RECENT DEVELOPMENTS IN BILOSOMES FOR DRUG DELIVERY

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ABSTRACT: In the current era numerous formulations have been developed in the present day that takes the form of vesicular carriers, such as liposomes and niosomes, which are Among the candidates for drug delivery Via oral administration. Bile salts and enzymes are Only occasionally used. These vesicular structures improve The formulation's stability in the Gastrointestinal tract and solubility of lipophilic medications. The ultra-Deformable Flexibility of bilosomes improves the permeability of the stratum corneum. Therefore, these Have Used in the transdermal and oral delivery of medication. These vesicles are used to Administer drugs topically, Such as ocular and intranasally. In conclusion, the stability, low Toxicity, and bioavailability of bilosomes make Them preferable to other traditional vesicular Carriers liposomes and niosomes.

KEYWORDS: Liposomes, Niosomes, Bilosomes, Vesicular carriers, Transdermal and Oral Delivery.

INTRODUCTION: Bilosomes are sealed, bilayered vesicles that transport lipids together With bile salts And nonionic surfactants. Their size spans from 5 to 200nm, and they are both Unilamellar and spherical Together with multilamellar vesicles. Conacher *et al*. from the University of Glasgow initially described Bilosomes in 2001. Under physiological Circumstances, bile acids exist as ionized bile salts and are produced in The liver and stored In the gall bladder. They are steroid-containing amphiphilic compounds with hydroxyl Groups and hydrophobic side chains containing methyl groups. Creating mixed micelles is Crucial in the Emulsification and solubilization of dietary lipids. Therefore, bile salts Improve The permeability of medication Molecules that are lipophilic across the plasma Membrane, Causingincreasedoral bioavailability of many Biologically active molecules**.**

TABLE:1 Comparative overview of vesicular carrier[2,4,5,8,11,15]

Vesicular systems	Composition	Size	Colour	Chemical stability	Oral / transdermal stability	Storage conditions	Preparation methods
Liposomes	Phospholipids and cholesterol	50-200nm	Colourless or translucent	Oxidative degradation over time, which may affect their stability	Orally Unstable	Require special conditions (liquid nitrogen storage)	TFH, RPE, LFH, Microfluidic method.
Niosomes	Non-ionic surfactants and cholesterol	100-500nm	Colourless or translucent	Stable and not prone to oxidative degradation	Orally unstable	Do not require special storage conditions	TFH, Ethanol injection method.
Bilosomes	Non-ionic surfactants and bile salts	50-200nm	Colourless or translucent	Stable and not prone to oxidative degradation	Orally Stable	Do not require special storage conditions	TFH, Solvent evaporation, Ethanol injection, RPE, Hot homogenization, Probilosomal method.
Glycerosomes	Phospholipids, glycerol, and water	50-200nm	Colourless or translucent	Stable and resistant to degradation	Orally Limited Stable	Do not require special storage conditions	Differential and Isopycnic centrifugation.
Cubosome	Lipid	50-500nm	Colourless	Stable and	Orally Stable	Do not	High-

s	bilayers arranged in a cubic or hexagonal lattice structure		or translucent	do not undergo oxidative degradation		require special storage conditions	pressure homogenization, Probe ultrasonication.
Transferosomes	Phospholipids, surfactants and water.	100-1000nm	Colourless or translucent	Transferosomes are relatively stable, but their chemical stability may vary depending on the specific composition.	Transdermally stable	Require special conditions	TFH, RPE, Ethanol injection, freeze-thaw sonication method.
Aquasomes	Poly hydroxyl oligomer, nanocrystalline calcium phosphate	60-300nm	Colourless	Solvent evaporation, spray drying, coacervation phase separation, and emulsion solvent diffusion	Orally Stable	Require special storage conditions	Solvent evaporation, spray drying, coacervation & phase separation, and emulsion solvent diffusion.
Sphingosomes	Sphingolipids and cholesterol(55:45)	0.05µm-0.45µm	Colourless	Very stable to acid hydrolysis	Orally Stable	Require special storage conditions	LHM, RPE, Sonication, solvent injection,

							microfluidization.
Ethosomes	Water, Phospholipid and Ethanol.	10nm-Few micron	_	Stable	Transdermally stable	Store in refrigerator conditions (4-8^{0}C)	Hot method, Cold method.
Herbosomes	Phospholipids, phosphatidylcholine, flavonoids	50nm-few hundred nm	Depends on the specific herb or extract used	Stable and do not undergo oxidative degradation	Orally Stable	Require special conditions	High-pressure homogenizer
Colloidosomes	Colloidal particles(hallow core and polymer shell)	1-4 µm	Coloured	Stable and covalently cross-linked	Orally stable	Specific storage conditions are necessary	Thermal annealing
Archeosomes	Archaea, synthetic archaeal lipids	200nm	_	Stability with ether linkages is more than esters	Orally stable	Specific storage conditions are necessary	TFM, RPE, micro fluidization, Polycarbonate membrane filter extrusion protocols.
Virosomes	Phospholipids, viral surface glycoproteins.	120-180nm	_	Stable	Orally stable	Require special storage conditions	Virosomes are stored at low temperatures(-20^0 or -

							80^0C)
Phytosomes	Phytoconstituents of herbs, phospholipids.	50nm-few µm	_	Stability depends on the type of phospholipid used	Orally Stable	Specific storage conditions are necessary	Solvent evaporation
Pharmacosomes	Phospholipid, Dichloromethane	79.9-620.2nm	Colourless	Stable but chemical stability varies depending on the specific formulation and drug or lipid used	Orally Stable	Controlled temperature($2\text{-}8^0$)	Solvent evaporation and ether injection method.

Because of their stability in the gastrointestinal tract, bilosomes are extremely biocompatible And increase the Therapeutic efficacy of medications. In the gastric intestine environment, The best mannan coating was utilized To stabilize the vesicles and serves as a targeting ligand For mannose receptors expressed on macrophages and Dendritic cells.

TYPES OF BILOSOMES:

Surface modified bilosome[18], Functionalized bilosomes[21], Self assembled bilosomes[23], Highly deformable bilosomes [19], Probilosomes[22], Nanobilosomes[20].

ADVANTAGES OF BILOSOMES:

- Increases the aqueous solubility of medications that aren't very water-soluble.
- Improved chemical and storage stability.
- Improved stability in the gastrointestinal tract.
- Enhance the permeability of the drug.
- Changes the corneum's permeability by weakening the lipid barriers between cells.
- Extremely deformable.
- Long-term medication release.

- Reduced doses and shorter intervals between the doses of the medicine.
- Drugs that are both lipophilic and hydrophilic can be encapsulated.
- In comparison to liposomes and micronized drugs, bilosomes have a higher Bioavailability of the medicine.

LIMITATIONS OF BILOSOMES:

- The lack of in vitro methods that accurately reflect in vivo conditions causes poor in Vitro in vivo Correlation, which makes it more difficult to characterization.
- Utilizing an anionic hydrophilic drug reduces the effectiveness of drug encapsulation By causing drug Migration to the external environment.

METHODS OF PREPARATION:

1. **REVERSE PHASE EVAPORATION METHOD:**

Water-in-oil emulsions are created using the reverse phase evaporation method, and the Medicine is present in The water phase while lipids make up the organic phase, forming a Bilosomal bilayer. In this procedure, bile salts And soyabean phosphatidylcholine are Dissolved in an organic solvent, such as buffer absolute ether, and a drop Of a buffer solution Containing protein is added by a fall. The mixture is sonicated in a water bath for 5min to Prevent the formation of an emulsion. The organic solvent is removed from the emulsion by Rotating it at a Speed of 50rpm. The dry lipids are subsequently hydrated with a buffer until A Uniform dispersion is created. Finally,bilosomes containing the medicine are obtained by Extruding this dispersion through a high-pressure Homogenizer, which is then further Purified by ultracentrifugation. This technique creates bilosomes containing Protein Medications such as recombinant human insulin and swine insulin. [1,2,5].

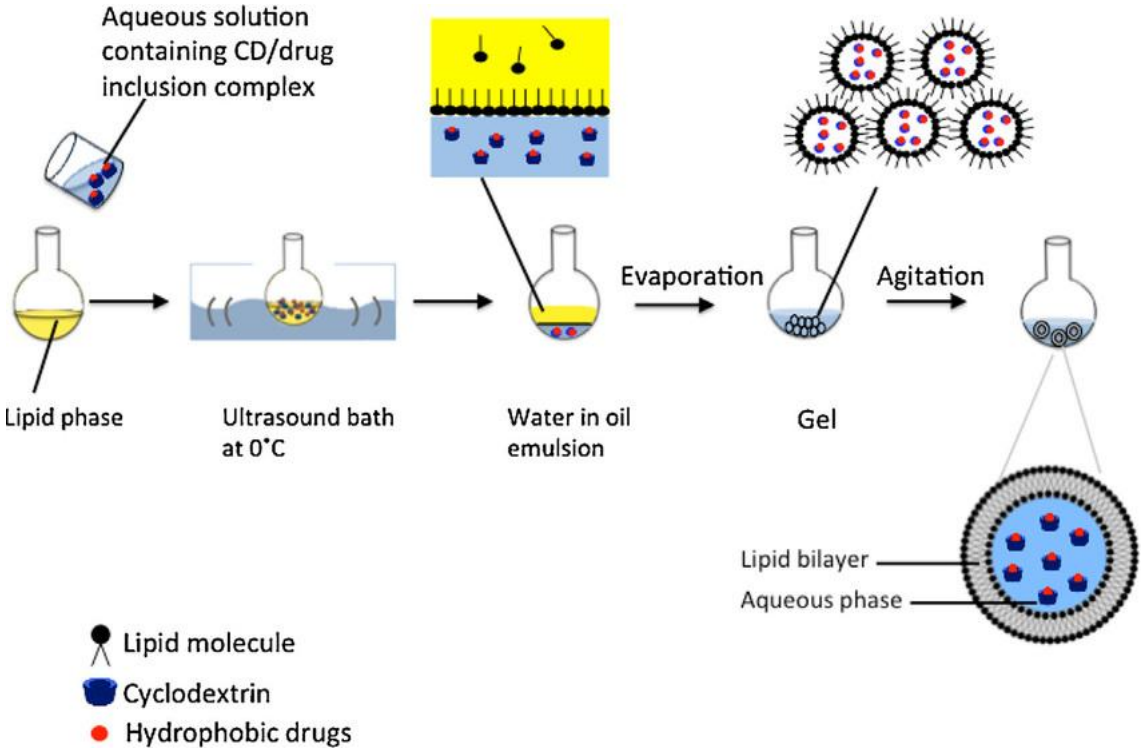

Figure 1: Reverse phase evaporation method [6].

ADVANTAGES:

- Increased capacity for aqueous loading internally.
- To get rid of the leftover solvent, try dialysis or centrifugation.

- **LIMITATIONS:**
- Organic solvent traces can interfere with the chemical or biological stability of lipids Or medicines that Have been loaded.

2. <u>Thin Film Hydration method</u>:

When creating drug-loaded bilosomes using the thin film hydration process, the medication Is dissolved in an Organic solvent together with the lipid component, Soyabeanphosphotidylcholine. The resulting thin film is Subsequently hydrated with a buffer containing bile salt to create big multilamellar vesicles, which then spilt Into smaller Unilamellar vesicles with high-pressure homogenization. Then, these vesicles are purified to Produce bilosomes that contain medication. Bilosomes containing tacrolimus, fenofibrate,

Cyclosporine A, Diphtheria toxoid, hepatitis B antigen, tetanus toxoid, etc, are prepared using This technique. [1,2,5].

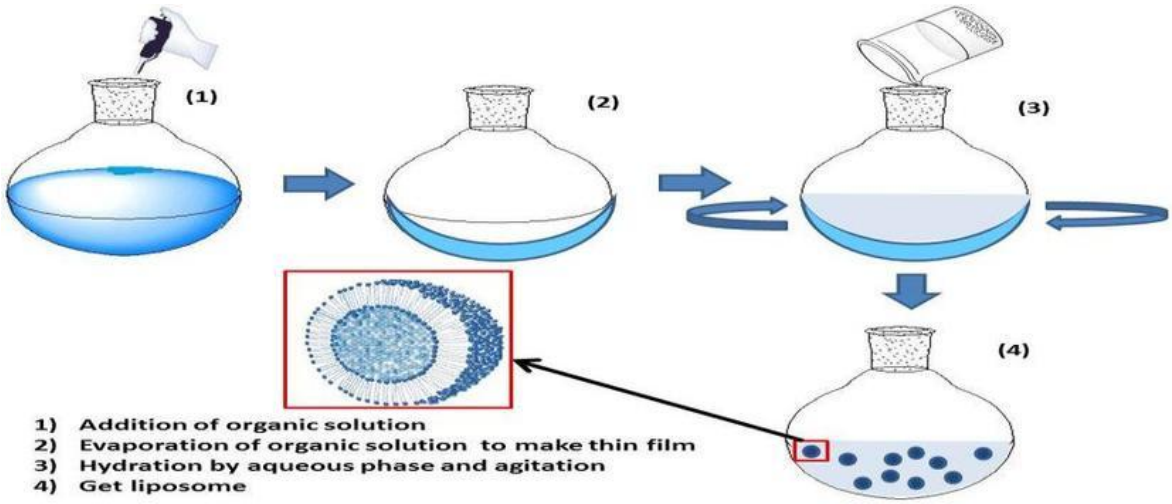

Figure 2: Thin film hydration method [6].

ADVANTAGES:

- On a laboratory size, feasible.
- High effectiveness of trapping for hydrophobic medicines.

LIMITATIONS:

- Experiencing high temperatures can harm phospholipids and/or drugs.
- Little to no encapsulation.
- Challenging to scale up**.**

3. Ethanol injection method:

Ethanol, non-ionic surfactant and cholesterol are dissolved in ethanol in a water bath. The Ethanolic solution Was slowly injected into phosphate buffer PH7.4 and is magnetically Stirred. Bile salts and edge activators Are Added formerly to the aqueous phase. Bilosome Dispersions are formed which are indicated by the turbidity of The solution. Stirring was Continued to ensure complete volatilization of ethanol. Dispersions are cooled at room temperature and sonicated. [1].

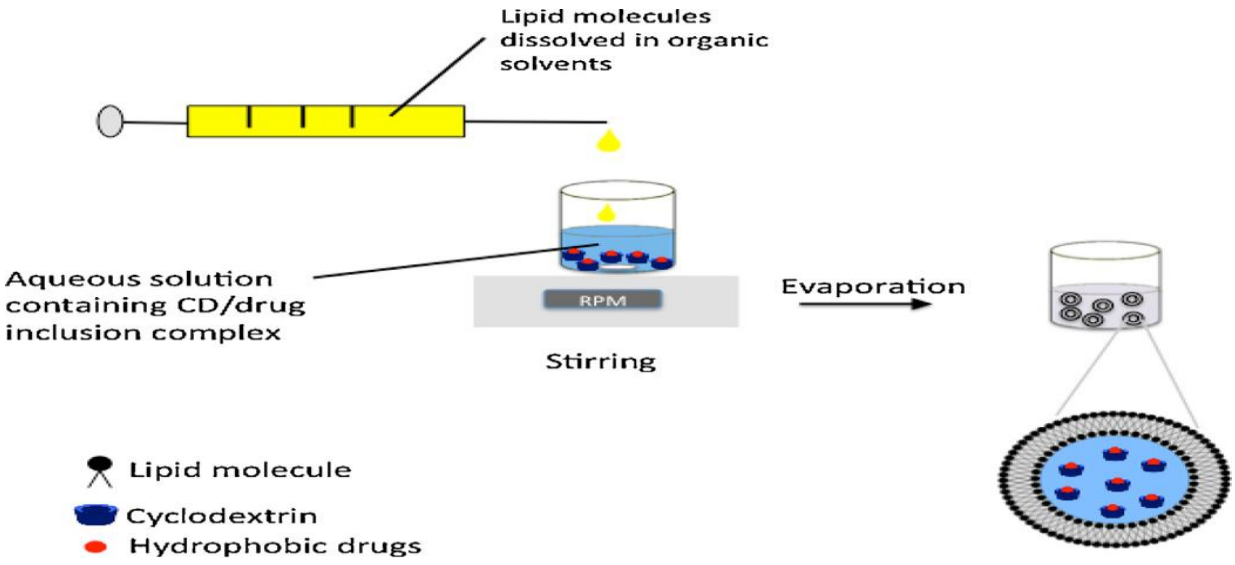

Figure 3: Ethanol injection method [6].

ADVANTAGES:

- This method is simple, fast, implemented, and reproducible as well as does not Cause lipid Degradation or oxidative alterations.

LIMITATIONS:

- It is a time-consuming process.
- The final suspension contains a large amount of organic residue, and it is Challenging to Remove ethanol because it creates an azeotropic combination With water.

4. HOT HOMOGENIZATION METHOD:

The lipid components, such as mono palmitoyl glycerol, cholesterol, and diacetyl phosphate, Are melted at 1400C to prepare bilosomes using the hot homogenization process for five minutes, then hydrated with the Buffer solution. After homogenization of the mixture, a bile Salt solution is added to create a dispersion that Contains empty vesicles. The mixture is then Homogenized once more the antigen follows the homogenate is Mixed with a buffered Solution, and numerous freeze then cycles are used to capture the protein. The antigen is Applied at the very end to reduce prolonged homogenization exposure. This technique is Utilized to capture TTX (Tetrodotoxin), rHA (recombinant influenza antigen), and H3N2 Subunit protein. [1],[2],[3]

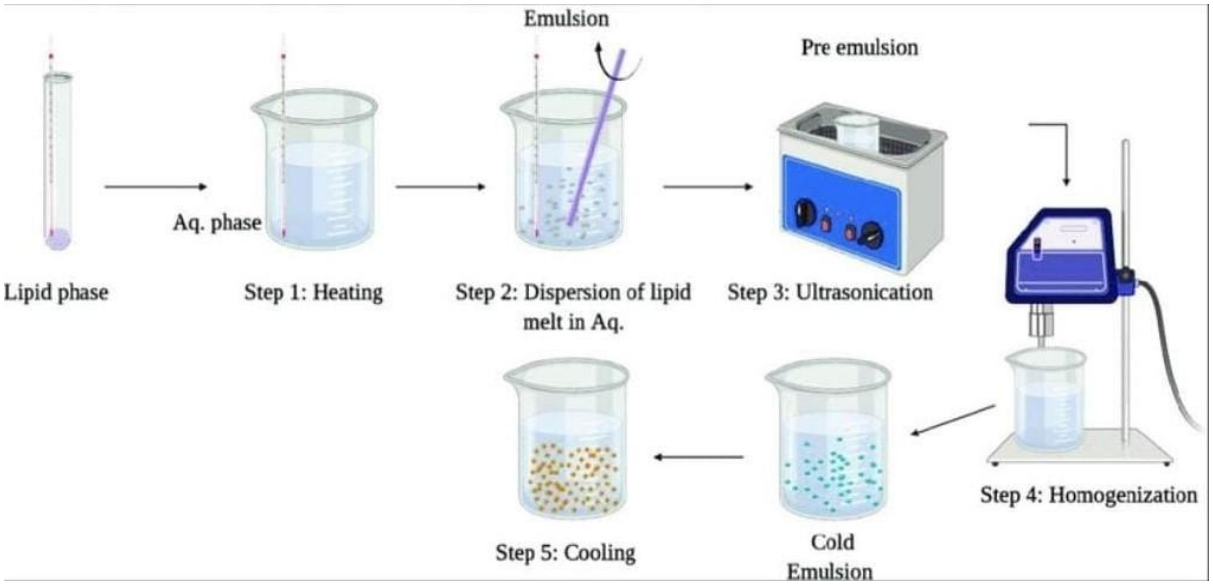

Figure 4: Hot Homogenization method [7].

ADVANTAGES:

- Simple to handle.
- It is a procedure without solvents

LIMITATIONS:

- Temperature-induced medication deterioration

5.PROBILOSOMAL METHOD:

In this method, sorbitol particles were located in a round bottom flask. This is then vacuum Dried in a rotatory Evaporator. Then the solution of phosphotidylcholine, bile salt and drug Was dissolved in an organic solvent Were added in a dropwise manner into the round bottom Flask to load them onto sorbitol particles. Loaded Sorbitol particles are freeze-dried to obtain Probilosomal powder which is then converted into bilosome by Manual agitation in water.[1]

CHARACTERIZATION OF BILOSOMES

A) PARTICLE SIZE:

The particle size of bilosomes exerts a substantial impact on their in vitro and in vivo Performances. The Vesicles size of bilosomes ranges from 90 Nanometers – 3 Micrometres. Greater uptake within the Peyer's Patches was demonstrated by larger Bilosomes vesicles (6 versus 2 m in diameter), which were also able to In an influenza Challenge research, lower the medium temperature differential change and encourage a Decrease in viral cell load. Analytical instruments constructed on the dynamic light Scattering principle, i.e., proton

correlation spectroscopy, are used to estimate particle size of bilosome vesicle dispersion. This Technique measures time-dependent Fluctuations in the intensity of scattered light which occurs because of The particles that Undergo Brownian motion. The diffusion coefficient of the particles can be determined By analyzing these intensity fluctuations, and results are provided in terms of size Distribution.[1,2]

B) POLYDISPERSITY INDEX(PDI):

The term polydispersity is used to describe the degree of non-uniformity of particle size Distribution. A Polydispersity index of 0.3 and less is seen to be appropriate for Drug Delivery applications using lipid-base carriers, such as liposomes and nanoliposome Formulations, and denotes a homogeneous population of phospholipid vesicles [1,2].

C) ZETA POTENTIAL(ZP):

Zeta potential means the overall charge acquired by the particles in a particular medium. Vesicles with Surface charge are more stable against accumulation than uncharged ones. Bilosomes acquire a negative charge due to the presence of bile salts that stimulate zeta Potential and avoid aggregation of the vesicles. The Peyer's patches favourably take up Negatively charged vesicles. Generally speaking, a system is thought to be stable when Its zeta potential equals due to electrostatic repulsion between the particles, Around + 30mv. A description of numerous techniques/ methods utilized to examine the Morphological Features of bilosomes as vesicular systems[1,2].

D) PERCENTENCAPSULATION EFFICIENCY:

1ml of the bilosome dispersion was taken and centrifuged at 15,000 rpm for 2 hours at 4^0C. The Supernatant was taken, suitably diluted and determined spectrophotometrically For the drug content[1,2].

E) TRANSMISSION ELECTRON MICROSCOPY(TEM):

Surface morphology is determined by transmission electron microscopy. Before TEM Examination, one drop Of a selected bilosome dispersion was air dried at room temperature for 10 min after being negatively Stained with 1% phosphotungstic acid[1].

F) DIFFERENTIAL SCANNING CALORIMETRY (DSC):

The apparatus was calibrated. Bile salts, cholesterol, non-ionic surfactant, drug-loaded Bilosomes and blank Bilosomes are investigated. 3mg samples were placed in standard Aluminium pans and heated from 10^0C to 200^0C at a scanning rate of 10^0C /min.[1]

G) INVITRO DRUG RELEASE STUDIES :

The dialysis bag method is used. Dialysisnbag was overnight immersed in the Releasemedium. the Medium is 50ml phosphate buffer p^H 6.8 and maintained at 37±0.5^{0}C. 3ml samples were withdrawn At1,2,4,6,8,10 and 24 hours and substituted With an equal volume of the medium. Withdrawn samples Are suitably diluted and Analysed spectrophotometrically to determine the drug release.[2]

H) STORAGE STABILITY:

Stability studies are carried out to explore the leaching of entrapped agents from Vesicles during Storage. The produced bilosomes are kept for 90 days at room temperature (25+2^0 C)and 4+0.5^{0}C in a Refrigeratory with a 70% relative humidity At 0,45 and 90 days, the prepared bilosomes' stability was Assessed.[1]

CONCLUSION:

Bilosomes are nano vesicular carriers for drug delivery. Bilosomes not only enhance THE Bioavailability of the drug but also increase the efficacy of drugs and the ability to entrap Proteins, peptides and antigens. Thus they have biomedical and pharmaceutical applications In drug delivery, cancer therapy and diagnostics. They can be given by various routes Including oral, nasal, ocular, and buccal. The bilosomes have profound applications in drug delivery and therapeutics.

CONFLICT OF INTEREST:

All the authors have no conflict of interest.

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