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Bilosomes in Antidiabetic Therapy: A Comprehensive Review on Sitagliptin Formulation by Thin Film Hydration Method

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ABSTRACT

Bilosomes have emerged as a novel vesicular drug delivery system designed to overcome the limitations of conventional carriers such as liposomes and niosomes. Their unique composition, incorporating bile salts into the lipid bilayer, enhances stability, protects drugs against enzymatic degradation, and improves gastrointestinal resistance. This structural innovation enables bilosomes to encapsulate both hydrophilic and lipophilic drugs, offering improved permeability, sustained release, and superior oral bioavailability. The review highlights the formulation processes, characterisation techniques, and comparative advantages of bilosomes, with a particular focus on Sitagliptin, a BCS Class III antidiabetic drug that suffers from poor intestinal permeability despite high solubility.

The article further discusses the methods of preparation, workflow optimisation, and evaluation strategies, while addressing challenges such as scale-up, GMP compliance, regulatory clarity, and long-term stability. Future perspectives emphasise the role of Quality by Design (QbD), probilosomes technology, and advanced manufacturing approaches in bridging laboratory success with clinical translation. Overall, bilosomes represent a promising and rational platform for oral delivery of Sitagliptin, offering enhanced therapeutic efficacy, patient compliance, and potential expansion into broader pharmaceutical applications.

Keywords: Bilosomes, Niosomes, Liposomes, Sitagliptin Phosphate, Thin film Hydration, Bile Salts, Oral Bioavailability, Nanocarriers.

INTRODUCTION

Vesicular drug delivery systems represent one of the most innovative approaches in modern pharmaceutics, designed to overcome the limitations of conventional dosage forms.(1) These systems are based on microscopic carriers that encapsulate therapeutic agents within a vesicle structure, typically composed of lipids, surfactants, or polymers.(2) By mimicking biological membranes, vesicles provide a protective environment for drugs, shielding them from degradation and enhancing their stability during transit through the body.(3)(4)

The concept originated with liposomes, spherical vesicles formed from phospholipid bilayers, which revolutionised drug delivery by enabling controlled release and targeted distribution. Over time, other vesicular systems such as niosomes (non-ionic surfactant vesicles), transferosomes (ultra-deformable vesicles), and bilosomes (bile salt-stabilized vesicles) were developed to address specific challenges like poor bioavailability, enzymatic degradation, and limited permeability across biological barriers.(5) Each system offers unique structural and functional advantages, making vesicular carriers versatile platforms for both small molecules and macromolecules.(6)

The primary strength of vesicular drug delivery lies in its ability to enhance therapeutic efficacy while minimising side effects.(7) By encapsulating drugs within vesicles, these systems can improve solubility, prolong circulation time, and facilitate site-specific delivery. Moreover, vesicles can be engineered to respond to physiological triggers such as pH, enzymes, or temperature, enabling controlled and sustained release.(1) This adaptability has made vesicular systems highly relevant in diverse therapeutic areas, including oncology, infectious diseases, neurology, and metabolic disorders.(8)

Traditional dosage forms such as tablets and capsules often suffer from poor bioavailability, especially for drugs that undergo extensive first-pass metabolism or degradation in the gastrointestinal tract. They typically provide rapid release, leading to fluctuations in plasma drug concentration and requiring frequent dosing to maintain therapeutic levels. While vesicular systems like liposomes and niosomes were developed to address these issues, they too present challenges.(9) Liposomes, though effective in encapsulating both hydrophilic and lipophilic drugs, are prone to instability, leakage, and high production costs, making large-scale application difficult.(4) Niosomes, prepared

from non-ionic surfactants, offer better stability and lower cost but still face low encapsulation efficiency, limited reproducibility, and vulnerability to GI degradation when used for oral delivery.(5)

Bilosomes, the bile salt-stabilized vesicular systems, represent a more advanced alternative with improved resistance to enzymatic breakdown and enhanced permeability across intestinal barriers. However, they are not free from limitations. Issues such as variable drug loading capacity, potential irritation due to bile salts, and scale-up difficulties remain significant hurdles.(10) Moreover, regulatory pathways for bilosome-based formulations are still evolving, which slows their clinical translation. Thus, while each system has advanced drug delivery in important ways, their limitations highlight the need for continued innovation and optimisation, particularly for drugs like Sitagliptin, where stability and bioavailability are critical for therapeutic success.(11)

Oral drug delivery remains the most preferred route due to its convenience, patient compliance, and cost-effectiveness. However, many therapeutic agents, particularly hydrophilic drugs and peptides, face poor stability and low bioavailability when administered orally. They are often degraded by gastric enzymes, destabilised by bile salts, or subjected to extensive first-pass metabolism, which significantly reduces their therapeutic efficacy. Sitagliptin, a DPP-4 inhibitor used in type II diabetes management, exemplifies these challenges, as its absorption and bioavailability are limited by gastrointestinal conditions.(12) This has created a strong need for advanced carriers that can protect the drug, enhance permeability, and ensure sustained release.(13)(14)

Bilosomes provide a compelling solution by incorporating bile salts into vesicular membranes, which confer remarkable stability against enzymatic degradation and improve resistance to harsh GI conditions. Their unique structure enhances drug encapsulation, facilitates lymphatic transport, and promotes better absorption across intestinal barriers. Compared to liposomes and niosomes, bilosomes demonstrate superior oral bioavailability, mucoadhesion, and permeability, making them particularly suitable for drugs like Sitagliptin that require consistent plasma levels for effective glycemic control.(15) Thus, the rationale for bilosomes in oral delivery lies in their ability to overcome conventional limitations, offering a promising platform for the development of next-generation antidiabetic formulations.(16)

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor widely prescribed for the management of type II diabetes mellitus. Its therapeutic action is based on prolonging the activity of incretin hormones, which stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner.(17) This mechanism helps achieve better glycemic control without causing significant hypoglycaemia, making Sitagliptin a valuable option either as monotherapy or in combination with other antidiabetic agents such as metformin. Clinically, Sitagliptin improves postprandial glucose regulation, enhances β-cell function, and contributes to long-term management of diabetes with relatively few adverse effects.(18)(19)

From a biopharmaceutical perspective, Sitagliptin is classified under the Biopharmaceutics Classification System (BCS) as Class III, meaning it exhibits high solubility but low permeability. While its aqueous solubility facilitates formulation development, the limited intestinal permeability restricts its oral bioavailability. This classification underscores the need for advanced drug delivery strategies that can overcome permeability barriers and ensure consistent absorption. Bilosomes, with their bile salt-stabilized vesicular structure, provide a rational approach to address these limitations by enhancing intestinal transport, protecting the drug from enzymatic degradation, and improving systemic exposure. Thus, the therapeutic importance of Sitagliptin combined with its BCS profile strongly justifies the exploration of bilosomes as an optimised oral delivery system.(20)(21)

Conventional oral dosage forms like tablets often struggle to deliver Sitagliptin effectively due to its BCS Class III profile (high solubility but low permeability). In tablet form, Sitagliptin undergoes limited absorption across the intestinal epithelium, resulting in reduced bioavailability and variable plasma concentrations. This not only affects therapeutic consistency but also

necessitates higher or repeated dosing, which can increase the risk of side effects and reduce patient compliance. Similarly, while vesicular carriers such as liposomes and niosomes have been explored to improve oral delivery, they face challenges of instability in the gastrointestinal tract, susceptibility to enzymatic degradation, and poor reproducibility during scale-up.(22)

Bilosomes, however, offer a distinct advantage by incorporating bile salts into their vesicular membranes, which enhances their stability in the harsh GI environment and improves permeability across intestinal barriers. The bile salts act as permeation enhancers, facilitating transcellular and paracellular transport of Sitagliptin, while also protecting the drug from enzymatic breakdown.(5) This results in improved oral bioavailability, sustained release, and better therapeutic outcomes compared to conventional tablets or other vesicular systems. Additionally, bilosomes demonstrate strong mucoadhesive properties, allowing prolonged residence time in the gut and more efficient absorption.(23) Thus, bilosomes represent a rational and promising alternative for Sitagliptin delivery, addressing the shortcomings of conventional oral formulations and paving the way for more effective diabetes management.(24)

COMPARATIVE ASSESSMENT:

Table 1: Comparative Assessment

Parameter	Liposomes	Niosomes	Bilosomes
Basic Composition	Phospholipid bilayers with aqueous core	Non-ionic surfactants + cholesterol	Non-ionic surfactants + cholesterol + bile salts(25)
Stability in the GI Tract	Poor - prone to enzymatic degradation and bile salt disruption	Moderate - more stable than liposomes but still vulnerable	High - bile salts confer resistance to enzymatic and bile salt degradation(26)
Encapsulation Efficiency	Good for both hydrophilic and lipophilic drugs	Moderate; lower for hydrophilic/anionic drugs	Variable; reduced for highly hydrophilic/anionic drugs(27)
Bioavailability	Limited oral bioavailability	Improved but inconsistent	Superior oral bioavailability due to enhanced permeability and lymphatic transport(26)
Cost & Scalability	High cost, complex manufacturing	Lower cost, easier to scale	Moderate; scale-up challenges due to bile salt incorporation(28)
Mucoadhesion	Limited	Moderate	Strong mucoadhesion, prolonged GI residence(26)
Clinical Translation	Established but limited oral applications	Some progress, mainly topical/transdermal	Emerging, promising for oral delivery, but regulatory pathways are evolving.(26)

Liposomes, niosomes, and bilosomes differ significantly in composition, stability, resistance to GI degradation, bioavailability, and storage requirements. Liposomes consist of phospholipid

bilayers enclosing an aqueous core, making them versatile carriers for both hydrophilic and lipophilic drugs.(29) However, they are inherently unstable, prone to aggregation, fusion, and leakage, and are readily degraded by bile salts and enzymes in the GI tract.(30) This instability limits their oral use and results in poor bioavailability. Niosomes, prepared from nonionic surfactants and cholesterol, offer better stability and lower production costs than liposomes. They show moderate resistance in the GI tract but remain vulnerable to enzymatic breakdown, leading to inconsistent bioavailability.(31)

Bilosomes, in contrast, incorporate bile salts into their vesicular membranes, which significantly enhances their structural integrity and resistance to enzymatic degradation. This unique composition allows bilosomes to withstand the harsh GI environment, improve permeability across intestinal barriers, and facilitate lymphatic transport. As a result, they provide superior oral bioavailability compared to liposomes and niosomes. In terms of storage, liposomes generally require cold storage and have a short shelf life, while niosomes are more stable and can be stored at room temperature(32). Bilosomes demonstrate moderate storage stability better than liposomes, but still require optimisation for long-term preservation. Overall, bilosomes stand out as a rational alternative for oral delivery of drugs like Sitagliptin, where enhanced stability, GI resistance, and bioavailability are critical for therapeutic success.(26)

Structure and composition

Bilosomes are specialised vesicular carriers characterised by a core-shell architecture. At the centre lies an aqueous core, which serves as the reservoir for hydrophilic drugs such as Sitagliptin. This core is surrounded by a lipid bilayer, typically composed of phospholipids and cholesterol, which provides structural integrity and accommodates lipophilic molecules within its hydrophobic regions. The defining feature of bilosomes is the incorporation of bile salts into the lipid bilayer. These amphiphilic molecules intercalate within the membrane, enhancing vesicle stability, protecting against enzymatic degradation, and improving permeability across intestinal barriers.(16)

This unique arrangement allows bilosomes to function as dual-purpose carriers, capable of encapsulating both hydrophilic and lipophilic drugs while simultaneously resisting the harsh conditions of the gastrointestinal tract. The bile salts not only stabilise the vesicular structure but also act as permeation enhancers, facilitating transcellular and paracellular transport. As a result, bilosomes demonstrate superior oral bioavailability, mucoadhesion, and sustained release profiles compared to conventional liposomes and niosomes. The core-shell design thus represents a rational and effective strategy for delivering drugs like Sitagliptin, where overcoming low permeability and ensuring consistent therapeutic levels are critical.(33)

Similar in structure to niosomes, bilosomes are nanoscale elastic colloidal transporters that hold bile salt and are mostly made of lipids and non-ionic surfactants.

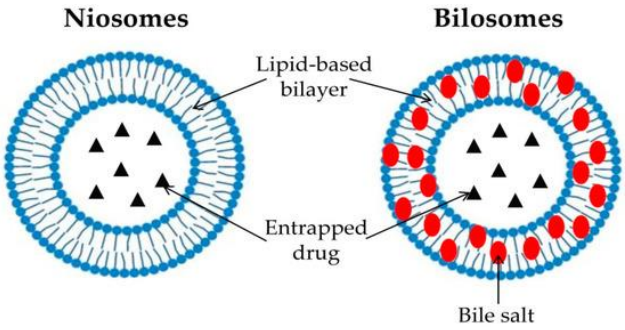

Fig. 1: Structure of Niosomes and Bilosomes

The hydrophilic drugs or antigens are trapped by the innermost layer (aqueous core) of bilosomes. In contrast, the hydrophobic drugs can be trapped by the outermost layer (lipid bilayer coated and implanted with bile salts). The bilosomal structure's distinctive closed form results from the bile salts' assembly in lipid layers. In a bilosome vesicle, the hydrophobic end of bile molecules is submerged in the hydrophobic portion of the lipid bilayer, while the hydrophilic end is oriented toward the hydrophilic region of the bilayer.(34)

The lumen of the gastrointestinal tract contains naturally produced biosurfactants called bile salts, which are necessary for the breakdown and absorption of fats. Sodium glycocholate (SGC), sodium deoxycholate (SDC) and sodium taurocholate (STC) are the most common bile salts employed in the creation of bilosomes.

These salts can effectively encapsulate hydrophobic medications and have exceptional solubility properties, particularly for lipophilic compounds. They are perfect for drug delivery since they are well-tolerated and biocompatible. They interact with cell membranes to facilitate drug absorption and improve the delivery of therapeutic ingredients.(35)

Because they are more compatible, stable and toxic than their anionic, amphoteric or cationic counterparts, non-ionic surfactants such as Span 40, Span 60, Span 80, Tween 60 and Tween 80 are the most commonly used surfactants in vesicle formation. They serve as wetting agents, emulsifiers, solubilisers, and permeation enhancers and show decreased irritation, haemolytic activity, and cytotoxicity.(36)

Because of their amphiphilic characteristics and high biocompatibility with biological membranes, cholesterol and phospholipids are frequently used among the various lipids that can be chosen for bilosome manufacturing. Because cholesterol improves bilosome properties such as greater stiffness, improved encapsulation efficiency, improved membrane stability, decreased toxicity and better rehydration of freeze-dried bilosomes, it is superior.(26)

Mechanism of Bile Salt-Mediated Permeation Enhancement:

Bile salts incorporated within the bilosomal bilayer do more than provide physical stability; they actively participate in overcoming the intestinal barrier that limits Sitagliptin's absorption. As natural biosurfactants, bile salts interact with the phospholipid components of the enterocyte membrane, transiently loosening the tight junctions between adjacent epithelial cells. This action opens the paracellular route, allowing hydrophilic molecules such as Sitagliptin to pass between cells rather than being restricted to the slower transcellular pathway. At the same time, bile salts solubilise membrane cholesterol and disrupt the ordered packing of the enterocyte lipid bilayer, which increases membrane fluidity and facilitates transcellular diffusion of the encapsulated drug.(36)

Beyond this direct membrane action, bile salts promote the formation of mixed micelles with dietary and endogenous lipids, assisting in the solubilisation and transport of vesicle contents across the unstirred water layer that lines the intestinal lumen. Bilosomes are also preferentially captured by the M-cells overlying the Peyer's patches of the gut-associated lymphoid tissue, directing a portion of the absorbed dose into the lymphatic circulation and thereby bypassing hepatic first-pass metabolism. Collectively, these complementary mechanisms membrane fluidisation, tight-junction modulation, micellar solubilisation, and lymphatic uptake explain why bilosomal encapsulation can substantially improve the effective permeability of a BCS Class III molecule like Sitagliptin without altering the drug's own physicochemical properties.(37)

Importantly, the extent of permeation enhancement is dose- and concentration-dependent: while moderate bile salt levels reversibly loosen tight junctions and are well tolerated, excessive concentrations can cause membrane damage and local irritation. This dual nature makes optimisation of bile salt type and concentration one of the most critical formulation decisions in bilosome development, forming the basis for the formulation variables discussed in the following section.(34)

Methods of Preparation:

1. Hot homogenization method

It is also called the melt method. Diacetyl phosphate, cholesterol and monopalmitoyl glycerol were heated to 130°C. The aforementioned mixture was mixed with bile salts, such as sodium deoxycholate, in buffer and vortexed. Entrapped bilosomes were resuspended in the proper buffer after no entrapped ones were separated by centrifugation.(38)

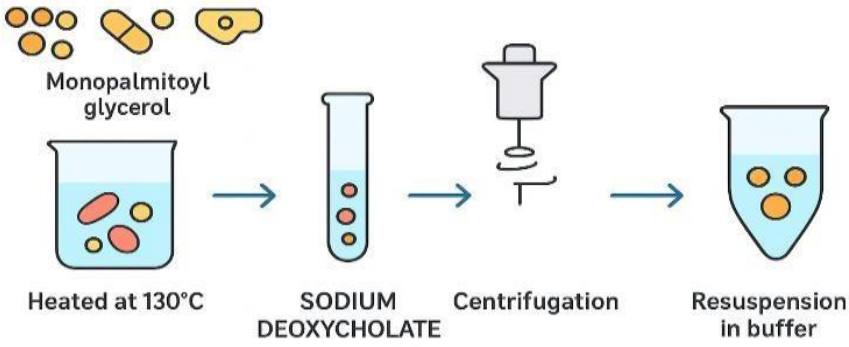

Fig.2: Hot homogenization method

2. Thin film hydration

Lipid film hydration is a common term for it. In a round-bottomed flask, the drug, nonionic surfactant, and cholesterol were dissolved in an appropriate organic solvent. To create a thin layer of lipid, the organic solvent was evaporated using a rota-evaporator. Make sure the solvent has completely evaporated. To achieve bilosomal dispersion, the produced film is hydrated with distilled water or a bile salt-containing buffer and agitated in a magnetic stirrer. Sonication was used to further reduce the particle size. Until it is characterised, the dispersion is kept at 4°C. Membrane extrusion, ultrasonication and homogenization can be used to transform multilamellar vesicles made via thin film hydration into tiny unilamellar vesicles.(39)(40)

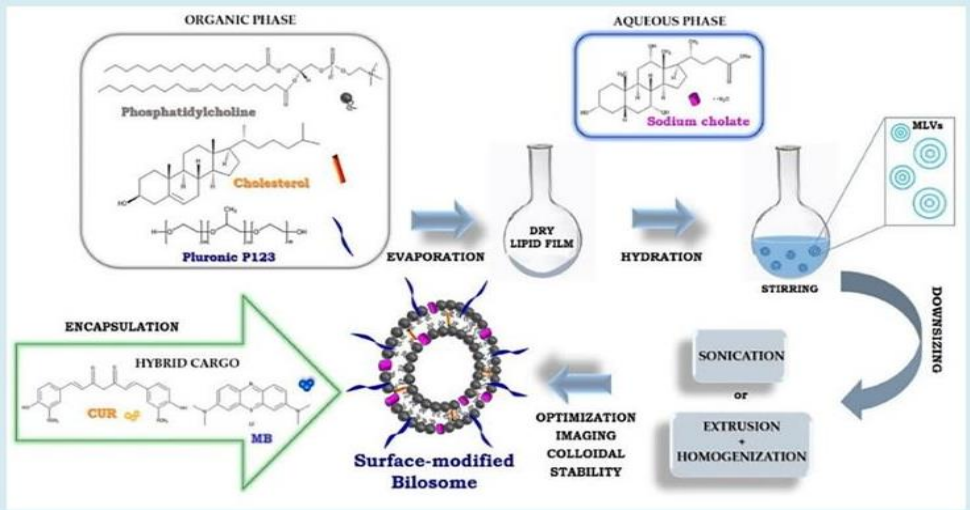

Fig.3: Thin film hydration

3. Ethanol injection method

In a water bath, ethanol was used to dissolve the drug, non-ionic surfactant, and cholesterol. Phosphate buffer pH 7.4 was gradually filled with the ethanolic solution, which was then magnetically agitated. The aqueous phase was previously supplemented with bile salts and other edge activators. Turbidity of the solution indicates the formation of bilosome dispersions. To guarantee that the ethanol was completely volatilized, stirring was kept up. After cooling to room temperature, dispersions are sonicated.(41)(42)

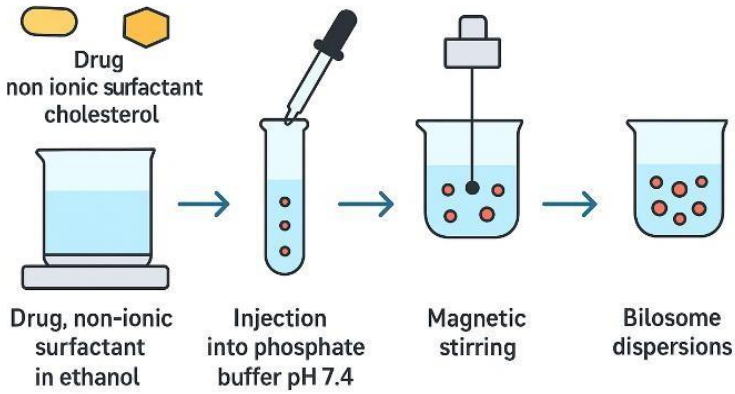

Fig.4: Ethanol injection method

4. Reverse phase evaporation

This approach involved dissolving bile salt and phosphatidyl choline in ethyl ether. The drug-containing buffer solution was added to it. Ultrasonication is applied to it. It causes reverse water to form in the oil emulsion. A rota-evaporator operating at low pressure removes the solvent. The resulting dried lipid is hydrated with buffer to create a uniform aqueous vehicle dispersion, which is then extruded using a high-pressure homogeniser.(43)(23)

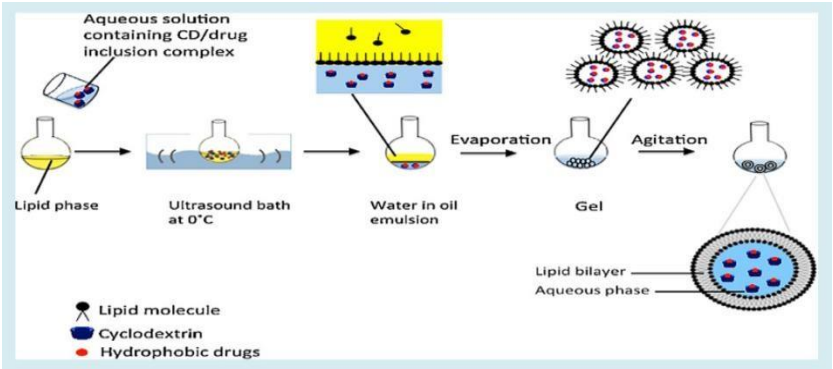

Fig.5: Reverse phase evaporation

5. Probilosomal method

Sorbitol particles were found in a flask with a circular bottom using this method. After that, a rotary evaporator is used to vacuum dry this. Next, the medication, bile salt and phosphatidyl choline solution were dissolved in an organic solvent and introduced dropwise to the round-bottomed flask to load them onto sorbitol particles. After being freeze-dried to produce Probilosomal powder, loaded sorbitol particles are manually agitated in water to create bilosomes.(44)

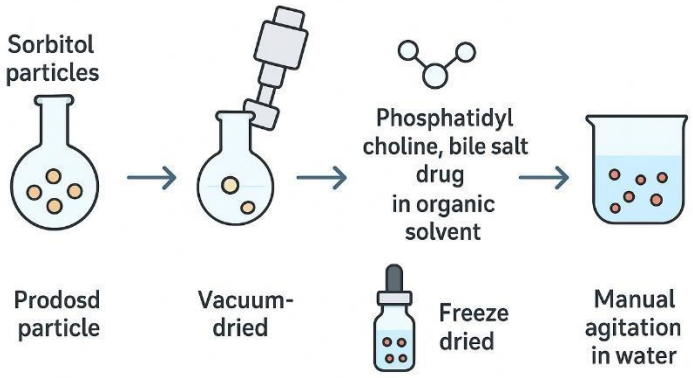

Fig.6: Probilosomal method

The thin-film hydration method is one of the most widely used techniques for preparing bilosomes because it offers simplicity, reproducibility, and versatility. In this method, lipids and bile salts are first dissolved in an organic solvent, which is then evaporated to form a thin lipid film. Upon hydration with an aqueous drug solution, the film spontaneously forms bilayered vesicles encapsulating the drug.(15) This approach enables efficient incorporation of both hydrophilic drugs (in the aqueous core) and lipophilic drugs (within the lipid bilayer), making it particularly suitable for molecules such as Sitagliptin that require protection and enhanced permeability.(3)

Advantages: Straightforward and cost-effective preparation process. High encapsulation efficiency for a wide range of drugs. Flexibility to modify vesicle size and composition by adjusting hydration conditions. Well-established technique with reproducible results, making it suitable for laboratory and pilot-scale studies.(11)(45)

Disadvantages and Limitations

Requires careful control of process parameters (hydration time, temperature, rotation speed) to ensure uniform vesicle formation. Organic solvent residues may remain if not properly removed, posing safety concerns. Scaling-up to industrial production can be challenging due to batch variability. Vesicles may exhibit instability during long-term storage, necessitating optimisation with stabilisers or conversion into probilosomes.(45)

Formulation Process

Table 2: Formulation Process(46)(11)

Step	Description
Selection of Excipients	Choose suitable phospholipids, cholesterol, bile salts, and stabilisers based on drug properties.
Thin Film Formation	Dissolve lipids and bile salts in an organic solvent; evaporate under reduced pressure to form a thin lipid film.
Hydration & Vesicle Formation	Hydrate the dry lipid film with an aqueous drug solution - spontaneous formation of bilayered vesicles with an aqueous core.
Downsizing & Stabilization	Reduce vesicle size using sonication, extrusion, or homogenization; stabilise with cryoprotectants or surfactants.
Drug Encapsulation & Evaluation	Encapsulate Sitagliptin in vesicles; evaluate particle size, zeta potential, entrapment efficiency, drug release, and stability.

Factors Affecting Bilosome Formulation and Performance:

Several formulation variables govern the size, entrapment efficiency, stability and in vivo performance of Sitagliptin-loaded bilosomes. Because these variables interact with one another, they are generally optimised together, often using statistical design-of-experiments approaches, rather than adjusted one at a time.(47)(48)

Type and concentration of bile salt: Sodium deoxycholate generally produces smaller, more rigid vesicles with higher entrapment efficiency than sodium glycocholate or sodium taurocholate, but higher bile salt concentrations beyond an optimum level can solubilise the bilayer and cause drug leakage rather than improving stability.(49)

Surfactant HLB value: Non-ionic surfactants with a hydrophilic-lipophilic balance in the intermediate range (such as Span 60 or Tween 60/80) favour bilayer formation; surfactants that are too hydrophilic tend to form micelles instead of vesicles, while overly lipophilic surfactants yield larger, less uniform vesicles.(15)

Cholesterol content: Increasing cholesterol up to an optimum ratio reduces membrane fluidity, decreases drug leakage, and improves vesicle rigidity, but excessive cholesterol can displace

the drug from the bilayer and reduce entrapment efficiency.(50)

Surfactant-to-bile salt ratio: A higher proportion of bile salt generally improves GI stability and permeation enhancement but reduces the mechanical rigidity of the vesicle, so this ratio is a key trade-off in formulation design.(50)

Drug-to-lipid ratio: As a highly water-soluble molecule, Sitagliptin's loading in the aqueous core is limited by core volume; increasing the aqueous phase or using remote/active loading approaches can improve entrapment without proportionally increasing lipid content.

Hydration medium, temperature and time: Hydration should generally be carried out above the phase transition temperature of the lipid to ensure complete film re-dispersion; inadequate hydration time results in larger, polydisperse vesicles and poor drug entrapment.(46)

Downsizing method (sonication/extrusion cycles): The number of sonication cycles or extrusion passes determines the transition from multilamellar to small unilamellar vesicles; excessive sonication can generate heat-induced drug degradation or vesicle fusion.

pH of the hydration medium: Because Sitagliptin phosphate solubility and bile salt ionisation are both pH-dependent, the hydration medium pH influences both drug loading and vesicle surface charge, which in turn affects colloidal stability.(51)

Characterisation technique:(48)

Particle size, Polydispersity index, Zeta potential

Particle size, polydispersity index and zeta potential are determined using a zeta sizer after diluting the bilosome dispersion ten times with purified water. Three measurements are made.

Encapsulation efficiency

1ml of the bilosome dispersion was centrifuged for two hours at 4°C at 15,000 rpm. The drug content of the supernatant was measured using spectrophotometry after it had been appropriately diluted.

Transmission electron microscopy (TEM)

Transmission electron microscopy is used to determine surface morphology. Before TEM observation, one drop of the chosen bilosome dispersion was adsorbed on a copper grid, negatively stained with 1% phosphotungstic acid and allowed to air dry at room temperature for ten minutes.

Differential Scanning Calorimetry (DSC)

The equipment was calibrated. Research is done on bile salts, cholesterol, non-ionic surfactant, drug-loaded bilosomes and blank bilosomes. Standard aluminium pans containing 3 mg samples were heated from 10°C to 200°C at a scanning rate of 10°C per minute.

In vitro drug release studies

The dialysis bag approach is employed. The dialysis bag was submerged in the release media for the whole night. The medium is kept at 37±0.5°C and contains 50 cc of phosphate buffer with a pH of 6.8. At 1, 2, 4, 6, 8, 10, and 24 hours, 3 ml samples were taken out and replaced with an equivalent volume of medium. To assess drug release, extracted samples were appropriately diluted and subjected to spectrophotometric analysis.

Storage stability

For 90 days, the manufactured bilosomes were stored at room temperature (25±2°C) with 70% relative humidity and in a refrigerator (4±0.5°C). At 0, 45 and 90 days, the prepared bilosomes' stability was assessed.

Confocal laser scanning microscopy (ex vivo study)

Rat dorsal skin was separated, with the donor compartment facing the subcutaneous layer. Bilosomes containing fluorescein diacetate (fluor-labelled bilosomes) were prepared and applied to the dorsal skin surface. Similarly, the dorsal skin surfaces of rats were treated with a 1% fluorescein diacetate solution (control) for six hours. After treatment with fluor-labelled bilosomes and the 1% fluorescein diacetate solution, longitudinal skin sections were fixed in paraffin wax and sectioned with a microtome. The presence of fluorescence in the skin layers was assessed. This technique, which requires ethical committee clearance, helps determine how bilosomes penetrate, move and travel through the skin.(48)

Advantages of Sitagliptin Bilosomes

The incorporation of Sitagliptin into bilosomes offers several distinct advantages compared to conventional oral dosage forms and other vesicular systems:

Enhanced Stability in the GI Tract

Bile salts integrated into the bilayer protect Sitagliptin from enzymatic degradation and bile salt disruption, ensuring better survival through the gastrointestinal environment.(14)(10)

Improved Oral Bioavailability

Bilosomes enhance intestinal permeability and facilitate lymphatic transport, overcoming Sitagliptin's BCS Class III limitation (high solubility but low permeability). This results in more consistent plasma concentrations and improved therapeutic efficacy.(52)(53)

Mucoadhesion and Prolonged Residence Time

Their surface properties allow bilosomes to adhere to the intestinal mucosa, extending the contact time and promoting sustained drug absorption.(11)

Controlled and Sustained Release

Sitagliptin encapsulated in bilosomes can be released gradually, reducing fluctuations in blood glucose levels and minimising the need for frequent dosing.(54)

Dual Drug Loading Capability

The aqueous core and lipid bilayer allow simultaneous encapsulation of hydrophilic and lipophilic drugs, enabling combination therapy if required.(55)

Patient Compliance Advantages of Sitagliptin Bilosomes

Enhanced Stability in the GI Tract, Improved Oral Bioavailability, Mucoadhesion and Prolonged Residence Time, Controlled and Sustained Release. Dual Drug Loading Capability. aqueous core and lipid bilayer allow . By improving bioavailability and reducing dosing frequency, bilosomes enhance convenience and adherence, which is crucial in chronic conditions like diabetes.(56)

Potential for Scale-up and Versatility: Although optimisation is needed, bilosomes can be adapted for different drugs and therapeutic areas, making them a versatile platform beyond Sitagliptin.(54)

Recent Research Advances in Bilosome-Based Oral Delivery

The rationale for applying bilosomes to Sitagliptin is reinforced by a growing body of work on structurally similar, permeability-limited or metabolically unstable drugs. Acyclovir, an antiviral nucleoside analogue with poor and erratic oral absorption, has been formulated as bilosomes prepared by thin film hydration and optimised using a Box–Behnken statistical design; the optimised formulation showed markedly higher in vitro drug release and greater ex vivo gut permeation than both a plain drug suspension and a marketed formulation, supporting the general principle that bile-salt vesicles can improve gut permeation of otherwise poorly absorbed hydrophilic drugs.(34)

Bilosomes have also been used to improve the oral delivery of poorly soluble neuroactive compounds. Luteolin-loaded bilosomes achieved a substantially higher in vitro drug release than a pure drug suspension, together with improved entrapment efficiency, while herbal extracts such as Bacopa Monnier have similarly been encapsulated in bilosomes to enhance their oral bioavailability relative to liposomal counterparts. These studies illustrate that the bile-salt-driven permeability advantage of bilosomes extends across a wide range of molecule classes, from small antiviral drugs to complex phytoconstituents.(50)

Within the antidiabetic space specifically, alternative lipid-based nanocarriers have also been explored for Sitagliptin and related DPP-4 inhibitors, underscoring the wider interest in overcoming their bioavailability limitations. Nanostructured lipid carriers have been developed for the co-delivery of Sitagliptin with lisinopril for comorbid diabetes and hypertension, optimised using Box–Behnken statistical design and characterised by dynamic light scattering and scanning electron microscopy.(57) Separately, Sitagliptin has been formulated as an oral polymeric nano scaffold, with process parameters systematically evaluated to enhance its anti-diabetic performance. Linagliptin, a closely related DPP-4 inhibitor

with low oral bioavailability arising from first-pass metabolism and P-glycoprotein efflux, has likewise been formulated as solid lipid nanoparticles incorporating P-glycoprotein inhibitors, which improved intestinal transport as measured by single-pass intestinal perfusion and Caco-2 permeability studies.(58)(59), this body of work situates bilosomal Sitagliptin within a broader and actively expanding effort to apply nanocarrier technology to DPP-4 inhibitors, and provides comparative benchmarks against which bilosome performance can be judged.(60)

Surface-Engineered and Targeted Bilosomes:

Beyond the conventional bile-salt-stabilised vesicle, several surface modification strategies have been investigated to further improve the performance of bilosomes for oral delivery, and these represent a logical next step for Sitagliptin bilosomes:

PEGylation: Coating the vesicle surface with polyethylene glycol chains can reduce recognition and clearance by the reticuloendothelial system, prolong circulation time after absorption, and create a steric barrier that further limits enzymatic access to the bilayer.(50)

Mucoadhesive polymer coating: Coating bilosomes with cationic mucoadhesive polymers such as chitosan increases electrostatic interaction with the negatively charged mucus layer, further prolonging intestinal residence time beyond the intrinsic mucoadhesion conferred by bile salts.

Ligand-conjugated bilosomes: Attaching targeting ligands (for example, lectins or vitamin receptor ligands) to the vesicle surface can direct bilosomes toward specific absorptive sites in the intestinal epithelium, such as M-cells of the Peyer's patches, further enhancing uptake.

Charge modification: Adjusting the surface charge of bilosomes through the choice of bile salt and surfactant influences both colloidal stability during storage and the extent of electrostatic interaction with the intestinal mucosa.

For Sitagliptin, where the primary bottleneck is intestinal permeability rather than solubility, mucoadhesive coating and M-cell targeting are of particular interest, as they would extend the vesicle's residence time at the absorption site without requiring changes to the drug's own formulation chemistry.(60)

Applications

Bilosomes have emerged as versatile nanocarrier systems with wide applications in drug delivery:

Oral Delivery of Poorly Permeable Drugs: Their bile salt-stabilized membranes enhance permeability and protect drugs from enzymatic degradation, making them ideal for BCS Class III and IV drugs.

Vaccine Delivery: Bilosomes can encapsulate antigens and improve mucosal immunity by enhancing uptake through Peyer's patches in the intestine.

Peptide and Protein Delivery: They protect sensitive biomolecules from degradation in the GI tract, enabling oral administration of molecules that are otherwise injectable.

Controlled and Sustained Release: Their vesicular structure allows gradual drug release, reducing dosing frequency and improving patient compliance.

Targeted Therapy: Bilosomes can be engineered for site-specific delivery, such as intestinal targeting, to maximise therapeutic outcomes.

When applied to Sitagliptin, bilosomes address its major limitation: low intestinal permeability despite high solubility (BCS Class III). By incorporating bile salts into the vesicular bilayer, bilosomes(61):

Enhance Permeability: Facilitate transcellular and paracellular transport of Sitagliptin across intestinal epithelium. Improve Bioavailability: Protect Sitagliptin from enzymatic breakdown, ensuring more consistent plasma concentrations. Provide Sustained Release: Reduce fluctuations in blood glucose levels by maintaining prolonged therapeutic action. Increase Mucoadhesion: Prolong residence time in the GI tract, allowing better absorption and reduced dosing frequency. Support Patient Compliance: By improving efficacy and reducing dosing burden, bilosomes make long-term diabetes management more convenient.

Comparative Perspective: Bilosomes versus Other Nanocarrier Platforms:

Sitagliptin's bioavailability challenge has attracted more than one nanocarrier solution, and it is useful to place bilosomes alongside the other lipid- and polymer-based platforms that have been explored for DPP-4 inhibitors and similarly permeability-limited drugs.(62)(63)

Table 3: Comparative perspective- Bilosomes v/s Nanocarriers

Feature	Bilosomes	Solid Lipid Nanoparticles / NLCs	Polymeric Nanoparticles
Core mechanism for BCS III drugs	Bile-salt-mediated permeation enhancement and tight-junction modulation	Lymphatic uptake and P-glycoprotein efflux inhibition	Mucoadhesion and controlled polymer erosion/diffusion
Typical entrapment efficiency	Moderate–high, sensitive to bile salt type	High for lipophilic actives, lower for hydrophilic drugs	Moderate, depends on polymer–drug affinity
GI stability	High, due to native bile salts in the bilayer	Moderate; lipid matrix can be disrupted by native bile salts	Variable; enteric coatings often required
Scale-up maturity	Early-stage, laboratory scale predominant	Relatively mature; several marketed SLN products exist	Mature; polymeric nanoparticle manufacturing is well established

Solid lipid nanoparticles and nanostructured lipid carriers rely primarily on lymphatic uptake and inhibition of P-glycoprotein-mediated efflux to improve bioavailability, and have already reached a comparatively mature stage of pharmaceutical development, with several marketed products validating their manufacturability.7 Polymeric nanoparticles offer robust, tunable release kinetics and established large-scale production methods, but often require additional enteric coatings to survive gastric conditions. Bilosomes occupy a distinctive niche: because their principal permeation-enhancing component, bile salts, is a naturally occurring intestinal biosurfactant, they achieve GI stability and permeability enhancement through a mechanism the gut is already adapted to tolerate, which may translate into a more favourable safety profile than carriers relying on synthetic permeation enhancers, even though their industrial scale-up is comparatively less mature.(64)

Challenges and Future Perspective

Scale-up and GMP Compliances

Despite their promise, bilosomes face several challenges in translation from laboratory research to clinical application. One major hurdle is scale-up and reproducibility: while thin film hydration and related methods work well at small scale, maintaining uniform vesicle size, entrapment efficiency, and stability during industrial production is complex. Incorporation of bile salts adds variability, and batch-to-batch consistency remains a concern. Additionally, Good Manufacturing Practice (GMP) compliance requires stringent control of excipients, solvents, and process parameters. Regulatory pathways for novel vesicular systems are still evolving, which slows down approval timelines. Long-term stability and storage optimisation also need further refinement to ensure commercial viability.(24)

Looking ahead, the future perspective for Sitagliptin bilosomes is highly encouraging. Advances in Quality by Design (QbD) approaches, continuous manufacturing, and microfluidic technologies may help overcome scale-up limitations. Incorporating stabilisers or converting bilosomes into probilosomes could improve shelf life and GMP compliance. Furthermore, bilosomes offer potential for personalised medicine, where formulations can be tailored to patient needs, and for combination

therapy, encapsulating Sitagliptin with synergistic antidiabetic agents. With ongoing research and regulatory adaptation, bilosomes could evolve into a mainstream oral delivery platform, providing more effective and patient-friendly diabetes management.(13)

Regulatory Clarity for Bilosomes

One of the most pressing challenges for bilosome technology is the lack of well-defined regulatory guidelines. Unlike conventional dosage forms such as tablets or capsules, bilosomes fall under the category of novel drug delivery systems (NDDS), where clear frameworks for approval are still evolving. Regulatory agencies such as the FDA (U.S.) and EMA (Europe) require extensive data on safety, stability, reproducibility, and scalability before approving. However, because bilosomes incorporate bile salts, which act both as excipients and permeation enhancers, their classification can be ambiguous, often requiring additional toxicological and pharmacokinetic studies.(65)(10)

Key regulatory challenges includes: Excipients Approval: Bile salts are not universally recognised as safe excipients in oral formulations, necessitating detailed safety dossiers. Manufacturing Standards: GMP compliance demands strict control of vesicle size, entrapment efficiency, and batch reproducibility, which are difficult to maintain during scale-up. Stability & Shelf Life: Regulatory bodies require long-term stability data under ICH guidelines, which bilosomes still lack in standardized form. Clinical Translation: Demonstrating in vitro–in vivo correlation (IVIVC) and consistent bioavailability is essential but remains a bottleneck.

Future Prospective

To achieve regulatory clarity, researchers and industry must Adopt Quality by Design (QbD) and Process Analytical Technology (PAT) frameworks to ensure reproducibility. Generate toxicological and pharmacokinetic data specific to bile salt-based carriers. Develop probilosomes formulations for improved stability and compliance with ICH storage guidelines. Engage with regulatory agencies early in development to establish standardised evaluation protocols for bilosome-based products.

Long-term Stability and Storage

One of the critical challenges for bilosome formulations, especially with drugs like Sitagliptin, is ensuring long-term stability and appropriate storage conditions. Because bilosomes are vesicular systems containing bile salts, phospholipids, and surfactants, they are prone to aggregation, leakage, and hydrolysis over time.(66)(67)

Key Issues in Stability and Storage: Physical Instability: Vesicle fusion, size enlargement, or precipitation during prolonged storage. Chemical Instability: Oxidation of phospholipids, hydrolysis of bile salts, and drug degradation. Temperature Sensitivity: Lipid bilayers are highly sensitive to heat; refrigeration is often required. Moisture Sensitivity: Aqueous dispersions may lose integrity; lyophilisation or conversion into probilosomes is often necessary.

Strategies for Improvement: Probilosomes: Converting bilosomes into dry, free-flowing granular forms that can be reconstituted before use improves shelf life and GMP compliance. Cryoprotectants: Addition of sugars (e.g., trehalose, sucrose) during freeze-drying stabilises vesicles. Controlled Packaging: Use of nitrogen flushing, amber vials, and moisture-proof containers to minimise oxidation and hydrolysis. ICH Stability Studies: Conducting accelerated and real-time stability studies under ICH guidelines ensures regulatory acceptance.

Future Perspective: Advances in nanotechnology and formulation science may enable bilosomes to achieve stability comparable to conventional solid dosage forms. Integration of Quality by Design (QbD) principles and continuous manufacturing could further standardise storage requirements, paving the way for clinical translation and commercialisation.(68)

Patent and Commercialization Landscape

Compared with liposomal and niosomal technologies, which already have several approved products and licensed manufacturing platforms, the intellectual property and commercial landscape for bilosomes remains nascent. Most published work on Sitagliptin and related bile-salt vesicular systems originates from academic and preclinical laboratory studies rather than from industrial or clinical-stage development, and no bilosome-based oral

antidiabetic product is currently marketed. This gap represents both a challenge and an opportunity: early movers who successfully resolve the scale-up, GMP, and stability issues outlined above stand to establish a differentiated position in the oral delivery of BCS Class III and IV antidiabetic and other chronic-disease medications. Strategic collaboration between academic formulation groups and pharmaceutical manufacturers, supported by contract development and manufacturing organisations experienced in liposomal production, could accelerate the translation of Sitagliptin bilosomes from bench-scale research toward investigational new drug filings.(69)(70)

CONCLUSION

Bilosomes represent a promising advancement in vesicular drug delivery systems, offering unique advantages over conventional liposomes and niosomes. Their incorporation into the lipid bilayer enhances stability, protects drugs against enzymatic degradation, and improves permeability across the gastrointestinal tract. For Sitagliptin, a BCS Class III drug with high solubility but poor permeability, bilosomes provide a rational solution by improving oral bioavailability, sustaining drug release, and ensuring more consistent therapeutic outcomes. The formulation process, characterisation techniques, and demonstrated advantages highlight bilosomes as a versatile and effective platform for oral antidiabetic therapy.

However, despite their potential, challenges remain in terms of scale-up, GMP compliance, regulatory clarity, and long-term stability. Addressing these hurdles through Quality by Design (QbD), advanced manufacturing technologies, and probilosomes approaches will be critical for clinical translation. With continued research, regulatory adaptation, and industrial optimisation, bilosomes could evolve into a mainstream oral delivery system, not only for Sitagliptin but also for a wide range of therapeutic agents. Thus, bilosomes stand at the intersection of innovation and practicality, offering a future pathway toward more effective, patient-friendly drug delivery in diabetes management and beyond.

Taken together, the mechanistic rationale, the breadth of preparation and characterisation techniques, and the growing comparative literature on bile-salt vesicles and related nanocarriers for DPP-4 inhibitors all point in the same direction: bilosomal Sitagliptin is a scientifically well-justified formulation strategy that is now ready to move from proof of concept studies toward systematic pharmacokinetic, toxicological and regulatory evaluation.

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