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Review of Liposomes as a Drug Delivery System

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ABSTRACT:

Liposome is a micro particulate colloidal vesicle, in which aqueous medium is surrounded by single or multiple concentric layers of phospholipids. Both hydrophilic & hydrophobic drug can be incorporated, water soluble drug being trapped in aqueous core and fat soluble drug in phospholipids. It offers controlled release, targeted drug delivery thus enhanced therapeutic efficacy and reduced dosing frequency.

Amongst various carrier systems, liposomes have generated a great interest because of their versatility. Liposomes not only deliver both hydrophilic and lipophilic medicaments for cancer, immunomodulation, diagnostics, antibiotics, antifungal, opthalmics, aniashamatic, vaccines, enzyme and genetic modification, but also gives wide choice of delivery like pulmonary, oral, vaginal, brain, transdermal, systemic, vaccine and antigen delivery with advantage of low cost, greater stability, purity of raw material, ease of storage. Although there are certain factors and hurdles that affect the development of liposome drug delivery system. About 40 years has been passed but still the delivery system is on R & D scale and only few countable liposome products have been reached to market.

1. INTRODUCTION-

When phospholipids are dispersed in water, they spontaneously form closed structure with internal aqueous environment bounded by phospholipid bilayer membranes, thus forms vesicular system called as Liposomes. About 40 years ago Bangham and co-workers defined Liposomes as the small vesicle of spherical shape that can be produced from cholesterols, non toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane protein., which has become the versatile tool in biology, biochemistry and medicine today. In 1960s, liposome has been used as a carrier to deliver a wide variety of compounds in its aqueous compartment. They can encapsulate and effectively deliver both hydrophilic and lipophilic substances,and may be used as a non-toxic vehicle for insoluble drugs.Liposome can be formulated and processed to differ in size, composition, charge and lamellarity. The most important use of liposomes expected to be in biotechnology, medicine and pharmacology, where they serves as vehicles for controlling delivery of entrapped medicament viz. immunomodulator, cancer hemotherapeutics, diagnostics, antibiotics, antifungal, opthalmics, aniashamatic, vaccines, enzyme and genetic material. Till the date liposomal formulations of antitumor drugs and antifungal agents have been commercialized on large scale. In coming years one sees an enormous potential in liposome manufacturing as more and more industrial manufacturing methods are developed. Though there are many hurdles in their formulation and developments, which are not negligible. The source of the lipids and stability of the phospholipids, which are considered critical excipients, plays a key role in the characterization of product performance. Moreover, its clinical use has found limited application due to the remarkable barrier properties of the stratum corneum, the outermost layer of skin (1)

1.1. History of the Liposome

The story of success of liposomes was initiated by Bangham and his colleagues in the early 1960s who observed that smears of egg lecithin reacted with water to form quite intricate structures. They were analyzed by electron microscopy showing that a multitude of vesicles were formed spontaneously. These more or less homogenous lipid vesicles were first called smecticmesophases. Later on, a colleague of Bangham termed them—more euphoniously liposomes. The physiochemical characterization of liposomes had been carried out in 196875. Moreover, thin lipid film hydration method had been developed to prepare multilamellar vesicles . Liposomes were widely used to study the nature of biological membrane because of close resemblance of bi-layered membrane with the biological membrane. During the late 1970s and early _80s, liposomes were re-engineered to maintain their stability so they could circulate in the blood for longer periods of time. While this was accomplished and stealth™ liposomes – ideal for delivering pharmaceutical drugs directly to cells - were developed, they remained very difficult to produce on a large scale. In 1975 – 85Liposome's utility was improved following basic research that increased the understanding of their stability and interaction characteristic within the system . This period also dealt with the discovery of various alternative methods for the preparation of liposomes. Also, due to the availability of vast knowledge about physio-chemical properties of liposomes, their behaviour within the body, their interaction with the cells, attempts had been made to improve their performance as drug carrier systems . The development of liposomal drugs with clinical utilityrelied on the development of techniques, which allowed the rapid generation of homogeneous small liposomes and efficient accumulation of drugs into liposomes. This was made possible by the extrusion technique and the pH gradient loading

techniques, which were developed in the late 1980s and early 1990s. The first liposomal drug formulation on the US market was the anticancer drug doxorubicin encapsulated in sterically stabilised liposomes [Doxil®]. Doxil® was approved by the FDA in 1995. It should be noted that it can take between 5 -10 years and 50 - 100 million US dollars to bring a liposomal drug from the research and development stage to the market. Today, liposomes are used successfully in various scientific disciplines, including mathematics and theoretical physics [topology of twodimensional surfaces floating in a three dimensional continuum], biophysics (properties of cell membranes and channels), chemistry [catalysis, energy conversion, photosynthesis], colloid science [stability, thermodynamic of finite systems], biochemistry [function of membrane proteins] and biology [excretion, cell function, trafficking and signal, gene delivery and function]. Ambisome TM, a parenteral amphotericin-B based liposomal product was first in the race, followed by number of other products which areeither at the stage of clinical trials or are already in the market. Moreover, renaissance in the liposome research is promising many more products tocome in the near future. (2)

1.2ADVANTAGE

- They offer targeted drug delivery.
- They are biocompatible, biodegradable and biologically inert.
- They are nonantigenic, nonpyrogenic and nontoxic.
- They can encapsulate both water soluble and water insoluble drugs.
- Drug toxicity is removed as other tissues and cells are protected.
- Cellular uptake of drug is enhanced.
- Size can be varied to incorporate smaller or larger drug molecules.(3)

1.3. Disadvantages

- Short half-life.
- Low solubility.
- Leakage and fusion of encapsulated drug/ molecules.
- Production cost is high.
- Fewer stables.
- Sometimes phospholipids undergo oxidation and hydrolysis-like reaction(4)

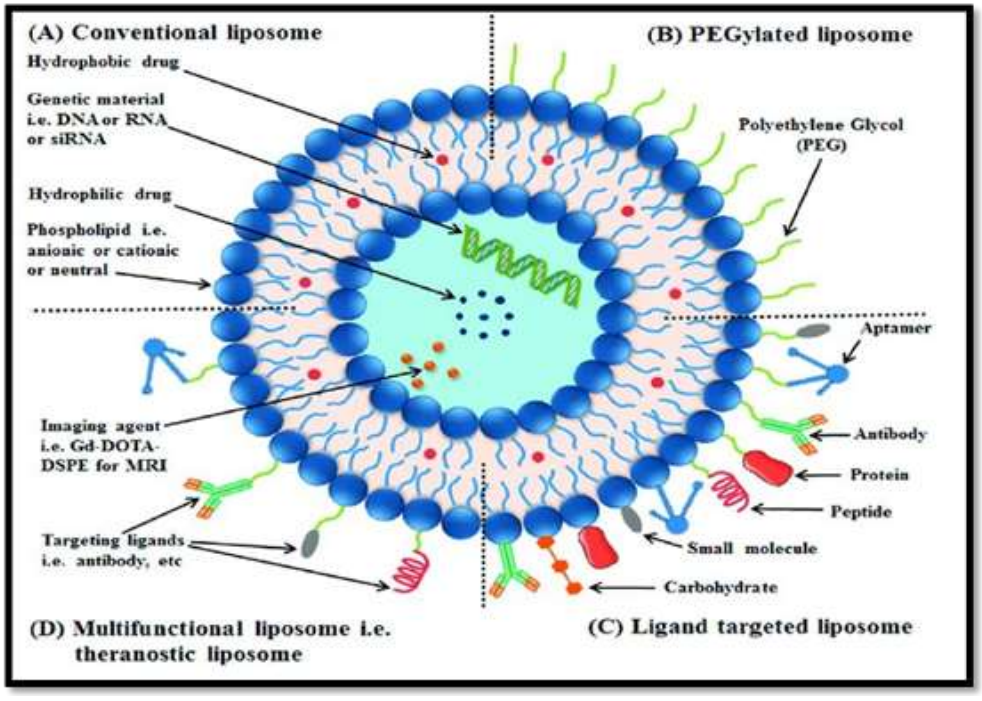

Fig no 1 Liposome

2. MECHANISM OF ACTION OF LIPOSOMES

1. Endoytosis - This take place by phagocytic cells of reticuloendothelial system such as neutrophils.

2. Adsorption - It occurs to the cell surface by nonspecific electrostatic forces or by interaction with cellsurface components.

3. Fusion- It occurs by the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm.

4. Lipid exchange- In this transfer of liposomal lipids to the cellular membrane without association of liposomal contents.(3)

3. Components of liposomes

3.1. Phospholipids

Glycerol containing phospholipids are most common used component of liposome formulation and represent greater than 50% of weight of lipid in biological membranes. These are derived from phosphatidic acid. The back bone of the molecule is glycerol moiety. At C3 position OH group is esterified to phosphoric acid. OH at C1 & C2 are esterified with long chain. Fatty acid giving rise to the lipidic nature. One of the remaining OH group of phosphoric acid may be further esterified to a wide range of organic alcohols including glycerol, choline, ethanolamine, serine and inositol. Thus the parent compound of the series is the phosphoric ester of glycerol. Examples of phospholipids are –

- Phosphatidyl choline (Lecithin) – PC
- Phosphatidyl ethanolamine (cephalin) – PE
- Phosphatidyl serine (PS
- Phosphatidyl inositol (PI)
- Phosphatidyl Glycerol (PG) For stable liposomes, saturated fatly acids are used. Unsaturated fatty acids are not used generally.(5)

3.2. Cholesterol

Typically, liposomes prepared by using only phospholipids are not sufficiently rigid primarily because of low phase transition temperature and/or unsaturation in the fatty ally! Irmal of Deng Daly & Therapies 2921,1115-3) 19chains creating defects in the cell membrane like packaging Dung packaging those liposome's leak the encapmalated drug One or two bilayer stabiliters are also used in most Tipoume formulation in order to avoid such leakage. The additives more widely used are cholesterol and alpha tocopherol Lipencaptation quality varies with variations in the composition of the phospholipid bilayer Cholster is indeed an abonistely vital component of natural lipid bilayers and its presence in bilayer liposomes induces drastic alteration in their characteristics Cholesterol by itself doesn't develop hatayer complexes, but can be integrated into high coscentrations of phosphoped membranes. Rigility is enhanced due to compact stacking of the layers, and permeability of water soluble molecules is roduce. By during hilayer pormeabilty, cholesterol enhances the durability of hydrophite drugs. Cholesterol reduces the flaidity above the phase transition temperature (Tc) to make the bilayer more ordered. The tricydic ring i wedged among the first few carbons of the fatty acyl chains and the hydroxyl group is exposed to the liquid phase, the cholesterol molecule fits in with the phospholipid molecules and orients itself among them. At very significant concentrations, cholesterol to phospholipids ratios if up to 1:1 or even 21 can be incorporated into the cellular membrane. Albumin, macroglobulin, and m-transferrin are blood proteins that intrat mars sasily and frequently with cholesterol-free liposomes enabling the vesicle to become unstable as a result its usage as a therapeutic delivery method has declined.(6)

4. Classification

Liposomes classifed into unilamellar, multilamellar, oligolamellar, and multi vesicular vesicles based on the number of phospholipid bilayers, . Various types of liposomes along with their particle sizes are given . The desirable size of liposomes for drug delivery applications ranges from 50 to 200 nm .Liposome size is the major factor for efcient delivery of drugs into the body. The size of liposomes shows signifcant efect on the pharmacokinetics of liposomes and drugs encapsulated into the liposomes. The size of liposomes less than 200 nm shows increased circulation and residence time f liposomes in the blood, enhanced in vivo drug release rom liposomes and signifcant accumulation into the tumour cells .(7)

4.1. Multilamellar vesicles (MLV)

MLV have a size greater than 0.1 µm and consist of two or more bilayers. Their method of preparation is simple, which includes thin – film hydration method or hydration of lipids in excess of organic solvent. They are mechanically stable on long storage. Due to the large size, they are cleared rapidly by the reticulo-endithelial system (RES) cells and hence can be useful for targeting the organs of RES [3]. MLV have a moderate trapped volume, i.e., amount of aqueous volume to lipid ratio. The drug entrapment into the vesicles can be enhanced by slower rate of hydration and gentle mixing . Hydrating thin films of dry lipids can also enhance encapsulation efficiency . Subsequent lyophilization and rehydration after mixing with the aqueous phase (containing the drug) can yield MLV with 40% encapsulation efficiency (8)

4.2. Unilamellar vesicles-

- Small unilamellar vesicles (SUV) (Size- 40-80nm)
- Medium unilamellar vesicles (MUV)(Size -40-80 nm)
- Large unilamellar vesicles (LUV)(Size100 nm-1,000 nm)

4.3. Oligolamellar vesicles (OLV)-

OLVs are made up of 10-20 lipid bilayers enclosed by internal volume.(9)

5. Method of liposome preparation and drug loading:

The following are used for the preparation of liposome:

1. Passive loading technique
2. Active loading technique.

5.1. Passive loading techniques **–**include three different methods:

1. Mechanical dispersion methods method.
2. Solvent dispersion method.
3. Detergent removal method.

5.1.1. Mechanical dispersion method:

Sonication:

Sonication is probably the most widely used method for creating an SUV. Here, MLV, Sonication is performed without a bath-type sounder or probe sounder in an inactive environment. The main drawbacks of this process are the presence of a very low internal volume / disability efficiency, the possibility of compiling phospholipids and compounds, the elimination of large molecules, probe scores, and metal pollution MLV with SUV13. There are two Sonication techniques:

Probe Sonication:

The note of the sonicator is direct indirect dispersion in the liposomes. The energy input into the lipid dispersion is much higher in this method. The energy connection at the tip generates local heat; therefore, the texture must be mixed with water / ice during lowing. Up to 1H, up to 5% of lipids can be de-activated. In addition, with the sonicator probe, Titanium will be released and the solution polluted. **A) Bath Sonication:**

The dispersion of liposomes in the cylinder is placed in a sniper bath. Controlling the temperature of the lipid dispersion is generally easy in this process, against the Sonitake using an active tip. Ultrasound treated material can be stored in sterile texture, under probe units or in an inert environment..(10)

5.1.2 Solvent dispersion methods:

Ether injection method:

This method involves dissolution of lipids in diethyl ether or ether/methanol. This lipid mixture is then injected into an aqueous solution containing material to be encapsulated. This is performed at a temperature of 55-65ºC or under reduced pressure. Evaporation of organic solvent is bought about by vacuum application. Finally, liposomes are obtained which is shown in fig 7.

Ethanol injection method:

Ethanol solution containing lipids is injected into excess of saline or aqueous solution through fine needle. Then mixing is done to produce SUVs

Reverse phase evaporation technique:

This method is generally used to encapsulate RNA and various enzymes. This technique involves injection of aqueous solution of drug into an organic solvent containing lipid followed by sonication of the biphasic mixture. This leads to the formation of water-in-oil type of emulsion. Later, the emulsion is dried in a rotary evaporator to obtain semisolid gel. The gel is then agitated mechanically due to which phase inversion occurs i.e., water-in-oil turns to oilin-water type of emulsion. During the process of agitation, some of the water droplets collapses to form the external phase, while remaining portion forms the entrapped aqueous volume .(11)

5.1.3. Detergent removal method-

Dialysis

The detergent at their critical Michelle concentration (CMC) is used to solubilize lipids. The detergent is detached, the micelles in phospholipid and last combine to form LUVs. The detergent can be removed by dialysis. The main benefit of detergent dialysis method is formation of liposome populations which are homogeneous in size. The main disadvantages of this method are possibility of retention of traces of detergents into the liposome.

Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption)-

Detergent absorption is attained by shaking of mixed micelle solution with beaded organic polystyrene absorbers such as XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Biobeads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA). The benefit of detergent absorber is removal of detergent at very low DilutionThe dilution of aqueous mixed micellar solution of detergent and phospholipids with buffer. The size ofmicellar and polydispersity is fundamentally increase.(12)

5.2. Active loading technique

5.2.1 Proliposome

Lipid and drug are coated onto a soluble carrier to form free-flowing granular material in proliposome which forms an isotonic liposomal suspension on hydration. The pro-liposome approach may provide an opportunity for cost-effective large scale manufacture of liposomes containing particularly lipophilic drugs.

5.2.2. Lyophilization

The removal of water from products in the frozen state at extremely reduced pressure is called lyophilization (freeze drying). The process is generally used to dry products that are thermolabile which may be destroyed by heat-drying This technique has a great potential to solve long term stability problems with respect to liposomal stability.Leakage of entrapped materials may take place during theprocess of freeze-drying and on reconstitution.(13)

6. CURRENT APPLICATIONS OF LIPOSOMES

Liposomes have demonstrated a wide range of applications in clinical settings. These applications ranged from therapeutic and diagnostic to, most recently, theranostic applications In this section, we summarize the potential application of liposomes in each field separately.

6.1. Therapeutic Applications of Liposomes:

A mounting body of literature has defined the viability of formulating a wide range of drugs in liposomes taking advantage of improved therapeutic efficacy and/or reduced systemic toxicity of the encapsulated drug compared with the free counterpart. Generally, alteration of the pharmacokinetics of liposomal drugs, via encapsulation, can lead to prolonged blood circulation characteristics, enhanced drug bioavailability, and/or preferential accumulation in disease sites.(14)

6.2. Clinical Application-

- Cancer chemotherapy.
- Gene therapy.
- Liposomes for topical application.
- Liposomes as a carrier of the drug in oral treatment.
- Liposomes for pulmonary delivery.
- Against leishmaniasis.
- Cell biological application.
- Metal storage disease.
- Ophthalmic delivery of drugs.(15)

6.3. Multi-functional, multi-component formulations-

Increasingly, the formulation and use of multi-functional, multi-component liposomal nanoparticles, sometimes referred to as theragnostics, is being explored — formulations that carry within an individual lipidic nanoparticle functions such as site-specific targeting, biomarker and imaging capabilities, delivery of combinations of therapeutics, and response to external or internal triggers to control drug release.(16)

6.4. Immunological adjuvants in vaccines-

Liposomes can be used for enhancing the immune response by encapsulating the adjuvants. Depending on the lipophilicity of antigens, the liposome can accommodate antigens in the aqueous cavity or incorporate within the bilayers. To enhance the immune response of diphtheria toxoid, liposomes were first used as immunological adjuvantsStealth liposomes contain few biological species as a ligand to enable binding with specific expression on the drug delivery site (targeted site) in addition to PED coating. These targeting ligands could be, vitamins, specific antigens or monoclonal antibodies (making an immuno-liposome), but it must be available. Naturally toxic drugs can be less toxic systemically if delivered to the diseased tissues or site. Ligands used for targeting to lungs for treatment of tuberculosis include maleylated bovine serum albumin (MBSA) and O-steroyl amylopectin.

Transfersomes (a type of liposomes) are highly deformable vesicles, used for transdermal material delivery (non-invasive method) . Doxorubicin (Doxil) and Daunorubicin (anticancer drugs) may be given via liposomes. Liposomes is used in cancer therapy, since cancer cells have overexpressed folate and transferrin receptors, making transferrin and folic acid as suitable ligands [32]. Other ligands used in cancer therapy are peptides and antibodies against VEGF, VCAM, matrix metalloproteases (MMPs), integrins etc. A recent Phase I/II study evaluating the safety and efficacy of a novel neoadjuvant combination treatment of paclitaxel, pegylated liposomal doxorubicin, and hyperthermia to treat locally advanced breast cancer. A phase II clinical trial of pegylated liposomal doxorubicin and carboplatin in Japanese patients with platinumsensitive recurrent ovarian, fallopian tube or primary peritoneal cancer. Its combination chemotherapy is done to treat patients .with platinum-sensitive recurrent ovarian cancer. The thermosensitive liposomal formulation ThermoDox®(Celsion Corporation, Lawrenceville, NJ), which contains lysophosphatidylcholine and is employed in the treatment of various cancers including primary liver cancer, recurrent chest wall breast cancer, colorectal, pancreatic and metastatic liver cancer, is currently in various stages of human clinical trials (Phase II/III) [.Lipoplatin is developed recently by using cisplatin as a carrier for treating cancer .Escheriosomes (a type of liposomes) prepared from lipids (polar) {obtained from the Escherichia coli} have shown high cytotoxic T lymphocyte (CTL) responses to deliver their entrapped molecules right into the cytosol of the APCs (Antigen Presenting Cells) .(17)

Conclusion-

The potential use of liposomes in man necessitates the production of sterile, pyrogen free preparations of liposomes which requires specific conditions for their preparation. For use as drug carriers, liposomes should be able to fuse with the arbitrary cells in a spontaneous and controllable manner. One major drawback of liposomal drug delivery system is poor encapsulation of certain drugs in which case the drug is derivise Application of liposomes medicine include encapsulation of both Lipid and water soluble drugs. Apart from use as drug carrier perhaps the most promising immunological property of liposomes is their cation as adjuvants. The development of 'pharmaceutical' liposomes is currently a growth area.

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