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Review Article

Advances in Bilosomal Drug Delivery Systems: Formulation Approaches and In Vitro Characterization for CNS Targeting

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Abstract

In order to overcome the drawbacks of traditional dosage forms, sophisticated nano-vesicular drug delivery systems have been developed as a result of recent advancements in pharmaceutical sciences. Because of their improved stability, flexibility, and capacity to promote medication absorption across biological barriers, bilosomes have drawn a lot of attention. Comprising non-ionic surfactants or phospholipids, cholesterol, and bile salts, bilosomes are bile salt-stabilized vesicular carriers that offer protection against enzymatic degradation and challenging physiological circumstances. Bilosomes are appropriate for oral, transdermal, and central nervous system (CNS) medication administration because of these special qualities. With an emphasis on formulation techniques and in vitro characterisation criteria, this review offers a thorough and critical analysis of bilosomes. The impact of preparation methods and formulation ingredients on drug release behaviour, entrapment efficiency, surface charge, and vesicle size are emphasised. To shed light on bilosome performance, a variety of in vitro evaluation techniques are compiled, such as particle size analysis, zeta potential measurement, morphological investigations, and cellular uptake evaluations. The dopamine agonist pramipexole, which is frequently used to treat Parkinson's disease, is described as a model medication to show how bilosomes can be employed in CNS therapy. Pramipexole has serious delivery concerns due to its short half-life, limited brain penetration, and dose-related side effects. These issues may be resolved by employing nano-vesicular devices. Overall, this review highlights the promise of bilosomes as effective drug carriers that can improve therapeutic results, increase bioavailability, and open up new avenues for CNS-targeted drug delivery.

Keywords: Dosage form; bilosomes; drug delivery; formulation.

1. Introduction

In order to increase treatment efficacy and patient compliance, pharmaceutical companies have progressively introduced state-of-the-art distribution systems in the drug delivery business, which has undergone substantial innovation in recent decades. This innovation boom is being driven by a desire to address problems with traditional medication administration, such as low bioavailability, rapid drug degradation, and poor patient adherence. The global market for drug delivery solutions is anticipated to grow quickly due to the rising incidence of complex and chronic illnesses including diabetes, cancer, and cardiovascular issues, which call for more precise and effective dosing systems.

Transdermal drug delivery systems (TDDS) provide several advantages over oral and injectable methods, including avoiding first-pass metabolism, providing longer drug release, improving compliance among patients, and enabling consistent plasma drug concentrations. The stratum corneum, the skin's outermost layer, is difficult for most therapeutic medications to penetrate, especially those that are hydrophilic or have a high molecular weight. Bilosomes

are nanovesicular systems made up of bile salts, cholesterol, and non-ionic surfactants. Bile salts have a few special benefits. First, compared to traditional carriers like liposomes, bile salts increase the bilosomes' flexibility and deformability, allowing them to more successfully navigate the densely packed lipid layers of the stratum corneum¹⁻⁵.

As an alternative to injectable therapy, oral drug administration is made possible by bilosomes, which stop therapeutic molecules from being broken down in the stomach. Because of their security in the gut, bilosomes improve the therapeutic efficacy and biocompatibility of medications^{6,7}. Reports state that bilosomes improve the GI tract's stability and the hydrophilic molecules' capacity to cross cell membranes, including proteins, peptides, and antigens^{8,9}. Because they are amphiphilic, bile salts like sodium glycocholate, sodium deoxycholate, and sodium taurocholate that are added to bilosomes enhance the system's penetration properties, which further enhances the oral bioavailability and biodistribution of drugs with poor aqueous solubility and permeability^{6,10}.

Advanced bilosomal formulations have been shown to have better penetration and bioavailability than other

vesicular systems when compared to traditional liposome and niosome formulations^{11–14}. Despite being vesicular drug delivery vehicles, liposomes and niosomes differ in terms of composition, structure, and properties. Liposomes are composed of amphiphilic molecules called phospholipids, which can be synthetic or natural and have a head that is hydrophilic and a hydrophobic tail. These substances self-assemble into bilayer structures in aqueous environments, forming vesicles with lipid bilayers surrounding aqueous cores. On the other hand, non-ionic surfactants amphiphilic molecules that mimic phospholipids but lack a phosphate group make up niosomes.

A hydrophilic head, like polyethylene glycol, and a hydrophobic tail, like alkyl chains, are the usual components of non-ionic surfactants. Similar to liposomes, niosomes also form vesicular structures with surfactant bilayers encasing water cores. Because natural phospholipids have distinct structures and packing arrangements, liposomes made of phospholipids are typically more stable. Enzymes in biological fluids, however, could be able to break them down. Because non-ionic surfactants may experience phase transitions or degradation under specific circumstances, niosomes are often less stable than liposomes. Bilosomes have a well-established therapeutic use as drug delivery vehicles for phytoconstituent, anticancer, CNS, protein/peptide, and vaccine medicines^{15–17}.

Importance of Pramipexole in Parkinson's Disease and CNS Therapy

Parkinson's disease and other neurological conditions are frequently treated with pramipexole, a non-ergot dopamine agonist. It has a strong affinity for dopamine D₂ and D₃ receptors, which are essential for controlling neurological signalling and motor function. Pramipexole can reduce bradykinesia, stiffness, and tremors three major Parkinson's disease symptoms by directly activating dopamine receptors. Pramipexole has several restrictions when used in clinical settings, despite its therapeutic success. Variable bioavailability, frequent dosage requirements, and systemic adverse effects such as nausea, dizziness, and somnolence are frequently caused by conventional dosage forms. Additionally, biological barriers like the blood–brain barrier, which limits medication entry into the brain, make it difficult to distribute Pramipexole to the central nervous system effectively. These difficulties demonstrate the necessity for cutting-edge drug delivery techniques that can enhance Pramipexole's pharmacokinetic profile and therapeutic efficacy. Because they improve drug stability, sustained release, and transport across biological barriers, nano-vesicular drug delivery devices have become potential platforms for CNS drug delivery. For assessing the potential of bilosomes in CNS-targeted therapy, pramipexole is an appropriate model medication^{18,19}.

Aim and Scope of the Review

This review's main goal is to give a thorough and critical overview of bilosomes as cutting-edge nano-vesicular

drug delivery systems, with an emphasis on their *in vitro* characterisation and formulation techniques. The structural characteristics, content, and functional benefits of bilosomes over traditional vesicular carriers are highlighted in the review. Additionally, this paper examines the usefulness of Pramipexole as a model medication to show how bilosomes can be used to deliver drugs that are active in the central nervous system. Recent developments in bilosome formulation methods, characterisation factors, and their possible contribution to improving medication bioavailability and therapeutic efficacy are highlighted. A discussion of the difficulties, constraints, and potential applications of bilosomal drug delivery systems is also included in the scope of this paper. This study attempts to give researchers and formulation scientists working on nano-vesicular systems for efficient medication delivery in neurological illnesses useful insights by compiling recent research findings.

2. Nano-Vesicular Drug Delivery Systems: An Overview

Because they can enhance the therapeutic efficacy of a variety of medications, nano-vesicular drug delivery devices have become more important in pharmaceutical research. Both hydrophilic and lipophilic medicinal molecules can be encapsulated in these systems' nanoscale vesicles, which are made of lipid or surfactant bilayers. Because of their structural similarity to biological membranes, they interact with cells and tissues more effectively, improving drug absorption, increasing bioavailability, and lowering systemic toxicity. Weak solubility, instability in biological fluids, fast clearance, and non-specific distribution are some of the difficulties that conventional drug delivery methods frequently encounter. By shielding the medication from deterioration, offering regulated or prolonged release, and enabling transport across physiological barriers, nano-vesicular carriers overcome these constraints. These methods have therefore been extensively studied for oral, transdermal, nasal, and parenteral delivery routes.

Over the years, a variety of nano-vesicular drug delivery systems have been created, each with unique structural traits and practical benefits. The earliest and most thoroughly researched vesicular carriers, liposomes, have good biocompatibility and the capacity to encapsulate both hydrophilic and lipophilic medications; nonetheless, stability problems and high production costs sometimes limit their practical use. When compared to liposomes, niosomes which are made with non-ionic surfactants offer better storage properties, lower costs, and increased chemical stability. Biological barriers like the stratum corneum can be effectively penetrated by transfersomes, which are ultra-deformable vesicles with edge activators that provide great membrane flexibility. Ethosomes, on the other hand, have a high concentration of ethanol, which greatly increases transdermal medication penetration and improves membrane fluidity. Bile salts stabilise bilosomes, an advanced type of vesicular carriers that are especially useful for oral and central nervous system

drug administration because they increase vesicle flexibility and resistance to enzymatic destruction²⁰⁻²⁴. Additionally, to these systems, other vesicular carriers such as pharmacosomes and sphenosomes have also

been studied for particular drug delivery applications. The most researched nano-vesicular systems, including liposomes, niosomes, transfersomes, ethosomes, and bilosomes, are compared in Table 1.

Table 1. Comparative Overview of Nano-Vesicular Drug Delivery Systems²⁵⁻³²

Vesicular System	Major Components	Key Characteristics	Advantages	Limitation	Major Applications
Liposomes	Phospholipids, cholesterol	Spherical vesicles with phospholipid bilayers enclosing an aqueous core	Biocompatible, capable of encapsulating hydrophilic and lipophilic drugs, targeted delivery potential	Physical and chemical instability, high cost, susceptibility to oxidation	Cancer therapy, gene delivery, CNS drug delivery
Niosomes	Non-ionic surfactants, cholesterol	Surfactant-based vesicles with enhanced chemical stability	Cost-effective, improved stability over liposomes, good entrapment efficiency	Aggregation, drug leakage on storage	Oral, topical, transdermal drug delivery
Transfersomes	Phospholipids, edge activators (Tween, Span)	Highly deformable vesicles with elastic membranes	Superior skin penetration, suitable for transdermal delivery	Formulation complexity, stability concerns	Transdermal and systemic drug delivery
Ethosomes	Phospholipids, high ethanol content, water	Soft, malleable vesicles with enhanced membrane fluidity	Excellent skin permeation, improved drug solubility	Skin irritation due to ethanol, limited non-topical use	Topical and transdermal drug delivery
Bilosomes	Non-ionic surfactants or phospholipids, cholesterol, bile salts	Bile salt-stabilized nano-vesicles with high membrane flexibility	Enhanced stability in GI conditions, improved bioavailability, protection from enzymatic degradation	Limited clinical data, scale-up challenges	Oral delivery, CNS drug delivery, vaccines

3. Bilosomes: Composition and Structural Characteristics

Bilosomes are sophisticated nano-vesicular drug delivery devices intended to improve therapeutic drugs' stability and bioavailability, especially in challenging physiological settings. Although bilosomes share structural similarities with other lipid-based vesicles like liposomes and niosomes, their inclusion of bile salts into the vesicular bilayer distinguishes them. Bilosomes differ from conventional vesicular carriers in that they have higher membrane flexibility, stability, and resistance to enzymatic degradation due to the inclusion of bile salts.

The fundamental concept behind bilosomes is to utilize the natural surfactant properties of bile salts to stabilize vesicles and improve their interaction with biological membranes. This feature allows bilosomes to maintain structural integrity in bile-rich environments and enhances drug absorption across epithelial barriers. Consequently, bilosomes have gained significant attention as promising carriers for oral drug delivery and are increasingly explored for central nervous system (CNS) targeting applications^{33,34,35}.

Components of a Bilosome

The physicochemical characteristics, stability, drug encapsulation effectiveness, and biological performance of bilosomes are all significantly influenced by their composition. Bile salts, cholesterol, and non-ionic surfactants or phospholipids are the main constituents of bilosomes.

Non-Ionic Surfactants

Given their low toxicity, good biocompatibility, and capacity to form persistent vesicular structures, non-ionic surfactants like the Span and Tween family are frequently utilised in the formulation of bilosomes. These surfactants are the main components of the bilayer membrane and help encapsulate both lipophilic and hydrophilic medications. Vesicle size, entrapment efficiency, and membrane rigidity are all strongly influenced by the surfactant's hydrophilic-lipophilic balance (HLB). For bilosome formulation to be optimised, surfactant selection is crucial.

Cholesterol

In order to increase membrane stiffness and decrease permeability, cholesterol is a crucial stabilising element

added to the bilosomal bilayer. It is essential for minimising medication leakage during storage and inhibiting vesicle aggregation. Cholesterol enhances vesicles' mechanical strength and adds to the bilosomal system's overall stability by adjusting bilayer fluidity. But too much cholesterol can make membranes less flexible and negatively impact how drugs release, so careful optimisation is required.

Bile Salts

The distinguishing elements of bilosomes are bile salts such sodium deoxycholate, sodium taurocholate, and sodium glycocholate. These amphiphilic molecules give the system special characteristics by integrating into the vesicular bilayer. Bile salts boost resistance to enzymatic degradation, increase vesicle deformability, and improve membrane elasticity. Bilosomes are especially useful for oral distribution of medications with low bioavailability because of their surfactant nature, which enables them to remain stable under gastrointestinal conditions.

Bile Salts' Role in Permeability and Stability

Bile salts are essential for enhancing bilosome stability and permeability. In bile-rich conditions, their absorption into the bilayer inhibits vesicle rupture and lowers interfacial tension. Bilosomes can withstand severe gastrointestinal conditions, where traditional vesicular systems frequently fail, because to their stabilisation effect.

By fluidizing biological membranes and encouraging vesicle–cell membrane contact, bile salts not only improve stability but also increase permeability. This characteristic contributes to increased systemic absorption and better drug transport across epithelial barriers. Bile salt-stabilized bilosomes are a better carrier system than conventional vesicular formulations due to the combined benefits of improved stability and permeability³⁶⁻⁴⁷.

Mechanism of Drug Encapsulation

Passive entrapment during vesicle production is how drugs are encapsulated in bilosomes. Lipophilic medications are integrated into the hydrophobic area of the bilayer membrane, while hydrophilic drugs are mainly confined within the watery core of the vesicles. Depending on their physicochemical properties, amphiphilic medicines may split between the two regions.

The type of surfactant, the amount of cholesterol, the amount of bile salt, and the preparation technique all affect how well drugs are encapsulated. Bile salts increase the membrane's flexibility, which makes it possible for medication molecules to be effectively accommodated inside the vesicular structure. In order to provide long-lasting therapeutic effects, this leads to enhanced entrapment efficiency and controlled drug release behaviour^{48,49}.

4. Bilosome Technologies

Studies on drug distribution and the assessment of new formulations both in vitro and in vivo. A number of liposomal formulations have been successfully sold and established in clinical practice, demonstrating the potential of liposomes as drug delivery systems throughout time. Successful occurrences, however, are mostly restricted to parenteral medication delivery. Despite being one of the most efficient drug delivery methods, patient pain and therefore limited compliance are some of its main downsides^{50,51}.

Bile salts integrated into the liposomal or niosomal membrane make up bilosomes, which are novel drug delivery vehicles. In the gut, conventional vesicles are known to be broken down by enzymes. However, by creating repulsion, the addition of bile salts to the formulation can assist stabilise the vesicle and shield it from the demoting effects of endogenous bile acids. Because of their greater stability in the gastrointestinal tract, which is further strengthened by their nanometric size, hydrophobicity, and negative surface charge, bilosomes have been found to improve the therapeutic efficacy of drugs. Additionally, bilosomes are easily absorbed into the portal circulation through the small intestine, potentially increasing the entrapped therapeutic's bioavailability. Biocompatibility and a good safety profile are further advantages. Bilosomes were first created to improve oral drug administration, but they have also been tested for various drug delivery methods. Technical viability to increase the production of bilosomes may facilitate the shift to broader use and possibly clinical practice^{52,53,54}.

Preparation Techniques and Industrial Potential of Bilosomes

These nanocarriers are obtained using a variety of techniques. Bilosome preparation was first accomplished using the Bangham method, a thin lipid film hydradrination technique (Figure 1)^{55,56}

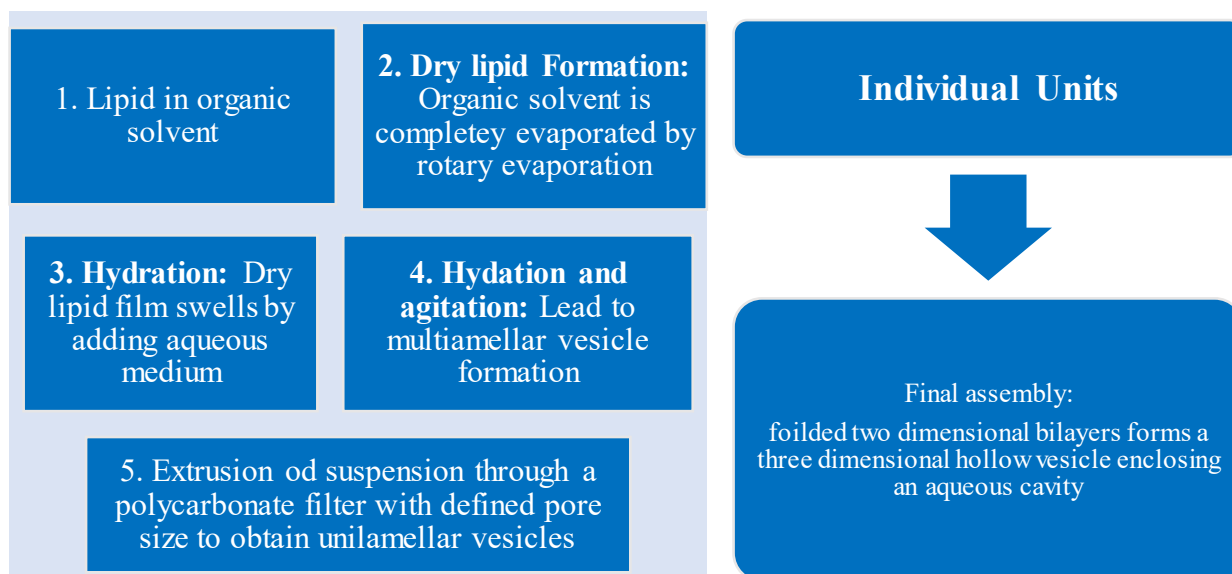


Figure 1: Diagrammatic illustration of the bilosome production process using thin film hydration

As the industrial manufacture of nanotechnology has become a reality and a necessity, new techniques for producing more bilosomes have been developed and tested. Heating techniques, microwave irradiation, freeze-drying (lyophilization), spray drying, supercritical reverse-phase evaporation, and several very desirable modified ethanol injection techniques, such as cross-injection, microfluidization, and membranes contactor application techniques⁵⁷.

5. In vitro characterizations and variables influencing vesicles bilosomes (BS)

Studies of vesicle size, polydispersity index (PI), zeta potential, vesicle morphology, entrapment efficacy, in vitro release, and cellular uptake investigations were all part of the in vitro characterisations of BS-vesicles. Below is a quick explanation of the characterisation methods and variables affecting some BS-vesicle characteristics. A variety of techniques for characterising BS-vesicles are displayed in Table 2.

Zeta potential, entrapment efficiency, particle size, PI, and form

Both in vitro and in vivo BS-vesicle performance are significantly influenced by particle size. Because of the vesicles' increased flexibility and decreased surface tension, an increase in bile salt levels was linked to a significant drop in the particle size and PI of BS-vesicles.

However, as the medium viscosity increased, a further increase in bile salt content led to vesicle expansion associated with an increase in PI. Because bile salts ionise at higher pH levels, increasing their surface activity, the hydration medium's pH also affects the vesicles' size. Several processing factors also affected the particle size of the vesicles.

The multilamellar micron-sized BS-vesicles produced by the thin film dispersion method were converted into tiny unilamellar nano-sized vesicles by extrusion via membrane, ultrasonication, or homogenisation. The preparation method has an impact on the vesicle particle size as well. Mann et al. claim that although the homogenisation procedure produced a single population of small vesicles, the thin film method produced a mixture of large and microscopic vesicles⁵⁸⁻⁶⁴.

Table 2: Major methods for BS-vesicles characterization⁵⁸⁻⁶⁸.

Parameter	Technique Used
Particle size	Measured using dynamic light scattering (DLS) and laser diffraction analyzers
Polydispersity index	Evaluated through dynamic light scattering to assess size distribution
Zeta potential	Determined by dynamic light scattering instruments for surface charge analysis
Morphology	Visualized using TEM, Cryo-TEM, SEM, and freeze fracture electron microscopy
Separation of free drug	Achieved by molecular exclusion chromatography and ultracentrifugation
Entrapment efficiency (%)	Estimated using HPLC, UV spectrophotometry, BCA, Micro-BCA, and modified ninhydrin assay
In vitro drug release	Studied using dynamic dialysis method
Cellular uptake	Analyzed using Caco-2 cells, corneal epithelial cells, and murine macrophage cell lines

6. Pramipexole as a Model Drug

Pramipexole's Pharmacological Profile

Dopamine D₂-like receptors, especially the D₃ subtype, are highly selectively targeted by the non-ergot dopamine agonist pramipexole. It is mostly recommended for the treatment of moderate to severe restless legs syndrome and Parkinson's disease. Pramipexole improves motor symptoms such as bradykinesia, stiffness, and tremors by directly activating dopamine receptors in the substantia nigra and striatum.

Pramipexole's antioxidant activity and suppression of mitochondrial oxidative stress are responsible for its pharmacodynamic neuroprotective qualities. The drug's favourable receptor selectivity profile is influenced by its low affinity for muscarinic, adrenergic, and serotonergic receptors. When taken orally, pramipexole has linear pharmacokinetics throughout the therapeutic dose range. It has a comparatively short elimination half-life of 8–12 hours due to its fast absorption, minimal plasma protein binding (<20%), and mainly renal excretion in unaltered form.

Biopharmaceutical Difficulties

Pramipexole has a number of biopharmaceutical drawbacks that limit its clinical performance despite its therapeutic efficacy. The medication's moderate oral bioavailability may be hampered by first-pass effects and gastrointestinal variability. Because of its brief half-life, frequent dosage is frequently necessary, which causes variations in plasma drug levels and decreased patient compliance, particularly in chronic neurological illnesses.

Furthermore, pramipexole's limited capacity to effectively penetrate the blood–brain barrier (BBB) poses a significant challenge to attaining the best possible central nervous system targeting. Additionally, dose-dependent side effects such as nausea, dizziness, somnolence, hallucinations, and impulse control issues may be linked to systemic delivery. These adverse effects are frequently associated with the drug's non-specific distribution outside of the brain.

Rationale for Model Drug Selection

Because of its physicochemical and pharmacokinetic properties, pramipexole is widely recognised as an appropriate model medication for nano-vesicular drug delivery studies. It is a perfect option for assessing how well nano-vesicular systems can improve brain targeting because of its low molecular weight, hydrophilic nature, and restricted BBB permeability. The medication was chosen for the development of sustained and regulated administration systems because of its short half-life and requirement for long-term therapy. Liposomes, niosomes, transfersomes, and bilosomes are examples of nano-vesicular carriers that have the potential to increase medication stability, extend circulation time, improve BBB penetration, and lessen systemic side effects. Additionally, pramipexole is a trustworthy probe for vesicular drug delivery because of its established analytical techniques and distinct

physiological endpoints, which enable precise evaluation of formulation performance.

Studies on Pramipexole in Nano-Vesicular Systems that have been reported

Numerous investigations have looked into nano-vesicular methods to increase pramipexole's therapeutic effectiveness. It has been found that liposomal and niosomal formulations produce prolonged release characteristics and improve drug encapsulation efficiency. With longer plasma residence times and less doses, these systems showed enhanced pharmacokinetic behaviour.

Because they can avoid the BBB through the olfactory and trigeminal pathways, intranasal nano-vesicular versions of pramipexole have also drawn interest. When compared to traditional oral formulations, these delivery methods demonstrated noticeably higher brain drug concentration. The potential of transfersomes and other deformable vesicular carriers to enhance mucosal penetration and brain targeting effectiveness has been further studied. Nano-vesicular delivery systems offer the potential to optimise pramipexole therapy for neurodegenerative illnesses because they have been demonstrated to decrease peripheral side effects, increase central drug availability, and improve patient compliance⁶⁹⁻⁷⁵.

7. Benefits of bilosomes^{76,77}

- When given, bilosomes increase the strength of weak antigens and facilitate the effectiveness of antigens, even in little amounts.
- Because they don't require the use of live pathogens, bilosomes provide a safe and effective substitute for traditional vaccines.
- There are advantages to this non-invasive technique in terms of user adherence and adoption.
- The traditional injection approach requires skilled staff for administration and is more expensive than alternatives.
- It is appropriate for a wide range of medicinal drugs due to its lower toxicity profile.
- The size of the carrier vesicle can be controlled to modulate the immunological response.
- For preparations like vaccinations, bilosomes remove the necessity for cold-chain storage.

Disadvantages of bilosomes^{78,79}

- The low correlation between in vitro and in vivo results, which stems from the absence of in vitro techniques that precisely mimic physiological settings, is a significant drawback of bilosome formulations.
- Vesicular digestion is impacted by the inadequacy of current in vitro release assays in simulating biological settings.
- These formulations also show limitations when used in cell lines and ex vivo permeation models to evaluate vesicular permeability.

• Bilosomes have low entrapment efficiency due to their inefficiency in entrapping anionic active chemicals, despite their effectiveness as carriers for cationic compounds. This is explained by the hydrophilic and negatively charged properties of bile salts, which prevent cationic actives from being entrapped or incorporated until membrane stabilisation effects are applied.

8. Application of bilosomes

8.1 System for Transdermal Drug Delivery The potential of bilosomes in transdermal medication administration, namely with Tenoxicam (TX), was examined by Al-mahallawi et al. Their results showed improved transdermal transfer of TX, providing a viable way to reduce oral administration's gastrointestinal adverse effects.

8.2 Oral Immunisation against Tetanus Using bilosomes loaded with tetanus toxoid, Mann et al. showed notable systemic and mucosal immunity. Similar to parenterally administered tetanus toxoid, the entrapped antigen triggered a Th2 response, leading to increased IgG1 and IgA antibodies.

8.3 Oral Drug Candidates: Bilosomes The relative bioavailability of insulin-loaded bilosomes containing various bile salts was assessed in male Wistar rats. Recombinant human insulin-containing bile salt formulations were evaluated, providing insight into their potential as oral medication candidates.

8.4 Ocular Drug Delivery Tacrolimus-containing liposomes have demonstrated potential for corneal penetration. However, their therapeutic efficacy is limited by inadequate transcorneal penetration, underscoring the necessity of improved drug delivery systems such as bilosomes in ocular applications^{80,81}.

9. Conclusion

A sophisticated and adaptable nano-vesicular drug delivery method, bilosomes have clear benefits over traditional vesicular carriers. Bile salts are incorporated into the vesicular membrane to promote stability, deformability, and permeability. This allows bilosomes to better transport drugs across cellular and epithelial barriers and resist harsh biological conditions. Bilosomes are especially promising for oral administration and drug delivery to the central nervous system because of these features. Vesicle size, surface charge, entrapment efficiency, and release behaviour are all significantly influenced by formulation variables such as bile salt concentration, surfactant type, cholesterol content, and preparation technique, as demonstrated by in vitro characterisation experiments. The potential of bilosomes for tackling important biopharmaceutical difficulties, such as limited brain targeting systemic side effects, is further supported by the use of pramipexole as a model medication. Notwithstanding its benefits, issues including the viability of scaling up, a lack of clinical data, and insufficient in vitro–in vivo correlation models still need to be resolved. Future studies should concentrate on refining formulation strategies, creating methods for

predictive assessment, and carrying out thorough in vivo and clinical studies. Bilosomes have a great potential to improve drug delivery and treatment efficacy in neurological and other chronic disorders with further development.

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