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BILOSOMES: SUPERIOR VESICULAR CARRIER TO ENHANCE ORAL AND TRANSDERMAL DRUG DELIVERY OF POORLY SOLUBLE ACTIVE DRUG MOLECULES

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ABSTRACT

Many pharmaceutical drugs, peptides and vaccines have less solubility/degradation in GIT due to this after oral intake permeation into systemic circulation is not significant, which in turn effects their pharmacological action. Vesicular drug delivery by liposomes and niosomes can defend entrapped agent to certain extent from degradation. Even though gastro intestinal environment pH, enzyme degradation limits their capability. Similarly, in transdermal route stratum corneum is the major barrier for permeation. In view of all these concerns BS-vesicles were developed by researchers. This review is based on out and out overview of BS-vesicles as a superior pharmaceutical carrier through oral delivery and transdermal of biological therapeutic macromolecules, poorly soluble drugs and vaccines. Insights all the possible research done on the BS-vesicles and their applications, characterization, storage. In addition, methods of preparation and modified BS-vesicles are described. Lastly, the gap in the scientific researches tackling bilosomes that needs to be addressed is highlighted.

KEYWORDS: BS-vesicles, lipophilic drugs, Bile salts, proteins and peptides, vesicular carriers, transdermal route.

INTRODUCTION

We are in an era of advanced drug development but recent techniques lead to introduction of many novel molecules with inadequate aqueous solubility. Due to low solubility drugs sediments in biological fluids which yields irreproducible pharmacological effects.

Oral delivery is the most convenient mode of drug intake due to ease-of-use. However, due to mucus secretion, strident acidic environment in the stomach, inconsistent pH in the intestine and enzymatic degradations the gastrointestinal tract have substantial physical and a biochemical barrier to the systemic bioavailability of oral drugs.[1] Besides, the systemic bioavailability of orals drugs rely on aqueous solubility and dissolution rate, permeability across gastrointestinal membranes.[2] Lipophilic drugs influences disintegration and the dissolution rate which in turn drug absorption. Within intestinal transit time limit dissolution process should be done to enhance drug absorption as dissolved drug may expose to absorptive cells.[3] The trans mucosal permeability via oral route can be enhanced by using permeation enhancers.[4] But enhancers should be biodegradable and biocompatible.

Stratum corneum (SC) is the barrier which protects the skin and prevents the absorption of drugs. However, recent research approaches to permeate SC through liposomes, ethosomes and transferosomes.

Liposomes and niosomes are unstable in the GIT. Bilosomes consists of nonionic surfactant correspond to niosomes but contains bile salts. Bile acids are biological compatible.[5] Bile acids increases drug absorption as it have drug solubilizing and permeation enhancing properties. Addition of bile salts to the vesicles enhances stability as bile salts helps in dissolution and breakdown of enzymes. Hence, Bilosomes have notable oral delivery of vaccines.[6-8] Bilosomes approach liver as they can easily absorbed through the small intestine to the hepatic circulation). So, they can be used as an effective tool for liver targeted drug delivery.[9] Bilosomes consists of nanosized PS which is needed for optimum transdermal drug delivery.[10]

3. ADVANTAGES OF BILOSOMES IN DRUG DELIVERY SYSTEMS

- Can induce both systemic and mucosal responses.
- Higher capacity for mass immunization.

- ❖ Simplified Production & Storage.
- ❖ It is a non-invasive system as it helps in patients acceptance and compliance and also eliminates needle associated risks.
- ❖ Oral intake eliminates multiple dosing.
- ❖ Less toxic and has wide range of therapeutic activity.
- ❖ No need of trained personnel during intake.

4. LIMITATION OF BILOSOMES IN DRUG DELIVERY SYSTEMS

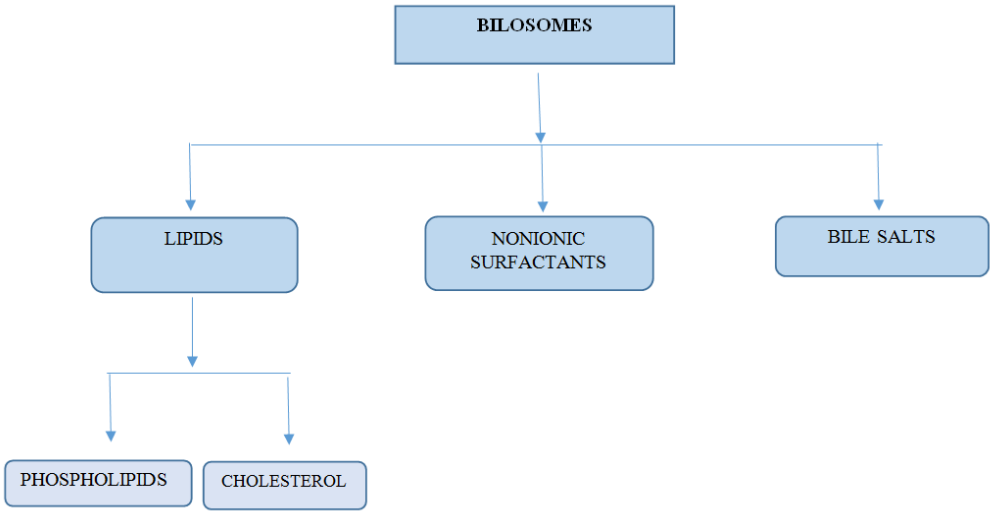
- ❖ Poor invitro-invivo correlation.

5. APPLICATIONS

1. The Apigenin loaded bilosomes enhances the absorption and stability of apigenin which is hydrophobic.[11] The Apigenin has anti-inflammatory property, inhibit the division and the migration of the breast cancer cells.
2. Bilosomes are the nanocarriers which are mostly used to deliver the proteins, vitamins, harmones and antibiotics through oral route[12]
3. Zolmitriptan loaded bilosomes are used for Intra-Nasal route which is used in treatment of migrane head-ache.[13]
4. Olmesartan loaded bilosomes which are coated with PEG show the enhanced solubility of poorly soluble drug olmesartan through Transdermal Route, used to treat hypertension.[14]
5. Bile salts and the colloidal micelles showed the improved bioavailability of Amphoterincin-B.[15]

6. COMPOSITION OF BILOSOMES

A) Lipids
B) Non-ionic surfactants
c) Bile salts.



A) Lipids include phospholipids and cholestrol.

- Phospholipids are amphiphilic in nature and have excellent biocompatibility with cellular membrane.

Dipalmitoyl Phosphatidyl choline.
Distearoyl Phosphatidyl glycerol

- Cholesterol increases the rigidity of bilosomes. Cholestrol is amphiphilic. Hydroxyl groups align towards the aqueous surface and in the centre of the bilayer the aliphatic chains orient parallel to the acyl chains.[8]

B) Non-ionic Surfactants

- They are less haemolytic and less irritant. Due to polar and non-polar segments non-ionic surfactants have high interfacial activity. Non-ionic surfactants which consists of stearyl (C18) chains show more entrapment efficacy than the lauryl (C12) chains.[9]

Alkyl esters and alkyl glyceryl ethers,
Polyoxymethylene 4 lauryl ethers

C) Bile salts

They are known as natural bio surfactants present in the gut lumen and helps in digestion and absorption of lipids. Bile salts increases stability of bilosomes in simulated fluids, by causing repulsion between the bile salts present in the bilosomes and external bile salts in the gut lumen.[3,17-19]: For more entrapment efficiency of hydrophilic drugs, combination of tweens(long alkyl chains) and cholesterol was used in 1:1 ratio. 8.6 HLB value non-ionic surfactant have superior entrapment efficacy and it get declines if HLB value decreases from 8.6 to 1.7. The commonly used nonionic surfactants for vesicles formation are as follows:

- Sodium Deoxycholate (SDC)
- Sodium Glycocholate (SGC).

6.2. Bilosomes are composed of two layers

- Innermost layer is of hydrophilic drugs and / or antigens
- Outermost layer is of bile salts and / or hydrophobic drugs.

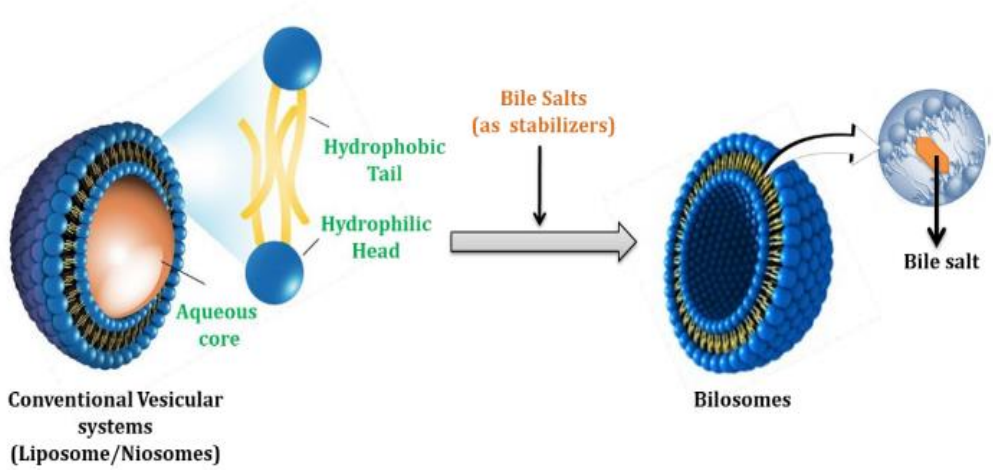


Figure 1: Representation of bilosomal system.[16]

7. PREPARATION OF BS-VESICLES

BS-vesicles were prepared using four methods.

REVERSE-PHASE EVAPORATION METHOD

Insulin /hexamethylmelamine BS- loaded liposomes.

In this approach, reverse w/o emulsion was formed by addition of soybean phosphatidylcholine (SPC) and bile salts to ethyl ether, to this buffered solution containing insulin was mixed and proceeded by ultra-sonication.[17-19] Then solvent by using a rota-evaporator under reduced pressure was removed. The dried lipids were hydrated formed by buffer to form homogenous aqueous vesicles dispersion that was expelled from high pressure homogenizer to get BS-liposomes entrapping protein. For loading hydrophobic drug in initial step hexamethyl melamine was dissolved with the lipid components in the organic solvent.

HOT HOMOGENIZATION METHOD: Hot paraffin oil bath was maintained at 120°C and a water bath at 50°C. Two Sodium bicarbonate buffers pH of 7.6 and the other one with a pH of 9.7 were prepared. Then a 100 mM bile salt solution was prepared by using bicarbonate buffer of pH 9.7. Accurate molar ratio of the lipids Mon propylene Glycol, bile and Dicalcium phosphate were taken in 25ml glass beaker, they were melted after 10min at 120°C for 10 minutes with occasional stirring. The emulsion was prepared by adding 5.2 ml of sodium bicarbonate of pH 7.6 buffer and homogenized at 8000 rpm. After few minutes of above step 0.25 mL (10 mg/mL) of the pre-heated (50°C) antigen solution was added and process continued for another 5 minutes. Antigen was added latter for minimize exposure to homogenization. Later the bilosome suspension was cooled down to 30°C, and left in an incubator/shaker (220 rpm) for 120 seconds.[20]

THIN-FILM HYDRATION METHOD: In this approach surfactant acts as a crucial ingredient. Span 80, methylidyne and sodium-dissolved organic carbon (Na-DOC) were mixed in a proportion of 2:1:0.1 along with 2% w/w stearyl amine in chloroform and methanol (8:2 v/v) in a round bottom flask. Thin film at the wall of the round bottom flask was formed by Solvent removal. Then film was by hydrated by 10ml of 10% w/v drug solution in water for 3 hours at 37°C, this step leads to formation of large multilamellar vesicles (LMVs). LMVs converted to small unilamellar vesicles (SUVs) by sonication.[21]

PRONIOSOMAL METHOD: sorbitol particles, the carrier was taken into round bottomed flask and by using rota-evaporator it was vacuum dried. Latter solution of PC, bile salt and drug which was dissolved in organic solvent were added drop wise into round bottom flask. Then, the loaded sorbitol particles were freeze-dried for complete evaporation of solvents residues. Finally, liposomes were formed from proliposomal powder by manual agitation in water.[22]

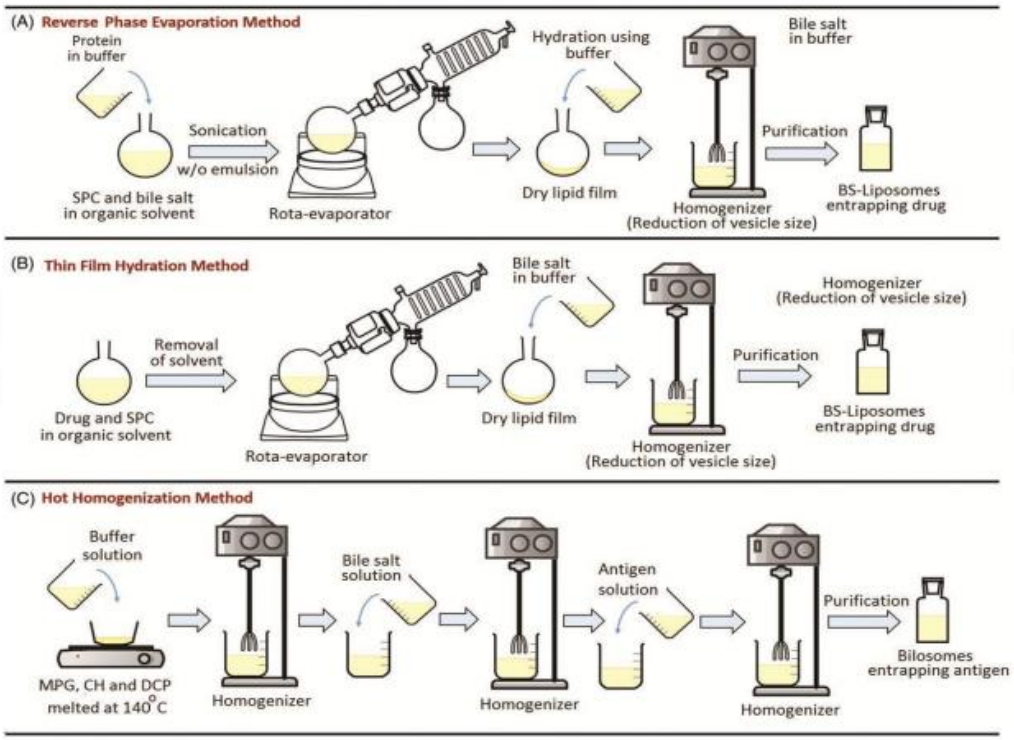


Figure 2: Representation of various methods for the preparation of bile salts-containing vesicles. (A) Reverse phase evaporation method (B) Thin film hydration method and (C) Hot homogenization method.

7. MODIFIED FORMS OF BILE SALTS VESICLES (BS-VESICLES)

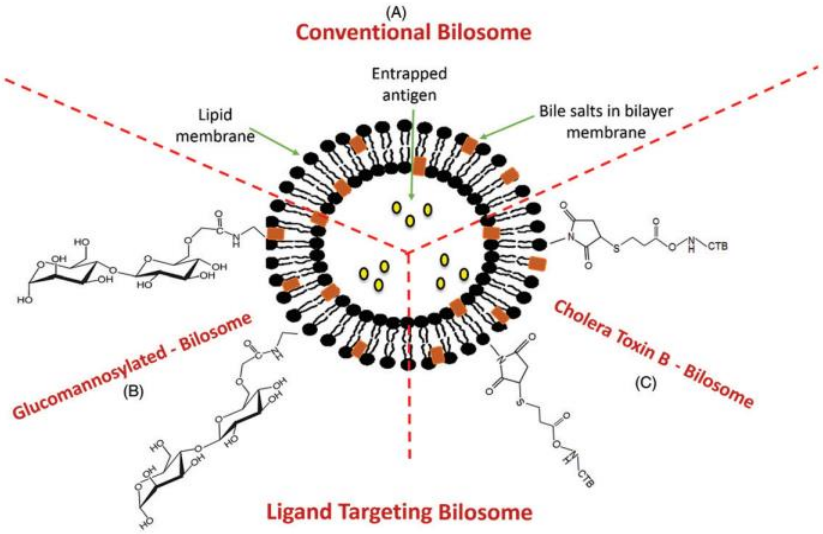


Figure 3: Structural composition of different types of bilosomes.

(A) Conventional bilosome, (B) Glucomannan (GM) bilosome and (C) Cholera toxin B-bilosome.[23]

To enhance their uptake by certain target cells BS-vesicles were modified via anchoring specific ligands to the vesicles surface.

Cholera toxin B-modified bilosomes

(CTB) is based on to their affinity to Glucomannan-modified (GM)1 ganglioside receptor on M-cells (Dertzbaugh & Elson, 1993). Surface of bilosomes was conjugated with CTB to make them to specifically bind to GM1 ganglioside receptors on M-cells membrane of Peyer's patches. The superiority of CTB-conjugated bilosomes was verified using fluorescence microscopy.[24]

GM bilosomes

The bilosomes surface conjugated with glucomannan (GM) increase their uptake through the mannosyl receptors of APCs, Jain et al. (2014a, b). Existence of high density of mannose over the surface of bilosomes

lead to precise recognition and binding to mannose receptors.[25]

Bile salt-coated liposomes (BSC-liposomes)

The formed bile salt coated liposomes (BSC-liposomes) having the covalently linked bile salt–lipid conjugate proved hepatocyte-specific targeting.

Table 1: Description of bile salt-containing liposomes formulation (BS-liposomes).

Vesicular carrier	Composition	Antigen	Preparation method	Vesicle size reduction	Ref
BS-liposomes	SPC: STC (5:1)	Tacrolimus (Poorly water soluble)	Thin film hydration method	Ultrasonication	[26]
BS-liposomes	SPC:bile salts (SGC/STC/SDC) (4:1)	Recombinant human insulin/ Protein drug	Reverse phase evaporation method	High-pressure homogenization	[19]
CTB-bilosomes	STS:CH:modified DPPE (7:3:1); 100 mg of SDC, Conjugation of CTB to bilosomes	Hepatitis B surface Antigen	Thin film hydration method	Extrusion through 200 nm pore membrane	[27]
GM-bilosomes	SMO:CH:SDC (2:1:0.1) GM-OCM-DSPE (10% w/w of total lipid content)	Tetanus toxoid	Thin film hydration method	Sonication	[28]

8. IN VITRO CHARACTERIZATIONS AND VARIABLES INFLUENCING BS-VESICLES

Table 2: In vitro characterizations and variables (BS-liposomes).

Characteristics	Methodology	Effect	Ranges	References
Particle size	Dynamic light scattering instrument	Decrease in particle size of bs-vesicles leads to increase in bile salt content and increased flexibility and decline in surface tension of the vesicle.	90nm-3µm	[26,22]
	Laser diffraction particle size analyzer.			[22]
Polydispersity index	Dynamic light scattering instrument	Increased PI of BS-vesicles leads to rupturing of the vesicles.	0.3 or below 0.3	
Zeta potential	Dynamic light scattering instrument.	zeta potential hinders the aggregation of the vesicles	+30 mV	[26]
	Electrophoretic mobility (EPM) measurements.			
Morphology	Transmission electron microscopy (TEM)	Spherical or nearly spherical		[26]
	Cryogenic-transmission electron microscopy (Cryo-TEM)			[29]
	Molecular exclusion chromatography			[30]
	Ultracentrifugation			[31]
Entrapment efficiency percent	High performance liquid chromatography (HPLC)	An increase in the bile salt content in the vesicles causes the leakage of an entrapped drug due to the fluidizing effect of bile salts on the lipid bilayers.		[29]
	UV spectrophotometer			[26]
	Bicinchoninic acid.			[30]
	Micro bicinchoninic acid (MicroBCA) method.			[31]
	Modified ninhydrin assay.			
In vitro release	Dynamic dialysis method	Helps to understand release kinetics from vesicular systems.		[29]
Cellular uptake	Human colon adenocarcinoma			[22]

	cell line (Caco-2 cells)			
	Spontaneously derived human corneal epithelial cells (SDHCECs)			[26] [32]

9. IN VIVO PERFORMANCE OF BILE SALT VESICLES (BS-VESICLES)

9.1 IMPROVEMENT IN ORAL DRUG BIOAVAILABILITY

Beagle dogs was given with BS-liposomes containing fenofibrate SDC-liposomes showed 1.57-fold increase in bioavailability relative to conventional liposomes.[29] Cyclosporine A (CyA) was given Male Wistar rats relative oral bioavailabilities of CyA-loaded SPC-liposomes and conventional liposomes were 120.3% and 98.6%, respectively. Facilitated absorption of intact BS-liposomes vesicles was the reason for the enhancement in cyclosporine A bioavailability. Hexamethylmelamine loaded bilosomes was 9.76- and 1.21-fold higher in bioavaliability than conventional liposomes. Using luminescence imaging, Niu et al. (2014) showed that orally uptake of SGC-liposomes loaded with recombinant human insulin (rhINS) were highly stable in vivo due to the dual protective effects imposed by SGC vesicles against damaging effects of bile salts and enzymes in the GIT. BS-liposomes containing Tacrolimus in rabbits showed less toxicity and increased permeability. Pro-BS liposomes containing salmon calcitonin 7.1-fold increase in the bioavailability was observed in Sprague Dawley rats. N iu et all observed that the hypoglycemic efficiency and oral bioavailability of insulin were in the sequence of SGC>STC>CH>SDC pointing out SGC in liposomes has better protection against enzymatic degradation. SGC-liposomes showed oral bioavailability of 8.5% and 11.0% when tested in both diabetic and non-diabetic rats.

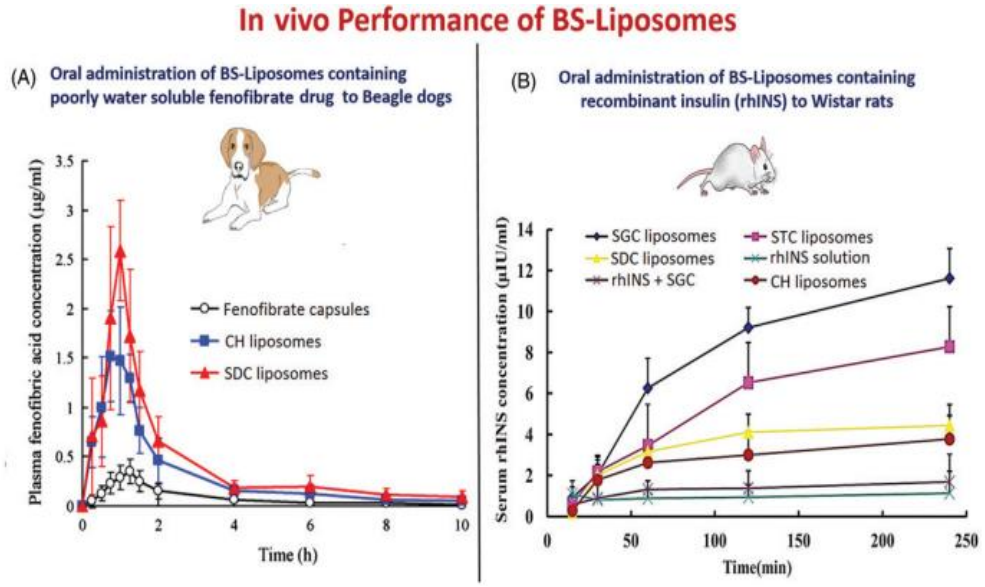


Figure 4. In vivo results of orally intake of bilosomes in comparison to conventional liposomes. (A) Fenofibrate-loaded bilosomes.[29] and (B) Recombinant insulin-loaded bilosomes.[14]

9.2 ENHANCEMENT OF VACCINE IMMUNOGENICITY

Bilosomes confirmed the suitability of using bilosomes as a carrier for vaccines to enable transmucosal vaccination. Bilosomes administered orally generated cell-mediated responses against synthetic peptides and high antibody titers against protein antigens comparable to those induced by subsequent systemic immunization.[33]

To boost their presence in the gut immune bilosomes with surface-attached ligands that can identify and connect to the cells of interest have been looked at. In this situation, Singh et al. portrayed the oral dose of bilosomes conjugated to CTB is very identical immunological response to that of administered parenterally and with Freund's full adjuvant. HBsAg-loaded CTB-conjugated bilosomes (20 mg) elicited anti-HBsAg IgG antibody titre response comparable to either IM alum-adsorbed HBsAg (10 mg) or HBsAg-loaded bilosomes (50 mg), according to research by Shukla et al. in 2010b. In order to provide transmucosal immunization, Shukla et al. (2008, 2011) looked at the potential of using SDC-bilosomes loaded with either HBsAg or DTx. bilosomes containing large concentrations of high molecular weight systemic immunoglobulin G (IgG) production dosage of the antigen similar to those brought on by intramuscular (IM) administration of antigens in mice. Production of anti-HBsAg-IgG and anti-TTx-IgG levels in mice serum was similar in both IM administered HBsAg and TTx and the combinatorial high dose of HBsAg and tetanus

toxoid (TTx) bilosomes formulation prepared Shukla etal.

Moreover, Mann et al detailed positive outcomes with respect to the viability of the bilosomes containing TTx in actuating noteworthy systemic and mucosal safe reaction after intake through oral route. TTx-loaded bilosomes were of superior quality to the oral intake of the un-entrapped antigen, but similar to parenterally administrated bilosomes. He assessed influence of particle size on the associated immune response. Outcome was that small and large vesicles entrapped influenza A antigen caused more protection measured as symptom score.

It was observed that baculovirus displaying VP1 (Bac-VP1) conjugated with bilosomes have significantly more immune responses than non-linked with Bac-VP1 conjugated with bilosomes which suggesting that bilosomes have intrinsic adjuvant characters when linked with antigen.[34]

It was found bilosomes to have a defensive property against antigens. Free antigen of 39% were measured across the GIT after oral intake in mice compared to 55% for antigen-loaded bilosomes.[35]

9.3 TRANSDERMAL DRUG DELIVER OF POORLY SOLUBLE DRUG

Lecithin-free proniosomal gel formulation Tween 20: cholesterol(9:1 and distilled water as aqueous phase) shows both the highest entrapment efficiency and stability with highest release efficiency.[36]

The bilosomal formulation in a 1:1 ratio with cholesterol and 20 mg SDC showed more permeation enhancement of TZN. It showed high zeta potential which lead to its greater stability after three months of storage at -4°C and 40°C/ 65% RH.[37]

10. STABILITY CONSIDERATIONS OF BILOSOMES

10.1. In Processing Stability

Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) procedure is used to separate proteins based on their electrophoretic mobility. To linearize proteins SDS, an anionic surfactant, is added to the protein substance and this leads to negative charge. Negative charge separates protein according to estimated size. In all the experimental studies, symmetrical shaped bands were observed between pure and extracted antigens. No new bands were present. Which confirms the method of preparation. Bile salts induce decomposition of entrapped agents.[32]

Circular dichroism spectroscopy analysis

CD is displayed by the molecules due to their levorotary and dextrorotary constituents. CD spectral signatures indicates their structures (Martin & Schilstra, 2008). By the superimposed CD spectra of test with standard samples it was confirmed that entrapped agents were stable. Hence, this indicates accuracy.[38]

Examples: Bovine serum albumin (BSA) and glucomamman (GM) bilosome size of 157 ± 3 nm, PDI of 0.287± 0.045, the zeta potential of −21.8 ± 2.01 Mv which were freeze-dried. They were found to retain its structural and conformational stability by SDS-PAGE and circular dichromism (CD) analysis.

10.2. STORAGE STABILITY

Stability studies were done to predict the leaching of the entrapped agent from the vesicles during storage. Shukla et al examined the retention of of Diphtheria toxoid in the bilosomes after storage at refrigerated (5±3°C) and room temperature of (25±2°C) at 70% RH. After 30 days storage, around 94% of the antigen was in bilosomes stored at room temperature, whereas greater than 98% of the antigen was detected in samples stored at refrigerated conditions. The stability of the formulations was due to the negative charge. This charge was induced by DCP on the bilosomes surface. This charge inhibit fusion and aggregation of the vesicles upon storage.[39]

10.3 STABILITY IN SIMULATED BIOLOGICAL FLUIDS

Bilosomes conjugated with either HBsAg or DTx retained significant amount of entrapped antigen during stability studies performed in simulated GI fluid and bile salts solutions of 5 mM and 20 mM concentrations.[39] SGC-liposomes retained considerable insulin load as compared with the conventional liposomes in both simulated GIF like pancreatin/pepsin in rats.[40] The defective effect was due to the enzyme inhibiting property of SGC and its associated membrane stabilization property. With respect to modified bilosomes) confirmed that CTB-bilosomes exhibited more stability when compared to niosomes incubated at 20 mM bile salt solution (retention 84%).[39]

Similarly, GM-bilosomes apparent added stability, in terms of more percent of TTx or BSA retained within the system, compared to bilosomes and niosomes due to the polymeric blanket barrier.[32]

14. CYTOTOXICITY OF BS-VESICLES

Bile salts causes irritation and toxicity when formulated with penetration enhancers leads to damaging of the intestinal epithelial barrier.[41] However, few researchers have shown that PL can reduce the noxiousness of bile salts.[28] By cell growth inhibition assay using Caco-2 monolayers cytotoxicity of bilosomes was evaluated in the range of 0.25– 6.25 mmol/L concentrations.[19] Although, there was a slight decrease in cell viability was observed due to increase in liposomes concentration, minor difference was observed among SGC, STC and SDC bile salts with different concentration after incubation for 4hrs. The obtained results indicate that bilosomes exhibit minor toxicity towards Caco-2 cells at the prepared concentrations.

Apoptosis induction was also estimated but non-siginficant difference was observed. SGC and STC has less toxicity confirming their suitability for ocular drug delivery than SDC-liposomes which had greater toxicity to corneal cells.[26]

15. PATENTS ON BILOSOMES

Table 3: Patents on bilosomes.

Patent no	Title	Inventors	Applicant	Claims	Composition	Method of preparation	Ref
11167033	Compositions and methods for treating viral infections	Anderson; David E	Variation Biotechnologies Inc.	Preparation of a thermostable lyophilized composition comprising an inactivated viral antigen and lipid vesicles (1-monopalmitoyl glycerol). A homogenized mixture of molten lipids and an aqueous solution of volume 6.25 mg/ml-25 mg/ml is obtained then lyophilized composition is thermostable when stored for a period of up to nine months at a temperature of 8. ° C to 40° C.	Non-ionic surfactant and inactivated hepatitis A virus	Lyophilisation and rehydration method	[42]
US9603920B2	Compositions and methods for treating influenza	Francisco Diaz-Mitoma Andrei Ogrel Jose V. Torres David E.	Anderson Variation Biotechnologies Inc	The vesicle comprises a transport enhancer which facilitates the transport of lipid-like molecules across mucosal membranes. The vesicle comprises a non-ionic surfactant.	Lipopolysaccharides, Orthomyxoviridae, CpG (5'— C—phosphate— G—3') containing adjuvants, Gastrins and Somatostatins	Hydration method	[43]
US20210316009A1	Methods for the preparation of a pharmaceutical-vesicle formulation and associated products and use		University of Strathclyde UK Secretary of State for Defence	The method for the preparation of a pharmaceutical-vesicle formulation, the method comprising the heating vesicle components comprising monopalmitoyl glycerol, cholesterol and dicetyl phosphate in a 5:4:1 molar ratio respectively at a temperature in the range of 50° C to 150° C	Esters of carboxylic acids, Togaviridae, steroids and proteins	Lyophilisation method	[44]
11,167,032	Methods and compositions for therapeutic agents	Kirchmeier; Marc J. Anderson	Variation Biotechnologies Inc.	Admixing the pre-formed vesicles with an aqueous solution that includes a thermolabile therapeutic agent, wherein preformed vesicles are prepared in the absence of thermolabile therapeutic agent	Therapeutic agents (e.g., live attenuated viral antigens, therapeutic proteins, etc.) and a lipid component.	Spray injection method used	[45]

16. CURRENT RESTRAINS AND FUTURE PERSPECTIVES

Deep insight of the literature two major constrains were observed during bilosomal development. Poor in vitro/ in vivo correlation is a major drawback with a lack of in vitro method. Although bilosomes confirmed to be a superior carrier for cationic water-soluble active drugs, sufficient loading of anionic active is still a hurdle.[45] By considering this negative charge and hydrophilicity of BSs, incorporation of cationic active would bind the BS in the bilayer to impart its membrane-stabilizing effect. Nevertheless, incorporation of anionic hydrophilic drugs would be lead to low entrapment efficiency and migration of both hydrophilic BSs and active to external phase.[47]

Proniosomal gel formulation enhances drug permeation through stratum corneum along with highest entrapment efficiency and stability.

Based on the reviewed articles, BS-liposomes were capable of increasing the bioavailability of poorly water soluble drugs in animal models and also they can protect the entrapped peptides and proteins after oral intake. Moreover, after the major breakthrough of using bilosomes for oral vaccines delivering by Conacher et al confirmed the usefulness of oral bilosomes entrapping antigens in both mucosal and systemic immune responses. In addition, CTB-bilosomes and GM-liposomes formulated via anchoring ligands to the bilosomal surface showed the ability of targeting the antigens into specific immune cells. The wide availability and low cost of bile acids, easily derivatized, proves these chiral templates into attractive building blocks for the design of novel drugs and drug carrier systems. The presented literature in this review showed that BS-vesicles have superior characteristics over conventional liposomes or niosomes for increasing the bioavailability of poorly soluble drugs through oral and transdermal route.

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