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Nanoliposomes As Drug Delivery Systems: A Brief Review

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ABSTRACT

Nanoliposomes are nanosized drug delivery systems which are primarily made up of phospholipid bilayers enclosing an aqueous core. They are amphiphilic, enabling many hydrophilic, lipophilic and amphiphilic therapeutic agents to be housed in various parts of the vesicle. Nanoliposomes have been greatly studied due to their ability to increase the solubility and stability of a molecule, its bioavailability, its pharmacokinetic properties and the distribution of a molecule in the tissues, and, possibly, to decrease the toxic effect of a drug on healthy tissues. Lipid composition, cholesterol concentration, surface charge, particle size and surface functionalization are methods used to modify the physicochemical properties of nanoliposomes. Modification with polyethylene glycol (PEG) may extend the circulation time, while ligands like antibodies, peptides, and other targeting molecules may allow selective binding to target cells. Drug release and cellular uptake can take place in a number of ways such as endocytosis, membrane fusion, adhesion and lipid exchange. The use of nanoliposomal formulations for anticancer drugs, proteins, peptides, vaccines and other bioactive molecules has been studied in great detail and a number of formulations have reached clinical trials. An important example of a PEGylated liposomal formulation of doxorubicin is Doxil®. Although nanoliposomes have many benefits, there are some drawbacks such as physical and chemical instability, drug leakage, complexity of production, scale-up, lack of reproducibility, immune interaction and translation from the experimental world to clinical application. The targeted, multifunctional and stimuli-responsive nanoliposomes may have even more application in the future in drug delivery.

KEY WORDS: nanoliposomes; liposomes; nanocarriers; drug delivery; targeted delivery; PEGylation; controlled release

1. INTRODUCTION

There are some disadvantages to the conventional drug administration such as poor aqueous solubility, low bioavailability, nonspecific distribution, rapid degradation, chemical instability and undesirable side effects. The restrictions may be especially significant for drugs which have a narrow therapeutic index and molecules that are prone to degradation in biological systems. Drug delivery systems are thus developed to alter the disposition and release of drugs and enhance the therapeutic efficacy of the active pharmaceutical ingredients [1,2]. Nanotechnology has played a significant role in the advancement of novel drug delivery systems. Liposomes have been the subject of high interest among the various nanocarriers due to the capacity to incorporate drugs with diverse physicochemical properties and the high degree of biocompatibility and biodegradability. Liposomes can be made of phospholipids and are spontaneously organized into bilayers in an aqueous environment [1,3]. Nanoliposomes are generally considered to be nanoscopic in size, with a hydrophilic, aqueous core and a lipid bilayer. Therefore, hydrophilic drugs can be included in the water compartment, while lipophilic drugs can be included in the lipid layer. Amphiphilic molecules can be located at the boundaries between the aqueous and lipid phases [1,4]. The structural flexibility of nanoliposomes opens up a wide range of possibilities for the transportation of small molecules as well as proteins and peptides. An important benefit of nanoliposomes is the potential to alter their physicochemical and biological properties by varying the type of lipids used and adding other lipids, such as cholesterol, polyethylene glycol (PEG) or targeting ligands. These changes may affect stability, circulation time, cell interaction and drug release [1,5]. Nanoliposomes can thus be used for targeted and controlled drug delivery, which has implications for the development of functionalized nanoliposomes. Targeted and controlled drug delivery can thus be achieved using nanoliposomes, which opens the possibility of developing functionalized nanoliposomes. This review covers the structure and classification of nanoliposomes, the most important components, drug incorporation methods, cellular uptake mechanisms, functionalization techniques, pharmaceutical applications, pros and cons as well as future prospects.

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2. THE STRUCTURE AND CLASSIFICATION OF NANOLIPOSOMES

In the presence of water, amphiphilic phospholipids self-assemble into liposomes. Polar head groups form hydrophilic interactions and hydrocarbon chains form van der Waals interactions, which help organize the lipid tails. The hydrophobic lipid chains have a tendency to stay away from water molecules, leading to spontaneous closed bilayer formation [1,6]. The vesicles produced have an internal aqueous compartment, bounded by one or more lipid bilayers. Liposomes may be unilamellar, multilamellar and multivesicular, depending on their structural organization and size.

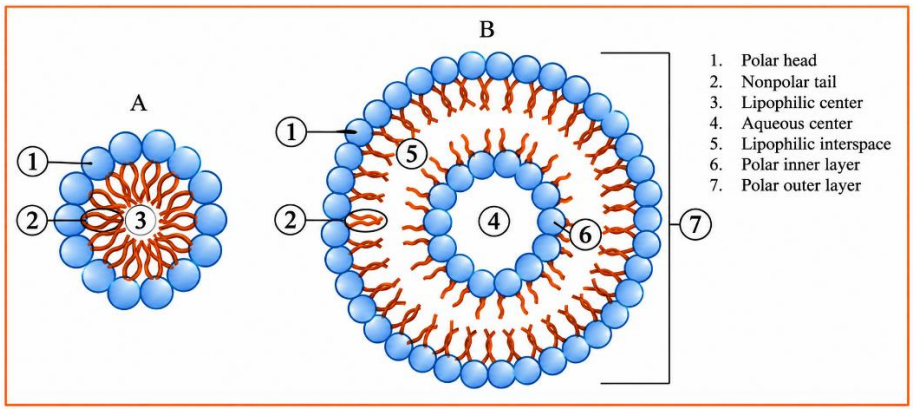


Fig 1: Structure of Nanoliposomes [7]

Table 1:Major types of liposomal vesicles [8]

Type	Structural characteristics	Typical size/feature
Small unilamellar vesicles (SUVs)	Single lipid bilayer	Approximately 30–100 nm
Large unilamellar vesicles (LUVs)	Single lipid bilayer with larger aqueous core	Approximately 100–300 nm
Giant unilamellar vesicles (GUVs)	Single bilayer, very large vesicles	Approximately 1–100 µm
Multilamellar vesicles (MLVs)	Multiple concentric lipid bilayers	Multiple bilayer structure
Multivesicular vesicles (MVVs)	Several smaller vesicles enclosed within a larger vesicle	Complex internal architecture

Liposomes can also be classified according to their surface charge as neutral, anionic or cationic systems. Surface charge influences interactions with biological membranes, proteins and other components of the biological environment [9]. For drug delivery, nanoliposomes are particularly attractive because nanoscale dimensions can be combined with surface modification and controlled drug encapsulation.

3. COMPOSITION OF NANOLIPOSOMES

3.1 Phospholipids

Liposomes are made up of the basic building blocks called phospholipids. They can self-organize to form stable bilayers in aqueous mediums because they are amphiphilic. Physicochemical characteristics of the selected phospholipid such as the phase transition temperature, the length of chain and the degree of saturation affects the rigidity, fluidity and/or drug retention of membranes [1,3]. Lipid composition can thus be varied depending on the route of administration and therapeutic goal. Stiffer bilayers could lead to the better retention of compounds encapsulated within them, while more fluid bilayers would be more suitable for the release of the drug or for interaction with the membrane.

3.2 Cholesterol

Cholesterol is commonly added to the liposomal membrane to enhance its stability. It binds with phospholipid molecules and facilitates closer packing of the bilayer. Incorporation of cholesterol may lead to decrease in

permeability of membranes and increase in physical stability [10]. However, the concentration of cholesterol needs to be carefully chosen as too much membrane stabilization could affect the release of the drug. Thus, the phospholipid-to-cholesterol ratio is an important formulation variable.

3.3 Polyethylene Glycol

PEG can be attached to the surface of liposomes, creating liposomes that are referred to as PEGylated or "stealth" liposomes. PEG is wrapped around the vesicle, creating a hydrophilic steric barrier that may decrease protein adsorption and recognition by the mononuclear phagocyte system. Thus, PEGylation can prolong the circulation of liposomes [1,8]. The biological restrictions are not completely overcome, however, with the PEGylation. Some PEGylated liposomes can give rise to an accelerated blood clearance phenomenon, due to immune recognition of PEG, with repeated administration [1]. So, it is important to take care of the amount, molecular weight and surface density of PEG.

3.4 Other Surface-Modifying Materials

Surface modification can be performed using polymers like chitosan, especially in cases where the system is for oral delivery. Other functional components can be incorporated to change surface properties, enhance stability or provide targeting [11].

The process of loading the drug and its subsequent release. The drug encapsulation by nanoliposomes is one of the significant features of nanoliposomes. Hydrophilic compounds usually become part of the aqueous core and lipophilic compounds become associated with the lipid bilayer. Amphiphilic molecules can be placed at the lipid-water interface [1,4].

4. DRUG RELEASE

The loading of drugs can be done at the time of liposome preparation or in the vesicles after preparation. Passive loading is the process whereby the drug is incorporated into the liposome in the process of formation. Active or remote loading, on the other hand, depends on the physicochemical difference between the interior and exterior of the liposome for the accumulation of the drug. The loading strategy can be selected based on the chemical and physical properties of the drug and the level of encapsulation or retention. A significant one is the PEGylated liposomal doxorubicin Doxil®. It is formulated as an ammonium sulfate gradient to achieve efficient and stable loading of the doxorubicin in the aqueous compartment [12]. Release of the drugs in nanoliposomes may be by diffusion, destabilization of the membrane, exchange of lipids, degradation of vesicles or interaction with cellular membranes. The release properties can be adjusted by modifying the lipid composition, membrane rigidity and surface properties. There is another way of controlling drug release by using stimuli responsive systems. They can be designed to react to the environment like pH, temperature or any biological stimulus. This is especially pertinent when the release of a drug at a particular tissue or cellular environment is desired.

5. FUNCTIONALIZATION, TARGETED DRUG DELIVERY.

Surface functionalization is a key approach for enhancing the biological activity of nanoliposomes. However, the classical liposomes can be cleared rapidly from the circulation and become trapped in the organs of the reticuloendothelial system, such as the liver and spleen [1,8]. PEGYlation decreases the clearance rate and increases the systemic half-life. The PEG layer is hydrophilic and creates a steric barrier that may reduce the interaction between the liposomal surface and plasma proteins, and minimize phagocytic cell recognition [1]. One way is to make targeting molecules bind to the surface of the liposomes. To facilitate binding to specific cellular receptors, antibodies, peptides, proteins, carbohydrates and other ligands can be included [5]. There are two types of targeting, passive and active. Passive targeting depends on the physicochemical properties and biodistribution of the nanocarrier. There are specific interactions between the surface ligands and receptors present on target cells, which is referred to as active targeting. Functionalization could also be utilized to create multifunctional systems that integrate drug delivery with targeting, imaging or diagnostic capabilities. This type of system can be referred to as a theranostic platform.

6. Cellular Uptake and Drug Delivery Mechanisms

Once administered, nanoliposomes come into contact with the biological fluid and cell membranes and extracellular components. They may be taken into the cells via various mechanisms depending on the characteristics of the particles and the cell types. Endocytosis is one of the significant internalisation pathways. The cellular entry may

occur via the clathrin-associated and caveolae-mediated endocytosis and/or macropinocytosis [13]. After this step, the nanoliposomes may be internalized and then undergo endocytosis, ultimately, releasing the drug inside the cells. The ultimate action of the drug will depend on its ability to get to the right intracellular or extracellular location. Besides endocytosis, the fusion between the liposomal membrane and the plasma membrane can be observed. Fusion allows the direct transfer of lipid and liposomal contents into cells. The increased attraction of nanoliposomes to the cell surface could also concentrate them in the vicinity of the cell, which may be conducive for transferring the drug. Another mechanism is the lipid exchange in which the lipid molecules are exchanged between the liposome, and the cell membrane [14]. Hence, the uptake of nanoliposomal drug delivery does not follow a single mechanism, it follows a combination of physicochemical and biological interactions.

Table 2: Major Nanoliposome Functionalization Strategies

Strategy	Main purpose	Potential benefit
PEGylation	Reduce rapid clearance	Prolonged circulation
Cholesterol incorporation	Improve membrane stability	Reduced permeability and leakage
Chitosan coating	Surface modification	Improved protection and potential oral delivery
Antibody/peptide ligand	Active targeting	Receptor-specific cellular interaction
Stimuli-responsive modification	Controlled release	Site- or condition-dependent drug release
Multifunctional modification	Combined targeting/therapy/diagnosis	Theranostic applications

The source review describes PEGylation as a means of extending circulation time, while ligands can be used to tailor interactions between nanoliposomes and target cells.

7. PHARMACEUTICAL APPLICATIONS OF NANOLIPOSOMES

7.1 Anticancer Drug Delivery

One of the more widely applied uses of liposomal drug delivery is for cancer therapy. Traditional anticancer drugs can be systemic toxic drugs due to the fact they are delivered to both tumor tissue and healthy tissue. Liposomal encapsulation can alter the distribution of the drug in vivo and pharmacokinetics and can minimize exposure to non-target tissues. One of the more well known clinically proven PEGylated liposomal formulations containing doxorubicin is called Doxil®. It was the first FDA-approved PEGylated liposomal nanodrug delivery system, and first used in clinical practice in 1995 [1,9]. Doxil® is made of hydrogenated soy phosphatidylcholine, cholesterol and MPEG-DSPE, with the doxorubicin in the aqueous core. It is reported that over 90% of the drug is encapsulated and used for active loading with a gradient of ammonium sulfate [1]. Other liposomal anti-cancer drugs have been created too, such as liposomal daunorubicin, and nanoliposomal irinotecan. These examples illustrate the possibility of altering the pharmacological properties of well-known anti-cancer agents with liposomal systems.

7.2 The delivery of proteins and peptides

The therapeutic potential of proteins and peptides is challenging due to enzymatic degradation, instability and low permeability. It is demonstrated that nanoliposomes can provide protection from unfavourable biological conditions and aid in targeting to target tissues [15]. Liposomes are amphiphilic, making it possible to encapsulate various kinds of biomolecules. Surface functionalization can be further optimized for better targeting cell interaction. Liposomes with nanometer dimensions are considered as systems that could be used for the delivery of protein and peptide drugs through the parenteral, oral, pulmonary, nasal, ocular and topical routes, overcoming the physiological barriers.

7.3 Vaccine Delivery

Liposomes also have been studied as vaccine delivery systems. They can be antigen carriers and immunomodulatory molecules; they may have a role in antigen presentation and immune responses. The versatility of composition and surface structure of liposomes offers possibilities to create vaccine delivery systems that control interactions with immune cells. [16]

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7.4 Delivery of Natural Bioactive Compounds

The large number of natural bioactive compounds with interesting pharmacological properties are subject to degradation, low bioavailability and limited permeability. Such constraints can limit their use in the pharmaceutical area [17].

Nanoliposomes are capable of offering a protective container for such molecules, and may enhance its delivery to biological tissues. The uploaded review specifically highlights the significance of nanoliposomes for natural bioactive molecules, and suggests their possible use for delivering compounds with antioxidant, anti-inflammatory, antitumor, antidiabetic and neuroprotective properties.

8. Advantages and Limitations

Nanoliposomes have several characteristics which make them desirable drug delivery vehicles. They have the following main benefits: they can be used to encapsulate hydrophilic and lipophilic drugs, they are biocompatible and biodegradable, they may be functionalized on their surface and can modify the drug release and/or its pharmacokinetic properties [18,19].

Table 3: Advantages And Limitations of Nano liposomal Drug Delivery

Advantages	Limitations
Encapsulation of hydrophilic and lipophilic drugs	Physical instability
Protection of sensitive molecules	Drug leakage
Potential for controlled release	Oxidation and hydrolysis of lipids
Surface functionalization	Aggregation during storage
Potential targeted delivery	Manufacturing complexity
Improved pharmacokinetic properties	Scale-up and reproducibility challenges
Biocompatibility and biodegradability	Potential immune interactions
Potential reduction of nonspecific toxicity	Translational and regulatory challenges

Although these benefits, formulation stability is still on the major challenges. If liposomal system is stored, it can undergo aggregation, fusion, leakage, oxidation or hydrolysis. These changes may impact particle size, encapsulation efficiency and drug release. Other concerns include manufacturing and scale-up. The composition, particle size, surface properties and drug loading efficiency should be reproducible in the large-scale production. The product(s) may be affected by the difference between laboratory scale and industrial scale manufacture. However, careful consideration of the biological interactions is also needed. The prolonged circulation is provided by PEGylated formulating, but in some cases repeated exposure leads to immune-mediated accelerated clearance from circulation [20]. Moreover, successful outcomes in experimental models cannot be assured for successful clinical translation.

9. FUTURE PERSPECTIVES

Nanoliposomes will be developed in the future for improved targeting, stability, controlled release, and manufacturing reproducibilities. Specific targeting of cellular receptors will be possible using functionalized nanoliposomes, which will aid more selective delivery. Another promising approach is the stimuli-responsive nanoliposomes. Such systems may be tailored to discharge their payload under predetermined conditions of either the physical or biological environment. These can be used to enhance the spatial and temporal release control. Multifunctional liposomes and theranostic liposomes can have both therapeutic delivery and imaging/diagnostic functions. This may aid in tracking drug distribution and response to treatment. Another key area of development is the delivery of biological therapeutics, such as proteins, peptides and nucleic acids. Liposomal systems are interesting vehicles for advanced therapeutics because they can provide protection for sensitive molecules and alter their biological distribution [4]. However, additional studies are needed to establish strong correlations between the composition of the liposomes, the physicochemical properties, the biological properties, and the clinical efficacy. The general principles for successful translation will continue to be important issues for large-scale manufacturing, quality control, long-term stability and regulatory standardization.

10. CONCLUSION

Nanoliposomes are versatile drug delivery systems that can be used to load molecules with very different physicochemical properties. They have a phospholipid bilayer and aqueous core which allows for inclusion of lipophilic, hydrophilic and amphiphilic compounds. The stability and circulation behavior and cellular interactions of these can be modified by cholesterol, PEG, polymers, and targeting ligands. Applications to anticancer therapy, protein and peptide delivery, vaccine development and delivery of natural bioactive molecules have been shown to be the pharmaceutical potential of nanoliposomes. Liposomal technology has been shown to evolve from the experimental stage to well-known pharmaceutical products as shown by the success of formulations like Doxil®. However, there are certain challenges such as physical and chemical instability, drug leakage, manufacturing complexity, scale-up, and reproducibility and biological interactions. The development of new generation of targeted, stimuli-responsive and multifunctional nanoliposomes, as well as the development of new manufacturing and characterization methods, may further make nanoliposomes a significant vehicle for the contemporary drug delivery systems.

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