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A review on Bilosomes- Nanocarriers for targeted delivery system.

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ABSTRACT:

Bilosomes come under Targeted drug delivery which involves the controlled release of the drug in predetermined rate at the target size. The various vesicular nanocarriers are nvolved in the targeted drug delivery like liposomes, niosomes and bilosomes. Liposomes, Niosomes are vesicular nanocarriers used for the oral administration of vaccines. The main isadvantage is that the instability in stomach due to low pH, presence of bile salts and enzymes. These problems can be overcome by using bilosomes which are bilayered vesicular carriers of lipids incorporating non-ionic surfactants and bile salts. The article contain the information about bilosomes Introduction, Advantages, Disadvantages, Different methods for preparation of bilosomes, characterization of bilosomes, evaluation f bilosomes and applications.

KEY WORDS: Bile salts, Vesicular carriers, Absorption, Mucosal permeation, Penetration enhancers, Biosurfactants.

INTRODUCTION:

Various types of nanocarriers are involved in the targeted drug delivery such as liposomes, niosomes [1,2,3]. Liposomes are most widely used vesicular nanocarriers of spherical shape and size vary from 25nm to few microns [4,5]. The main drawback of liposomes was found to be lack of physical and chemical stability in stomach [6]. Bilosomes are the vesicular carriers that protect the vaccines from degradation in stomach [7]. Bilosomes are the bilayered vesicular carriers of lipids incorporating non-ionic surfactants and bile salts, which are spherical in structure and the size vary from 5-200nm [8]. Bile acids are the facial amphiphiles that are synthesized in liver and stored in gall bladder in the ionized bile salt form [9]. The bile salts are the biosurfactants used in bilosomes are involved in mucous permeability of drugs [10,11].

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Table: Different types of nanocarriers and their properties

S.NO:	CHARACTER	LIPOSOMES	NIOSOMES	BILOSOMES
1	Composition	Phospholipids with cholesterol and charge inducer	Non-ionic surfactant with cholesterol and charge inducer	Non-ionic surfactant, bile salt and charge inducer
2	Chemical stability	Oxidative degradation occurs	Oxidative degradation is not observed	No oxidative degradation occurs
3	Stability in simulated intestinal fluid	rickety	unstable	robust
4	Antigen dose	High antigen dose is required due to instability.	High antigen dose is required due to instability	low antigen dose is required due to instability
5	Storage stability	Require liquid nitrogen for storage	Special conditions are not required	Special conditions are not required

ADVANTAGES:

1. On modifying the size of the vesicle the immune response can be optimized [13]

2. On changing the concentration, the aggregation is done accordingly with the respect to concentration [14,15,16].

3. The bilosomes are used to deliver both the hydrophilic and hydrophobic drugs [17].

4. The bilosomes constituting pluronic polymers reduce the uptake of nanocarriers by Mononuclear Phagocyte System [MPS][18].

5. The drug loaded bilosomes show greater bioavailability than the liposomes and micronized form [19].

6. Oral administration is convenient than the parenteral route of administration, which is observed in bilosomes[20].

DISADVANTAGES:

1. The main disadvantage of bilosomes was found to be poor invitro-invivo correlation

[21].**APPLICATIONS:**

1.The Apigenin loaded bilosomes increases the absorption and stability of apigenin which is poorly soluble or has solubility and greater metabolism [22,23]. The Apigenin has anti-inflammatory property and also inhibit the increase in the number and the migration of cancer cells and also promote apoptosis of the breast cancer cells [24].

2.Bilosomes are the nanocarriers which are widely applied to deliver the proteins, vitamins, harmones and antibiotics through oral route [25,26].

3. Zolmitriptan loaded bilosomes are used to deliver the drug through Intra-Nasal route which is used in treatment of migrane head-ache [27,28],

4. Olmesartan loaded bilosomes which are coated with Poly Ethylene Glycol show the improved solubility of poorly soluble drug olmesaretan through Transdermal Route, used to treat hypertension [29].

5. Bilosomes are used to deliver the vaccines effectively when given by oral route due to increased stability than liposomes and niosomes[30].

6. The colloidal micelles which is formulated by the addition of bile salts showed the improved bioavailability of Amphoterincin-B, when given through oral route [31].

7. The size adjustable cholate nanocarriers which generally come under the class of amphiphilic copolymer by using bile salts is used to treat cancer [32].

DIFFERENT METHODS FOR PREPARATION OF BILOSOME:

1.) REVERSE PHASE EVAPORATION METHOD :-

In this method water phase consists of drug or protein and the oil phase consists of phospholipids like soya lechithin and bile salts dissolved in ether(organic solvent). The buffer solution into which the drug is added is dropped drop by drop into the oil phase and then this mixture is sonicated for 5min in water till W/O emulsion is obtained. To remove the organic solvent in W/O emulsion, it is rota evaporated with rotating speed of 50rpm. Then to the dried form add the buffer solution and extruded through high pressure homogenizer [33].

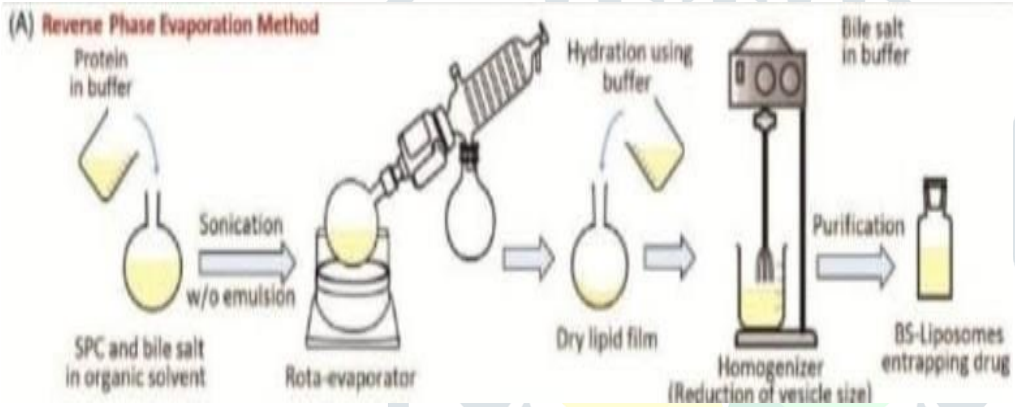

Figure 1: Reverse phase evaporation method[39]

2.) THIN FILM HYDRATION METHOD :-

In this method the phospholipid and the drug are dissolved in organic solvent and the solvent is evaporated by using rotary evaporator and results in formation of thin film. The thin film is hydrated with buffer containing bile salt to form bilosomes of large multilamellar vesicles. By using, high pressure homogenizer the large multilamellar vesicles are converted into small unilamellar vesicles. By ultra-centrifugation process, the bilosomes can be purified and separated.

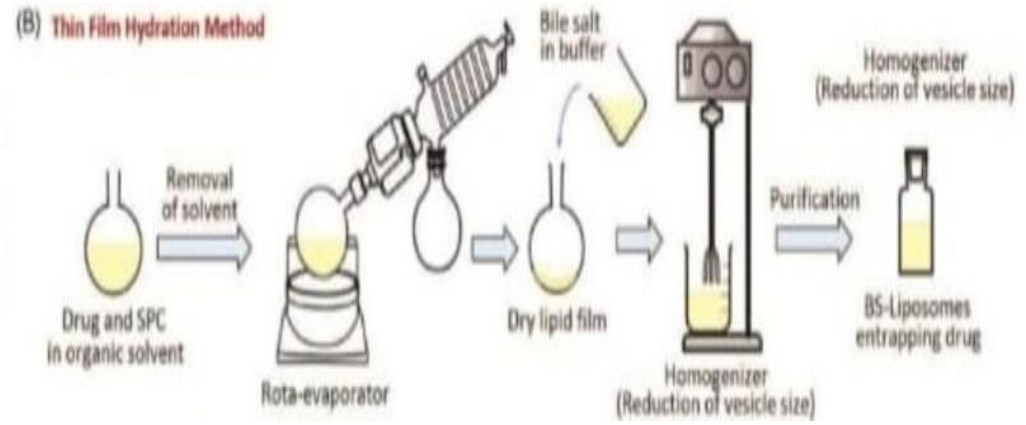

Figure 2: Thin film hydration method[39]

3.) HOT HOMOGENIZATION METHOD:-

In the method the mono palmitoyl glycerol, cholesterol, di-cetyl phosphate melted at 140 for 5minutes and then hydrated with buffer solution containing bile salts to obtain empty vesciles. The formed empty vesicles are homogenized by homogenizer and the antigen buffered solution is added and after several freeze thaw cycles protein entrapment occurs [34,35,36,37]

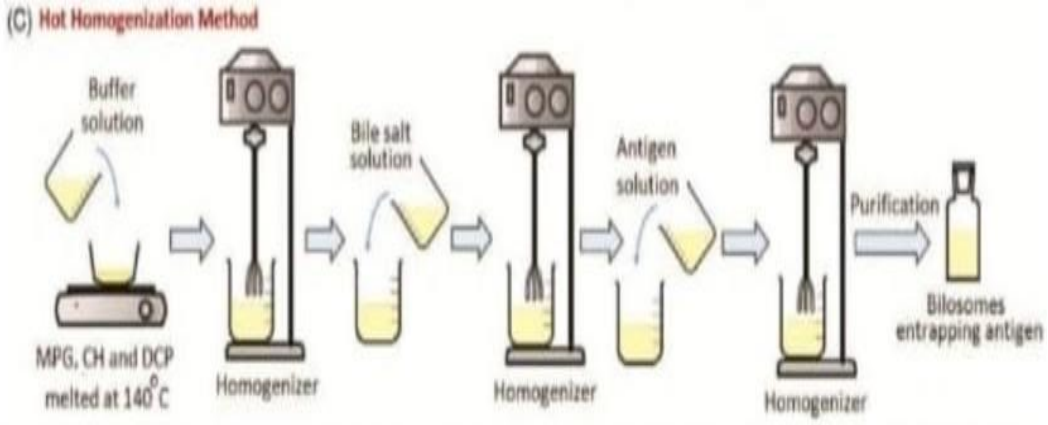

Figure 3: Hot homogenization method [38]

CHARACTERIZATION OF BILOSOMES:

1. MORPHOLOGY:- Transmission Electron Microscope is used to determine the morphological characteristics of bilosome. A drop of diluted bilosomal sample was placed on a glass slide and leave it to dry for 1hr and was observed in Transmission Electron Microscope[39,40]

2. PARTICLE SIZE:- Dynamic Light Scattering is used to determine the size of bilosome Vesicle. The bilosome vesicle size ranges from 90nm-3µm [39,40].

3.ZETA POTENTIAL:- The bilosomes acquire negative charge on the surface due to thepresence of bile salts which prevent the aggregation of vesicles. The overall charge acquired by the particles in a particular medium is called as zetapotential. The bilosomes are considered to be stable, if they possess ±30mV zeta potential[39].

4.PERCENTAGE ENTRAPMENT EFFICIENCY:- Spectroscopy methods or chromatographic methods are used to determine the percentage entrapment efficiency of the bilosomes. The prepared bilosomes are centrifuged at 18000 rpm for 30 minutes at $4^{O}C$ in centrifugation tube. The supernatant was collected and drug concentration was analysed by using UV visible spectrophotometer. % EE is calculated by using following formula [41,42].

$$\% \text{ Entrapment efficiency(EE \%)} = \frac{\text{Drug content in bilosomes}}{\text{Total drug added}} \text{ X100}$$

5. INVITRO RELEASE: Invitro release studies are used as an indicator for determined the Invivo performance [43]. Dynamic dialysis method is used to determine the Invitro release of drug from Vesicle. The drug release from the vesicle can be determined by the drug concentration in the receiver compartment by the diffusion across the dialysis membrane [44].

CONCLUSION:

Bilosomes are the targeted delivery systems in which the drug is delivered to the target site. They are vesicular nanocarriers which has the ability to increase mucosal permeability used in transdermal drug delivery systems and also due to the nano size of the carrier, the absorption of drug increases which leads to increased

bioavailability of drug due to which the therapeutic activity of drug is improved. Bilosomes have many advantages over liposomes and niosomes which include stability in the stomach used for oral immunization, protection of entrapped protein and peptides on oral administration, decrease the uptake of antigen by M cells, Improve the bioavailability of poorly soluble drugs. So, for painless, non-parentral administration with improved stability, mucosal permeability bilosomes are widely used nanocarriers for drug delivery.

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