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Review Article

LIPOSOMES: AN ADVANCE TOOLS FOR NOVEL DRUG DELIVERY SYSTEM

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Abstract: Use of liposome-encapsulated enzymes for delivery into cells was first reported in 1971. About the same time, a specific receptor on hepatocytes was demonstrated to mediate clearance of ß-galactose–terminated glycoproteins from circulation. A mannoside-specific receptor was recognized on the cell surface of the RES of rats (including the liver sinusiod and macrophages). Liposomes are microscopic vesicles composed of a bilayer of phospholipids or any similar amphipathic lipids They can encapsulate and effectively deliver both hydrophilic and lipophilic insoluble drug, because lipids are amphiphatic (both hydrophilic and hydrophobic) in aqueous media, their thermodynamic phase properties and self assembling characteristics evoke entropically driven sequestration of their hydrophobic regions into spherical bilayers are referred as lamellar. It provides controlled drug delivery. It should be biodegradable, biocompatible, and flexible, non ionic, can carry both water and lipid soluble drugs. Liposomes have been used to deliver anticancer agents in order to reduce the toxic effects of the drugs when given alone or to increase the circulation time and effectiveness of the drugs.

Key words: Liposome, controlled drug delivery, phospholipid

INTRODUCTION:

Today, clinical medicine possesses an extremely long list of different pharmaceutical products and every year many new drugs are added to the list with the understanding of molecular mechanisms of diseases. Scientists and physicians are never satisfied only with a favourable drug action against the disease under treatment. The task of avoiding undesirable drug actions on normal organs and tissues and minimizing side effects of the therapy is very important. Thus, screening of biologically active compounds became necessary, permitting the choice of drug with selective action on the appropriate organs or tissues. At the same time, many pharmacologically effective compounds cannot be used as drugs due to their undesirable action on normal tissues. Their specificity for the drug of choice is not based on their ability to accumulate selectively in the target organs.[1] normally, they are more or less evenly distributed in the whole body and to reach the target zone the drug has to cross many other organs, cells, intracellular compartments *etc.*, where it can be partially inactivated. To overcome this problem, a high concentration of drug has to be administered, which has a potential to cause undesirable complications and is sometimes expensive too. The ideal solution to such problems is the targeting of drugs using suitable carriers like serum proteins, immunoglobulins, synthetic polymers, liposomes, niosomes, microspheres, erythrocytes, reverse micelles, pharmacosomes, monoclonal antibodies, *etc.*[2]

DEFINITION:

Liposomes are defined as structure consisting of one or more concentric spheres of lipid bilayers separated by water or aqueous buffer compartments. (OR) Liposomes are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid bilayers. This represents a multilamellar liposome. It contains many layers of phospholipids with water in between the layers.[3]

DISCOVERY OF LIPOSOME:

Liposome was discovered about 40 years ago by Bangham and co-workers. This was an accidental discovery, when he dispersed Phosphatidyl choline molecules in water; he found that it was forming a closed bilayer structure containing an aqueous phase entrapped by lipid bilayers. It was defined as microscopic spherical vesicles that form when phospholipids are hydrated or exposed to an aqueous environment. Liposomes are microscopic vesicles composed of a bilayer of phospholipids or any similar amphipathic lipids.[4] They can encapsulate and effectively deliver both hydrophilic and lipophilic insoluble drug, because lipids are amphiphatic (both hydrophilic and hydrophobic)in aqueous media, their thermodynamic phase properties and self assembling characteristics evoke entropically driven sequestration of their hydrophobic regions into spherical bilayers are referred as lamellar. liposomes vary in charge and size depending on the method of preparation and the lipids used the multi lamellar vesicle [MLV] size range is0.1-5.0micrometres.the small unilamellar vesicle [SUV] size range is 0.02 0.05micrometres,and the large unilamellarvesicle [LUV] size range varies from0.06micrometre and greater. [5]

Advantages: [6]

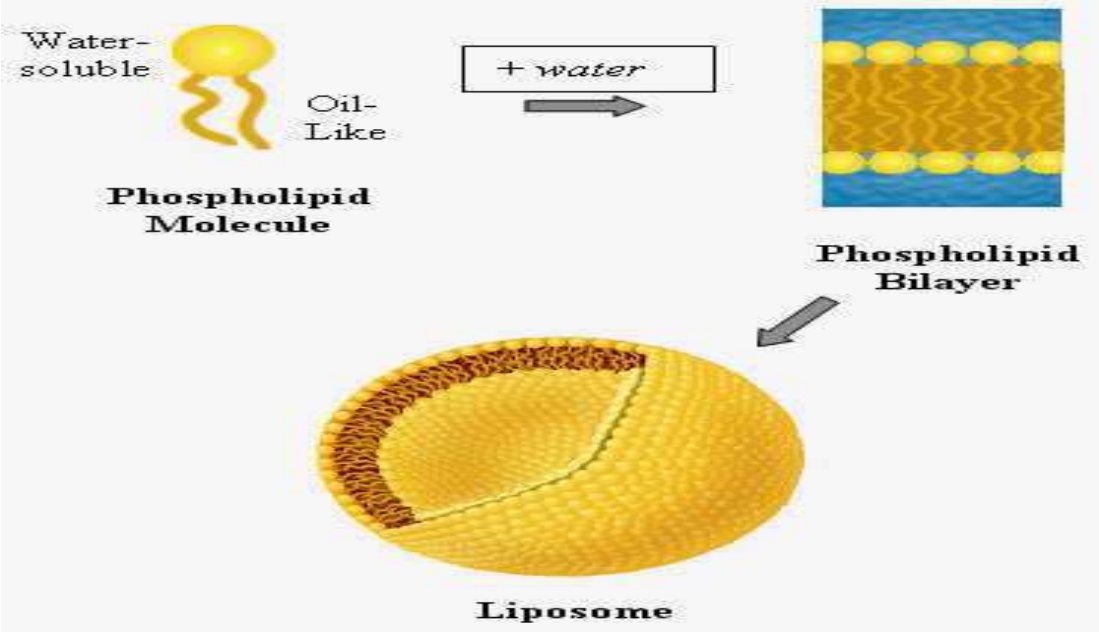
It provides controlled drug delivery.

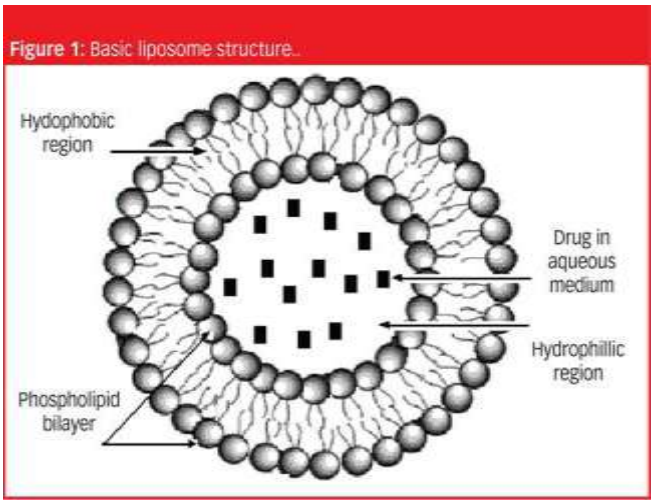
- It should be biodegradable, biocompatible, and flexible.
- It should be non ionic.
- It can carry both water and lipid soluble drugs.

- The drugs can be stabilized from oxidation.
- It should be improve the protein stabilization.
- It provides controlled hydration.
- It provides sustained release.
- It provides targeted drug delivery or site specific drug delivery.
- Stabilization of entrapped drug from hostile environment.
- Alter pharmacokinetics and pharmacodynamics of drugs.
- It can be administered through various routes.

Structure of Liposomes:

Liposomes are spherical lipid bilayers from 50nm to 1000 nm diameter that serve as convenient delivery vehicles for biologically active compounds. The field of liposome research has expanded considerably over the last 30 years. It is now possible to wide range of liposomes varying in size, phospholipid composition and surface characteristics to suit the specific application for which they are intended. This paper gives an overview of the main advances in liposome research from a point of view of their applications in medicine.[7]





Classification of Liposomes:

Liposomes can be classified either on the basis of their structural properties or on the basis of the preparation method used.

Liposome classification based on structural features:

MLV Multilamellar large vesicles
OLV Oligolamellar vesicles
UV Unilamellar vesicles
SUV Small unilamellar vesicles
MUV Medium sized unilamellar vesicles
LUV Large unilamellar vesicles
GUV Giant unilamellar vesicles
MVV Multivesicular vesicles

Liposome classification based on method of liposome preparation:

REV Single or oligolamellar vesicle made by reverse phase evaporation method
MLV / REV Multilamellar vesicles made by reverse phase evaporation method

SPLV	Stable plurilamellar vesicles
FATMLV	Frozen and thawed MLV
VET	Vesicles prepared by extrusion method
FUV	Vesicles prepared by fusion
FPV	Vesicles prepared by french press
DRV	Dehydration- rehydration vesicles
BSV	Bubblesomesa

Techniques of Liposome Preparation:

There are three stages for liposomes preparation

1) **Hydration stage:**

a) Mechanical Methods: MLVs were traditionally produced by hydrating thin lipids films deposited from an organic solution on a glass wall by shaking at temperatures above the phase transition temperature of the phospholipid with the highest Tc. The wide size distributions of the produced liposome dispersions were usually narrowed down by (low) pressure extrusion or ultrasoncation.[8]

b) Methods based on replacement of organic solvent by aqueous media: The lipid constituents are first dissolved in an organic solvent which is subsequently brought in contact with an aqueous phase. The organic solvent is removed later. During the removal of the organic phase, liposomes are formed. Their characteristics (size, organisation of bilayers) depend on the protocol used. If the organiic solvent with the dissolved lipids is not miscible with the aqueous phase (ether, chloroform, freons), then the intrmediate stage is an emulsion (immiscible solvent). Other organic solvents containing the dissolved lipid (s) can be mixedhomogenously with the aqueous phase (ethanol) in the first stage. Then lipoosmes formation occurs when the organic solvent concentration drops below a certain critical value (miscible solvents). The contents of residual organic solvent that is exceptable in the finished product depends on the solvent in question and the route of administration.[9]

c) Methods based on detergent removal: (Phospho) lipids, lipophilic compounds and amphiphatic proteins can be solubilized by detergents forming mixed micells. Upon removal of the detergent, vesicle formation can occur. This technique is well established for preparation of reconstituted virus envelopes[10] or reconstituted tumor membrane material.[11]Schreier and coworkers described a two step strategy for insertion of proteins into the outer layer of liposomes. First liposomes were formed by detergent dialysis method and subsequently proteins were inserted by partial resolubalization of the membrane by the detergent (deoxycolate) inthe presence of protein.[12]

d) Method based on size transformation and fusion : Sonication of phospholipds below their phase transition temperature (Tc) results in vesicles with defects in the bilayers. Heating the dispersion to Tc eliminates these structural defects and causes fusion resulting in large unilamellar liposomes with a wide size distribution.[13]

2) **Sizing stage**

There are two approaches, one without a special sizing step A and one with a special sizing step B

A-In liposome formation process, circumstances are selected and controlled in such a way that particle size distributions with an acceptable width are produced. High shear homogenization produces a size distribution which depends on operational pressure.[14,15]

B-For small dispersion volumes, the liposome dispersion can be fractionated by centrifugation as liposome density usually differs from the density of the medium. Gel permeation chromatography has also been used for subdividing wide particle size distribution. On an analytical or semi-preparative scale, the selection of the pore size of the chromatographic material provides an opportunity to manipulate the size class resolution within certain limits.[16]

3) **Removal of nonencapsulated material**

Many lipophilic drugs exhibit a high affinity to the bilayer and are completely liposome associated. However, for other compounds, the encapsulation efficiency is less than 100 percent. The nonencapsulated fraction of the active compound can causeunacceptable side effects or physical instability.[10] For removal of nonencapsulated material, the following techniques are used : a) dialysis and ultracentrifugation, b) Gel permeation chromatography, c) Ion exchange reactions.

Liposome for targeted delivery:

Use of liposome-encapsulated enzymes for delivery into cells was first reported in 1971. About the same time, a specific receptor on hepatocytes was demonstrated to mediate clearance of ß-galactose–terminated glycoproteins from circulation. A mannoside-specific receptor was recognized on the cell surface of the RES of rats (including the liver sinusiod and macrophages). By grafting different glycosides on the surface of liposomes, it is possible to direct the latter to different cell types of rat liver.[17] Galactosylated liposomes are mainly taken up by liver hepatocytes, whereas mannosylated liposomes are mainly taken up by nonparenchymal cells.[18] Grafting specific ligands to the liposome surface facilitates a fusion of the liposome with target cells by endocytosis, thus releasing material to be delivered. In cancer chemotherapy, the toxicity of anticancer drugs is of major concern. Liposomes could be used to deliver such drugs and minimize their toxic effects on healthy cells. Targeted delivery to cancer cells could be achieved by coating monoclonal antibodies (MAbs) raised against tumor-cell specific antigens. In vitro and in vivo studies by Ahmad et al. of squamous-cell carcinoma in mouse models provided evidence that antibody-coated polyethyleneglycol liposomes containing doxorubicin were more effective and less toxic than free drugs, drugs incorporated into antibody-free liposomes, and antibodycoated conventional liposomes.[19] The major concern in antibody-grafted liposome use is the induction of immune response to the grafted antibodies. Basten et al. suggested a novel approach to overcoming that difficulty.[20] They used 125I-labeled antigen to kill the cells responsible for immune induction (the "antigen suicide" technique). Other possible approaches to overcome the immune-system problem include immunosuppressive drugs and humanized antibodies or establishing neutral immune windows for subsequent injection. Liposomes can be designed to release

their entrapped contents under certain controlled conditions: pH-sensitive and temperature-dependent liposomal systems.[21] Drug targeting using liposomes as carriers holds much promise, especially in reducing toxicity and targeting delivery to disease sites. The future is bright for liposome research, with a large number of clinical trials ongoing in several countries with liposomal formulations of various anticancer drugs, cytokines, peptides and proteins. In the near future, several more liposome-based drugs will find their way into the pharmaceutical market.

CONCLUSION:

From the above article it is concluded that the considering the advantages of this Novel drug delivery system. A novel technology has been developed by which water-soluble substances can be solubilized in the absence of water into oils. The formation of anhydrous reverse micelles might play an important role in the solubilization and the resulting oil solutions are physically and chemically stable. Liposomes have developed into a viable pharmaceutical dosage form. Progress has taken place in quantum leaps, rather than in a continuum, over the last two decades. Vital progress have been made in the development of long circulating liposomes that are not immediately recognized and removed by the cells of mononuclear phagocyte system.

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