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Advantages and therapeutic applications of drug delivery vesicles: Bilosomes

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Abstract
Bilosomes, or bile vesicles, are bilayer vesicles that arise from the hydration of bile salts. They have received considerable attention in recent years for their potential applications in various sectors, including drug delivery and nutraceuticals. This review discusses the potential applications of Bilosomes, particularly their use as drug delivery systems for hydrophobic drugs, along with their roles in the food and nutraceutical industries. Moreover, we examine the current state of the Bilosomes market, including the commercial products that are available today. In conclusion, this review provides a comprehensive summary of the recent advancements in Bilosomes research and highlights the potential of Bilosomes in various areas.

Keywords: Bilosomes, vesicles, therapeutics, drug delivery, commercial

Introduction
Bilosomes represent a category of drug delivery systems that leverage bile salts to improve the stability and efficacy of medications, especially for oral and topical use. These nanovesicles are made up of phospholipids and bile salts, providing benefits such as increased drug solubility, better bioavailability, and precise delivery [1]. Due to their biocompatibility and capacity to shield drugs from degradation within the gastrointestinal tract, bilosomes are viewed as a promising option for a range of therapeutic applications. Bilosomes are flexible, nonionic, amphiphilic surfactant delivery systems that incorporate bile salts to enhance the oral and dermal delivery of medications at different dosages [2-3]. Given the challenges faced by liposomes and niosomes in the gastrointestinal tract, including poor stability and issues with drug loading or leakage, the advancement of bilosomes appears to be a promising alternative for achieving similar objectives.

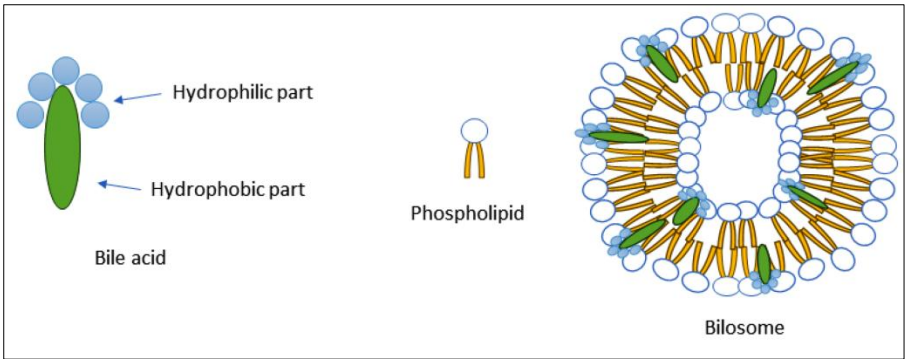

Fig 1: Basic Structure of Bilosomes

Bilosomes are vesicular carriers that are closed and have a double-layered structure, composed of lipids, non-ionic surfactants, and bile salts as their key components. These elements are mixed in various proportions to create the ideal vehicle for delivering

encapsulated drugs through the intended route of administration. Consequently, bilosomes can be derived from either liposomes (Bile salt-liposomes) or niosomes (bile salt-niosomes). Their dimensions typically range from 5 to 200 nm, and they often display a spherical shape, existing as either single or multi-layered vesicles. Bilosomes enhance the delivery of drugs and vaccines targeting various gastrointestinal infectious agents, including cholera toxin and diphtheria toxins [4-7]. Thanks to their intestinal stability and adaptability, bilosomes serve as effective carriers for vaccines and bioactive substances, as well as for antimicrobial, anticancer, and antifungal medications [6-8]. They are also utilized as alternative drug delivery systems for various other routes, including ocular and dermatological treatments [9-10]. Numerous studies have evaluated the antimicrobial efficacy of bilosomes by transporting antibiotics, natural bioactive compounds, or vaccines. Mice infected with Burkholderia pseudomallei were effectively treated with bilosome-encapsulated levofloxacin and doxycycline, showing no harmful effects on the microbiome. Furthermore, levofloxacin-bilosome significantly enhanced the bactericidal properties of the antibiotic [11]. The pegylated bilosomes loaded with luteolin (LL) demonstrated superior antibacterial, antioxidant, and anticancer properties compared to single luteolin [12]. Additionally, bilosomes that were surface-modified and synthesized via the solvent evaporation technique, loaded with quercetin, showed greater antibacterial, antioxidant, and anticancer effects than free quercetin delivery. This system proved to be more effective against Escherichia coli than Staphylococcus aureus [13]. Moreover, the moxifloxacin-loaded bilosome, referred to as MX-BSop in situ gel (MX-BSop-Ig4), exhibited enhanced permeation compared to single moxifloxacin, along with improved antibacterial effects and reduced tissue toxicity [14]. It also demonstrated two- and four-fold lower minimum inhibitory concentrations against E. coli and S. aureus, respectively. Other compounds, including quercetin, lycopene, and apigenin, as well as various drugs, have been developed for their antibacterial, antiviral, and antifungal properties [15-17]. The quercetin-loaded, surface-modified bilosome displayed a stronger antibacterial effect against E. coli than S. aureus [13].

Advantages of Bilosomes

The Bilosomes in the recent past have shown numerous advantages and this becomes a reason that this drug delivery vesicles to evolve at a rapid rate. These advantages have been explored by the researchers to develop the Bilosomes based formulation for the treatment and management of several diseases [18-20].

Table 1: Advantages of Bilosomes As Drug Delivery Carrier

S. No.	Parameter	Details
1.	Improved bioavailability	Bilosomes enhance the bioavailability of lipophilic drugs by safeguarding them from degradation and aiding their transport across cell membranes.
2.	Drug protection	Bilosomes provide protection to drugs against degradation caused by enzymes and other bodily factors.
3.	Decreased toxicity	Bilosomes can minimize the toxicity of drugs by ensuring their direct delivery to the intended cells or tissues.
4.	Targeted delivery	Bilosomes can be engineered to specifically target certain cells or tissues, thereby boosting the efficacy of the drug or genetic material.
5.	Biocompatibility	Composed of natural phospholipids and bile salts, bilosomes are regarded as biocompatible, which lowers the likelihood of adverse reactions
6.	Gene therapy applications	Bilosomes can facilitate the delivery of genetic material to cells, presenting potential applications in gene therapy.

Therapeutic Applications of Bilosomes

- **Cancer therapy:** Bilosomes are proposed as a delivery system for anticancer medications, as they can specifically target cancer cells and improve the bioavailability of these drugs. Alamoudi *et al*., optimized bilosome based nanoparticles enhance cytotoxic and pro-apoptotic activity of costunolide in LS174T colon cancer cells [21]. Hegazy *et al*., designed TPGS surface modified bilosomes as boosting cytotoxic oral delivery systems of curcumin against doxorubicin resistant MCF-7 breast cancer cells [22]. Alhakamy *et al*., formulated and optimized Piceatannol loaded bilosome stabilized zein protein exhibits enhanced cytostatic and apoptotic activities in lung cancer cells [23].
- **Antiviral therapy:** Bilosomes are also suggested as a delivery mechanism for antiviral medications, as they can safeguard the drugs from degradation and enhance their bioavailability. Zakaria *et al*., formulated Poly phenolic phytoceutical loaded nano-bilosomes for enhanced caco-2 cell permeability and SARS-CoV 2 antiviral activity [24]. Rawat *et al*., carried formulation, development and *in vitro* assessment of Rilpivirine Nanobilosomes [25].
- **Gene therapy:** Bilosomes have been proposed as a delivery system for genetic material, as they can provide protection for the material. Bilosomes are suggested as a means to prevent degradation and improve their transport through cell membranes.
- **Dermatology:** Bilosomes are being considered as a delivery mechanism for topical skincare products and cosmetics, as they can facilitate the absorption of active ingredients through the skin. El-Nabarawi *et al*., carried the preparation, characterization and *in vivo* skin deposition assay of Bilosomes as a novel carrier for the cutaneous delivery for dapsone as a potential treatment of acne [26]. Mosallam *et al*., fabricated the highly deformable bilosomes for enhancing the topical delivery of terconazole [27].
- **Ophthalmology:** Bilosomes are being explored as a delivery system for ocular medications, as they can safeguard the drugs from degradation and improve their transport across the cornea.
- **Cardiology:** Bilosomes are being proposed as a delivery system for cardiovascular medications, as they can protect the drugs from degradation and enhance their transport through cell membranes.

- **Neurology:** Bilosomes are being suggested as a delivery system for medications targeting neurological disorders, as they can shield the drugs from degradation and improve their transport across the blood-brain barrier. El Taweel *et al*., formulated intranasal zolmitriptan loaded bilosomes with extended nasal mucociliary transit time for direct nose to brain delivery [28]. Elsheikh *et al*., generated a brain-targeted approach to ameliorate memory disorders in a sporadic alzheimer's disease mouse model via intranasal luteolin-loaded nanobilosomes [29].

Commercial Status of Bilosomes

A variety of products are available in the market that utilizes Bilosomes as a fundamental element. These products are being made and available commercially to enhance the delivery of variety of drugs used to treat numerous disorders [30-32].

Table 2: Marketed products of Bilosomes

S. No.	Trade name	Drug Name	Details
1.	Vemlidy	Tenofovir Alafenamide	A nucleotide reverse transcriptase inhibitor (NRTI), it is utilized for the treatment of chronic hepatitis B virus (HBV) infection in adults who have compensated liver disease
2.	Marqibo	Vincristine Sulfate	It is a chemotherapy medication utilized for the treatment of acute lymphoblastic leukemia
3.	Onivyde	Irinotecan	A chemotherapy drug that is used to treat pancreatic cancer
4.	Abraxane	Paclitaxel	A chemotherapy medication utilized for the treatment of breast, non-small cell lung, and pancreatic cancers. It is encapsulated within Bilosomes, which assist in directing the drug specifically to cancer cells while minimizing side effects
5.	Doxil	Doxorubicin Hydrochloride	It is encapsulated in Bilosomes that help to target the drug to cancer cells and reduce side effects
6.	Amphotec	Amphotericin B	An antifungal medication utilized for the treatment of fungal infections, including aspergillosis and candidiasis

Conclusion

Bilosomes serve as a promising drug delivery mechanism, showcasing numerous advantages but also facing certain limitations. Further investigation is required to fully appreciate their potential and to confront the challenges that arise with their utilization. Additionally, more research is needed to analyze the safety and effectiveness of Bilosomes in various therapeutic scenarios. Notwithstanding the limitations, Bilosomes have the capacity to revolutionize the delivery of drugs and genetic materials to cells and tissues in the body, establishing them as a key focus of active research and development in the drug delivery field.

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