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BILOSOMES AS EMERGING NANOVESICULAR SYSTEMS: RECENT PROGRESS, APPLICATIONS AND CHALLENGES

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ABSTRACT

Bilosomes are bile salt-containing vesicular nanocarriers that have attracted interest as drug-delivery systems because of their potential to improve the stability, permeability, and bioavailability of encapsulated therapeutics. They are generally composed of phospholipids and/or non-ionic surfactants together with bile salts, which can modify membrane properties and help vesicles withstand physiologically challenging environments. This review summarizes the definition, structural features, composition, advantages, limitations, preparation methods, characterization techniques, and therapeutic applications of bilosomes. Recent studies involving oral, topical, transdermal, buccal, and intranasal delivery are highlighted. Particular attention is given to their potential for improving the delivery of poorly soluble or poorly permeable compounds and to emerging applications in cancer, neurological disorders, and metabolic disease. Despite encouraging preclinical findings, challenges remain regarding physical stability, reproducibility, scale-up, process control, and the limited amount of clinical evidence. Further systematic in vivo studies, standardized manufacturing approaches, and well-designed clinical investigations are needed to establish the translational potential of bilosomal drug-delivery systems.

KEYWORDS: Bilosomes; nanocarriers; oral drug delivery; vesicular drug delivery; bile salts; bioavailability enhancement.

1. INTRODUCTION

Vesicular nanocarriers are widely investigated for improving the delivery of drugs that are limited by poor aqueous solubility, instability, low permeability, or extensive presystemic metabolism. Liposomes, niosomes, and bile-salt-containing vesicles have been explored as strategies to protect incorporated molecules and improve their interaction with biological membranes.[1,2,3,4]

Conventional vesicles may show limited performance after oral administration because the gastrointestinal tract presents several barriers, including variable pH, digestive enzymes, mechanical stress, and interactions with endogenous bile components. Bilosomes were developed as bile-salt-stabilized vesicles to improve the resistance and functional performance of vesicular carriers in physiologically challenging environments.[1,5]

Bile salts can alter membrane fluidity and surface properties and may act as permeation-enhancing components. Their incorporation has therefore been investigated for improving intestinal absorption and, in some systems, supporting lymphatic transport. However, the magnitude of these effects depends on formulation composition, bile-salt type and concentration, drug properties, and the administration route.[1,5]

Bilosomes have also been investigated beyond oral delivery, including topical, transdermal, buccal, and intranasal applications. Recent studies demonstrate that formulation design can be tailored to the biological barrier and the physicochemical characteristics of the drug.[6,7]

1.1 Definition of Bilosomes

Bilosomes are bile-salt-containing vesicular drug-delivery systems formed from amphiphilic components such as phospholipids and/or non-ionic surfactants in combination with bile salts. Depending on their composition and preparation method, they can form closed vesicular structures capable of incorporating hydrophilic and lipophilic compounds in different regions of the vesicle.[1,2,8,9]

1.2 Structure of Bilosomes

Bilosomes are generally described as niosome-like or liposome-like vesicular systems in which bile salts are incorporated into or associated with the vesicular membrane. Hydrophilic molecules may be accommodated in the aqueous interior, whereas lipophilic molecules can partition into the hydrophobic membrane region. The exact architecture depends on the lipid/surfactant composition and manufacturing conditions.[1,2,6]

1.3 Advantages of Bilosomes

1.3.1 Enhanced Gastrointestinal Stability: Bile salts can improve the resistance of vesicular systems to physiologically relevant gastrointestinal conditions, although the degree of protection depends on formulation composition and experimental conditions.[1,5]

1.3.2 Potential Improvement in Oral Bioavailability: Bilosomes have been investigated for poorly soluble or poorly permeable drugs and bioactive compounds, with several preclinical studies reporting improved exposure compared with free drug or conventional formulations.[1,5,10,11]

1.3.3 Dual Drug-Loading Capability: The aqueous interior can accommodate hydrophilic compounds, while hydrophobic compounds may be incorporated into the vesicular membrane.[1,2,12]

1.3.4 Non-Invasive Administration: Oral, topical, transdermal, buccal, and intranasal routes have been investigated, potentially offering route-specific advantages over invasive administration.[6,7,13]

1.3.5 Enhanced membrane interaction and permeability: Bile salts can modify membrane properties and may enhance drug–membrane interactions and permeation.[1,5]

1.3.6 Potential Biocompatibility: Phospholipids and bile salts are physiologically relevant components; however, biocompatibility and safety must be established for each formulation rather than assumed solely from composition.[1,5]

1.3.7 Controlled or Sustained Drug Release: Depending on vesicle composition and drug–carrier interactions, bilosomes can modify the release profile of incorporated drugs.[10,14,15]

1.4 Limitations of Bilosomes

1.4.1 Physical Instability During Storage: Vesicles may undergo aggregation, fusion, leakage, or changes in particle size and surface characteristics over time.[1,5,16]

1.4.2 Scale-up Challenges: Laboratory preparation methods may be difficult to translate directly to reproducible industrial manufacturing because mixing, energy input, phase ratios, and process conditions can change with scale.[5,17]

1.4.3 Variable Entrapment Efficiency: Drug loading and entrapment depend on drug physicochemical properties and the composition and preparation conditions of the vesicles[1,10,14]

1.4.4 Manufacturing Cost and Material Quality: Pharmaceutical-grade lipids, surfactants, bile salts, process controls, and analytical characterization can contribute to manufacturing complexity and cost.[5,17]

1.4.5 Sensitivity To Formulation And Storage Conditions: Changes in temperature, pH, ionic environment, or other storage variables may affect vesicle integrity and drug retention; therefore, stability conditions should be established experimentally.[1,16]

2. COMPOSITION OF BILOSOMES

The composition of bilosomes is selected to obtain vesicles with suitable size, membrane characteristics, drug-loading capacity, and stability. Common components include phospholipids or non-ionic surfactants, bile salts, optional cholesterol or other membrane modifiers, the therapeutic agent, and an aqueous phase.[1,2]

2.1 Phospholipids: Phosphatidylcholine, lecithin, and soybean-derived phospholipids may provide the structural framework of lipid-based bilosomes.[1,2]

2.2 Bile Salts: Bile salts such as sodium cholate, sodium deoxycholate, and sodium taurocholate are characteristic components of bilosomal systems and can influence membrane fluidity, surface properties, and stability.[1,5,10]

2.3 Cholesterol: Cholesterol may be incorporated in some bilosomal formulations to modify membrane packing, rigidity, and permeability. Its inclusion is formulation-dependent and is not an obligatory component of every bilosome.[1,6,10]

2.4 Non-ionic Surfactants: Non-ionic surfactants may be used to form or modify the vesicular membrane and to tune vesicle characteristics.[1,2,15]

2.5 Therapeutic Agent: The drug or bioactive compound may be located predominantly in the aqueous compartment or within the hydrophobic membrane, depending on its physicochemical properties.[1,2]

2.6 Aqueous Medium: Water, buffer, or another suitable aqueous phase is used for vesicle formation or hydration, depending on the preparation technique.[1,14]

3. FORMULATION AND PREPARATION METHODS

3.1 Thin Film Hydration Method: Lipids and other organic-soluble components are dissolved in an appropriate organic solvent system and the solvent is removed under reduced pressure to form a thin film. The film is then hydrated with an aqueous phase containing the required components, followed by size reduction where necessary.[1,10,14]

3.2 Hot Hydration Method: Lipid or surfactant components are processed at an elevated temperature and hydrated with a suitable aqueous phase. Mixing and sonication may be used to obtain a more uniform dispersion. Process temperature should be selected according to the thermal characteristics of the formulation components.[1]

3.3 Solvent-Evaporation Method: Organic-soluble components are dissolved in an organic phase and combined with an aqueous phase containing suitable surfactant/bile-salt components. Subsequent solvent removal and size-reduction steps can yield vesicular dispersions.[1]

3.4 Modified Hot Homogenization Method: In some formulations, lipid components are melted or processed at elevated temperature and homogenized with an aqueous phase, followed by incorporation of bile salts and other formulation components and subsequent cooling. The method is formulation-specific and requires control of temperature and shear conditions.[1]

3.5 Probe Sonication Method: Sonication can be used as a size-reduction step after mixing the drug, membrane-forming components, bile salt, and aqueous phase. Sonication time and energy can influence particle size, PDI, temperature, and vesicle integrity.[14,15]

3.6 Reverse-Phase Evaporation Method: An aqueous phase containing the drug is emulsified with an organic phase containing vesicle-forming components. Removal of the organic solvent under reduced pressure can produce vesicular structures. The method requires careful control of phase composition and solvent removal.[1]

3.7 Ethanol Injection Method: An ethanolic solution of suitable lipid/surfactant components and drug is injected into an aqueous phase containing bile salts under controlled stirring.

Rapid solvent dilution promotes self-assembly of vesicular structures. Ethanol concentration, injection rate, mixing, and downstream size reduction can affect the final product.[15]

4. CHARACTERIZATION TECHNIQUES

4.1 Particle Size and Polydispersity Index (PDI): Dynamic light scattering (DLS) is commonly used to determine the hydrodynamic particle size and PDI. These parameters provide information about vesicle size and dispersion uniformity.[1,10,14]

4.2 Entrapment Efficiency (EE%): Unentrapped drug is separated from the vesicular fraction using an appropriate separation technique, and the amount of incorporated drug is quantified by a validated analytical method. EE% is generally expressed as the percentage of total drug associated with the vesicular formulation.[10,14,18]

4.3 Zeta Potential: Zeta potential provides information about the electrokinetic surface characteristics of the vesicles and can be useful for assessing colloidal stability. Interpretation should consider the formulation medium and ionic strength.[1,10]

4.4 Vesicular Morphology: Transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), or related techniques may be used to examine vesicle morphology, depending on the formulation and study design.[1,14,15]

4.5 In Vitro Drug Release: Release can be evaluated using dialysis-based or other validated membrane/separation methods under appropriate sink and experimental conditions. Release data may be fitted to kinetic models when justified by the study design.[10,14,15]

4.6 FTIR and DSC: Fourier-transform infrared spectroscopy (FTIR) can be used to investigate chemical interactions and compatibility between the drug and excipients, while differential scanning calorimetry (DSC) provides information about thermal transitions and changes in the physical state of formulation components.[14]

4.7 Stability Studies: Stability studies should monitor relevant attributes such as particle size, PDI, zeta potential, drug content, entrapment efficiency, appearance, and drug leakage under defined storage conditions.[1,16]

5. APPLICATIONS

5.1 Cancer Therapy: Bilosomal formulations have been investigated to improve the delivery and biological activity of anticancer compounds. For example, costunolide-loaded bilosomes

showed enhanced cytotoxic and pro-apoptotic effects in LS174T colon cancer cells in a preclinical study.[19] TPGS-coated curcumin bilosomes have also been investigated for oral anticancer delivery.[20,21] Chitosan-coated apigenin bilosomes have similarly shown notable antimicrobial and cytotoxic activity in vitro.[22]

5.2 Neurological Disorders: Intranasal bilosomal systems have been explored for nose-to-brain delivery. Zolmitriptan-loaded bilosomes were designed to improve nasal residence and direct brain delivery, while luteolin-loaded nanobilosomes were evaluated in a mouse model of memory impairment.[7,23]

5.3 Cardiovascular and Metabolic Applications: Bile-salt-enriched vesicles have been investigated for the delivery of carvedilol, with studies reporting improved oral bioavailability compared with conventional formulations.[11, 24] Lovastatin-loaded bilosomes have also been investigated as a strategy for improving the delivery of a poorly water-soluble lipid-lowering drug.[14]

5.4 Antidiabetic and Nutraceutical Delivery: Bilosomes have been studied for oral delivery of bioactive compounds with poor aqueous solubility or limited bioavailability. An alkaloid nutraceutical-loaded bilosomal system demonstrated an improved pharmacokinetic profile and hypoglycemic effect in diabetic rats.[11]

5.5 Topical and Transdermal Delivery: Highly deformable bilosomes have been investigated for topical delivery of terconazole, while other bile-salt-containing vesicles have been studied for cutaneous delivery and enhanced skin deposition of poorly permeable drugs.[15,25]

5.6 Vaccine and Macromolecule Delivery: Bilosomes have also been investigated as adjuvant-free carriers for oral vaccine antigens, with studies reporting protection against gastrointestinal pathogens and improved mucosal immune responses.[26,27] Bile salt-stabilized vesicles have similarly been explored for the oral delivery of therapeutic proteins and peptides, which are otherwise degraded by gastrointestinal enzymes.[28]

6. CHALLENGES IN TRANSLATION AND COMMERCIALIZATION

Despite promising preclinical findings, the translation of bilosomes into commercial products remains challenging. Long-term physical stability, drug leakage, batch-to-batch

reproducibility, control of critical process parameters, and scale-dependent changes in mixing and energy input must be addressed.[1,5,16,17]

Manufacturing at larger scale requires robust and reproducible processes capable of controlling vesicle size, PDI, drug loading, and other critical quality attributes. Recent work on continuous and in-line homogenization of vesicular systems illustrates the importance of scalable process engineering for reproducible nanovesicle manufacture, although such approaches should not be considered specific validation of every bilosomal formulation.[17]

Another important limitation is the relatively limited clinical evidence compared with the large body of formulation and preclinical research. Standardized characterization protocols, appropriate in vivo studies, toxicological assessment, stability-indicating methods, and well-designed clinical investigations will be important for establishing the safety, efficacy, and regulatory acceptability of bilosomal products.[1,5]

7. CONCLUSION

Bilosomes are versatile bile-salt-containing vesicular systems with potential for improving the delivery of poorly soluble, poorly permeable, or biologically unstable therapeutics. Their performance can be tailored through the selection of membrane-forming components, bile salts, drug-loading strategy, and manufacturing method. Evidence from recent preclinical studies supports their investigation across oral, topical, transdermal, buccal, and intranasal delivery routes. However, formulation instability, scale-up, reproducibility, process control, and limited clinical evidence remain important barriers to translation. Future work should focus on standardized manufacturing and characterization, rigorous in vivo evaluation, long-term stability, safety assessment, and clinically relevant studies to determine whether the promising laboratory findings can be translated into robust pharmaceutical products.[1,5,17]

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