WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 22, 319-333. Review Article ISSN 2277–7105

BILOSOMES: EMERGING VESICULAR CARRIERS IN DRUG DELIVERY -A COMPREHENSIVE REVIEW

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Article Received on 19 October 2025,
Article Revised on 08 Nov. 2025,
Article Published on 16 Nov. 2025,

https://doi.org/10.5281/zenodo.17615877

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How to cite this Article: *Geethashree S. C., Dr. T S Nagaraja, Dr. R Yogananda, Pooja B C, Kavyashree N J, Pavithra. (2025) BILOSOMES: EMERGING VESICULAR CARRIERS IN DRUG DELIVERY -A COMPREHENSIVE REVIEW. "World Journal of Pharmaceutical Research, 14(22), 319–333.

ABSTRACT

Recently, several nano-vesicular delivery systems such as liposomes, nanoparticles, and niosomes have been developed to enhance drug delivery. However, their effectiveness—particularly through biological routes like oral, transdermal, and nasal administration—is often limited by physiological barriers such as pH variations, bile salts, and metabolic enzymes. Bilosomes—non-ionic surfactant-based nanovesicles incorporating bile salts— represent an advanced alternative capable of protecting drugs from degradation and improving bioavailability through multiple administration routes. The combination of non-ionic surfactants and bile salts enhances bilosomal stability, flexibility, and tissue penetration, allowing them to efficiently cross biological barriers. Bilosomes have demonstrated strong potential for delivering vaccines, biological therapeutics, and small- molecule drugs via oral, transdermal, nasal, ocular, and parenteral routes. This review outlines the unique characteristics, composition, preparation, and evaluation methods of bilosomes, emphasizing factors influencing their performance. It also discusses their broad therapeutic applications, the impact of formulation variables on efficacy, and future prospects including clinical translation and commercialization.

KEYWORDS: Bilosomes, Deformable vesicles, Bile salt stabilized vesicles, Vesicular carriers, Bile salt.

INTRODUCTION

Recent trends in drug development have introduced a variety of compounds with limited bioavailability. A key obstacle is the lipophilic nature of many therapeutic agents, which hinders their ability to dissolve in gastrointestinal (GI) fluids and thus impairs their absorption. Furthermore, orally administered biological substances, including proteins, peptides, and vaccines, often undergo significant degradation in the digestive system, limiting their effectiveness. To address these issues, alternative drug delivery strategies have been developed. Among them, vesicular systems such as liposomes and niosomes have shown potential in shielding active pharmaceutical ingredients from enzymatic breakdown and enhancing their stability during GI transit.[1]

Bilosomes represent an advanced modification of traditional liposomes and niosomes, distinguished by the inclusion of bile salts, which enhance their flexibility, absorption, and permeability. These nanovesicular carriers are particularly suited for delivering highly lipophilic and poorly permeable drugs, offering a promising approach to overcoming common barriers in oral drug administration. Bilosomes are the bilayered vesicular carriers of lipids incorporating non-ionic surfactants and bile salts, which are spherical in structure and the size vary from 5-200nm. Bile acids are the facial amphiphiles that are synthesized in liver and stored in gall bladder in the ionized bile salt form. The bile salts are the biosurfactants used in bilosomes are involved in mucous permeability of drugs.

Bilosomes are synthetic vesicular systems designed to resemble natural phospholipid bilayers in both structure and composition. They consist primarily of phospholipids and bile salts, enabling them to encapsulate therapeutic agents or genetic material for improved bioavailability and targeted delivery to specific cells or tissues. Due to these properties, bilosomes have gained attention as a versatile platform for various therapeutic applications, including cancer treatment, antiviral therapies, gene delivery, and dermatological interventions.[2,3]

One of the main advantages of Bilosomes is their ability to protect drugs or genetic material from degradation and enhance their transport across cell membranes. This can improve the bioavailability and efficacy of the encapsulated material. They can also be designed to target specific cells or tissues, which can increase the specificity of therapy. Bilosomes are especially promising for drug and gene delivery due to their capacity to shield encapsulated agents from degradation and improve their translocation across cellular membranes.

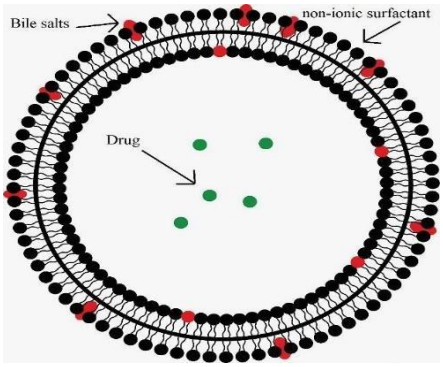
Comparative studies have shown that bilosomal formulations offer superior bioavailability and permeation capabilities when compared to conventional liposomes and niosomes. Although liposomes and niosomes are both classified as vesicular drug delivery systems, they vary in terms of their structural components and characteristics. Liposomes are made from phospholipids—either naturally derived or synthetically produced—which are amphiphilic molecules comprising a water-attracting (hydrophilic) head and a water-repelling (hydrophobic) tail. In aqueous settings, these molecules spontaneously form bilayer vesicles with an internal aqueous compartment surrounded by lipid layers.[4]

In contrast, niosomes are constructed from non-ionic surfactants, which are also amphiphilic but differ from phospholipids by lacking a phosphate group. These surfactants often feature hydrophilic polyethylene glycol heads and hydrophobic alkyl chain tails. Like liposomes, niosomes form vesicles with aqueous interiors enclosed by bilayers. While liposomes generally demonstrate higher stability due to the organized structure of natural phospholipids, they can be vulnerable to enzymatic degradation in physiological environments. Niosomes tend to be less stable than liposomes, as their surfactant components are more prone to physical or chemical changes under certain conditions.[5]

Bilosomes: Structural Aspects and composition[6-8]

Conacher et al. were the pioneers in introducing bilosomes, which are vesicular structures formed by non-ionic amphiphilic compounds. These structures are similar to niosomes—non-ionic surfactant vesicles—but are uniquely characterized by the presence of bile salts. The bile salts play a crucial protective role, helping bilosomes resist the harsh acidic and basic environments encountered in the gastrointestinal (GI) tract. Moreover, their inclusion enhances the permeability of the intestinal membrane, thereby improving the oral bioavailability of the encapsulated drug molecules. Bilosome formulations typically incorporate non-ionic surfactants—commonly from the Span series (e.g., Span 40, Span 60, Span 80)—in combination with cholesterol and bile salts. These vesicular nanostructures were examined for their capacity to encapsulate both hydrophilic and hydrophobic compounds within their aqueous core and phospholipid bilayer. Bilosomes consist of two distinct layers: the innermost layer houses hydrophilic drugs and antigens, while the outermost layer contains bile salts and hydrophobic medications. The bile salts are encapsulated within the lipid layers of the bilosomal structure, giving the system its characteristic closed form. In the bilosome vesicle, the hydrophilic end of the bile acid

molecules faces the aqueous core of the lipid bilayer, while the hydrophobic end is embedded in the hydrophobic region of the bilayer. This unique structure enables bilosomes to effectively deliver a variety of drugs via different routes.



Schematic overview of bilosomal structure and constituent elements/

Bile salt

The inclusion of bile salts in the vesicular shell offers bilosomes several advantages over other vesicular nanosystems, particularly in terms of enhanced gastrointestinal stability and superior transdermal permeability. As natural endogenous surfactants, bile salts exhibit excellent biological compatibility, low toxicity, and biodegradability. Additionally, bile salts can facilitate drug transport across biological membranes by promoting drug dissolution and/or modifying the permeability of cell membranes.

The most frequently used bile salts in the formulation of bilosomes are **sodium glycocholate (SGC), sodium deoxycholate (SDC),** and **sodium taurocholate (STC)**. These specific bile salts are preferred due to their distinctive characteristics and benefits in drug delivery systems. Notably, they exhibit strong solubilizing capabilities, which enhance the encapsulation and delivery of both hydrophilic and hydrophobic drugs, contributing to improved bioavailability and therapeutic effectiveness.

Lipids

Phospholipids are highly biocompatible with biological membranes, making them ideal components for drug delivery systems. Their amphiphilic nature allows them to spontaneously self-assemble into concentric bilayer structures, which facilitates wetting, emulsification, and the formation of stable vesicles for encapsulating therapeutic agents.[6] Commonly used components include **soybean phosphatidylcholine, dicetyl phosphate,**

distearoyl phosphatidylglycerol, and **monopalmitoyl glycerol**. Cholesterol, an amphiphilic molecule when incorporated into bilosome formulations. Its hydrophilic hydroxyl group aligns toward the aqueous surface, while the hydrophobic aliphatic chains integrate into the bilayer membrane. Due to its ability to interact with non-ionic surfactants, cholesterol can significantly affect the structural and physical characteristics of bilosomes. Specifically, it enhances the cohesion between the non-polar regions of the bilayer, resulting in increased compactness and stability of the bilosomal membrane.

Non-iconic surfactants

Non-ionic surfactants are commonly employed in bilosome formulations because they offer greater stability and biocompatibility compared to anionic, cationic, or amphoteric surfactants. They function as effective solubilizers, wetting agents, emulsifiers, and permeability enhancers, contributing to the overall efficiency and stability of the bilosomal drug delivery system. Commonly used non-ionic surfactants in bilosome formulations include **Tween 60, Span 60**, and **Span 80**.

Bilosomes preparation methods

Thin Film Hydration Method

The thin film hydration method is a widely used technique for preparing drug-loaded bilosomes. In this process, the lipid component—typically soybean phosphatidylcholine—along with the drug, is first dissolved in an organic solvent. The solvent is then evaporated under reduced pressure using a rotary vacuum evaporator, forming a thin lipid film on the walls of the flask. This thin film is subsequently hydrated with a buffer solution containing bile salts, resulting in the formation of large multilamellar vesicles (LMVs). These LMVs are then subjected to high- pressure homogenization to produce small unilamellar vesicles (SUVs). The resulting vesicles are purified to yield bilosomes loaded with the drug.

This method has been successfully used to prepare bilosomes loaded with various agents such as tacrolimus, fenofibrate, cyclosporine A, diphtheria toxoid, hepatitis B antigen, and tetanus toxoid.

Advantages

- Suitable for laboratory-scale preparation
- High entrapment efficiency, especially for hydrophobic drugs

Disadvantages

- Exposure to high temperatures may degrade phospholipids and/or the drug
- Low encapsulation efficiency for hydrophilic drugs
- Challenging to scale up for industrial production

Reverse phase evaporation

The reverse phase evaporation method is used to prepare bilosomes by forming a water-in-oil (w/o) emulsion, where the aqueous phase contains the drug and the organic phase includes lipids like soybean phosphatidylcholine and bile salts.[20] In this process, lipids are dissolved in an organic solvent (e.g., absolute ether), and the drug- containing buffer is added gradually. The mixture is then sonicated in a water bath to form a stable emulsion. The organic solvent is removed using a rotary evaporator (50 rpm), and the remaining lipid film is hydrated with buffer to form a uniform dispersion. This is followed by high-pressure homogenization and ultracentrifugation to obtain purified, drug-loaded bilosomes.

This technique is commonly used for encapsulating protein-based drugs such as porcine insulin and recombinant human insulin.

Advantages

- Efficient removal of residual solvent using centrifugation or dialysis.
- Higher capacity1 for loading the internal aqueous phase.

Disadvantages

- Residual organic solvent may affect the stability of lipids or the biological integrity of the drug.

Hot Homogenization Method

In the hot homogenization method, the lipid components, including mono-palmitoyl glycerol, cholesterol, and dicetyl phosphate, are first melted at 140°C for 5 minutes, then hydrated with a buffer solution. The mixture is homogenized, followed by the addition of a bile salt solution to form a dispersion of empty vesicles, which is then homogenized again. To achieve protein entrapment, the antigen-containing buffered solution is introduced, and multiple Freeze-Thaw cycles are used. Antigen is added at the final step to reduce prolonged exposure to the homogenization process. This method is typically used for encapsulating influenza A antigen, recombinant influenza antigens.

Advantages

- Solvent-free and easy to perform.
- Straightforward handling process.

Disadvantages

- Degradation of the drug due to temperature exposure.

Solvent Injection Method

This method is known as ethanol injection or ether injection method, The solvent injection method generally yields a relatively low entrapment efficiency. In this technique, non-ionic surfactants, lipids, and hydrophobic drugs are dissolved in an organic solvent. This solution is then slowly injected into an aqueous phase containing pre-dissolved bile salts, which is preheated above the boiling point of the organic solvent. As the organic solvent evaporates under continuous stirring, a turbid appearance in the hydroalcoholic mixture signals the formation of bilosomal vesicles. The resulting dispersion is allowed to cool to 25 ± 2°C, then subjected to sonication using an ultrasonic water-bath sonicator to achieve a uniform and fine bilosome dispersion.

This method has been successfully used to develop PEGylated bilosomes loaded with resveratrol.[9,10]

Characterization of Bilosomes vesicles

- **Particle size**

Particle size (PS) plays a pivotal role in the evaluation of bilosomal formulations, as it strongly influences their physical stability and physicochemical properties. Moreover, both the *in vitro* and *in vivo* performances of bilosomal vesicles are highly dependent on PS. Typically, photon correlation spectroscopy is employed to determine the PS and polydispersity index (PDI) of the prepared formulations.

Several formulation and processing parameters are known to affect the PS of bilosomes. These include the type and concentration of surfactants, the nature and level of bile salts, the proportion of cholesterol, as well as the homogenization or ultrasonication conditions applied during the preparation process.

The reduction in particle size (PS) of the developed vesicles achieved through

homogenization or sonication processes is often associated with a significant decrease in the entrapment efficiency (EE%). However, this reduction simultaneously enhances the drug's solubility and improves its *in vitro* release profile.

Polydispersity Index (PDI)

The polydispersity index (PDI) serves as an indicator of particle size distribution, reflecting the degree of homogeneity and uniformity within a formulation. Lower PDI values, approaching zero, denote a narrow and homogeneous size distribution, whereas values closer to one indicate a broad and heterogeneous distribution. PDI is typically determined using the same analytical technique employed for particle size measurement, such as photon correlation spectroscopy, laser light scattering, or dynamic light scattering.

Entrapment Efficiency (EE%)

The entrapment efficiency (EE%) of bilosomal formulations represents the percentage of drug successfully incorporated within the bilosomal vesicles. It can be determined using either direct or indirect methods.

In the indirect method, the amount of unentrapped (free) drug is quantified and subtracted from the total drug content of the formulation. The total drug content is typically determined by withdrawing a known volume of the formulation and analyzing it using an appropriate analytical technique. Conversely, in the direct method, EE% is measured by rupturing the precipitated vesicles with an organic solvent, followed by analysis of the released drug using validated techniques.

Spectroscopic and chromatographic methods, such as UV–visible spectrophotometry and High-Performance Liquid Chromatography (HPLC), are commonly employed for drug quantification. Meanwhile, separation of the unentrapped drug may be achieved through exhaustive dialysis, gel filtration, or centrifugation.

The EE% by the indirect method can be calculated using the following equation:

Zeta Potential (ZP)

$$\%EE = \frac{total\ amount\ of drug\ loaded - Free\ drug\ in\ supernatant}{Total\ added\ amount\ of drug\ used\ in\ formulation} \times 100$$

Zeta potential (ZP) represents the overall surface charge acquired by vesicles in a given medium. It is a critical parameter for assessing the stability of bilosomal dispersions, as it provides insights into the electrostatic repulsion between particles. ZP is commonly measured by evaluating electrophoretic mobility in an applied electric field, using instruments such as the Zetasizer, dynamic light scattering systems, the Nano ZS-90 Zetasizer, or Malvern Zetasizer.

Bilosomes typically exhibit a negative surface charge due to the incorporation of bile salts as formulation constituents. This negative charge is attributed to the presence of hydroxyl (–OH) groups, which increase the magnitude of the ZP, thereby reducing the likelihood of vesicle aggregation and enhancing dispersion stability.

In Vitro Release Study

In vitro release studies are conducted to predict the performance of a drug delivery system under *in vivo* conditions. These studies are commonly performed using techniques such as the membrane diffusion method, dialysis method, or Franz diffusion cell method. All of these approaches are based on monitoring the diffusion of drug-loaded bilosomal vesicles from dialysis bags into an external dissolution medium.

Homogenization and ultrasonication processes have been shown to positively influence the *in vitro* release of drugs from bilosomal vesicles. This effect is primarily attributed to the significant reduction in particle size (PS) achieved during these processes, which increases the surface area of the vesicles and thereby enhances both drug dissolution and *in vitro* release profiles.

Morphological Study

The structural characteristics and morphology of bilosomal vesicles are typically examined using microscopic techniques. Various electron microscopy methods are employed depending on the physical state of the formulation. Scanning Electron Microscopy (SEM) is commonly used for vesicles in the solid state, where surface images are obtained by directing a focused electron beam across the sample. In contrast, Transmission Electron Microscopy (TEM) is preferred for characterizing vesicles in the liquid state, as it provides detailed internal structural information at high resolution.

Stability Study

Stability assessment is a critical parameter in evaluating the suitability of bilosomal formulations as drug delivery systems. Bilosomal vesicles must be examined for different types of stability, including physical, chemical, and biological stability. The major challenges during storage are vesicle aggregation, fusion, and drug leakage, all of which may compromise the integrity and performance of the formulation. Therefore, stability studies are essential to ensure that the developed bilosomes retain their physicochemical characteristics under defined storage conditions over a specified period.[11,12]

According to the International Council for Harmonisation (ICH) guidelines, stability testing is performed under the following conditions:

- **Long-term stability study:** 25 ± 2 °C / 60 ± 5% RH or 30 ± 2 °C / 65 ± 5% RH.
- **Intermediate stability study:** 30 ± 2 °C / 65 ± 5% RH.
- **Accelerated stability study:** 40 ± 2 °C / 75 ± 5% RH.

Applications of Bilosomes in various drug delivery system

Delivery of Antidepressant Drug

Sertraline hydrochloride (SER), a selective serotonin reuptake inhibitor (SSRI), is classified as a Class II drug under the Biopharmaceutical Classification System (BCS).[82] To enhance its oral delivery, Ismail et al. developed and optimized bilosomal formulations encapsulating SER. The optimized freeze-dried bilosomes demonstrated a diffusion-controlled release profile, with 23.75 ± 0.58% drug release in the first 2 hours, followed by 66.82% release in simulated intestinal fluid (Table II). Furthermore, bilosomes enhanced intestinal penetration and diffusion by approximately five-fold, achieving a 222% relative bioavailability compared with pure SER. These findings suggest that bilosomal encapsulation can effectively reduce gastrointestinal side effects while significantly improving the oral bioavailability of SER.

Treatment of Acne

El-Nabarawi et al. investigated bilosomes as vesicular carriers for the topical delivery of dapsone in acne management. The ex vivo skin permeation study revealed a 1.5-fold higher retention of dapsone in the bilosomal formulation compared to a dapsone alcoholic solution. Moreover, in vivo histopathological evaluation confirmed the safety of the developed topical formulation, showing no evidence of inflammation or tissue damage. These findings highlight the potential of bilosomes as an effective and safe vesicular carrier for the topical delivery of dapsone in the treatment of acne and other dermatological disorders.

Drug delivered via bilosomes	Therapeutics efficacy	Route of delivery	Conclusion
Insulin	Diabetic treatment	Oral Delivery	Prove the safety of the oral administration of insulin.
Cyclosporin A	Immunosuppressant	Oral Delivery	More effective and safer for oral delivery.
Tacrolimus	Immunosuppressant	Oral Delivery	More efficient and safer in comparison with free drugs.
Eprosartan mesylate	High blood pressure treatment	Oral delivery	Showed a nephroprotective effect after oral administration.
Apigenin	Anti-inflammatory And anti-carcinogenic effects	Oral Delivery	Enhanced ssolubility, dissolution, and oral bioavailability.
Acyclovir	Antiviral agent	Oral Delivery	Improved absorption and bioavailability of acyclovir through gastrointestinal tract.
Risedronate	Postmenopausal osteoporosis treatment	Oral Delivery	Improved stability to digestive media with enhancement in the permeation and reduced drug toxicity more than drug solution.

Therapeutic Applications of Bilosomes Through Oral Route.

Delivery of Antifungal Drug

Zafar et al. developed butenafine-loaded bilosomes (BN-BSo) to enhance antifungal efficacy via the transdermal route. The optimized formulation was incorporated into Carbopol 940 (1% w/v) to prepare a bilosomal gel (BN- BSog), which was subsequently evaluated for pH, viscosity, in vitro release, diffusion, antifungal activity, and skin irritation. The BN-BSo formulation demonstrated a higher in vitro drug release compared to BN-BSog and pure butenafine. Meanwhile, BN-BSog exhibited a 2.36-fold increase in permeation flux relative to the pure drug dispersion. Importantly, BN-BSog displayed strong antifungal activity, producing a zone of inhibition > 20 mm against *Candida albicans* and *Aspergillus niger*, while maintaining a non-irritant profile. These results confirm the potential of bilosomal gels as effective transdermal antifungal delivery systems.

Drug delivered via bilosomes	Therapeutics efficacy	Route of delivery	Conclusion
Olmesartan medoxomil	Anti- hypertension drug	Transdermal Delivery	Exhibited enhanced in skin permeation and higher skin deposition in comparison with the drug suspension.
Lornoxicam	Anti- inflammatory drug.	Transdermal Delivery	Superior *in vivo* permeation and showed that bilosomes could enhance the transdermal delivery of lornoxicam.
Tizanidine	Skeletal muscle relaxant agent.	Transdermal Delivery	Improved permeation through the skin barrier and thus improved the

			bioavailability of the drug.
Berberine	Rheumatoid arthritis treatment.	Transdermal Delivery	Showed a delayed-release effect and increased in skin permeability. Also, reduce inflammation and exhibited a dramatic reduction in edema swelling.
Metformin hydrochloride	Diabetes type II treatment.	Transdermal Delivery	Improved skin permeation and enhanced the bioavailability of the drug.

Therapeutic Applications of Bilosomes Through Transdermal Route.

Transdermal Delivery of an Antidiabetic Drug

Salem et al. developed metformin hydrochloride-loaded bilosomes for active transdermal delivery in the management of type II diabetes. The in vitro release study demonstrated a biphasic release profile, with a permeation flux ranging from 198.79 to 431.91 ng cm^{-2} h^{-1}, compared to 154.26 ng cm^{-2} h^{-1} for the metformin hydrochloride solution. The optimized bilosomes exhibited a high deformability index (6.5), confirming their vesicular flexibility and suitability for transdermal application. These findings suggest that bilosomes represent a promising vesicular carrier for improving the transdermal delivery of metformin and potentially other therapeutic agents.

Ocular Delivery of an Antifungal Agent

Janga et al. formulated in situ ion-sensitive hydrogels incorporating natamycin-loaded bilosomes for ocular drug delivery. The developed system was evaluated through in vitro cytotoxicity, permeation, and corneal histology studies. Results demonstrated that the bilosome-based hydrogels provided enhanced corneal permeability, along with favorable viscoelastic and adhesive properties, supporting prolonged ocular retention. Moreover, cytotoxicity and histological evaluations confirmed the safety and compatibility of the formulation with ocular tissues. These findings highlight bilosome-based hydrogels as a promising platform for the ocular delivery of antifungal agents.[4,8,13]

Future Perspectives

Based on the reviewed literature, bilosomes represent a promising platform for oral vaccine delivery. Conacher et al. demonstrated that bilosomes are effective in entrapping antigens and eliciting both mucosal and systemic immune responses. Moreover, bilosomes have shown the capacity to protect entrapped peptides and proteins from degradation following oral administration. Although bilosome-based vaccine systems have not yet reached

commercialization, two patents concerning their application in oral vaccine delivery (US 5,876,721 and EP 0722341B1) have been granted, with additional patents under development for the delivery of small molecules and biologics.

Superficial modification of bilosomes through ligand attachment on the vesicular surface has revealed their potential to selectively target immune cells. Future research should focus on the selective transfer of antigens to the intestinal lymphatic system using bilosomal carriers. Furthermore, the versatility of bilosomes in accommodating a broad spectrum of antigens with varying physicochemical properties and susceptibility to gastrointestinal degradation warrants further investigation. This adaptability positions bilosomes as attractive building blocks for next-generation drug delivery systems.

To advance this field, clinical studies are essential to validate the safety, efficacy, and immunological mechanisms of bilosomes in humans. Such investigations will pave the way for their translation into effective oral vaccine carriers and broaden their application across diverse therapeutic areas.

CONCLUSIONS

This review highlights the current state-of-the-art in the development of bilosomes as nano-vesicular drug delivery systems. Conventional drug delivery strategies continue to face major challenges, including low solubility, poor absorption and penetration, hepatic first-pass metabolism, enzymatic degradation, and overall reduced bioavailability. Bilosomes have emerged as a promising alternative, offering improved solubility, membrane permeability, and bioavailability of therapeutic agents.

In addition to enhancing pharmacokinetic properties, bilosomes provide structural stability, flexibility, and compatibility for encapsulating a wide range of therapeutic molecules, including small drugs, peptides, proteins, and antigens. Their ability to withstand harsh gastrointestinal conditions and target specific tissues underscores their potential for both systemic and localized delivery.

Taken together, the versatility and effectiveness of bilosomes position them as next-generation vesicular carriers, paving the way for innovative applications in oral vaccines, transdermal formulations, and the treatment of diverse diseases. Continued preclinical and clinical research will be essential to fully realize their translational potential and move bilosome-

based therapeutics closer to commercialization.

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