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Enhancing Drug Delivery Efficiency with Bilosomes: Formulation, Applications, and Future Perspectives

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Abstract: Bilosomes are lipid-based vesicular carriers incorporating bile salts, offering targeted drug delivery with enhanced bioavailability. These innovative carriers address limitations of conventional systems, improving drug stability and efficacy. Despite challenges in in vitro-in vivo correlation, bilosomes show promise in transdermal, oral, and ocular drug delivery, revolutionizing pharmaceutical formulations.

IndexTerms **- Bilosomes, Liposomes, Drug delivery systems, Drug stability, Applications of bilosomes.**

1. INTRODUCTION

Vesicular systems represent innovative drug delivery platforms designed to target therapeutic agents to specific sites of action [1]. Traditional vesicular carriers have garnered significant interest for their ability to enhance the bioavailability and permeation of drugs via various administration routes, including oral, parenteral, and transdermal/topical routes. Among these carriers, liposomes have emerged as prominent nanocarriers for drug delivery, underscored by their historical significance as the first nanoscopic drug delivery system to receive clinical approval with Doxil® in 1995 [2]. Despite their efficacy, conventional vesicular carriers face challenges such as gastrointestinal instability, low entrapment efficiency, and limited drug retention within the stratum corneum [3]. To address these limitations, novel lipid vesicular systems, including transfersomes, ethosomes, and more recently, bilosomes, have been developed. Transfersomes and ethosomes, comprising phospholipids with edge activators or high ethanol content, respectively, offer enhanced drug delivery capabilities. Bilosomes represent a newer class of soft lipid vesicular systems, highlighting ongoing efforts to innovate and improve drug delivery technologies. These advancements hold promise for optimizing drug delivery strategies and improving therapeutic outcomes in various medical applications [4].

Bilosomes are comprised of deoxycholic acid integrated into the membrane structure of niosomes. Typically employed as penetration enhancers in the pharmaceutical sector, bile salts play a crucial role in enhancing oral bioavailability [5]. Bilosomes represent closed bilayered vesicular carriers composed of lipids combined with nonionic surfactants and bile salts. They exhibit a size range of 5-200 nm, characterized by spherical shapes and the presence of both unilamellar and multilamellar vesicles [6]. First described in 2001 by Conacher et al. at the University of Glasgow, bilosomes utilize bile acids synthesized in the liver and stored in the gallbladder [7]. These amphiphilic molecules possess a steroid nucleus with a hydrophilic side chain containing hydroxyl groups and a hydrophobic side chain containing methyl groups. Bile salts play a critical role in emulsifying and solubilizing dietary fats by forming mixed micelles. Consequently, they enhance the permeability of lipophilic drug molecules across cellular membranes, thereby increasing the oral bioavailability of various biologically active compounds. Encapsulation of proteins, peptides, or vaccines in bilosomes has demonstrated the ability to induce both systemic and mucosal immunity upon administration, offering advantages such as enhanced immunogenicity and protection against pathogens at mucosal surfaces without eliciting undesirable interactions between pathogens and host cells [8].

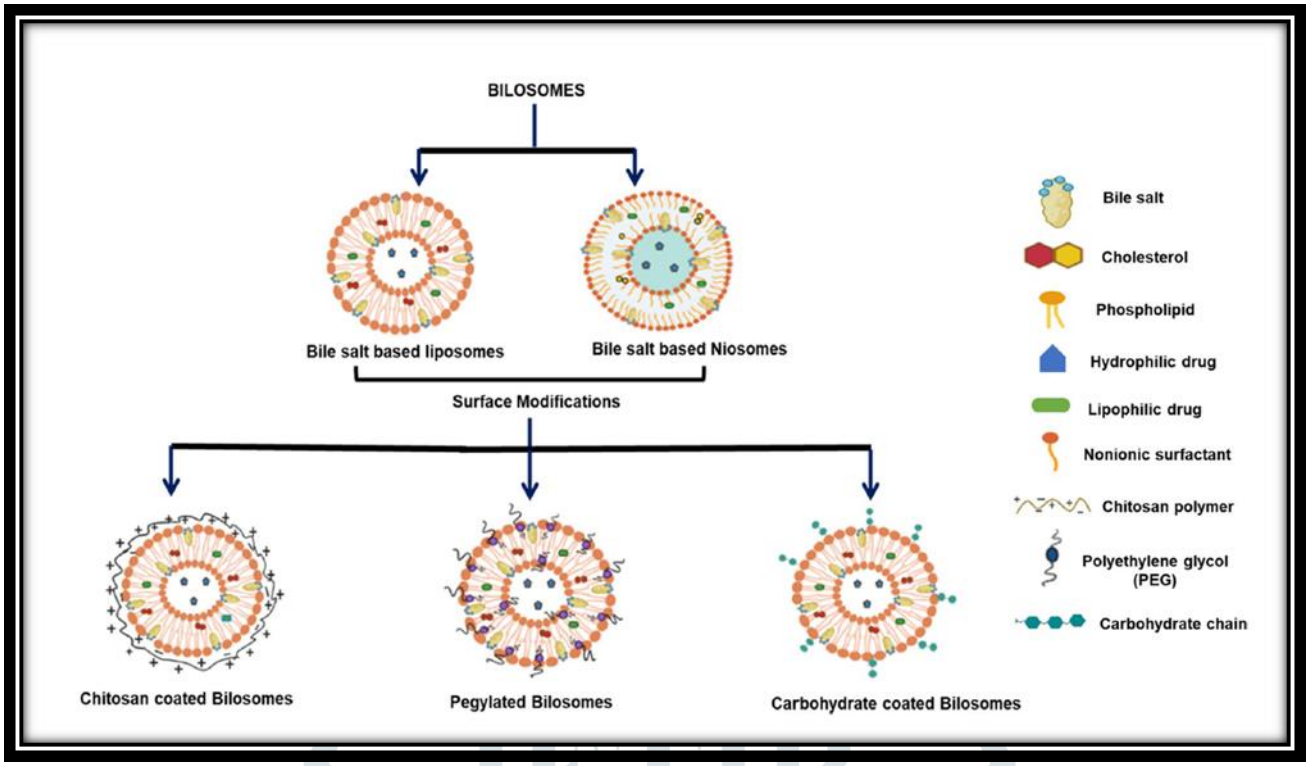

Fig 1: Bilosomes with their surface modifications

2. COMPOSITION OF BILOSOMES [9]

Bilosomes typically consist of two layers:

- An inner layer containing hydrophilic drugs or antigens
- An outer layer comprising bile salts or hydrophobic drugs.

2.1 Materials Used in the Preparation of Bilosomes

The materials utilized in bilosome preparation include lipids, nonionic surfactants, and bile salts.

2.1.1 Lipids

a. Phospholipids

Phospholipids exhibit remarkable biocompatibility with cellular membranes due to their amphiphilic nature, allowing them to self-assemble and promote wetting and emulsification. Their amphiphilic properties enable the formation of closed concentric bilayers in aqueous environments. Additionally, phospholipids possess excellent emulsifying capabilities, making them effective stabilizers for emulsions. Commonly employed phospholipids in bilosome formulations include [10]:

- Dicetyl Phosphate
- Soybean Phosphatidylcholine
- Mono Palmitoyl Glycerol
- Dimyristoyl Phosphatidylcholine
- Dilauroyl Phosphatidylcholine

b. Cholesterol

Cholesterol, possessing amphiphilic properties, integrates into cellular membranes, with its hydroxyl groups aligning towards the aqueous surface and its aliphatic chains orienting parallel to the acyl chains within the bilayer's core. This incorporation enhances the rigidity of bilosomes[11] .

2.1.2. Nonionic Surfactants

Nonionic surfactants are favored in bilosome preparation due to their stability and compatibility compared to anionic, cationic, or amphoteric forms. They exhibit reduced hemolytic activity and irritation to cellular surfaces while helping maintain physiological pH levels. Serving as solubilizers, wetting agents, emulsifiers, and permeability enhancers, they also act as potent P-glycoprotein inhibitors, facilitating drug absorption and tissue-specific targeting. Nonionic surfactants possess polar and non-polar segments, ensuring high interfacial activity. The chain length and size of hydrophilic head groups influence drug entrapment efficacy. Surfactants with stearyl (C18) chains demonstrate greater entrapment efficacy compared to those with lauryl (C12) chains. Commonly used nonionic surfactants for vesicle formation include [12]:

- Alkyl esters and alkyl glyceryl ethers
- Polyoxyethylene 4 lauryl ethers

- Polyoxyethylenecetyl ethers and stearyl ethers
- Sorbitan fatty acid esters – Span 40, Span 60, Span 80
- Polyoxyethylene fatty acid esters - Tween 20

2.1.3. Bile Salts

Bile salts, natural biosurfactants found in the gastrointestinal tract, aid in lipid digestion and absorption. They stimulate bile secretion, thereby enhancing the absorption of biologically active molecules. Mixed micelle systems leverage this property to improve the solubility of highly lipophilic drugs. Additionally, bile salts contribute to the stability of bilosomes in simulated fluids by inducing repulsion between the bile salts within bilosomes and those in the gut lumen. Bile salts commonly utilized in bilosomes include [13].

- Sodium Deoxycholate (SDC)
- Sodium Glycocholate (SGC)
- Sodium Taurocholate (STC)
- Sodium Taurodeoxycholate (STDC)

3. METHODS USED FOR PREPARATION OF BILOSOMES

3.1 Thin film Hydration Method

The preparation of bilosomes, commonly known as lipid film hydration, involves dissolving a mixture of drug, non-ionic surfactant, and cholesterol in an organic solvent, followed by evaporating the solvent to form a thin lipid film. After ensuring complete solvent evaporation, the lipid film is hydrated using distilled water or a buffer solution containing bile salt. This hydration process, conducted under stirring, results in the formation of multilamellar vesicles (MLVs) or large unilamellar vesicles (LUVs). Subsequently, the particle size is further reduced through sonication. The resulting bilosomal dispersion is stored at 4°C until characterization. Additionally, multilamellar vesicles produced via this method can be converted into small unilamellar vesicles using techniques like membrane extrusion, ultrasonication, or homogenization. Overall, this method provides a systematic approach to fabricate bilosomes, lipid-based nanoparticles crucial for drug delivery applications [14], [15]

3.2 Ethanol injection method

The ethanol injection method is a technique utilized for the preparation of bilosomes, specialized lipid-based nanoparticles for drug delivery purposes. In this method, a mixture comprising the drug, non-ionic surfactant, and cholesterol is dissolved in ethanol under controlled conditions, typically in a water bath. Subsequently, this ethanolic solution is gradually injected into a phosphate buffer solution with a pH of 7.4 while being stirred magnetically. Prior to injection, bile salts and other edge activators may be incorporated into the aqueous phase. As the ethanolic solution is introduced into the buffer, bilosome dispersions begin to form, evidenced by the turbidity of the solution. Stirring is sustained to ensure complete volatilization of ethanol, and the resulting dispersions are cooled to room temperature. Finally, sonication may be employed to further refine the particle size distribution and enhance the uniformity of the bilosomes. This method offers a controlled and reproducible approach for the preparation of bilosomes, which play a crucial role in targeted drug delivery systems [16], [17].

3.3 Reverse phase evaporation method

The formulation of bilosomes incorporating a triblock copolymer and varying concentrations of sodium cholate was achieved through the thin film hydration method. In a round-bottom flask, a mixture of chloroform phosphatidylcholine, cholesterol, and pluronic P123 was dissolved, followed by the evaporation of the organic solvent under reduced pressure. Distilled water containing sodium cholate was then added to hydrate the formed lipid thin film, with the addition of glass beads to enhance film detachment. The resulting suspension of multilamellar vesicles was stirred for 2 hours and further reduced in particle size using a probe sonicator. These bilosomes, stored at 4°C, were prepared for drug loading. By incorporating curcumin into the lipid phase and methylene blue into the aqueous phase, double-loaded vesicles were produced using a similar procedure. This method, employing a combination of organic and aqueous phases followed by sonication, offers a controlled approach for the preparation of bilosomes, crucial for targeted drug delivery systems [18].

3.4 Hot homogenization method

The hot homogenization method was employed for the preparation of bilosomes, a lipid-based nanoparticle system. Initially, a hot paraffin oil bath was set up at 120°C, while a water bath at 50°C was prepared. Sodium bicarbonate buffers with pH values of 7.6 and 9.7 were also prepared. A 100 mM bile salt solution was then made using 25 mM sodium bicarbonate buffer of pH 9.7. Lipids including MPG, Chol, and DCP were melted by heating at 120°C for 10 minutes. Subsequently, an emulsion was formed by adding sodium bicarbonate buffer of pH 7.6 and homogenizing immediately. After homogenizing for 3 minutes, an antigen solution was added and further homogenized for 5 minutes. To minimize antigen exposure, it was added at the final stage of homogenization. The bilosome suspension was then allowed to cool to 30°C and incubated for 2 hours in an incubator/shaker at 220 rpm. This method ensures proper encapsulation of the antigen within the bilosomes, enhancing their stability and efficacy for targeted drug delivery [19].

3.5 Probilosomal method

In the probilosomal method, sorbitol particles are initially placed in a round-bottomed flask and vacuum dried using a rotary evaporator. Following this, a solution containing phosphatidylcholine, bile salt, and the desired drug dissolved in an organic solvent is added dropwise into the flask to load them onto the sorbitol particles. Subsequently, the loaded sorbitol particles undergo freeze drying to yield probilosomal powder. This powder is then manually agitated in water to convert it into bilosomes.

In summary, the probilosomal method involves vacuum drying sorbitol particles, followed by the addition of a solution containing phosphatidylcholine, bile salt, and drug onto the sorbitol particles. After freeze drying, the resulting probilosomal powder is converted into bilosomes through manual agitation in water. This method offers a controlled approach for the preparation of bilosomes, potentially enhancing drug delivery efficacy [20].

4. ADVANTAGES OF BILOSOMES [21]

- Bilosomes facilitate the efficacy of antigens, even in small quantities, and enhance the potency of weak antigens when administered.
- Bilosomes offer a safe and efficient alternative to conventional vaccines as they do not necessitate the use of live pathogens.
- This non-invasive system provides benefits in terms of user acceptance and adherence.
- The conventional injection method is burdened by elevated costs relative to alternatives and necessitates trained personnel for administration.
- The reduced toxicity profile makes it suitable for a broad spectrum of therapeutic agents.
- Modulation of the immune response can be achieved by controlling the size of the carrier vesicle.
- Bilosomes eliminate the need for cold-chain storage requirements for preparations like vaccines.
- Bilosomes offer a novel delivery system that enhances patient compliance, facilitates ease of administration, and potentially extends patent life.

5. DISADVANTAGES OF BILOSOMES [22]

- One major limitation of bilosome formulations is the poor correlation between in vitro and in vivo results, stemming from the lack of in vitro methods that accurately replicate physiological conditions.
- Existing in vitro release assays do not adequately mimic biological environments, impacting vesicular digestion.
- Additionally, when applied to ex vivo permeation models and cell lines to assess vesicular permeability, these formulations exhibit drawbacks.
- Despite their efficacy as carriers for cationic substances, bilosomes demonstrate inefficiency in entrapping anionic active agents, resulting in low entrapment efficiency. This is attributed to the negatively charged and hydrophilic nature of bile salts, which hinder the entrapment or incorporation of cationic actives, unless membrane stabilization effects are exerted.

6. APPLICATION OF BILOSOMES

6.1 Transdermal Drug Delivery System

Al-mahallawi et al. investigated the potential of bilosomes in transdermal drug delivery, particularly with Tenoxicam (TX). Their findings indicated enhanced transdermal transport of TX, offering a promising strategy to mitigate gastrointestinal side effects associated with oral administration.

6.2 Oral Immunization against Tetanus

Mann et al. demonstrated significant systemic and mucosal immunity through oral immunization with tetanus toxoid-loaded bilosomes. The entrapped antigen induced a Th2 response, resulting in elevated IgG1 and IgA antibodies, comparable to parenterally delivered tetanus toxoid.

6.3 Bilosomes as Oral Drug Candidates

Evaluation of insulin-loaded bilosomes with different bile salts in male Wistar rats revealed insights into their relative bioavailability. Various bile salt formulations incorporating recombinant human insulin were assessed, shedding light on their potential as oral drug candidates [23].

6.4 Ocular Drug Delivery

Liposomes containing tacrolimus have shown promise in corneal penetration. However, insufficient transcorneal permeation limits their therapeutic efficacy, highlighting the need for enhanced drug delivery systems like bilosomes in ocular applications [23]

7. FUTURE PERSPECTIVES

Vesicular drug delivery systems offer diverse applications across pharmaceuticals, cosmetics, cosmeceuticals, and food industries. They enable targeted drug delivery to infection sites, reducing drug toxicity without adverse effects [24]. Additionally, they enhance drug biopharmaceutical properties, improving bioavailability, particularly for poorly soluble drugs. Despite the preference for oral administration by patients, many drugs struggle with absorption through the gastrointestinal tract, limiting their effectiveness. This challenge is particularly significant for vaccines and biologic therapeutics, with only a 1% uptake rate. Moreover, approximately one-third of small molecule drugs, especially those targeting the central nervous system, face obstacles in oral absorption. Thus, vesicular drug delivery systems offer a promising approach to overcome these limitations and enhance therapeutic outcomes.

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