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Review Article

**BILOSOMES: A NOVEL VESICULAR CARRIER FOR DRUG  
DELIVERY – A REVIEW**

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**Abstract:**

*Vesicular drug delivery systems are promising agents with diverse applications in pharmaceuticals, cosmeceuticals and cosmetics. Bilosomes are bilayered vesicles of non-ionic surfactants and bile salts which are similar to niosomes. Bile salts are endogenous surfactants which act as a double-edged sword by increasing the aqueous solubility and permeability of active pharmaceutical ingredient. These vesicular structures increase the solubility of lipophilic drugs and increase the stability of the formulation in the gastrointestinal tract. Bilosomes are ultradeformable flexible structures which increases the stratum corneum permeability. Thus these have applications in both oral and transdermal drug delivery. These vesicles are utilised for topical drug delivery like ocular and intranasal drug delivery. In addition, bile salt integrated nanomedicines like probilosomes, surface engineered bilosomes and non-oral bilosomes have been surveyed. Tremendous research in the last decade has made bilosomes a potential carrier system. The extensive search has been presented related to the formulation and characterisation of bilosomes. Bilosomal systems have profound application in biological therapeutics and vaccine delivery. This review offers a comprehensive and informative data focusing on the great potential of bile acid and their salts for therapeutic application. In conclusion, bilosomes are superior to other conventional vesicular carriers (liposome and niosome) with regards to the stability, low toxicity and bioavailability.*

**Key words:** Vesicular drug delivery system, bilosome, endogenous surfactants, aqueous solubility, permeability, ultradeformable, nanomedicines, biological therapeutics, vaccine delivery, bioavailability

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## INTRODUCTION:

Pharmaceutical nanotechnology is the most innovative and highly specialized field which will revolutionize the pharmaceutical industry in near future. Nanocarriers have been used to circumvent problems associated with the conventional drug delivery systems. Vesicular carriers like liposome and niosome have gained great attention during the last few decades in biomedicine [1]. Even though they have many advantages, they have disadvantages also. It includes problems associated with stability and leakage of the encapsulated drug. Bilosome a novel vesicular carrier composed of non-ionic surfactant and bile salt are very useful in overcoming the limitations of the conventional vesicular carriers [2]. Bilosomes were first described by Conacher et al [3]. It was stated that 70% of new drug candidates were discarded in early stages due to poor solubility in water. Poor solubility leads to problems with bioavailability [4]. These bile salts stabilized vesicles are capable of enhancing the solubility of poorly water soluble drugs thereby enhancing the bioavailability. Increased solubility is due to bile salt micelle formation at critical bile salt micellar concentration. Due to their amphiphilic property they can associate in water and form micelle when their concentration is greater than critical micellar concentration.

The stability of the bile salt vesicles in gastrointestinal tract make it as wonderful carrier for the delivery of proteins, peptides and antigens [5]. The stability in gastrointestinal environment is due to repulsion between bile salts in the vesicle and the external bile salts in solution. Bilosomes have profound application not only in oral drug delivery. It is an effective transdermal drug delivery carrier. These are nano sized formulations which is optimum for transdermal delivery [6]. The conventional bilosomes contain span 60 as non-ionic surfactant and sodium deoxycholate as bile salt. Bile acids are endogenous surfactants synthesised in liver and stored in gall bladder and exists as salts. They have surface active and interfacial properties. They adopt flat conformation at interfaces with rigid steroidal backbone parallel to the interface to allow contact of hydroxyl groups with the aqueous environment. They have emulsifying, solubilising and wetting properties [7]. It acts as a penetration enhancer in topical dosage forms including buccal, ocular, nasal, transdermal routes of administration. Negatively charged bile salts increases the stability of the formed vesicular system. It has fluidizing effect which enhances the permeability of the drug. Thus bile salt stabilized vesicles improve stratum corneum permeability [8]. Sodium deoxycholate is the most commonly used bile salt due to its lipophilic, anionic nature and high

membrane permeability [9]. Span 60 is used in the conventional bilosomal systems because they have higher alkyl chain length and saturated thus imparting increased surfactant lipophilicity and thus increasing the efficiency of encapsulation of the drug. Bilosomal systems show biphasic release profiles which shows an initial burst followed by sustained release of drug [10]. Actually these bilosomes are modifications of the conventional vesicular carriers. The basic difference between bilosomes and conventional vesicles is their composition and structure. Bilosomes consists of edge activators like bile salts whereas conventional carriers are deprived of it. Edge activators act by lowering the surface tension of the vesicle bilayer resulting in the destabilization of vesicles which improves tissue penetration. Bilosomes exhibit lowest *in vitro* drug release but highest bioavailability. This is because the *in vitro* release media are usually deprived of any bio surfactants, enzymes or bile content and thus fails to mimic *in vivo* conditions [11].

## COMPOSITION OF BILOSOMES

- Non-ionic surfactants
  - Span 60
  - Span 40
  - Span 80
  - Tween 80
  - Tween 40
- Cholesterol
- Bile salts
  - Sodium deoxycholate
  - Sodium taurocholate
  - Sodium lithocholate
  - Sodium tauroglycocholate
  - Sodium glycocholate [5,12]

## ADVANTAGES OF BILOSOMES

- Increases aqueous solubility of poorly water soluble drugs
- Enhanced chemical and storage stability
- Enhanced stability in gastrointestinal tract
- Improves permeability of drug
- Small particle size
- Increased encapsulation efficiency
- Alters stratum corneum permeability by loosening intercellular lipid barriers
- Highly deformable
- Prolonged drug release
- Extended duration of action
- Reduced dose, dosing interval of drug
- Both hydrophilic and lipophilic drugs can be encapsulated

- Bioavailability of drug from bilosome is greater than liposome and micronized form of drug
- Easy availability of excipients, low cost
- Oral, ocular, buccal, nasal, transdermal delivery is possible
- Topical application helps to overcome systemic side effects, prevents first pass, avoids degradation of drugs in the stomach by acids and enzymes [11,13]

#### LIMITATIONS OF BILOSOMES

- Poor *in vitro in vivo* correlation due to lack of *in vitro* method that mimic *in vivo* condition thereby increasing the difficulty in characterization
- Incorporation of anionic hydrophilic drug cause migration of drug to external space thereby decreasing the encapsulation efficiency of drug
- Minor irritation [5,14]

#### VARIETIES OF BILOSOMES

##### a) Probilosomes

These are dry, free flowing granular products that instantaneously form bilosomal dispersion on ingestion. Due to its dry nature their stability is high. They have high permeability also. Formation of a lipophilic ion pair between the drug and the bile salt increases the encapsulation efficiency of drug [15, 16].

##### b) Non oral bilosomes

Transdermal permeation of drug is increased by bile salt containing vesicles. Ultra deformable liposomes for transdermal application are called as transferosomes. These are otherwise referred as non oral bilosomes because these ultra deformable structures contain bile salts [17].

##### c) Surface engineered bilosomes

The surface of the bilosomes are modified for drug targeting and to improve the stability of the drug. Glucmannan modified bilosomes are used for oral administration of Tetanus Toxoid. This enhances the chemical and conformational stability of entrapped Tetanus Toxoid. The immunological response of the encapsulated drug also can be improved. The stability of Glucmannan against digestive enzymes is attributed by its polymeric nature. Better immune response was elicited after oral administration of Glucmannan bilosomes compared to conventional bilosomes. This was related to the existence of high density of mannose molecules over the bilosome surface that resulted in more precise recognition and binding of bilosomes to mannose receptors [3,5,18].

##### d) Bile salt liposome

Liposomes are vesicular carriers commonly used for drug delivery. Orally administered liposomes have low solubility in the gastrointestinal tract because of the acids and enzymes present in the stomach. The physiological bile salts have membrane disruptive effects thereby producing premature drug release prior to intestinal absorption. Thus liposomal vesicles are stabilized by addition of bile salts. The increased stability is due to repulsion between bile salts present in the vesicles and external bile salts [19-21].

#### FORMULATION VARIABLES

##### a) Type of non-ionic surfactant

Span type surfactant is commonly used. This is because they have high phase transition temperature and thus increases the efficiency of encapsulation. Among the span type surfactant span 60 is commonly used. Span 60 has higher alkyl chain length than span 40 and thus will have increased surfactant lipophilicity and increased encapsulation efficiency. Span 80 has unsaturation and thus its vesicle permeability is high and reduces the encapsulation efficiency. Absolute zeta potential of bilosomes prepared by using span 60 as surfactant is high [22-24].

##### b) Amount of lipid

Cholesterol is the lipid component. It also increases the flexibility of the vesicle and imparts fluidizing effect. The amount of cholesterol determines the particle size and encapsulation efficiency. When the amount of cholesterol is high there is increased interaction of cholesterol with hydrophobic tail of span 60 which result in close packing and decreases the particle size of vesicles. Due to this close packing the encapsulation efficiency is also increased. But when the cholesterol concentration is increased further it causes perturbation of bilayer and expulsion of drug from vesicles. Increased concentration of cholesterol reduces drug leakage thereby decreasing the percentage drug release [22-24].

##### c) Type and amount of bile salt

Anionic bile salts are commonly employed because they can produce stabilized vesicles. Sodium deoxycholate is commonly used because it is more anionic, lipophilic and can form ion pair with drugs. Bile salts increases the flexibility of bilosomes and reduces the membrane tension resulting in small particle size. It also reduces leakage of the encapsulated drug. Incorporation of bile salts produce a sustained release of drug. Anionic bile salts improves stability by reducing

the aggregation and maintains optimum zeta potential [22-24].

d) Sonication time

Increasing sonication time reduces vesicle size increasing the lamellar diffusion area thereby increasing the drug release. Sonication method also affects the particle size.

## METHODS OF PREPARATION

### 1. Hot homogenization method

It is also called as melt method. Monopalmitoyl glycerol, cholesterol, diacetyl phosphate were heated at 130°C. Bile salts like sodium deoxycholate in buffer was taken and added to the above mixture and vortexed. Non entrapped bilosomes were removed by centrifugation and entrapped one's were resuspended in appropriate buffer [25,26].

### 2. Thin film hydration

It is often referred as lipid film hydration. Drug, non-ionic surfactant and cholesterol were taken in round bottomed flask and dissolved in suitable organic solvent. The organic solvent was evaporated using rota-evaporator to obtain a thin film of lipid. Ensure complete evaporation of the solvent. The formed film is hydrated using distilled water or buffer containing the bile salt and stirred in a magnetic stirrer to obtain bilosomal dispersion [27-29]. The particle size was further reduced by sonication. The dispersion is stored at 4°C until characterisation. Multilamellar vesicles prepared by thin film hydration can be converted into small unilamellar vesicles by using membrane extrusion, ultrasonication, and homogenization [27-29].

### 3. Ethanol injection method

Drug, non-ionic surfactant and cholesterol were dissolved in ethanol in a water bath. The ethanolic solution was slowly injected into phosphate buffer pH 7.4 and is magnetically stirred. Bile salts and other edge activators are added formerly to aqueous phase. Bilosome dispersions are formed which are indicated by turbidity of solution. Stirring was continued to ensure complete volatilization of ethanol. Dispersions are cooled at room temperature and sonicated [24,30].

### 4. Reverse phase evaporation

In this method phosphatidyl choline and bile salt were dissolved in ethyl ether. Buffer solution containing the drug was added to it. It is subjected to ultrasonication. It results in the formation of reverse water in oil emulsion. The solvent is removed by rota-evaporator under reduced pressure. Dried lipid thus obtained is hydrated by buffer to form homogenous aqueous vehicle dispersion that was extruded through a high-pressure homogenizer [31,32].

### 5. Probilosomal method

In this method sorbitol particles were located in a round bottomed flask. This is then vacuum dried in a rotary evaporator. Then the solution of phosphatidyl choline, bile salt and drug were dissolved in organic solvent were added in drop wise manner into the round bottomed flask to load them onto sorbitol particles. Loaded sorbitol particles are freeze dried to obtain probilosomal powder which is then converted into bilosome by manual agitation in water [33].

## CHARACTERISATION OF BILOSOMES

a) Particle size, Polydispersity index, Zeta potential  
Bilosome dispersion is diluted to 10 fold using distilled water and measured the particle size, poly dispersity index and zeta potential using zeta sizer. The measurements are taken in triplicate [6,34].

b) Encapsulation efficiency

1ml of the bilosome dispersion was taken and centrifuged at 15,000 rpm for 2hour at 4°C. The supernatant was taken, suitably diluted and determined spectrophotometrically for the drug content.

c) Transmission electron microscopy (TEM)

Surface morphology is determined by transmission electron microscopy. One drop of selected bilosome dispersion was adsorbed on copper grid, negatively stained with 1% phosphotungstic acid and then air dried at room temperature for 10 min before TEM observation [6,10,24].

d) Differential Scanning Calorimetry (DSC)

Apparatus was calibrated. Bile salts, cholesterol, non-ionic surfactant, drug loaded bilosomes and blank bilosomes are investigated. 3mg samples were placed in standard aluminium pans and heated from 10°C to 200°C at a scanning rate of 10°C/min [6,10,24].

e) *Invitro* drug release studies

Dialysis bag method is used. Dialysis bag was overnight immersed in the release medium. The medium is 50 ml phosphate buffer p<sup>H</sup> 6.8 and maintained at 37±0.5°C. 3ml samples were withdrawn at 1, 2, 4, 6, 8, 10 and 24 hour and substituted with equal volume of medium. Withdrawn samples are suitably diluted and analysed spectrophotometrically to determine the drug release [4,35].

f) Storage stability

The prepared bilosomes are stored at refrigerated temperature ( $4\pm 0.5^{\circ}\text{C}$ ) and at room temperature ( $25\pm 2^{\circ}\text{C}$ ) at 70% relative humidity for 90 days. The stability of the prepared bilosomes was evaluated at 0, 45, 90 days [3,14].

g) Confocal laser scanning microscopy (*ex vivo* study)

Dorsal rat skin was isolated with its subcutaneous layer confronting the donor compartment. Fluorescein diacetate incorporated bilosomes (fluorolabelled bilosomes) were prepared and applied to dorsal rat skin surface. Similarly 1% fluorescein diacetate solution (control) was prepared and added to dorsal skin surface of rats and remained for 6 hours. Longitudinal sections of skin that were exposed to fluorolabelled bilosomes and 1% fluorescein diacetate solution were stored in paraffin wax and sliced using a microtome. The existence of fluorescence in skin layers was evaluated. This method helps to determine the permeation, movement and path of bilosomes through skin and this method requires ethical committee approval [4,28,36].

### CONCLUSION AND FUTURE PERSPECTIVES:

Bilosomes are nanovesicular carriers for drug delivery. They have applications in vaccine delivery, protein/peptide delivery, direct nose to brain delivery for treatment of brain diseases like Alzheimer's and migraine. Thus they have biomedical and pharmaceutical application in drug delivery, cancer therapy and diagnostics. As they improve the solubility and permeability, they enhance the bioavailability of drug thereby increasing therapeutic effectiveness. They can be given by various routes including oral, transdermal, nasal, ocular, buccal. Thus bilosomes have profound application in drug delivery and therapeutics.

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