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Review Article

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Bilosomes: Emerging Vesicular System for Enhanced Drug Delivery - A Comprehensive Review

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ABSTRACT
The development and application of bile salts or bile acid-based delivery systems, such as stabilized bile acid liposomes, chemical conjugates, micelles, complexes, etc., has significantly increased in the last few years. These components collectively constitute a unique delivery system known as bilosomes. These systems have special advantages over other delivery systems because of their unique molecular structure. The bilosomes of the new generation exhibit better mucosal penetration and stability in the gastrointestinal tract. Through transdermal administration, this composition aids in the suppleness and deformability of the skin barrier, allowing bilosomes to penetrate deeper layers of the skin and pass through the stratum corneum layer.

Keywords: Bilosomes, Vesicular Carriers, Drug Delivery System, Bile Salts, Targeted Delivery

Introduction

The drug delivery industry has seen significant innovation in recent decades, with pharmaceutical companies gradually introducing cutting-edge delivery systems to improve therapeutic efficacy and patient compliance. This innovation boom is being driven by the need to address problems with traditional medication administration, such as low bioavailability, rapid drug degradation, and low patient adherence. The global market for drug delivery solutions is anticipated to grow quickly due to the rising prevalence of chronic and complex diseases like diabetes, cancer, and cardiovascular conditions, which call for more precise and effective dosage systems [1-5]

The advantages of transdermal drug delivery systems (TDDS) over oral and injectable methods include avoiding first-pass metabolism, providing sustained drug release, improving patient compliance, and enabling consistent plasma drug concentrations. The stratum corneum, the outermost layer of the skin, is difficult for the majority of therapeutic agents to penetrate, especially those that are hydrophilic or have a large molecular weight.

Bilosomes are nanovesicular systems made up of bile salts, cholesterol, and non-ionic surfactants. Bile salts provide a number of special benefits. First off, unlike traditional carriers like liposomes bile salts increase the bilosomes' flexibility and deformability, which helps them move more effectively through the densely packed lipid layers of the stratum corneum. Second, by altering the skin's lipid matrix, bile salts increase penetration by weakening the skin's barrier and promoting deeper drug absorption.

Structural Aspects

The distinctive vesicular nanocarriers known as bilosomes share structural similarities with niosomes and liposomes, but they differ significantly in that they contain bile salts. By improving the stability, permeability, and ultimately the body's bioavailability of bioactive molecules, these vesicular systems are intended to enhance their oral and mucosal administration. Beyond their structural benefits, bilosomes are remarkably versatile in their ability to encapsulate a wide range of medicinal agents, including macromolecules like proteins, peptides, vaccines, and nucleic acids, as well as hydrophilic and hydrophobic small molecules. These bioactives are shielded by the special lipid-bile salt bilayer, which offers improved stability against the acidic and enzymatic conditions seen in the GI tract. Additionally, the bile salt component is essential for the interaction of bilosomes with biological membranes in addition to adding to structural robustness. This encourages specialized uptake through M cells in Peyer's patches and improves mucosal adhesion and penetration [6-10].

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Fundamental Composition

Non-Ionic Surfactants: Sorbitan monostearate or Span 60, Sorbitan monopalmitate, Span 40,Tween (polyoxyethylene sorbitan esters) 60 or 80 Cholesterol

Bile Salts: Sodium Deoxycholate, Sodium Taurocholate, Sodium glycocholate

Morphology and Architecture

Depending on how they are prepared, bilosomes usually produce unilamellar or multilamellar vesicles with spherical or multilayered structures that range in size from 100 nm to 1 μm. The aqueous core is where hydrophilic medications are primarily trapped. The lipid bilayer incorporates lipophilic medications. The lamellarity, size, and mechanical characteristics of vesicles can differ depending on the bile salt content and formation technique.

Properties of the Surface

Bile salts provide the vesicles a negative surface charge, or zeta potential, which increases particle stability through electrostatic repulsion. Mucoadhesion and entrance into epithelial cells, especially M cells in Peyer's patches, which are essential for mucosal immunity are similarly influenced by this surface charge.

Integrity and Stability

Bilosomes have substantially greater structural stability than traditional vesicles, especially in:
pH of the stomach that is acidic
Bile fluid and digestive enzymes are present. Extended storage circumstances

Bile salts and cholesterol cooperate to preserve the integrity of vesicles by:
Diminished permeability of the bilayer
Osmotic pressure differential resistance
Resistance to the effects of surfactant aggregation

Preparation Method

Bilosomes are prepared using a number of well-established methods, each of which has a unique impact on the stability, structural characteristics, vesicle size, and drug entrapment effectiveness. They are Reverse phase evaporation, Ethanol injection, High pressure homogenization, thin film hydration technique [11-15].

Reverse-Phase Evaporation Method

Organic solvents breakdown lipids and bile salts, and sonication is used to emulsify an aqueous phase with or without drug into this organic phase. Reduced pressure causes the organic solvent to evaporate, causing the emulsified droplets to collapse into vesicles that trap water-soluble medications inside the aqueous core.Large unilamellar vesicles (LUVs) with a high entrapment efficiency of hydrophilic compounds are produced using this technique. Benefits: The large aqueous core allows for high encapsulation efficiency for hydrophilic agents.

Limitations

The approach is more complicated and time-consuming than thin-film hydration, and it uses organic solvents, which could compromise the stability of the medicine.

Ethanol injection method

After being dissolved in ethanol, lipids are quickly injected into an aqueous phase typically water or a buffer that contains bile salts-while being stirred. Lipids self-assemble into bilosomes when ethanol and water combine, resulting in the instantaneous spontaneous production of vesicles. Evaporation or dialysis are then used to eliminate the ethanol [16-20].

Benefits

Easy to use, repeatable, and rotary evaporation is not required.

Limitation

Usually results in smaller vesicles but occasionally has less drug loading than thin-film techniques. Its simplicity makes it useful for scaling up.

High Pressure Homogenization Method

High pressure is used to process a suspension of lipid and bile salts via a homogenizer, where cavitation and strong shear forces cause the produced vesicles to shrink in size. Small, homogeneous vesicles with good stability can be produced using this technique.

Benefits

Narrow size distribution and industrial scalability. Limitations include the need for a lot of equipment and the possibility of heat generation that must be managed to avoid lipid or medication degradation.

Thin Film Hydration Method

This is the most widely used and conventional technique for making both liposomes and bilosomes. An organic solvent mixture, such as chloroform/methanol, is used to dissolve lipids, such as cholesterol, bile salts, and nonionic surfactants. A thin lipid coating forms on the flask's inner wall as a result of the solvent being evaporated at lower pressure using a rotary evaporator. After that, the film is hydrated at temperatures higher than the lipid transition temperature using an aqueous bile salt solution (or buffer containing medication). Multilamellar vesicles (MLVs) are formed when the film peels off due to agitation and hydration. After hydration, sonication or extrusion may be used to decrease vesicle size and produce more homogeneous, unilamellar vesicles.

Benefits

High repeatability, ease of use, and compatibility with both lipophilic and hydrophilic medications.

Limitations

For hydrophilic medications, this may lead to a heterogeneous size distribution and comparatively low entrapment efficiency.

Physiochemical Properties and Characterization

Parameter	Key points
Flexibility of membranes	Bile salts facilitate deformation and passing of biological barriers by increasing the fluidity and flexibility of the bilosome membrane.

Capability of Membrane	Fusion increased flexibility facilitates the direct transport of drugs into cells by improving the fusing of bilosomes with cell membranes.
Enhancement of Absorption	Bile salts improve permeability by relaxing tight junctions and facilitate cellular uptake by endocytosis or transcytosis
Stability of Membranes	Despite enhanced membrane fluidity, bile salts protect bilosomes against GI tract degradation caused by bile salts. practicalresult stability and flexibility work together to enhancefusion, penetration, and effective drug administration.
Particle size and Range	Effect on bilosome stability, biodistribution, cellular absorption, and bioavailability. Tissues are more deeply penetrated by smaller particles. Ideal size range is between 100 and 400 nm.
Entrapment Efficiency	Generally ranges from 50% to over 90%. High entrapment ensures optimal drug disposition which enhances therapeutic efficiency.

Mechanism of Drug Delivery

As sophisticated vesicular nanocarriers for oral and mucosal medication administration, bilosomes have drawn a lot of interest. Because of their special structure, which is defined by the presence of bile salts in the lipid bilayer, encapsulated medications can be delivered, absorbed, and treated more effectively

Defence in the GI Tract Against Enzymatic Degradation

With a very acidic pH in the stomach and a range of digesting enzymes (proteases, nucleases, and phospholipases) in the intestine, the gastrointestinal (GI) environment is harsh. The majority of medications are quite vulnerable to these degradative circumstances, particularly peptides, proteins, and nucleic acids. Bilosomes' multi-component bilayer serves as a strong physical barrier that shields encapsulated medications from low pH and harmful enzymes right away.

Improved Permeation via Membrane Fluidization Induced by Bile Salts

Bile salts increase fluidity and decrease stiffness by interfering with the lipid molecules' natural packing in the bilosome membrane. Vesicles become more flexible and deformable as a result of this fluidization, making it simpler for them to pass through or fuse with cellular membranes. Bile salts also improve paracellular transport by momentarily relaxing tight connections between epithelial cells. When combined, these actions enhance the ability of big and small molecules to pass through biological barriers.

Lymphatic Absorption and First-pass Bypass

The portal vein, which passes through the liver, or the intestinal lymphatic system, which first avoids the liver, are the two ways that drugs absorbed in the intestine can enter the bloodstream. Bilosomes are preferentially absorbed by the lymphatic system because of their lipid-rich and bile salt-containing membranes. Drugs that are prone to fast liver breakdown can achieve larger systemic concentrations thanks to this circumvention of first-pass hepatic metabolism, which enhances their therapeutic efficacy.

Challenges and Limitations

Inadequate In Vivo Clinical Information

In vitro and in animal investigations, bilosome-based therapies have demonstrated encouraging outcomes, enhancing immunological responses, permeability, and bioavailability. Strong human clinical data are still lacking, nevertheless crucial elements like toxicity, immunogenicity, pharmacokinetic variability, and long-term safety are still poorly understood.

Stability for Long-Term Storage

During long-term storage, bilosomes may experience physical instability, such as vesicle fusion or aggregation. Vesicle integrity and medication stability may also be impacted by chemical degradation, which includes lipid and bile salt hydrolysis or oxidation. Shelf life is further impacted by sensitivity to pH and osmotic conditions; poor bile salt maintenance may hasten decay.

High Cost of Production

Bilosomes are reasonably easy to prepare in a lab, but it can be difficult to manufacture them on a big scale for commercial use. The hydration technique, bile salt concentration, and lipid-to-drug ratio are all critical factors that need to be closely regulated for batch uniformity. High-priced raw materials and specialized machinery raise production costs.

Complexity in Regulatory Categorization

Bilosomes may have delays or ambiguity in regulatory categorization due to their hybrid nature, which combines the principles of synthetic surfactant-based systems and vesicular nanocarriers. Their approach to market may be slowed as a result of ambiguity surrounding testing, labelling, and approval procedures.

Conclusion

Utilizing the special qualities of bile salts, bilosomes have become a very promising nanocarrier system that improves medication delivery through a variety of administration routes. The oral bioavailability and therapeutic efficacy of encapsulated medications are greatly increased by their capacity to enhance membrane stability, encourage penetration, and enable lymphatic absorption. Bilosomes can also be used to administer hydrophobic medications, peptides, proteins, and vaccines with a variety of advantages, including targeted administration, controlled release, and fewer systemic side effects. Bilosomesin particular have demonstrated encouraging findings in transdermal drug administration due to their ability to penetrate the epidermal barrier, improve drug retention, and improve therapeutic outcomes for both systemic and local application.

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