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Review Article

Bilosomes: A specialized bile salt based nanocarrier drug delivery system in cancer therapy

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Abstract

Over the past several years, advances in nanotechnology have given rise to diverse nanocarrier systems tailored for site specific drug delivery. Among these, bilosomes a bile salt stabilized vesicles have emerged as a superior alternative to conventional liposomes and niosomes. This review explores the structural advantages of bilosomes, specifically their enhanced stability within the harsh gastrointestinal (GI) milieu, resistance to enzymatic degradation, and superior mucosal permeability, which collectively enhance the bioavailability of lipophilic and poorly permeable drug therapeutics. A comparative analysis of bilosomal structure relative to liposomal and niosomal frameworks is provided, highlighting the role of various bile salts in modulating vesicle elasticity and drug absorption. The discussion further extends to the preparation methods employed in bilosome formulation and their applications in targeted oncology, evaluating their efficacy in treating breast, skin, lung and liver cancers. Through a synthesis of contemporary case studies, this review examines the mechanistic pathways underlying bilosomes mediated anticancer therapy, while critically assessing their advantages, inherent limitations, and regulatory considerations. Graphical representations are included to illustrate current concepts in bilosomal delivery, offering a comprehensive roadmap for future research in targeted nanomedicine

Keywords: Bilosomes, Nanocarrier, drug delivery system, cancer.

1. INTRODUCTION:

Targeted drug delivery system is widely used platform for treating various disease across the globe. Drug targeting concept was first coined by Paul Ehrlich a German scientist in the late 19th and early 20th centuries. This targeting approach is then terms as Magic bullet [1]. His study finally led to the discovery of arsphenamine in 1909, the first effective 'targeted' treatment for syphilis, which regarded as the practical implementation of his magic bullet notion and the basis for contemporary chemotherapy [2]. Drug targeting enables the medicine to reach its target site and produce the desired pharmacological reaction as per the therapeutic necessity. A precise grasp of the level of targeting makes it simple to select the appropriate targeting moiety, ligand, or carrier system [3]. Furthermore, focused delivery enables for a minimal amount of medicine to reach non target organs and tissues, resulting in an effective and safe drug delivery system [4]. A carrier system can be used to deliver medications in a targeted manner. A carrier is a distinct molecule or system that is fundamentally required for the efficient delivery of a loaded drug to predetermined areas [5]. These are specially engineered vectors that transport medicine to the desired location by encapsulating or attaching to it with a spacer moiety. Drug carrier is nothing but the nanotechnology used in the targeting which involves liposomes, ethosomes, cubosomes, transferosomes, bilosomes, polymeric micelles and dendrimers [6]. Targeted approach is highly suitable techniques as compared to traditional drug administration methods because this system reduces the systemic toxicity and lowers side effects as well as improve the bioavailability, accumulation of drug at targeted site which significantly improves the therapeutic index of drug [7].

Bilosomes are emerged as a recent development of advanced targeted drug carrier or novel targeting approach based on bile salt and phospholipids which are nano carrier that created to get around some of the

drawbacks of traditional liposomes , namely instability in the digestive system .Because of their extreme flexibility, they can encapsulated medications or genetic material to improve absorption, stability ,and targeted delivery via a variety of methods ,including oral, transdermal or ocular administration[8]. This is accomplished by the bile salts improving penetration through biological membranes and protecting the vesicles against deterioration. They are incorporated bile salts into the bilayer membrane. Bilosomes in particular enhance the stability and oral absorption of medications in GI malignancies [9].

Bilosomes have several advantages over other targeting drug delivery systems such as more stability and biocompatibility due to presence of nonionic surfactant also Cholesterol to make the membrane stiff (Fig.1). Bile salts to improve penetration and provide stability against GI deterioration. High entrapment efficiency and capacity to deliver a range of mediation and biological substances. Bilosomes amphililic properties enable them to shield their contents from GI tract acid and enzymatic degradation, promoting excellent medication absorption when taken orally. By improving medication uptake and transport across epithelial barriers, bilosomes facilitate targeted distribution. They can be further modified foe better targeting and controlled release [10]. Increased stability and resistance to GI breakdown when compared to traditional vesicles. Adaptability in delivery methods, including as oral, transdermal and mucosal [11]. The mechanism of bilosomes are involved bile salts change the characteristics of vesicular membranes by functioning as edge activators that improve fluidity, reduces surface tension ,and encourages tissue penetration[12].

According to the World Health Organization (WHO), cancer is the leading cause of illness and death worldwide. Between 2005 and 2020, an estimated 85 million people are expected to die from cancer [13].In September 2025 recent study shows that by 75% death rate expected to rise in next 25 years [14]. Patient morbidity and mortality rates are rarely reduced by the conventional chemotherapeutics used in cancer treatment. This result is caused by the chemotherapeutics since they seriously damage healthy tissues. One intriguing development in cancer treatment is the ability of nanoparticles to overcome resistance in cancer cells [15]. Research has looked into using nanoparticles as a possible drug delivery method to solve these issues in cancer treatment. While simultaneously increasing the intracellular concentration of drugs within cancer cells, nanoparticles can protect healthy cells from harm [16]. In order to improve pharmaceutical formulations and treatment approaches, the future will offer customized nanomedicine, artificial intelligence, and real-time imaging[17] .One of the main objectives of cancer treatment is to target the specific cancer cells while sparing as many healthy cells as possible. Chemotherapy administration is hampered by several significant clinical obstacles because of the wide body distribution, MDR mechanism, poor absorption, increased metabolism, excretion, and poor diffusion across the tumor mass [18]. In this regard, improving nanoparticle absorption depends on EPR in solid tumors and the physiological drug resistance of the cancer micro environment [19]. This enhancement was made possible by increasing encapsulation efficiency, using artificial intelligence algorithms to model nanocarrier drug release kinetics, and predicting interactions between drug incorporation, nanocarriers, cell membranes, and biological mediators [20].

Hepatocellular carcinoma, breast cancer, colon cancer, melanoma and have all demonstrated encouraging outcomes when treated with bilosomes [21].Their longer circulation duration improves the like hood of targeting distant tumor location and invasive cells in metastatic malignancies and also in breast cancer [22]. Both hydrophilic and hydrophobic anticancer medications are encapsulated in bilosomes, which increases their solubility and stability and boosts their therapeutic action and bioavailability [23]. This review article involves potentially use of bilosomes as a targeting drug delivery system in various cancer types such as melanoma or skin cancer, hepatic or liver cancer, colon cancer, breast cancer also collectively study of mechanism of bilosomes.

2. STRUCTURE AND COMPONENTS:

The primary structural components of bilosomes formulation includes

Bile salts: these are the key component of bilosomes system. Common bile salts used are sodium deoxycholate (SDC), sodium Glycocholate (SGC), and sodium Taurocholate (STC). Bile salts are integrated into the phospholipid bilayers and nonionic surfactants

Amphiphilic Lipids / Nonionic surfactants: These are Main framework of bilayer phospholipid membrane. Examples includes phospholipids like phosphatidylcholine and soybean and nonionic surfactants like span 60, 80 or tween 60, 80 etc.

Cholesterol: This is important for maintain membrane fluidity and rigidity and hence it can effects permeability and stability bilosome structure.

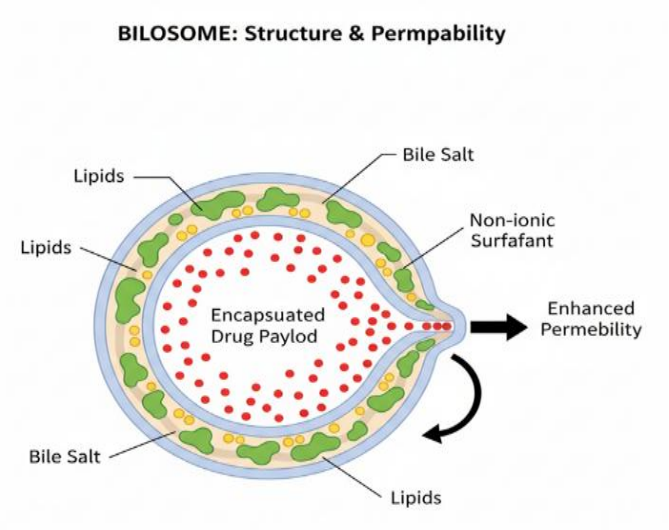

Figure 1: Structure of bilosomes

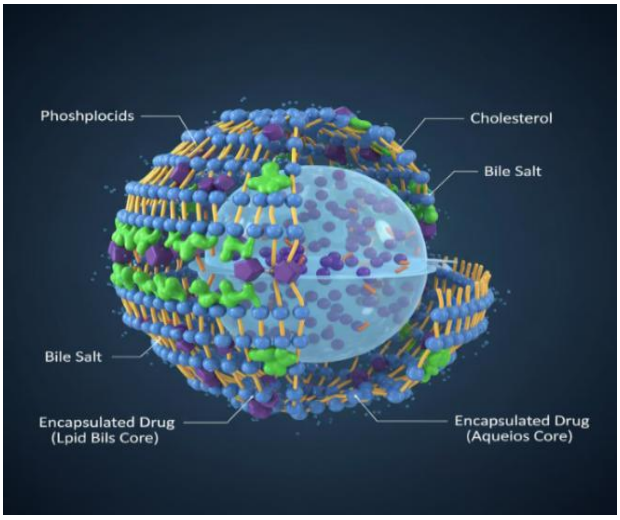

Figure 2: 3D structure of bilosomes

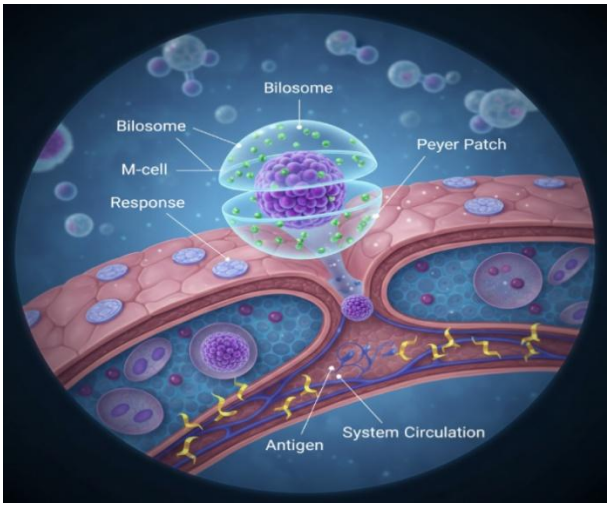

Figure 3: Bilosomes in targeted drug delivery

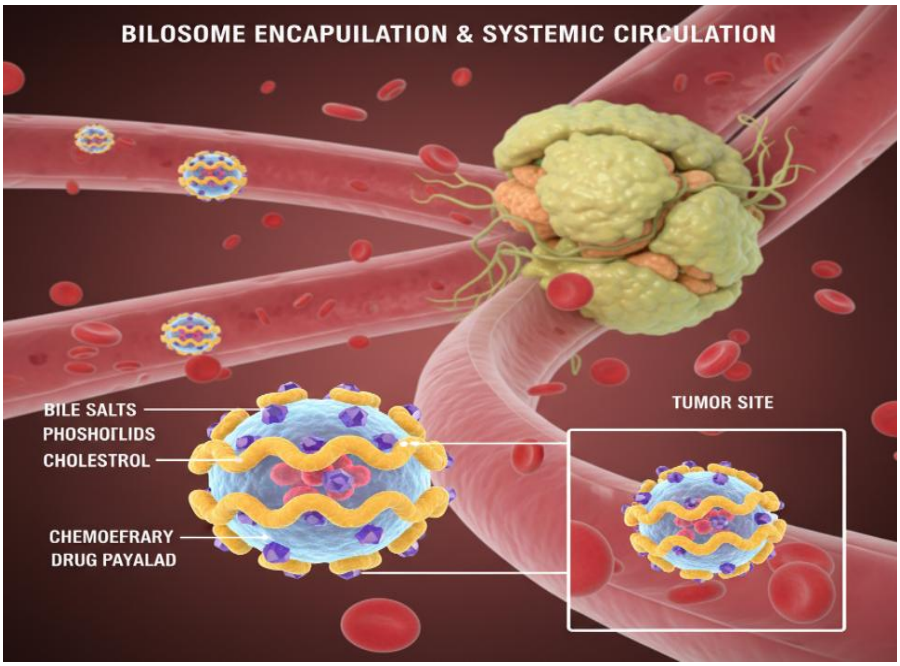

Figure 4: Bilosomes at tumor site

3. MECHANISM OF ACTION OF BILOSOMES:

Encapsulation: Drugs are trapped within a stable lipid bilayer modified with bile salts which shown Fig.2. structure of bilosomes.

Protection: The bile salts shield the drug form degradation by stomach acid and enzymes.

Penetration: High flexibility allows bilosomes to squeeze through biological barriers and skin pores to entered into systemic circulation through Meyers patch that present in endothelial cells that leads to bypass the first pass hepatic metabolism .As shown in Fig. 3.

Absorption: They promotes uptake via M cells in the intestine or direct cell membrane fusion. As shown in (Fig. 4).

Release: The cargo is delivered into the systemic circulation or specific target tissues.

In the formulation of bilosomes the main ingredient is a bile salt. In below Table 1 various types of Bile salts are mentioned that also involving in treatment specifying related to cancer.

Table 1: Type of Bile salts used in Cancer

Sr.No	Bile Salt	Structure	pH	Cancer Treatment	Ref
1.	Sodium Deoxycholate	Steroid structure with 2 hydroxyl groups	pH >7	Colorectal and other cancers	24
2.	Deoxycholic acid	Steroid structure having 2 hydroxyl groups & 1 carboxyl group	pH~8.3	Breast and Colorectal	25
3.	Sodium Glycocholate	Glycine trihydroxyl sodium salt	pH 6-8	Lung cancer , liver cancer, skin cancer	26
4.	Sodium Chenodeoxycholate	Steroid nucleus , hydroxyls at C-3, C-7 positions	pH ~ 6.7	Colon & skin cancer	27
5.	Sodium Ursodeoxycholate	Epimerized CDCA at C-7, more hydrophilic	pH ~ 8	Gastric , liver and prostate cancer	28
6.	Sodium Taurocholate	Cholic acid steroid linked with amino acid taurine	pH 6-8	Colorectal cancer	29
7.	Sodium Taurodeoxycholate	Deoxycholic acid steroid with 2 OH group linked with amide-taurine bond	pH 6-8	Colorectal & Gastric Cancer	30
8.	Sodium cholate	Steroidal 3 OH & 1 COOH	pH 6-10	Liver & Pancreatic cancer , Breast cancer	31
9.	Conjugated Bile Salts	Glycerin/taurine conjugation increases solubility	pH 5.5-7	Liver cancer	32
10.	Lithocholic Acid (least commonly used salt farm)	Hydroxycholan-24-oic acid	Unstable / oxidize easily under acidic & neutral pH	Breast , pancreatic & prostate	32
11.	Tauro-chenodeoxycholic acid(TCDCA)	Dihydroxyl ethanesulfonic acid	p H 4.5-5	Gastric cancer	33

4. PREPARATION METHODS:

There are various preparation methods used to formulate Bilosomal nanoparticles. In below table 2 preparation methods are characterizes based on their advantages, disadvantages and types of cancer treated most.

Table 2. Preparation methods of Bilosomes

There are primarily four to five methods used in the preparation of bilosomes which summarizes in below Table 2 with their advantages and disadvantages.

S.N	Technology	Description	Reason behind	Cancer Type	Advantages	Disadvantages	Ref
1.	Thin Film Hydration	A thin film of phospholipids and bile salts is hydrated ,foaming bilosomes after agitation and sonication	Enables encapsulation of hydrophobic and hydrophilic drugs for enhanced stability and targeted delivery	Colon , Lung , Prostate , GI cancers	Simple process Low cost for lab scale %EE increases Flexible	Hard to remove solvent fully Uneven vesicle sizes Hard to scale up	[34]

2.	Solvent Evaporation	Phospholipids and bile salts are dissolved in organic solvent and then mixed with water , foaming bilosomes upon solvent removal	Produces Bilosomes with encapsulation efficiency, improving drug bioavailability in tumors.	Colon, Pancreatic	Easy preparation with std equipment %EE high due to bile salts Good Stability	Toxic organic residue heterogeneous vesicles Limitated scalability	[35]
3.	Ether Injection Method	Solution of lipids /bile salts in organic solvent is injected into aqueous phase to form bilosomes after agitation.	Simple method for encapsulating sensitive anticancer drugs, providing protection.	General (Reported in various studies)	Forms unilamellar vesicles with good uniformity Simple, quick process High %EE Reduced residual solvent	Low % EE for hydrophobic drugs Large vesicle sizes Ether toxicity Poor scalability	[36]
4.	Hot Phase Homogenization	Lipid mixture and aqueous phase are homogenized at high temperature, then cooled to form bilosomes.	Suitable for large scale production and drugs requiring high tempura stability.	General	Produces uniform small unilamellar bilosomes High reproducibility and good colloidal stability Suitable for heat stable compounds	Risk of drug degradation Limited to thermo stable , scalability challenging Needs specialized homogenizer	[37]
5.	Freeze Drying Method	Bilosomes spontaneously form with preserved size, structure and encapsulated drug. use of lyoprotectants and	It improves shelf life and makes oral or systemic administration feasible , crucial for cancer requiring	Various , including oral delivery for GI cancers	Enhanced long term stability Protect sensitive drugs	Expensive in nature Low yield Chance of vesicle aggregation Time consuming	[38]

5. ROLE OF BILOSOMES IN CANCER

5.1 Liver cancer or Hepatocarcinoma

Primary liver cancer is a condition characterized by the formation of malignant (cancer) cells in liver tissues[39]. Bilosomes in liver cancer treatment serve as advanced nanocarrier, improving anticancer agent oral delivery and therapeutic efficacy. These bilosomes are frequently coated with lactoferrin (LF) to allow active targeting, as LF can bind to receptors overexpressed on HCC cells, such as glycoprotein receptors, hence increasing cellular internalization[40]. The mechanism consists of passive targeting via the increased permeability and retention (EPR) effect and active targeting via LF receptor-mediated endocytosis [41].The bilosomal formulation increases stability, bioavailability, and targeted administration to liver cancer cells, resulting in enhanced death via caspase-3 activation. This results in much better anticancer potency than free medicines, with a noticeable increase in tumor cell cytotoxicity without increased damage to normal cells [42]. Bilosomes are a promising oral drug delivery strategy for liver cancer because they improve targeting, cellular uptake, and therapeutic results through both passive and active mechanisms, using particular ligands[43].

5.2 Lung Cancer

Lung cancer is a condition characterized by uncontrolled cell proliferation in the lungs[44]. It was considered relatively rare in the early twentieth century, but by the end of the century, it had become the top cause of cancer-related death among males in more than 25 developed countries. Bilosomes have showed promise as nanocarrier in lung cancer treatment, enhancing drug delivery and efficacy[45]. Their mode of action in lung cancer mostly involves increasing drug permeability and cellular uptake, which results in enhanced cytotoxicity against lung cancer cells. For example, piceatannol-loaded bilosome-zein protein formulations (PIC-BZ) had much stronger lethal effects on A549 lung cancer cells than the pure drug [46]. By

boosting caspase-3 protein expression, this formulation increased medication absorption while also inducing cell cycle arrest in the G2-M phase and apoptosis [47]. Similarly, bilosomes loaded with medications such as trametinib demonstrated enhanced penetration and cytotoxicity against lung cancer cells, as well as increased apoptotic activity when compared to the drug alone[48]. In summary, bilosomes operate as effective nanocarriers in lung cancer by improving anticancer drug delivery, cellular uptake, and apoptosis-inducing properties, resulting in better treatment outcomes in lung cancer models such as the A549 cell line [49]

5.3 Breast Cancer:

Breast cancer is leading cause of cancer deaths among women globally, rate vary by fivefold over the world, but they are increasing in areas where the disease was formerly uncommon. Nanotechnology is utilized to diagnose molecular cancer through the use of biomarker and nanoparticles, resulting in multivalent effect that increases specificity and binding affinity, making them an appropriate diagnostic agent[50]. Bilosomes have demonstrated promising efficacy in breast cancer treatment as drug delivery vehicles. They improve the absorption and targeting of anticancer medicines while minimizing side effects and treatment resistant. Bilosomes have been investigated for transdermal delivery of tamoxifen to the breast, which improves local drug concentration while reducing systematic side effects compared to oral treatment [51]. According to recent study, bilosomes loaded with medications such as axitinib and methotrexate cause higher cytotoxicity and apoptosis in breast cancer cell lines such as MF7, showing increased anticancer activity [52]. Bilosomal formulations improves drug stability, allow for controlled release penetration, resulting in greater therapeutic efficiency.

5.4 Skin cancer:

Skin cancer is an abnormal development of skin cells that is most commonly induced by exposure to ultraviolet radiation from sunlight or tanning beds. The most prevalent forms include basal cell carcinoma, squamous cell carcinoma and melanoma [53]. Bilosomes improved skin penetration and shield encapsulated medications or photosensitizing from deterioration. Bilosomes have been shown in recent research to be efficient transporters of photosensitizers and anticancer drugs in skin cancer, particularly metastatic melanoma. For example, niosomes containing a mix of natural carotenoids (astaxanthin) and second – generation photosensitizers (such as Rose Bengal) have demonstrated potent antitumor effectiveness against human melanoma cell lines [55]. By dramatically decreasing cancer cell viability upon light activation, inducing apoptosis by modifying pro and anti-apoptosis proteins, and decreasing metastasis, these formulations make use of photodynamic treatment (PDT) [56]. Their surface characterization and Nano scale (size less than 100 nm) enable cellular absorption and transdermal administration. They target cancer cell more successfully than free medications, increasing selectivity and lowering toxicity [57-58]. Bilosomes offer regulated activation and synergistic anticancer effects, such as melanoma cell death and mitochondrial damage, when used in conjugation with photodynamic therapy [59]. By improving delivery and therapeutic efficacy, this novel bilosomes based method shows great promise a skin cancer therapy alternatives, particularly for difficult melanoma cases.

6. COMPARATIVE STUDY:

Bilosomes are comparatively more efficient and stable formulation among other nanoparticles or nano formulations. In Table 3 comparatively study are described between Bilosomes and traditional Nano formulations like liposomes or niosomes focuses mainly on important features.

Table 3: Comparative study of bilosomes with other nanotechnology

Sr.no	Key features	Bilosomes	Other nanotechnology (Liposomes, Niosomes)	Ref
1.	Stability and Bioavailability	More stable due to bile salt, enhance bioavailability.	Least stable in gastric and During GI degradation	60
2.	Encapsulation Versatility	Bilosomes provide better protection and controlled release mechanism	Less protection compared to bilosomes	61
3.	Safety and Biocompatible	Bilosomes are biodegradable, biocompatible and tend to have lower toxicity, making them suitable for repeated or long term use.	Not likely suitable for long term use.	10
4.	Targeting and Flexibility	Reduces systemic side effects by enables specific delivery of drug at targeted site hence more flexible in nature	Least flexible than bilosomes	54
5.	Comparative size and drug release	May provide Greater permeability and stability	Have slow release pattern and least permeable than bilosomes	62

7. CHARACTERIZATION BILOSOMES :

Bilosomes require comprehensive characterization to evaluate their size , stability , charge , Morphology and drug loading for effective drug delivery applications[62] Common parameters are mentioned in below Table 4.

Table 4: Characterization of Bilosomes

Parameter	Description	Typical Methods
Particle Size	Measures vesicle diameter distribution	Dynamic Light Scattering (DLS)
Polydispersity Index (PDI)	Indicates Size Uniformity	DLS
Zeta Potential	Assesses Surface charge and stability	Zeta sizer
Entrapment Efficiency (%EE)	% of drug encapsulated	Centrifugation
Morphology	Vesicle shape and lamellarity	Transmission Electron Microscopy (TEM)

8. REGULATORY CONSIDERATIONS:

Bilosomes, as novel drug delivery nanocarriers offers advantages for cancer treatment, but their regulatory pathway present specific complexities. Bilosome components, which are often bile salts and phospholipids, are widely acknowledged as safe, biodegradable, and biocompatible, indicating that they are pharmaceutically acceptable [63] that are summarized in Table 5 .

Bilosomes and other lipid-based drug delivery systems, are subject to the same regulatory scrutiny as nanocarriers by agencies such as the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) to established efficacy and safety, these nanocarriers must be thoroughly characterized, tested for toxicity and validated clinically[64]. Regulatory guidance mandates comprehensive evaluation through in vitro and in vivo toxicological studies to address potential risks and to ensure patient safety [65].

Table 5: Regulatory bodies and their role in regulation

Sr.no	Body	Region	Role in bilosome Regulations	Ref
1.	FDA	USA	Drug /device/ biological evaluation ., clinical trials , GNP, Nano guidance	64
2.	EMA	EU	Approval of nanomedicine, GMP , safety /efficacy standards	65
3.	ISO/OECD	Global	International risk, safety and process standard	65
4.	EPA/Other	National	Oversight for non-pharmaceutical uses and environmental health	66

9. CASE STUDIES:

9.1 Breast Cancer:

1. Zafar A et al., designed Lute Olin loaded Peglyated bilosome using thin-film hydration method and optimized them for enhanced anti-cancer activity. The percentage entrapment efficiency, particle size, poly-dispersity index, and zeta potential were found to be '75.05±0.65%, 252.24±3.54nm, 0.24, 32mV' respectively. In vitro antioxidant activity of the Luteolin loaded pegylated bilosome compared to free drug was found to be 96.87±3.32% and 70.31±2.11% respectively. In cytotoxicity testing, the IC_{50} value of the Luteolin loaded Peglyated bilosome was found to be 390mM and 510 mM against MCF7 and MDA-MB-231 cancer cells, respectively at 48 h. In cytotoxicity testing, the IC_{50} value of Luteolin loaded Peglyated bilosome was found to be 370 µM and 510 µM whereas that of the free drug was 820 µM and 980 µM against MCF7 and MDA-MB-231 cancer cells, respectively at 48 h, demonstrating that luteolin loaded pegylated bilosome had a lower IC_{50} value than the free drug . Overall, the results of the study indicated that luteolin loaded pegylated bilosome are promising in the treatment of Breast cancer [67].

2. Zaki I et al., developed acrylamide derivatives loaded Peglyated bilosomes using the thin-film hydration method and optimized them for enhanced anti-cancer activity against 'MCF-7' breast cancer cells. The percentage entrapment efficiency, particle size and zeta potential, of optimized formulation were found to be '100 5.6%, 280.3 15.4 nm, 22.5 3.4 mv' respectively. In cytotoxicity testing, the IC_{50} value of acrylamide derivatives loaded Peglyated bilosomes compared to that of the free drug was 0.75 0.03 µM and 2.11 0.19 M respectively against MCF7 indicating that acrylamide derivatives loaded Peglyated bilosomes had a lower IC_{50} value than the free drug. The findings of this study show that acrylamide derivatives loaded Peglyated bilosomes significantly better approach in the treatment of Breast cancer [68].

9.2 Lung Cancer:

1. Alhakamy NA et al., Formulated Piceatannol-Loaded Bilosome Stabilized Zein Protein using the thin-film hydration method and optimized them for enhanced anticancer efficacy. The percentage entrapment efficiency and particle size were found to be 93.14 2.15% and 157.45 1.62 nm respectively. . In cytotoxicity testing, the IC_{50} value of the pure Piceatannol and Piceatannol-Loaded Bilosome Stabilized zeta potential was found to be 22.3±3.4 µM and 5.78±2.3 µM respectively against A549 lung cancer cell line demonstrating that Piceatannol-Loaded Bilosome Stabilized Zein Protein had a lower IC_{50} value than the free Piceatannol. The wound coverage of free Piceatannol and Piceatannol-Loaded Bilosome Stabilized Zein 59.64%, and 35.87% respectively. Overall, the study revealed that Piceatannol-Loaded Bilosome Stabilized Zein Protein are highly promising for improving the oral bioavailability and anticancer efficacy of Piceatannol in lung cancer treatment [46].

2. Chettupalli A. et al., designed Trametinib-loaded nano-bilosomes using the thin-film hydration method and optimized them for enhanced anticancer efficacy. The percentage entrapment efficiency, particle size, poly-dispersity index, and zeta potential were found to be 94.27 ± 2.16%, 158.32 ± 10.24 nm, 0.132 ± 0.03, and −46.57 ± 1.06 mV respectively. Ex vivo permeation studies revealed free drug and Trametinib-loaded nano-bilosomes solution exhibited 89.36 ± 4.95 µg and 1159.36 ± 4.81 µg permeation respectively which indicated markedly higher intestinal permeability and penetration compared to pure Trametinib. In cytotoxicity testing, the IC_{50} value of the pure Trametinib and Trametinib-loaded nano-bilosomes was found to be 28.61 ± 3.56 µM and 9.74 ± 1.52 µM respectively demonstrating that Trametinib-loaded nano-bilosomes had a lower IC_{50} value than the free Trametinib. Overall, the study revealed that Trametinib-loaded nano-bilosomes are highly promising for improving the oral bioavailability and anticancer efficacy of Trametinib in lung cancer treatment [69].

9.3 Liver Cancer:

1. Kharouba M et al., developed Pitavastatin loaded bilosomes using the thin-film hydration method and optimized them for treatment of hepatocellular carcinoma. The percentage entrapment efficiency, particle size, poly-dispersity index, and zeta potential were found to be '90.56% ± 3.22, 112.28 nm ± 6.35, 0.229 ± 0.06, −7.86 mV ± 1.13' respectively. In a comparative cytotoxicity investigation lactoferrin coated Pitavastatin loaded bilosomes exhibited IC_{50} values of 2.82 µg/mL and 39.8 µg/mL whereas free drug solution exhibited IC_{50} values of 124.9 µg/mL and 169 µg/mL against 2D HepG2 cancer cells, 3D HepG2 spheroids respectively which indicated superior selective anticancer activity. The In vivo studies demonstrated LF-coated PIT-loaded bilosomes produced the strongest anticancer effect, with 3-fold decrease tumor size and increasing caspase-3 expression by 4 to 5-fold. Generally, the study revealed that Pitavastatin loaded bilosomes are highly promising for improving the oral bioavailability and anticancer efficacy of Pitavastatin in treatment of hepatocellular carcinoma[14].

2. Abbas H et al., designed cur cumin analog nano-bilosomes using the thin-film hydration method and optimized them for treatment of hepatocellular carcinoma. The percentage entrapment efficiency, particle size, poly-dispersity index, and zeta potential were found to be '90.21 ± 1.0%, 111.6 ± 1.4 nm, 0.006, 27.05 ± 1.08mV' respectively. In a comparative cytotoxicity investigation, PIP-loaded bilosomes and cur cumin suspension exhibited showed an IC_{50} of 0.0895 µg/mL and 0.346 µg/mL against Huh-7 hepatocellular carcinoma cells indicating superior anticancer potency of the bilosomal formulation. The in-vivo safety study demonstrated that PIP-loaded bilosomes were significantly less toxic to normal Wi-38 cells with an IC_{50} of 37.64 µg/mL compared to curcumin suspension and doxorubicin with 6.56 µg/mL and 2.02 µg/mL respectively. Overall, the study revealed that PIP-loaded bilosomes are highly promising for improving the solubility, selectivity, and anticancer efficacy of cur cumin analogs in hepatocellular carcinoma treatment [70].

9.4 Skin Cancer:

1. Waglewska E *et al.,* formulated Rose Bengal (RB) and Astaxanthin (AST) co-loaded positively charged bilosomes using the thin-film hydration method followed by sonication and optimized them for melanoma therapy. The particle size, poly-dispersity index, and zeta potential were found to be '69 ± 1 nm, 0.29 ± 0.01, +44 ± 1 mV' respectively with entrapment efficiency of '85 ± 3%' and '95 ± 2%' for RB and AST respectively. In vitro cytotoxicity study was carried out using A375 and Me45 melanoma cells exhibited 20% and 30% reduction in viability against A375 and Me45 cell line respectively while maintaining >80% viability in normal HaCaT cells, confirming strong and selective photo cytotoxicity. Overall, the study indicated that Rose Bengal and Astaxanthin loaded cationic bilosomes represent a promising and biocompatible nano photodynamic platform with superior tumor-selective activity for melanoma treatment [54].

10. LIMITATIONS:

Bilosomes, or bile salt incorporated nanocarriers like liposomes, have numerous significant drawbacks in drug delivery applications. These issues have an impact on the formulations, stability and performance.

1. Entrapment Issues:

Anionic hydrophilic medicines frequently move to the exterior aqueous space, lowering %EE.

A negative charge on bile salts makes it difficult to incorporate certain drug.

2. Stability and scale up :

Bilosomes are more sensitive to preparation conditions, influencing vesicle size and stability. High production costs and challenges in large scale manufacturing hinder commercial viability. Capable production using micro fluidization remains challenging, as do long-term

stability challenges such as aggregation and regulatory gaps for clinical approval. Safety profiling and clinical studies are required for human validation [71].

3. GI simulation Models:

There is poor association between in vivo and in vitro models that simulated GI conditions. This leads to more difficult to accurately characterize and anticipate real world behavior.

11. FUTURE DIRECTIONS:

Bilosomes a bile salt-stabilized vesicular nanocarriers hold significant promise for drug delivery due to their enhanced stability relative to liposomes and niosomes, particularly via oral, transdermal, and mucosal routes. A 2025 study highlights their potential to improve bioavailability, enable targeted drug delivery, and support vaccine administration.

Bilosomes are particularly effective for the oral delivery of peptides, proteins, and biologics, as they resist gastrointestinal degradation and enhance absorption. They facilitate anticancer targeting through ligand modifications such as folic acid conjugation, reduce toxicity associated with anti-inflammatory medications, and support ophthalmic, nasal, and vaccine applications through controlled release mechanisms. While polymer incorporation improves stability and mucoadhesion, nano sized bilosomes enhance tissue penetration and cellular uptake. In the context of oncology, bilosomes are emerging as a viable nanocarrier platform for cancer therapy, offering enhanced stability. Targeted tumor delivery, and improved bioavailability of anticancer drugs compared to free drug formulations. Preclinical studies have demonstrated superior cytotoxic and pro apoptotic effects in colon, breast, and lung cancer cells relative to conventional treatments. These vesicles protect drugs from gastrointestinal degradation, enable precise targeting of cancer cells via bile salt receptors, and reduce systemic toxicity through strategies such as PEGylation and ligand modification. Potential applications extend to gastrointestinal malignancies, melanoma, and solid tumors requiring stimuli responsive drug release.

12. CONCLUSION:

Bilosomes are emerging as a promising nanocarrier platform for cancer therapy, offering enhanced stability, targeted tumor delivery, and improved bioavailability of anticancer drug compared to free drug formulations. Preclinical studies have demonstrated superior cytotoxic and pro- apoptotic effects in colon, breast, and lung cancer cells relative to conventional treatments. These vesicles protect drugs from gastrointestinal degradation, enables precise targeting of cancer cells via bile salt receptors, and reduce systemic toxicity through strategies such as PEGylation and ligand modification. Potential applications include gastrointestinal malignancies, melanoma, and solid tumors requiring stimuli- responsive drug release. However, current evidence remains limited to preclinical studies, with no human trials conducted to date. Challenges related to scalability, long term stability, and regulatory approval continue to hinder clinical translation. Future research should prioritize GMP- compliant manufacturing, clinical validation, and the development of hybrid formulations to fully realize the potential of bilosomes in transforming oncology drug delivery.

CONTRIBUTION STATEMENT

Shagufta Shikalgar: original drafting, formal analysis, reviewing. **Natalin Veg:** draft, editing and conceptualization. **Ashwini Delekar, Shreya Sangale, and Vikas Powar:** reviewing and verifying. **Sunita Shinde:** Final editing and reviewing of main draft.

DECLARATION OF USING SOFTWARE

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CONFLICT OF INTEREST

All authors have declare that they have no conflict of interest

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