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LIPOSOMES: A REVIEW

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ABSTRACT

The efficacy of drugs depends on the method by which the drug is delivered. Liposomes have been considered to be the most successful nanocarriers for drug deliver. A liposome is a tiny bubble (vesicle), made out of the same material as a cell membrane. Liposomes provide an established basis for the sustainable development of different commercial products for treatment of medical diseases by the smart delivery of drug Liposomes, the vesicles of phospholipid bilayer, can encapsulate both hydrophilic and lipophilic drugs and protect them from degradation and have made their way to the market. This review of literature discusses about the liposome components, methods of production of liposomes, their stability, biodistribution and the potential therapeutic applications as drug delivery systems.

KEYWORDS: Liposome, Encapsulate, Toxicity, Efficacy, Phospholipid

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1. INTRODUCTION:

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.[1]So to get the required concentration new techniquesare required to develop. Liposomal encapsulation is a new technique for increasingthe efficacy of drugs. Liposomal encapsulation technology (LET) is adelivery technique used to transmit drugs that act as curative promoters for the body organ by medical investigators. This form of delivery system proposal targeted the delivery of vital combinations to the body.[2]

LET is a method of generating sub-microscopic foams called liposomes.Liposomes have shown great potential as a drug delivery system. The therapeutic index of new or established drugs is modifying by improving the drug absorption,metabolism by using liposomes. Liposomes also prolonging biological half-life or reduce toxicity. Drug distribution, absorption, metabolism and excretion is alsocontrolled by properties of the carrier (liposomes) and nolonger by physio-chemical characteristics of the drug substance only. [3]

Liposomes are small artificial vesicles of spherical shape they have hydrophobic and hydrophilic character. They have one or more phospholipid bilayer membranes can transport aqueous or lipid drugs, depending on the nature of those drugs andalso protect the drug from degradation and reduce drug-related nonspecific toxicity. They have a numerous use in cosmetic and pharmaceutical industries.[4]

Liposomes are spherical self-closed structures, composed of curvedlipid bilayers, which enclose part of the surrounding solvent into theirinterior. The size of a liposome ranges from some 20 nm up to severalmicrometres and they may be composed of one or several concentric membranes, each with a thickness of about 4 nm. Liposomes possess unique properties owing to the amphiphilic character of the lipids, which make them suitable for drug delivery [5].

The name liposome is derived from two Greekwords: 'Lipos' meaning fat and 'Soma' meaning body.Structurally, liposomes are concentricbleedervesiclesin which an aqueous volumeis entirely enclosed by a membranous lipid bilayer. Membranes are usually made of phospholipids, which are molecules that have a hydrophilic head

group and a hydrophobic tail group. The head is attracted to water, and the tail, which is made of a long hydrocarbon chain, is repelled by water.When membrane phospholipids are disrupted, they can reassemble themselves into tiny spheres, smaller

than a normal cell, either as bilayers or monolayers. The bilayer structures are liposomes. The monolayer structures are called micelles. [6]

In this review article we discuss about the liposome components, methods of preparation, drug encapsulation mechanism and the potential therapeutic applications advantages and disadvantages of liposomes.

2. CLASSIFICATION

Liposomes can be classified in number of ways. depending upon their composition, size and number of bilayers.[7]

2.1 Depending upon composition

a)Conventional liposomes
b) pH-sensitive liposomes
c)Cationic liposomes
d)Immuno-liposomes
e)long-circulating liposomes.

2.2 Based on the method of preparation

a) REV- Reverse phase evaporation vesicles

b) MLV-REV- Multi lamellar vesicle by REV

c) DRV-Dehydration- rehydration method

d) VET- Vesicle prepared by extraction method

e) SPL- Stable plurilamellar vesicles

f) FAT-MLV- Frozen and thawed MLV

2.3 Depending upon size

a) Small unilamellar vesicles (SUV): 20–100 nm

b) Large unilamellar vesicles (LUV): >100 nm

c) Giant unilamellar vesicles (GUV): >1000 nm;

d) Oligolamellar vesicle (OLV): 100–500 nm and

e) Multilamellar vesicles (MLV): >500 nm.

New developed types of liposomes, designated as doubleliposome (DL)[8] and multivesicular vesicles (MVV),[9]were recently reported. These liposomes, which could be prepared by novel preparative technique, are thought to improve drug protection.

3.METHOD DRUG LOADING IN LIPOSOMES

The main aim of the liposome is to increase the therapeutic index, biological half-life and to reduce the toxicity. An ideal liposome formulation should efficient in drug entrapment, narrow particles size distributionand long-term stability of liposome products. Liposomes preparation methods involve hydrating of thelipid,sizing of the particles and removing of the non-encapsulated drug. The following methods are used for the drug loading in liposomes.

3.1. Passive loading techniques-In the passive loadingmethod the drug is encapsulated by introducing an aqueous phase of a water-soluble drug or an organic phase of a lipid-soluble drug, before or at some stage during the preparation of the liposomes. The high drug encapsulation efficiency can be achieved by usingpassive loading method for lipid-soluble drugs with a high affinity tothe lipid membrane.

3.2. Active loading technique. -In the active loading method, the drugs can beloaded by creating diffusion gradients for the ions or drugs acrossthe external and internal aqueous phases.

4. METHODS OF LIPOSOMES PREPARATIONS:

The correct choice of liposome preparation methoddepends on the following parameters:

1)Thephysicochemical characteristics of the material to beentrapped and those of the liposomal ingredients

2) The nature of the medium in which the lipid vesiclesare dispersed

3) The effective concentration of theentrapped substance and its potential toxicity

4) Additional processes involved during application/delivery of the vesicles

5) Optimum size,polydispersity and shelf-life of the vesicles for theintended application

6) Batch-to-batchreproducibility and possibility of large-scaleproduction of safe and efficient liposomalproducts. [3,4]

4.1. Mechanical dispersion method.
4.2. Solvent dispersion method.
4.3. Detergent removal method [10,11,12]

4.1.Mechanical dispersion method

4.1.1. Preparation of liposomes bythin film hydration method

The thin-film hydration procedure is the most common and simplemethod for preparation of MLV by dissolving the phospholipids inthe organic solvents: dichloromethane, chloroform ethanoland chloroform-methanol mixture (2:1 v/v; 9:1 v/v; 3:1 v/v). A thin and homogeneous lipid film is formed when solvent isevaporated under vacuum at the temperature: 45-60 ºC. Nitrogengas is involved in order to completely remove the residualsolvent. A solution of distilled water, phosphate buffer,phosphate saline buffer at pH 7.4 and normal saline buffer areused in hydration step. The time for the hydration process variedfrom 1 h to 2 h at the temperature 60-70 ºC. In order to obtain fulllipid hydration, the liposomal suspension is left overnight at 4 ºC24. Fig. 1The thin-film hydration method can be used for all different kinds oflipid mixtures. The main drawbacks of the method are related to lowencapsulation, difficulty of scaling up and the size distribution isheterogeneous[13].Once a stable, hydrated MLVsuspension has been produced, the particles can bedownsized by a variety of techniques as shown below:

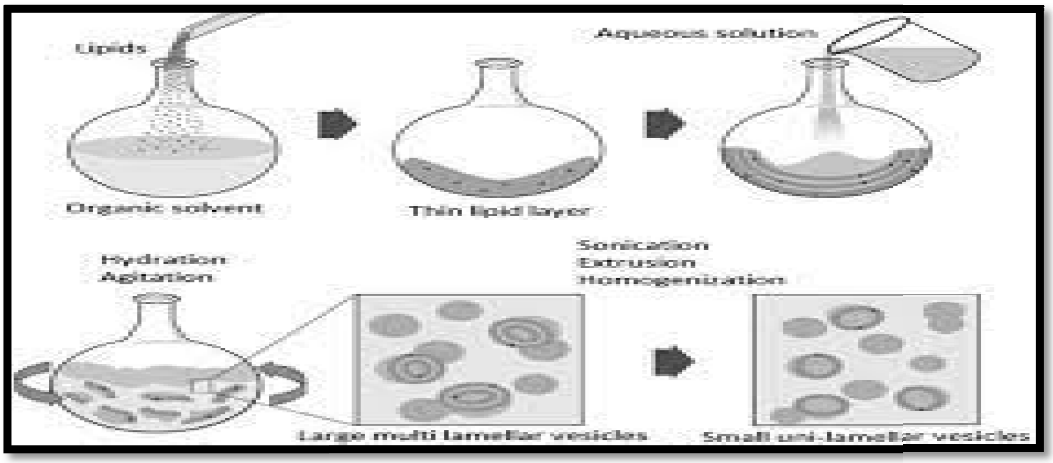

Fig 1: Liposomes prepared by thin layer hydration method

1.1. Sonication
1.2. French pressure cell: extrusion
1.3. Freeze-thawed liposomes
1.5. Micro-emulsification
1.6. Membrane extrusion
1.7. Dried reconstituted vesicles [19,20].

1.1 Sonication Method

The sonication method is based on size transformation andinvolves the subsequent sonication of MLVs prepared by thin-filmhydration method, using sonic energy usually under an inertatmosphere including nitrogen or argon. The sonication method enables homogenous dispersion of small vesicles using bath typeor probe type sonicator with a potential for greater tissuepenetration. The probe tip sonicator delivers high energy to the lipidsuspension.(Fig. 2) The possibility of overheating of the lipid suspensioncauses degradation [14,15,16]. Sonication tips tend to release titaniumparticles into the lipid suspension which must be removed bycentrifugation prior to use. The bath sonicators are the most widelyused instrumentation for preparation of SUV[17,18]. They areused for large volume of dilute lipids. The oxidation of unsaturatedbonds in the fatty acid chains of phospholipids and hydrolysis to lysophospholipids and free fatty acids, as well as denaturation ofthermolabile substances and very low encapsulation efficiency ofinternal volume are the main drawbacks of the method. [19,20]

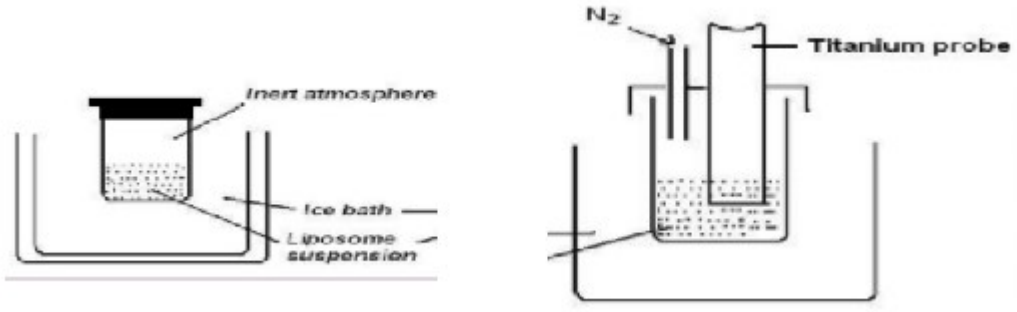

Fig 2: Probe Sonicator and Bath Sonivator

1.2French pressure cell:

Extrusion French pressure cellinvolves the extrusion of MLV through a small orifice. (Fig.3) An important feature of the French press vesiclemethod is that the proteins do not seem to be significantlypretentious during the procedure as they are insonication. An interesting comment is that Frenchpress vesicle appears to recall entrapped solutes significantlylonger than SUVs do, produced by sonication ordetergent removal. [21,22,23,24]

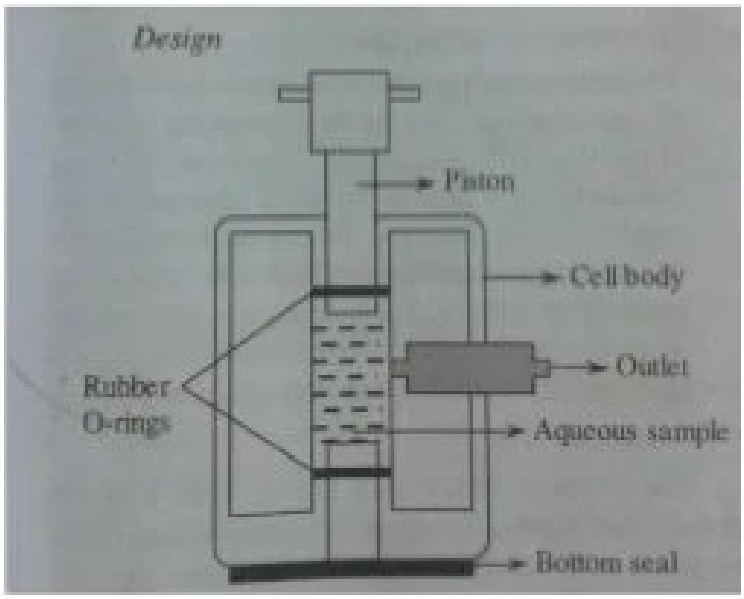

Fig. 3: Liposomes prepared by French Pressure Cell Method

The method involves gentle handling of unstablematerials. The method has several advantages over sonicationmethod. The resulting liposomes are ratherlarger than sonicated SUVs. The drawbacks of themethod are that the high temperature is difficult to attain,and the working volumes are comparatively small(about 50 mL as the maximum) [8,23].

1.3Freeze-thawed liposomes:

SUVs are rapidly frozen andthawed slowly. The short-lived sonication dispersesaggregated materials to LUV. The creation ofunilamellar vesicles is as a result of the fusion of SUVthroughout the processes of freezing and thawing. This type of synthesis is strongly inhibited byincreasing the phospholipid concentration and by increasingthe ionic strength of the medium. The encapsulationefficacies from 20% to 30% were obtained [25-26].

1.4Micro Emulsification

This method is provided for preparing small lipid vesicles in commercial quantities by micro emulsifying lipid compositions using very high shear forces generated in a homogenizing apparatus operated at high pressures at a selected temperature. At least 20 circulations (approximately 10 minutes) but not greater than 200 circulations (100 minutes) are sufficient to produce a micro emulsion of small vesicles suitable for biological application.

1.5 Membrane Extrusion

Liposomes passed through membrane of defined pore size. Lower pressure is required (<100 psi). LUVs as well as MLVs can be processed. Vesicle contents are exchanged with dispersion medium during breaking and resealing of phospholipid bilayers as they pass through the polycarbonate membrane. (Fig. 4) For high entrapment, the water-soluble compounds should be present in suspending medium during the extrusion process.[27]

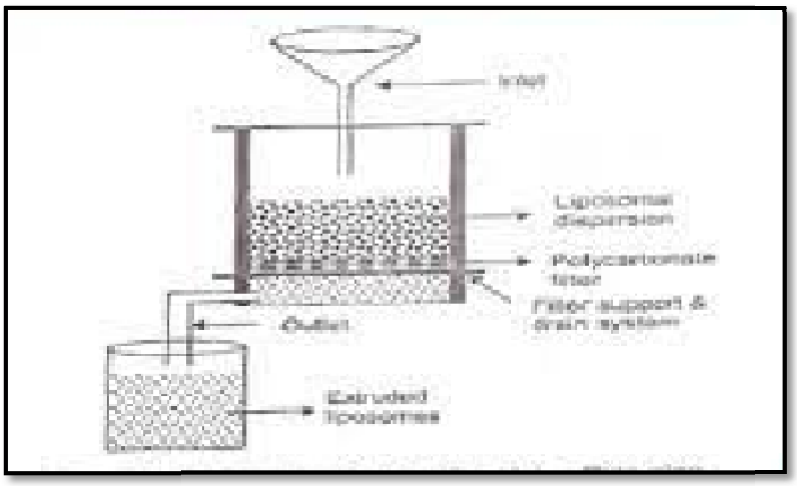

Fig. 4: Liposomes Prepared by Membrane Extrusion Method

2. Solvent Dispersion Methods-

2.1 Ether Injection Method:

A solution of lipids dissolved in diethyl ether orether/methanol mixture is slowly injected to anaqueous solution of the material to be encapsulated at55-65°C or under reduced pressure. The subsequentremoval of ether under vacuum leads to theformation of liposomes. The main drawbacks of themethod are population is heterogeneous (70-190 nm)and the exposure of compounds to be encapsulated toorganic solvents or high temperature.[28]

2.2 Ethanol Injection Method:

A lipid solution of ethanol is rapidly injected to avast excess of buffer. The MLVs are immediatelyformed. The drawbacks of the method are that thepopulation is heterogeneous (30-110 nm), liposomesare very dilute, it is difficult to remove all ethanolbecause it forms azeotrope with water and thepossibility of various biologically active.

2.3.Reverse Phase Evaporation Method:

By briefsonication of a two-phase system containingphospholipids in organic solvent (diethyl ether orisopropyl ether or mixture of isopropyl ether andchloroform) and aqueous buffer emulsion is formed. The organicsolvents are removed under reduced pressure,resulting in the formation of a viscous gel. From that viscous gel complete solvent is remove by rotary evaporator under reduced pressure, it give formation of liposomes. With this method 655 efficacy of highencapsulation can be obtainedin a medium of low ionic strength for example0.01M NaCl. The method has been used toencapsulate small and large macromolecules. Themain disadvantage of the method is the exposure ofthe materials to be encapsulated to organic solventsand to brief periods of sonication. [29]

3. Detergent Removal Method-

The detergents at their critical micelle'sconcentrations have been used to solubilize lipids. Asthe detergent is removed the micelles becomeprogressively richer in phospholipid and finallycombine to form LUVs. The detergents can beremoved by dialysis. A commercial device calledLIPOPREP (Diachema AG, Switzerland) which is aversion of dialysis system is also used to remove the detergents. Other techniques which are used to remove the detergents are (a) by using GelChromatography involving a column of Sephadex G-259 (b) by adsorption or binding of Triton X-100 (adetergent) to Bio-Beads SM-210 (c) by binding ofoctyl glucoside (a detergent) to Amberlite XAD-2beads. The advantages of detergentdialysis method are excellent reproducibility andproduction of liposome populations which arehomogenous in size. The main drawback of themethod is the retention of traces of detergent(s)within the liposomes.[30]

4. Advantages of liposomes-Liposomes offer several advantages in drugdelivery system.

1. Provide controlled drug delivery
2. Biodegradable, biocompatible, flexible and non ionic
3. Can carry both water soluble and lipid soluble drugs
4. Drug can be stabilized from oxidation
5. Controlled hydration
6. Improve protein stabilization
7. Provide sustained release
8. Targeted drug delivery and site-specific drugdelivery
9. Stabilization of entrapped drug fromhospital environment
10. Altered pharmacokinetics andpharmacodynamics
11. Can be administered through various route
12. Act as reservoir of drug
13. Therapeutic index of drug is increased[31]

5. Disadvantages of liposomes-Liposomes offer several advantages but still has some disadvetages as the production cost is high, short half-life, Low solubility,Leakage and fusion of encapsulated drug / molecules and Sometimes phospholipid undergoes oxidation and hydrolysis-like reactions.[32]

6. Application of liposomes-

Both hydrophilic and hydrophobic drugs can be encapsulated in liposomes. Liposomesare also relatively non-toxic and biodegradable**.**Application of liposome in pharmacology and medicine can bedistinguished between diagnostic and therapeutic application ofliposome. That containing various drug or markers, and theiruse as a tool, a reagent or a model in the basic studies ofinteraction of cell, recognition processes, and mode of action ofcertain substances. Unfortunately, many drugs have a verynarrow therapeutic window, meaning is to the therapeuticconcentration is not much lower than the toxic one. In varioucases, the efficacy can be enhanced or the toxicity can bereduced by the use of a suitable drug carrier which alters thespatial and temporal delivery of the drug, i.e., itspharmacokinetics and bio distribution.[33]

6.1.Applications of Liposomes in Cancer:

Liposomes have been successfully used in cancer therapy. A number of different liposomal formulations of anti-cancer agents have been shown to deliver the drug at the site of solid tumors with minimum toxicity as compared to free drug.Currently, there are a many products in the market and in clinical development for use as anti-cancer drug delivery vehicle. Doxil, a PEGylated liposomal formulation, is the first liposomal product that was approved by the FDA for the treatment of kaposi's sarcoma in AIDS patients.[34]

6.2. Treatment of human immunodeficiency virus (HIV) infections by liposomes:

Several antiretroviral nucleotide analogues have beendeveloped for the treatment of patients sufferingfrom the acquired immune deficiency syndromes (AIDS). These include antisense oligonucleotide,which is a new antiviral agent that has shownpotential therapeutic application against HIV-1.[34]

6.3. Topical drug delivery:

The application of liposomes on the skin surface hasbeen proven to be effective. Liposomes increase the permeability of skin forvarious entrapped drugs and at the same timediminish the side effect of these drugs because lowerdoses are now required.

6.4. Enhanced antimicrobial efficacy/safety:

Antimicrobial agents have been encapsulated inliposomes for two reasons. First, they protect theentrapped drug against enzymatic degradation. E.g., the penicillins and cephalosporin aresensitive to the degradative action of J-lactamase, which is produced by certain microorganisms.Secondly, the lipid nature of the vesicles promotesenhanced cellular uptake of the antibiotics into themicroorganisms, thus reducing the effective dose andthe incidence of toxicity as exemplified by theliposomal formulation of amphotericin B.[35]

6.5.Liposomes in parasitic diseases and infections :

From the time when conventional liposomes are digested byphagocytic cells in the body after intravenous management,they are ideal vehicles for the targeting drug molecules intothese macrophages. The best-known instances of this 'Trojanhorse like mechanism

are several parasitic diseases which normally exist in the cell of MPS. They comprise leishmaniasisand several fungal infections.

6.6. Liposome as carrier of drug in oral treatment:

Steroids used for arthritis can be incorporated into largeMLVs. Alteration in blood glucose levels in diabetic animals wasobtained by oral administration of liposome-encapsulated insulin.

6.7. Liposome for pulmonary delivery:

Inhalation devices like nebulizer are used to produce anaerosol of droplets containing liposomes.

6.8. OcularApplication :

The eye is protected by three highly efficient mechanisms (a) anepithelial layer that is a formidable barrier to penetration (b) tearflow (c) the blinking reflex. All three mechanisms are responsible forpoor drug penetration into the deeper layers of the coenea and theaqueous humor and for the rapid wash out of drugs from the corneal
surface. Enhanced efficacy of liposomes encapsulated idoxuridine inherpes simplex infected corneal lesions in rabbits was first reported andconcluded that ocular delivery of drugs couldbe either promoted or impeded by the use of liposome carriers.[35]

6.9. Liposomes in cosmetics:

Developers would now have to deal very intensively with questions of raw material selection, characterization of raw and finished formulations, and clinical safety of
these unique formulations. They suggested that soya phospholipids in the form of
liposomes satisfy many of these
requirements.[35].

7. CONCLUSION

Liposomes have been used in a broad range of pharmaceutical applications and cosmetics arena. Several drug candidates which are highly potent and have low therapeutic indication can be targeted to the required diseased site using the liposomal drug delivery system. Liposomes were the first nanotechnology-based drug delivery systems approved for the clinical applications because of their biocompatibilityand biodegradability like featuresThis review showed that liposomes have beenprepared from a variety of synthetic andnaturally occurring phospholipids Several methods of preparingliposomes were identified, which couldinfluence the particle structure, degree of drugentrapment Furthermore, liposomes are tools for drug targetingin certain biomedical situations and for reducing the incidence of dose-related drug toxicity.

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