigorous optimization is necessary since the density, orientation, and stability of the ligand on the liposomal surface can affect targeting efficiency.[25]

10. PHARMACEUTICAL AND THERAPEUTIC APPLICATIONS

10.1 PEGylated and Stealth Liposomes

PEGylated liposomes, which include polyethylene glycol chains on their surface, are frequently created to slow down the mononuclear phagocyte system's quick detection and clearance. The hydrophilic PEG layer can lengthen circulation duration by reducing interactions with clearance-related cells and plasma proteins. The liposome may have a better chance of reaching the target region with longer circulation. One well-known example of a PEGylated liposomal medication is Doxil®. The biological effects of PEG must be taken into account during development even though PEGylation offers significant benefits because repeated treatment may cause anti-PEG immune responses in some people.[26]

10.2 Immunoliposomes and Ligand-Modified Liposomes

Immunoliposomes are liposomes that have been altered to recognize particular biological targets by adding antibodies or antibody fragments. Peptides, folate, carbohydrates, or aptamers may be present in other ligand-modified liposomes. These technologies aim to enhance intracellular medication delivery and selective cellular uptake. The target receptor's expression, the ligand's accessibility, and the stability of the ligand-liposome bond all affect how effective they are. The molecular complexity of human tissues and illness situations makes consistent clinical performance difficult, despite the fact that many ligand-modified systems have shown encouraging results in laboratory and animal research.[18]

10.3 Stimuli-Responsive and Hybrid Liposomes

AIt is possible to create advanced liposomes that react to changes in the environment, including pH, temperature, enzymes, and redox conditions. In order to provide better stability, targeting, or controlled-release characteristics, hybrid liposomes may also include lipid vesicles with polymers, nanoparticles, or other functional elements. These multipurpose systems may integrate imaging or diagnostic capabilities with medicinal delivery. In order to obtain more accurate medication administration while preserving acceptable stability and manufacturability, research is increasingly focused on creating such intelligent liposomal systems.[19]

11. ADVANTAGES OF LIPOSOMES

Major advantages include

1. The capacity to encapsulate both hydrophilic and hydrophobic medications.
2. Enhanced medication solubility.
3. Preventing drug deterioration.
4. The potential for continuous and regulated release.
5. Pharmacokinetic behavior modification.
6. The possibility of customized medication delivery.
7. Less exposure of certain harmful medications to healthy cells.
8. A higher therapeutic index for some medications.
9. Many lipid components are biocompatible.
10. Surface modification potential.
11. Possible transport of nucleic acids and macromolecules.
12. Applicability via various administration channels.

The clinical success of a number of liposomal products has been attributed to these qualities.[28]

Liposomes have several limitations

1. Instability in the body
2. Phospholipids' chemical breakdown
3. Oxidation
4. Hydrolysis
5. Leakage of drugs
6. Combination
7. Vesicle fusion
8. A comparatively high cost of production
9. Challenges in large-scale production
10. Variability from batch to batch
11. Problems with sterilization
12. Complicated requirements for characterization
13. Some formulations have limited stability
14. Potential immunological responses
15. Efficiency of variable targeting
16. Possible immunological effects of frequent PEG administration
17. The need for specialist production and quality assurance [17]

12. SAFETY, TOXICITY AND STABILITY STUDIES

12.1 Safety and Toxicity

The active medication, lipid constituents, particle properties, contaminants, and mode of administration all affect a liposomal formulation's safety profile. Despite the good biocompatibility of many pharmacological lipids, liposomal medicines may nonetheless result in immunological interactions or infusion-related complications. Certain formulations may trigger complement activation and other immunological reactions. Concerns about anti-PEG reactions after repeated exposure may also be raised by PEGylated systems. Therefore, the medicine and the entire carrier system should be taken into account while evaluating safety. To determine each formulation's safety profile, appropriate preclinical and clinical research is required.[20]

12.2 Physical Stability

Aggregation, fusion, sedimentation, vesicle size fluctuations, and drug leakage are examples of physical instability. Temperature variations, ionic conditions, lipid content, and extended storage can all cause these alterations. Because it might alter the desired release profile and decrease the amount of medicine that is still encapsulated, drug leakage is especially significant. Particle size, polydispersity, zeta potential, encapsulation effectiveness, drug content, and appearance are frequently observed in stability investigations. For the product to function consistently over the course of its shelf life, physical stability must be maintained.[21]

12.3 Chemical Stability

Drug retention and membrane structure may be impacted by the oxidation and hydrolysis of phospholipids. Oxygen, light, and high temperatures can all encourage oxidation, whereas inappropriate pH or moisture levels can enhance hydrolysis. Therefore, choosing the right lipids, shielding them from light and oxygen, maintaining controlled storage conditions, and using appropriate formulation techniques can all help to increase chemical stability. Because changes in the lipid components can ultimately impact the product's therapeutic function, stability studies should track lipid degradation in addition to drug content and release.[26]

13. REGULATORY CONSIDERATIONS

13.1 Quality Attributes

Because the performance of liposomal products depends on both the active ingredient and the carrier system, they need to be well characterized. Particle size, particle-size distribution, shape, lipid composition, drug content, encapsulation effectiveness, drug-to-lipid ratio, free-drug concentration, and release behavior are all significant quality factors. Depending on the formulation, other features including internal pH, surface qualities, and lipid degradation products may also be significant. Because different characterization approaches can make it challenging to compare data across laboratories, standardized analytical methodologies are required.[14]

13.2 Manufacturing Controls

For liposome quality to remain constant, manufacturing controls are crucial. The final product's properties can be affected by factors like lipid concentration, temperature, mixing circumstances, hydration, drug-loading conditions, purification, and size reduction. Controlling endotoxins and microbiological contamination is especially crucial for sterile items. Validation of manufacturing procedures is necessary to show that they reliably generate liposomes that satisfy predefined requirements. Information on chemistry, manufacturing, and controls for liposome drug products is specifically covered in the FDA guidance.[24]

13.3 Pharmacokinetics and Regulatory Evaluation

Chemistry, production and controls, human pharmacokinetics, bioavailability or bioequivalency, and labeling for liposome medicinal products are all covered in the FDA's liposome guidance. This illustrates how liposomal formulations, as opposed to traditional formulations, might change a drug's pharmacokinetic behavior. Therefore, both the active medicinal ingredient and the carrier's qualities must be taken into account in regulatory assessment. Regulatory approval requires constant product quality, suitable pharmacokinetic behavior, and dependable manufacturing.[14]

14. CHALLENGES AND RESEARCH GAPS

14.1 Stability and Drug Leakage

One of the biggest obstacles in the development of liposomal drugs is still long-term stability. Aggregation and fusion can result from physical instability, and membrane integrity can be impacted by phospholipid chemical breakdown. Drug leakage might alter the planned pharmacokinetic profile and decrease encapsulation. For some formulations, it is still challenging to maintain long-term stability while keeping suitable drug-release characteristics, despite the investigation of many stabilizing strategies. To create more stable lipid compositions and better storage techniques, more research is needed.[25]

14.2 Scale-Up and Reproducibility

A liposomal composition that works well in the lab might not behave the same way when manufactured on a big scale. Particle size and drug encapsulation can be affected by variations in mixing, temperature, processing time, lipid concentration, and purification. The number of crucial quality characteristics that must be managed also rises due to the complexity of liposomal products. As a result, standardized procedures and scalable production technology are crucial research goals. Although continuous manufacturing and microfluidics show promise, more industrial validation is needed.[17]

14.3 Targeting and Clinical Translation

Although targeted liposomes have shown a great deal of promise in experimental research, successful clinical translation is still difficult. In addition to being diverse within a single tumor or sick tissue, receptor expression can differ between patients. Additionally, liposome accumulation and cellular

uptake may be restricted by biological barriers. Furthermore, not every patient benefits equally from the improved permeability and retention effect. Therefore, in order to improve clinical performance prediction, future research must better integrate laboratory characterisation, animal investigations, and human pharmacology.[19]

15. CONCLUSION

One of the most significant and clinically proven innovative medication delivery methods is liposomes. Both hydrophilic and hydrophobic medications can be accommodated by their phospholipid bilayer structure, and their surface and composition can be changed to offer targeted distribution, controlled release, and extended circulation.

To create liposomes with the appropriate physicochemical properties, a number of preparation procedures have been devised, such as thin-film hydration, reverse-phase evaporation, ethanol injection, freeze-thawing, and microfluidic approaches. To guaranty formulation quality, it is crucial to characterize particle size, PDI, zeta potential, morphology, encapsulation efficiency, drug loading, release, and stability.

The medical applications of liposomes have expanded dramatically, particularly in the fields of cancer treatment, antifungal therapy, analgesia, pulmonary treatment, ocular administration, vaccination, and nucleic acid delivery. Many medications, such as Doxil®, AmBisome®, Onivyde®, Vyxeos®, Marqibo®, Exparel®, and Arikayce®, have successfully undergone clinical translation.

Physical and chemical instability, drug leakage, manufacturing complexity, scale-up, cost, characterisation, and variable targeting efficiency are still significant obstacles, nevertheless. Stimuli-responsive systems, active targeting, microfluidic manufacturing, RNA delivery, hybrid nanocarriers, and personalized nanomedicine are the main areas of focus for future study.

All things considered, liposomes have developed from basic phospholipid vesicles into complex, multipurpose drug delivery systems. Continued improvements in formulation science, nanotechnology, analytical characterisation and regulatory science are likely to significantly improve their safety, effectiveness and clinical value.

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