



## Review Article

# Emerging Applications of Bilosomes in Nanomedicine and Targeted Therapy : A Review

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### ARTICLE INFO

Published: 18 Oct 2025

#### Keywords:

Bilosomes, Nanocarriers, Drug delivery systems, Bile salts, Targeted drug delivery, Oral vaccines, Bioavailability enhancement, Transdermal delivery, Mucosal delivery Phospholipid vesicle

#### DOI:

10.5281/zenodo.17383247

### ABSTRACT

Bilosomes are advanced nano-vesicular drug delivery systems composed of phospholipids, non-ionic surfactants, cholesterol, and bile salts that provide enhanced stability, permeability, and bioavailability compared to conventional carriers such as liposomes and niosomes. Their unique composition allows protection of encapsulated drugs from enzymatic and acidic degradation, particularly within the gastrointestinal tract, while enabling effective delivery of both hydrophilic and hydrophobic agents. Bilosomes have demonstrated significant potential across multiple therapeutic areas, including oral vaccines, cancer therapy, antiviral treatment, gene and protein delivery, neurological disorders, ocular therapy, mucosal delivery, and transdermal applications. Their ability to exploit passive and active targeting mechanisms, as well as stimuli-responsive release, further enhances therapeutic precision and reduces systemic side effects. Despite challenges related to formulation stability, large-scale manufacturing, and regulatory approval, bilosomes remain a promising platform for next-generation targeted and patient-friendly drug delivery systems.

## INTRODUCTION

### TARGETED THERAPY<sup>[1,2,3]</sup>

By concentrating on genetic or protein biomarkers, targeted therapy is a type of precision or personalised medicine intended to target specific alterations in cancer cells that facilitate their growth, division, and metastasis. Targeted therapy seeks to interfere with signals or processes specific

to the disease, potentially controlling or curing it with fewer side effects than traditional chemotherapy, which generally affects both healthy and cancerous cells. Small molecule inhibitors, which stop cell functions inside cells, and monoclonal antibodies, which attach to particular cell surface proteins, are common medications used in targeted therapy.

### NANOMEDICINES<sup>[4,5,6]</sup>

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



In order to better understand biological processes and to diagnose, prevent, and treat disease, nanomedicine uses materials that are nanoscale, usually between 1 and 100 nanometres. Drugs can be delivered more effectively by nano-objects such as liposomes, polymers, micelles, and nanoparticles because they increase the drugs' solubility, stability, and capacity to reach particular body locations, like tumours, while reducing adverse effects on healthy tissues. Both passive targeting (using natural accumulation in tumour tissues) and active targeting (attaching drugs to molecules that bind specifically to receptors on disease cells) are possible with nanocarrier engineering.

## BILOSOMES [10,11,30,31]

Bilosomes are novel nano-vesicular systems made of phospholipids and bile salts that are intended to enhance the oral, transdermal, ocular, and other routes of drug and bioactive agent delivery.

Phospholipids, non-ionic surfactants, and bile salts make up the majority of bilosomes, which are sophisticated vesicular drug delivery systems that offer improved stability, flexibility, and permeability above conventional liposomes and niosomes.

In order to increase the bioavailability of different therapeutic agents, particularly through oral, transdermal, and ocular routes, bilosomes are closed, bilayer nanovesicles. By adding bile salts,

they greatly increase the vesicles' ability to withstand the harsh gastrointestinal environment, which makes it easier to deliver medications that are both hydrophilic and hydrophobic. Because of their enhanced absorption and permeation capabilities, bilosomes have demonstrated value in the delivery of proteins, peptides, vaccines, anticancer medications, and phytoconstituents.

## COMPOSITION OF BILOSOMES

1. **Phospholipids:** The main bilayer structure of bilosomes is made up of these naturally occurring or artificially produced amphiphilic molecules, which resemble biological membranes and promote biocompatibility and self-assembly.
2. **Bile Salts:** The lipid bilayer incorporates endogenous biosurfactants such as sodium taurocholate, sodium glycocholate, and sodium deoxycholate to improve stability, flexibility, and drug permeability as well as shield encapsulated medications from gastrointestinal deterioration.
3. **Non-ionic Surfactants:** Amphiphilicity, biocompatibility, low toxicity, and vesicle structure stabilisation are the reasons for the inclusion of molecules like those in the Span or polysorbate families.
4. **Cholesterol:** Frequently added to improve membrane stability and rigidity, which lessens vesicle contents leakage.

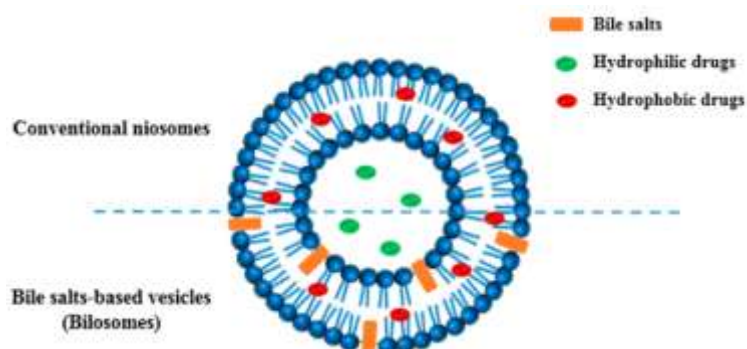


FIG NO:1 STRUCTURE OF BILOSOMES

Bilosomes can be single or multilayered, and their typical sizes fall between 5 and 200 nm. Hydrophilic agents can be encapsulated in the aqueous core and hydrophobic agents can be encapsulated in the bilayer due to the structural arrangement.

## INTRODUCTION OF APPLICATION OF BILOSOMES

Initially, bilosomes were created to improve the stability and absorption of medications, particularly those that are poorly permeable or lipophilic. Because bile salts are incorporated into their structure, these carriers are more flexible, absorbable, and permeable, which makes them ideal for overcoming biological barriers such as the skin and gastrointestinal tract.

## METHOD OF PREPARATION

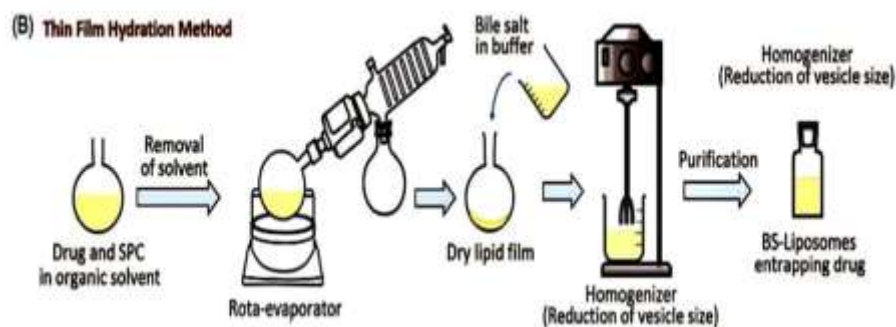


FIG NO: 2 METHOD OF PREPARATION

### 2. Method of Reverse Phase Evaporation:

To create a water-in-oil emulsion, lipids and bile salts are dissolved in an organic solvent and combined with an aqueous phase. Vesicles with a high encapsulation efficiency are created when the organic phase gradually evaporates under lower pressure. To purify the bilosomes and decrease particle size, the resultant dispersion is subjected to additional processing.

### 3. Method of Ether Injection:

Although bile salts are a crucial component of the vesicular structure, bilosome formulations are typically made using methods similar to those for conventional liposomes. Thin film hydration, reverse phase evaporation, and ether injection are the primary preparation techniques.

### 1. Thin film hydration

An organic solvent is used to dissolve phospholipids and bile salts, and the solvent is then evaporated to create a thin layer. Bilosomes are created when the dried film is agitated or sonicated after being hydrated with an aqueous buffer that frequently contains the medication. Centrifugation is used for harvesting, and if necessary, size reduction follows. Because of its ease of use and adaptability in encapsulating a broad range of medications and biotherapeutics, this technique is frequently employed.

Bilosomes form quickly when an organic solution of phospholipids and bile salts is gradually injected into a heated aqueous phase. The dispersion is then processed for size homogeneity and purification after the organic solvent is eliminated.

Alternative Techniques As an environmentally friendly substitute, probe sonication is becoming more and more well-liked, particularly for compounds that are sensitive to drugs. For better particle size control and reproducibility,

techniques like hot homogenisation and microfluidics are also investigated.

## MECHANISM OF DRUG DELIVERY

### Stability in gastrointestinal tract<sup>[6,7]</sup>

**Bile Salt Integration:** Bile salts, such as sodium taurocholate, sodium glycocholate, or sodium deoxycholate, are incorporated into the bilayer of bilosomes. By protecting both hydrophilic and hydrophobic medications from the GI tract's harsh acidic and enzymatic conditions, this design significantly lowers leakage and early drug degradation.

**Structural Resilience:** Bile salts make the vesicle membrane more flexible and fluid, which improves its resistance to the damaging effects of digestive enzymes and stomach acid. Bilosomes protect medications as they pass through the stomach and into the intestines by maintaining chemical and structural stability, in contrast to traditional liposomes and niosomes, which are frequently unstable in the GI environment.

**Enhanced Permeability:** By making it easier for bile salts to pass through the intestinal epithelium, they increase absorption in addition to improving the bilosomes' physical stability. Bilosomes provide better protection for medications (like insulin), according to studies, which results in a much longer GI residence and increased bioavailability.

## CELLULAR UPTAKE AND TARGETING PATHWAYS<sup>[8,9,10,11]</sup>

### Cellular uptake mechanisms

- **Endocytosis:** The main way that bilosomes can enter cells is by endocytosis, which includes both macropinocytosis and clathrin-mediated pathways. Functionalisation, like

hyaluronic acid (HA) coating, has been demonstrated to enhance receptor-mediated uptake, especially through CD44 receptors, which are highly expressed in some cancer cells.

- **Paracellular Transport:** Larger and more hydrophilic molecules can pass through the paracellular pathway because the bile salts in bilosomes temporarily relax tight junctions in epithelial cells. This improves the absorption of drugs at mucosal surfaces, such as the gastrointestinal tract.
- **Transcellular Transport:** Because bilosomes are lipid-rich, they can fuse with cellular membranes and release their contents straight into the cytoplasm, which helps internalise medications that are otherwise poorly absorbed.

### Targeting pathways

- **Receptor-mediated Targeting:** To facilitate selective targeting and uptake by cells expressing corresponding receptors (e.g., CD44 for HA-modified bilosomes), bilosomes can be surface-modified (e.g., with ligands like HA or sugars like dextrose).
- **Mucoadhesion and Extended Residence:** Bilosomes exhibit potent mucoadhesive qualities. This leads to a prolonged local release and improved absorption by increasing their retention at mucosal sites (intestine, skin, and ocular surface).

## Emerging Applications in Nanomedicines

### 1. ORAL VACCINE THERAPY APPLICATION OF BILOSOMES:

- Using Bilosomes to Deliver Vaccines Orally By preventing membrane destabilisation and degradation by digestive enzymes, bilosomes—vesicles made of bile salts and



non-ionic surfactants—stabilize the vesicles in the gastrointestinal (GI) tract. As the vaccine antigens pass through the hostile environment of the stomach and intestines, this helps shield them. M cells in the intestines' Peyer's patches, which trigger mucosal immune responses, including the production of secretory IgA, can more easily absorb the vesicles. Oral vaccination with bilosome-encapsulated antigens results in a robust mucosal and systemic immune response. Studies have shown that by enhancing antigen stability and delivery, bilosomes can improve the effectiveness of oral vaccines for a range of antigens, including influenza, tetanus toxoid, diphtheria toxoid, and hepatitis B.<sup>[11,12]</sup>

- Bilosomes support lower antigen doses to achieve an effective immune response, have superior chemical and GI tract stability, and don't need special storage conditions when compared to liposomes and niosomes.<sup>[13,14]</sup>
- **Antigen Protection:** Bile salts are incorporated into the bilayer structure of bilosomes, providing increased stability against harsh gastric acids and digestive enzymes. This stops the vaccine antigens from degrading too quickly as they pass through the intestines and stomach.<sup>[15,16]</sup>

## 2. CANCER THERAPY APPLICATION OF BILOSOMES<sup>[17,18,19]</sup>

- **Improved Drug Stability and Permeability:**

Bilosomes shield anticancer medications from gastrointestinal breakdown, increasing their bioavailability and therapeutic impact. For targeted delivery to cancer cells, they can transport a variety of chemotherapeutic agents, including pitavastatin, doxorubicin, methotrexate, and 5-fluorouracil (5-FU).

- **Targeted Delivery and Overcoming Resistance:**

Surface alterations like ligand conjugation increase drug uptake and cytotoxicity while decreasing systemic toxicity by improving targeting to tumour cells. Additionally, bilosomes can overcome chemotherapy resistance in cancers by inhibiting multidrug resistance proteins, such as P-glycoprotein.

- **Photodynamic Therapy:**

By co-delivering natural substances like curcumin and photosensitisers like methylene blue, bilosomes have been used to enable synergistic photodynamic therapy for aggressive cancers like melanoma with improved selectivity and fewer side effects.

- **Oral and Non-invasive Delivery:**

Bilosomes make it easier to administer anticancer medications orally, increasing patient compliance and providing a non-invasive substitute for intravenous chemotherapy.

- **Versatility across cancer types:**

Many cancers, including those of the gastrointestinal tract, breast, lungs, pancreas, and skin melanoma, have shown demonstrated efficacy.

## 3. ANTI-VIRAL THERAPY APPLICATION BILOSOMES<sup>[20,21,22]</sup>

- By shielding antiviral medications from gastrointestinal tract degradation and improving their absorption through epithelial barriers, bilosomes enhance their oral and mucosal delivery. Increased bioavailability and therapeutic efficacy result from this. They have been employed as carriers to enhance the



controlled release and oral absorption of antiviral medications such as acyclovir.

- Additionally, bilosomes are efficient nanocarriers for antiviral vaccines, such as those against the human enterovirus 71 (HEV71), influenza A (H3N2), and hepatitis B virus. Both systemic and mucosal immune responses are enhanced by their stability and targeting capabilities.<sup>[23]</sup>
- By improving targeting to immune cells like M cells in Peyer's patches, surface modifications like mannosylation can boost vaccine effectiveness and protection against viral infections.
- Bilosomes have demonstrated potential delivery benefits for antimicrobials, antifungals, and naturally occurring bioactive compounds with antiviral properties in addition to antiviral medications.

#### 4. GENE AND PROTEIN THERAPY APPLICATIONS OF BILOSOMES<sup>[24,25,26,27,28,29]</sup>

- Bilosomes enhance bioavailability and therapeutic efficacy by preventing enzymatic degradation of therapeutic genes, siRNA, microRNA, and proteins and facilitating their passage across cellular membranes. By altering the surface of bilosomes, targeted delivery to particular tissues or cells can be made possible, improving the accuracy of gene and protein therapies while reducing off-target effects.
- In clinical settings, they are appropriate carriers for genetic medicines and protein drugs due to their biocompatible composition of natural phospholipids and bile salts, which lowers toxicity risks. According to recent research, bilosomes can be designed to release genetic material gradually and under control, which could improve treatment outcomes for

genetic disorders, infectious diseases, and cancer.

- Sustained ocular and other targeted delivery routes are becoming more applicable thanks to developments in engineered bilosome carriers combined with stimuli-responsive release and in situ gel systems.

#### 5. APPLICATIONS IN NEUROLOGICAL DISORDERS<sup>[32,33,34]</sup>

##### • ALZHEIMER'S DISEASE

When given orally and intranasally, resveratrol-loaded bilosomes showed decreased neuroinflammatory markers and enhanced memory function in mouse models of Alzheimer's disease (AD).

Bilosomes loaded with luteolin improved spatial memory and inhibited tau hyperphosphorylation and amyloid  $\beta$  aggregation, suggesting that they may be used as a treatment for AD.

##### • Brain Injury and Stroke

When compared to plain formulations, glibenclamide-loaded bilosomes in mucoadhesive in situ gel administered intranasally dramatically raised brain drug concentrations, providing a potentially effective treatment for ischaemia, stroke, and traumatic brain injury.

##### • Treatment for Migraines

Delivered in mucoadhesive gels, zolmitriptan-loaded bilosomes demonstrated direct nose-to-brain targeting and superior brain bioavailability, suggesting that they could be used to treat acute migraines.

#### 6. TRANSDERMAL THERAPY APPLICATIONS<sup>[35,36,37]</sup>



An overview of bilosome applications in transdermal therapy reveals that they are sophisticated vesicular carriers that improve drug penetration through the stratum corneum, the skin's natural barrier, providing a viable method for topical and systemic delivery. Bile salts are incorporated into lipid vesicles to form bilosomes, which offer enhanced permeability, flexibility, and deformability for efficient transdermal medication delivery.

- **Mechanism of Action:** The disruption and fluidisation of skin lipids by bile salts in bilosomes increases vesicle flexibility and facilitates effective drug transport across the epidermal barrier. Bypassing gastrointestinal metabolism, this enhances drug permeability and solubility.
- **Enhanced Permeability and Bioavailability:** Bilosomes have been demonstrated to enhance the transdermal permeation of various pharmaceuticals exhibiting suboptimal oral bioavailability. For instance, bilosomal formulations of diacerein, olmesartan medoxomil, tizanidine hydrochloride, terbutaline sulphate, and diclofenac sodium exhibited enhanced skin deposition, retention, and bioavailability relative to traditional formulations or oral administration.
- **Safety and Skin Compatibility:** Histopathological evaluations verify that bilosomal formulations do not induce skin irritation or inflammation, rendering them safe for topical application.
- **Formulation and Characterization:** Thin-film hydration and other similar methods are often used to make bilosomes. The goal of optimisation is to improve particle size, entrapment efficiency, and stability. Characterisation techniques encompass TEM, DSC, FTIR, as well as *ex vivo/in vivo*

permeation and pharmacokinetic/pharmacodynamic investigations.

### Examples of Applications:

- **Diacerein loaded bilosomes:** Bilosomes loaded with diacerein made osteoarthritis treatment better by making drugs stay in the body longer and get through the skin better.
- **Olmesartan bilosomes:** Olmesartan bilosomes made the drug twice as available as oral tablets.
- **Lornoxicam bilosomes** exhibited improved anti-inflammatory and analgesic properties with increased dermal penetration. New bilosomal gels made for anti-inflammatory, antihypertensive, antidiabetic, and antifungal drugs have better therapeutic profiles and controlled release.
- **Research Trends:** In order to optimise therapeutic efficacy, ongoing research focusses on PEGylated bilosomes, chitosan-coated bilosomal gels, and the addition of penetration enhancers.

### 7. MUCOSAL THERAPY:<sup>[38,39,40,41,42,43]</sup>

The deliberate administration of therapeutic agents that target the mucosal surfaces of the human body, including the gastrointestinal tract, respiratory tract, urogenital tract, and oral cavity, is known as mucosal therapy. These mucosal surfaces play vital roles in immune defence, absorption, and barrier function, acting as vital barriers and interfaces where the body interacts with the outside world.

- **Mucosal Barrier:** The mucosa is a complex structure made up of protective mucus layer, underlying immune cells (collectively referred to as mucosa-associated lymphoid tissue, or MALT), and epithelial cells joined



by tight junctions. This barrier keeps homeostasis stable and stops pathogen entry.

- **Immune Defence:** The balance between active defence against infections and immune tolerance to innocuous substances (such as food and commensal microbes) is regulated by mucosal immune cells. Both adaptive immune responses and innate immunity mechanisms are involved in this.
- **Healing and Homeostasis:** In order to heal wounds and preserve integrity, the mucosa has built-in repair mechanisms that include tight junction restoration, inflammation modulation, and epithelial cell proliferation. To restore barrier integrity and avoid chronic inflammation, mucosal healing is promoted by modifying cellular and immune responses.
- **Protection and stability:** Bilosomes shield encapsulated medications from acidic environments in the saliva, nasal secretions, or gastrointestinal tract as well as from enzyme-induced degradation. Their membranes' bile salts offer protection from bile salt-mediated dissolution, increasing vesicle stability and extending the duration of residence at mucosal sites.
- **Enhanced Mucosal Penetration:** Deeper penetration into mucosal tissues is made possible by the bile salts' fluidisation of mucosal lipid membranes and increase in vesicle deformability. This characteristic facilitates the efficient delivery of medications that normally have low mucosal bioavailability, such as proteins, peptides, and vaccines, and enhances both local and systemic drug absorption.
- **Targeted Immune Activation:** It has been demonstrated that bilosomes conjugated with targeting moieties, such as the cholera toxin B subunit, target M cells in the gut-associated lymphoid tissue (GALT), improving antigen uptake and triggering potent systemic and

mucosal immune responses. Bilosomes are therefore promising vehicles for nasal and oral vaccines that prevent infectious diseases.

### THERAPEUTIC APPLICATIONS:

- **Oral Vaccines:** Bilosomes have the potential to be used in needle-free oral vaccines because they effectively transport antigens to mucosal immune cells, eliciting IgA-mediated mucosal immunity.
- **Antimicrobial Delivery:** Ciprofloxacin and moxifloxacin, two antibiotics that have been loaded into bilosomes, have shown enhanced penetration and greater effectiveness in treating mucosal infections, including infections of the eyes.
- **Anti-inflammatory and Neuroprotective Agents:** Intranasal bilosomes containing medications such as luteolin and zolmitriptan target the brain through mucosal pathways, exhibiting improved brain bioavailability and therapeutic effects in models of neurodegeneration.
- **Delivery of Phytochemicals:** Bilosomes enhance the oral bioavailability and therapeutic effectiveness of substances derived from plants that are used as antidiabetic, anti-inflammatory, and antioxidant agents.
- **Safety and Biocompatibility:** According to studies, bilosomal formulations are safe for mucosal administration, non-irritating, and biocompatible, making them appropriate for long-term or recurrent use.

### Challenges and Advances:

- **Obstacles and Progress** Effective therapy requires specially designed delivery systems because mucosal environments present difficulties such as enzymatic degradation and mucociliary clearance.



- Bilosomes are one type of nanocarrier that enhances drug penetration and stability in mucosal tissues.
- To create safer and more efficient mucosal therapies, ongoing research aims to comprehend mucosal immunoregulation and microbiota-immune crosstalk.
- Uses in Diseases of the Anterior Segment Acetazolamide and pilocarpine, which lower intraocular pressure (IOP), are two examples of enhanced delivery.
- Bilosomal formulations improve IOP control with fewer doses and fewer systemic side effects by increasing ocular retention time, corneal penetration, and sustained release.
- Bilosomes can be coupled with mucoadhesive polymers, like chitosan, to enhance adhesion to the corneal surface and extend the duration of medication action.

## **BILOSOMES APPLICATION IN OCULAR THERAPY**<sup>[44,45,46,47,48,49]</sup>

The unusual structure of bilosomes, which incorporate bile salts to improve drug stability, penetration, and retention on different areas of the eye, makes them attractive for use in ocular therapy. They serve as a flexible nanocarrier system that enhances bioavailability and therapeutic effects while reducing adverse effects for both anterior and posterior segment ocular medication delivery.

### **Bilosomes in ocular drug delivery**

- Bilosomes improve drug absorption and retention on the ocular surface by shielding encapsulated medications from enzymatic breakdown and physiological barriers of the eye, such as tear dilution and corneal impermeability.
- Their bile salt content improves the ability to pass through ocular barriers, such as the cornea and conjunctiva, by increasing membrane fluidity and permeability.
- The ability of bilosomes to encapsulate hydrophilic and hydrophobic medications makes them versatile for a range of ophthalmic agents, including proteins, antibiotics, anti-glaucoma medications, and anti-inflammatory drugs.

### **Applications in Anterior Segment Disease**

### **Applications in Posterior Segment Diseases**

- The retina and vitreous humour are difficult targets because of anatomical barriers, but bilosomes enhance drug delivery to these areas.
- Drugs encapsulated in bilosomes, like gene therapy molecules or antivascular agents, have a longer half-life, lower clearance, and sustained release when administered intravitreally.
- Experimental ocular gene therapy and the delivery of neuroprotective peptides that reduce inflammation in conditions like uveitis have both made use of bilosomes.

### **Advantages**

- Benefits Compared to Traditional Carriers greater stability in ocular tissues and tear films when compared to liposomes devoid of bile salts.
- Better therapeutic efficacy is the result of increased bioavailability and penetration.
- Decreased systemic and ocular toxicity as a result of prolonged and targeted drug release. flexibility for improved efficacy across several administration routes, including topical, intravitreal, and systemic.



## ROLES IN TARGETED THERAPY

Biosomes, also known as liposomes or bilayer vesicles, are nanoscale drug carriers that are essential to targeted therapy because they allow for the precise delivery of drugs to diseased cells, especially in the treatment of cancer.

### Mechanisms of Targeted Therapy<sup>[50,51,52,53]</sup>

Biosomes distinct structural makeup, surface characteristics, and interactions with biological systems all work together to improve the specificity and effectiveness of drug delivery in targeted therapy.

- Structural Composition and Stability
- Passive Targeting
- Active Targeting
- Enhanced Mucosal Permeation and Bioavailability
- Stimuli-Responsive Drug Release
- Overcoming Drug Resistance and Enhancing Intracellular delivery

### Passive Targeting: The Role of the Enhanced Permeability and Retention (EPR) Effect

- In biosome-mediated drug delivery, passive targeting takes advantage of the pathophysiology of tumour vasculature. Wide fenestrations, impaired lymphatic drainage, and aberrant, disorganised, and highly permeable vasculature are common features of solid tumours. The Enhanced Permeability and Retention (EPR) effect is the term used to describe the preferential extravasation and retention of nanoparticles, which are usually between 10 and 400 nm in size, within tumour tissues due to this aberrant vasculature.
- By passively accumulating at tumour sites following intravenous administration, biosomes that have been engineered to

optimal nanosizes take advantage of the EPR effect. They have a longer half-life and better accumulation because of their bilayer structure and the composition of bile salts, which increase stability in circulation. Bile salts are also added to promote membrane flexibility and fluidity, which aids in post-extravasation transmigration through the tumour interstitium.

- The EPR effect reduces systemic toxicity and side effects, which have been a significant problem with traditional chemotherapy, by increasing local drug concentrations at the tumour while limiting exposure to healthy tissues. However, because of microenvironmental factors like stromal density and vessel permeability, the EPR effect's magnitude can differ greatly among tumour types, stages, and individual patients.
- Therefore, tumour selectivity and therapeutic efficacy may not always be achieved by passive targeting via EPR alone. To increase the EPR effect, a number of tactics have been investigated, such as combination therapies that alter the tumour microenvironment, restore normalcy to aberrant vessels, or break down extracellular matrix components to allow for deeper penetration of nanoparticles. Because of their increased stability and capacity to interact with biological membranes, biosomes are ideal candidates for these enhanced EPR-based strategies.<sup>[52,53]</sup>

### Active Targeting: Ligand-Functionalized Biosomes for Enhanced Specificity

- Active targeting greatly improves selectivity and drug delivery precision, whereas passive targeting allows for some tumour accumulation. Using ligands that selectively bind receptors or antigens that are overexpressed on pathological cells, such as



monoclonal antibodies, aptamers, peptides, vitamins, or small molecules, active targeting entails chemically altering the bilosome surface.

- By decorating the bilosome lipid bilayer or PEGylated surface with targeting moieties, ligands can functionalise bilosomes through covalent attachment or adsorption methods. Examples include antibodies that target HER2 or EGFR, transferrin for cells that express iron receptors, and folate for cancers that are folate receptor-positive.
- By improving cellular uptake through receptor-mediated endocytosis, this receptor-mediated targeting increases intracellular drug delivery to tumour cells or other diseased cells. By preserving healthy cells, it also increases selectivity and reduces off-target side effects. Bile salts in bilosomes help to maintain membrane stability in spite of changes rather than interfering with ligand attachment.
- In a number of preclinical models, active targeting with ligand-functionalized bilosomes has demonstrated significant improvements in therapeutic outcomes. Bilosomes functionalised with epidermal growth factor (EGF) peptides, for instance, have shown notably effective increased uptake in colon and lung cancer cells that overexpress EGFR. Dual-functionality systems, which combine targeting and stimuli-responsive release for more intelligent drug delivery, are also made possible by ligand-functionalized bilosomes.<sup>[51,53]</sup>

### Stimuli-Responsive Bilosomes: Controlled and Spatiotemporal Drug Release

The precise temporal and spatial control of drug release is made possible by stimuli-responsive bilosomes, which are designed to release their

payload in response to particular internal or external triggers that are typical of diseased tissues.

Common stimuli exploited for bilosomes based drug delivery include:

- **pH – responsive release:** In contrast to normal tissues, tumour microenvironments and intracellular compartments (lysosomes, endosomes) frequently have an acidic pH. The therapeutic agent can be released selectively in tumour tissue or inside target cells by bilosomes containing pH-sensitive lipids or polymers that destabilise in acidic environments.
- **Enzyme-triggered release:** Enzymes (such matrix metalloproteinases) that are overexpressed in tumours or inflammatory tissues can break down delicate connections or bilosome bilayer elements, causing cargo release.
- **Thermo-responsive release:** Bilosomes temperature-sensitive components enable them to release medications in response to localised hyperthermia treatments.
- **Redox-responsive systems:** Bilosomes can be engineered to release drugs through disulphide bond cleavage in response to the increased intracellular glutathione levels found in cancer cells.<sup>[50,52]</sup>

By avoiding early drug release into the bloodstream, these stimuli-responsive characteristics enhance the therapeutic window and reduce systemic toxicity. When paired with such responsive elements, the presence of bile salts improves bilosome flexibility and membrane dynamics, which is advantageous.

### LIMITATIONS<sup>[11,12,23,30]</sup>



Although bilosomes, novel lipid vesicles containing bile salts, have many benefits for drug delivery, they also have significant drawbacks and difficulties.

### Preparation and Formulation Sensitivity

Size, stability, and encapsulation efficiency can vary depending on the formulation parameters (lipid composition, bile salt type, and hydration method) used in bilosome preparation. It is still difficult to optimise and scale up reproducible bilosome formulations for consistent manufacturing.

### Stability Issues

Bilosomes still experience physical and chemical instability during storage, such as vesicle aggregation, leakage, and drug degradation, even though bile salts improve vesicle stability against bile and enzymatic degradation. This can shorten shelf life and call for careful stabiliser selection or lyophilisation.

### Invitro-In vivo Correlation

Because bilosomes interact intricately with biological fluids and membranes, in vitro release or permeation studies frequently do not correlate well with in vivo performance. This makes predictive evaluation and formulation optimisation more difficult.

### Biological Barriers and Immune Interaction

Although bilosomes enhance mucosal penetration, it is still challenging to get past all biological barriers in complex tissues, such as mucus clearance and enzymatic breakdown. Additionally, unless bilosomes are surface-modified, reticuloendothelial systems' immune recognition and clearance shorten circulation times and target accumulation.

### Toxicity and Safety Concerns

Excessive bile salt concentrations can cause membrane irritation or cytotoxicity, which restricts dosage and delivery methods. Thorough long-term safety studies are still necessary, particularly for systemic or repeated dosing.

### Limited clinical data and Regulatory Challenges

Clinical translation of bilosome formulations is limited despite encouraging preclinical results because of scale-up issues, complicated regulatory requirements, and insufficient safety and efficacy data.

### FUTURE PERSPECTIVES<sup>[11,49,56,57]</sup>

Future estimates of bilosomes as drug delivery systems demonstrate their enormous potential for a wide range of therapeutic uses and administration routes, which is bolstered by continuous developments in pharmaceutical sciences and nanotechnology.

Future directions	Description	Impact
Broadening applications	Exploring new delivery routes and disease areas	Increase therapeutic potential across fields
Advanced formulations	QbD, mucoadhesive coating	Improves stability, targeting and release
Personalized medicines	Tailored drug release and combination therapy	Enhance therapy precision and outcomes
Clinical regulatory progress	Safety studies, evolving regulations	Facilitates approval and market adoption



Digital & AI Integration	AI-guided formulation and smart drug delivery	Accelerates development and individualized care
Sustainability Focus	Efficient manufacturing and Eco-friendly materials	Reduces environmental impact

## CONCLUSION:

Bilosomes represent a versatile and innovative approach in nanomedicine, bridging the gap between traditional vesicular carriers and modern targeted drug delivery needs. Their bile salt-stabilized structure not only improves drug stability and absorption but also enables site-specific and sustained release across diverse routes of administration. Emerging applications in vaccines, cancer, neurological, and ocular therapy highlight their wide-ranging clinical potential. However, limitations such as formulation reproducibility, long-term stability, and limited clinical translation must be addressed to facilitate their broader adoption. Future research integrating quality-by-design approaches, surface functionalization, artificial intelligence-driven formulation strategies, and sustainable manufacturing practices could accelerate their transition from laboratory to clinical use. Overall, bilosomes hold strong promise as next-generation nanocarriers for improving therapeutic efficacy, patient compliance, and precision in drug delivery.

## ACKNOWLEDGEMENT

We would like to thank Prof. Dr. A .Meena, Principal , Prof. Dr. A. Shanthy, Vice Principal, K.K.College of Pharmacy for motivating us for our review work.

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**HOW TO CITE:** Suresh K, Laura S L, Gopinath E, Vignesh R, Emerging Applications of Bilosomes in Nanomedicine and Targeted Therapy : A Review, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 10, 1952-1966. <https://doi.org/10.5281/zenodo.17383247>

