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REVIEW ARTICLE

LIPOSOMES IN DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Amongst various medicament carrier systems, liposomes have generated a great interest because of their versatility. Liposomes not only used in delivery of both hydrophilic and lipophilic medicaments for cancer, diagnostics, antibiotics, antifungal, opthalmics, enzyme and vaccine, but also provide wide choice of delivery of medicament to various routes like pulmonary, oral, vaginal, brain, transdermal with advantage of low cost, greater stability, purity of raw and ease of storage. Liposomes are one among the various drug delivery systems used to target the drug to the particular tissue. Because there is a structure similarity between the lipid bilayer and cell membrane, liposome can penetrate effectively deliver drug such that a free drug would not penetrate.

The success of liposomes as drug carrier has been reflected in a number of liposome-based formulation, which are commercially available or are currently undergoing clinical trials.

KEYWORDS: Liposomes, structural component of liposomes, preparation of liposomes.

INTRODUCTION:

The method by which a drug is delivered to the diseased organ can have a significant effect on its efficacy. Some of the 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. On the other side, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, and efficacy of drugs were generated. The new strategies, often called drug delivery systems (DDS), which are based on some approaches that combine polymer science, pharmaceutics and molecular biology. To minimize the drug degradation and loss or to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among some of the drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, lipoproteins, liposomes, and micelles. These carriers can be made slowly degradable and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest)[1]. Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. The example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumour tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. As the ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest. Improving delivery techniques that minimize toxicity and improve efficacy offers the great potential benefits to patients, and opens up the new markets for pharmaceuticals and drug delivery companies. Liposomes are the sub-micron particles that are finding important applications in fields such as biotechnology (in applications like siRNA delivery, antibody delivery), cosmetology (emulsions and creams etc.) and the pharmaceutical industry (chemotherapeutic delivery)[2]. The Liposomes are composed of phospholipids bilayer have a polar end attached to a non-polar chain. When these phospholipids are introduced into an aqueous medium, they self-assemble into bilayer vesicles with the polar ends facing the aqueous medium and nonpolar ends forming a bilayer[3]. In pharmaceutical applications the active molecule or drug is usually incorporated into liposome either into the hydrophilic pocket or sandwiched between the bilayers depending on the hydrophilicity or lipophilicity of the drug. Chemotherapeutics such as Paclitaxel and Doxorubicin have been used to treat cancers of various kinds for over two decades.

Drugs which are encapsulated within a nanocage are functionalized with channel of proteins are effectively protected from premature degradation by some

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proteolytic enzymes. The drug molecule is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage. Liposomes have distinct many advantages of being both nontoxic and biodegradable because they are composed of naturally occurring substances. Biologically active materials or drugs encapsulated within liposomes are protected to varying extent from immediate dilution or degradation, suggesting drug carrier systems for the transport of drugs and other bioactive capsules to disease-affected organs or to the targeted site[4,5]. The unique property of the liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs. Because of advancements in the methods of preparing and formulating liposomes, high-entrapment efficiencies are possible for incorporating drugs into liposomes that create a tremendous pharmaceutical impact. Furthermore, such encapsulation has been shown to reduce drug toxicity while retaining or improving the therapeutic efficacy[6].

CLASSIFICATION OF LIPOSOMES:

Liposomes can be classified on the two bases either on the basis of their structural properties or on the basis of the preparation method used. These two classification system are independent of each other.

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)

CLASSIFICATION BASED ON METHOD OF 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 (Bubblesomes)

STRUCTURAL COMPONENTS OF LIPOSOMES:

1) PHOSPHOLIPIDS:

Glycerol containing phospholipids are the most common components of the liposomes and represent 50% of the weight of lipids in biological membrane. These are derived from phosphatidic acid. The backbone of the molecule is glycerol moiety. For stable liposomes saturated fatty acids are used

Examples of some phospholipids are:

- Phosphatidyl choline (lecithin)
- Phosphatidyl ethanolamine (cephalin)
- Phosphatidyl serine
- Phosphatidyl inositol
- Phosphatidyl glycerol

2) SPHINGOLIPIDS:

The backbone of liposomes is sphingosine or a related base. Sphingosines are the important constituents of plant and animal cells. The most common Sphingolipids are Sphingomyelin and Glycosphingolipid. These contain 3 characteristic building blocks.

- A molecule of fatty acid.
- A molecule of sphingosine.
- A head group that may be a simple alcohol like choline or a very complex carbohydrate.

3) STEROLS:

In sterols cholesterol and its derivatives are included in liposomes for

- Decreasing the fluidity or microviscosity of the bilayer.
- Reducing the permeability of the membrane to water soluble molecules.
- To stabilize the membrane in presence of biological fluids such as plasma.

Liposomes without plasma interact rapidly with plasma proteins like albumin, transferring and microglobulin. These proteins try to extract bulk phospholipid from liposomes thus depleting the outer monolayer of vesicles leading to physical instability. The cholesterol substantially reduces this type of interaction.

4) SYNTHETIC PHOSPHOLIPIDS:

Synthetic saturated phospholipids are:

- Dipalmitoyl Phosphatidyl choline (DPPC)
- Distearoyl Phosphatidyl choline (DSPC)
- Dipalmitoyl Phosphatidyl ethanolamine (DPPE)
- Dipalmitoyl phosphatidic acid (DPPA)
- Dipalmitoyl Phosphatidyl serine (DPPS)

Synthetic unsaturated phospholipids are:

- Dioleoyl Phosphatidyl choline (DOPC)
- Dioleoyl Phosphatidyl glycerol (DOPG)

5) POLYMERIC MATERIALS:

The synthetic phospholipid having diactylanic group in the hydrocarbon chain polymerizes when exposed to U.V leading to formation of polymerized liposomes. These liposomes have significantly higher permeability barriers to entrapped aqueous drugs. Such as for other polymerisable lipids are – lipids containing conjugated diene, methacrylate. The several polymerisable surfactants are also synthesized.

6) CATIONIC LIPIDS

Some cationic lipids are:

- Dioctadecyl dimethyl ammonium bromide or chloride (DODAB/C)
- Dioleoyl propyl trimethyl ammonium chloride (DOTAP)

This is an analogue of DOTAP and the various including other analogues of DOTMA and cationic derivatives of cholesterol.

7) OTHER SUBSTANCES

- Variety of other lipids of surfactants is used to form the liposomes.
- Non ionic lipids.
- Many single chain surfactants.
- Sterylamine and dicetyl phosphate.
- Polyglycerol and polyethoxylated mono and dialkyl amphiphiles generally used in some cosmetic preparations.
- Single or double chain lipids having fluoro carbon chain can form very stable liposomes.

MECHANISM OF LIPOSOMES FORMATION:

Liposomes are vesicular structures that consisting of the hydrated bilayers. Liposomes structures used for pharmaceutical purposes consist of a phospholipid backbone. But some other classes of molecules can also form bilayer based vesicular structures. On other hand not all the hydrated phospholipids form bilayer structures. Other forms of self aggregation such as inverted hexagonal phases or micelles with completely different properties can occur. The amphilicity is the common feature that all bilayer forming compounds share. They have defined polar and nonpolar regions. In water the hydrophobic regions tend to self aggregate and the Polar Regions tend to be in contact with the water phase. Their head groups are hydrophilic and their fatty acyl chains are hydrophobic. The lipids capable of forming the liposomes exhibit a dual chemical nature.

This can be understood by taking the CMC of Dipalmitoyl P.C found to be 4.6^{-10} M in water, which is a small no. indicating the over whelming preference of this molecule for a hydrophobic environment such as found in that core of micelle bilayer and there is a free energy transfer from water to micelle. This large energy change between a water and hydrophobic environment explains the over whelming preference of typical lipids to get assemble in bilayer structures, including water as much as possible from the hydrophobic core in order to achieve the lowest energy level so as to acquire the highest stability for the aggregate structure[7,8].

PREPARATION OF LIPOSOMES[9,15]:

- General method of preparation.
- Specific methods of preparation.

A) GENERAL METHOD OF PREPARATION:

In the general method the lipid is dissolved in organic solvent. The solvent is evaporated leaving a small film of lipid on the wall of container. Then an aqueous solution of drug is added. In the first procedure the mixture is agitated to produce multi lamellar vesicles and then sonicated further to get SUV's. In the second procedure the mixture is sonicated and the solvent is evaporated to get LUV's. After the extrusion SUV's are formed. Drug can be incorporated into the aqueous solution or buffer if it is water soluble. Free drug and liposomes can be separated by gel chromatography.

B) SPECIFIC METHODS:

These methods are classified in three types based on the mode of dispersion as given below:

1) PHYSICAL DISPERSION METHODS:

In the physical dispersion methods the aqueous volume enclosed within the lipid membranes is about 5-10%, which is very small proportion of total volume used for preparation. So large amount of drug is wasted during preparation. But lipid soluble drug can be encapsulated to high percentage. In these methods, MLV's formed and further treatment is required for preparation of unilamellar vesicles. In physical dispersion method the following techniques are used[10]:

- Hand shaken method.
- Non-shaking method.
- Freeze drying.

The processing of lipids hydrated by physical means is done by following methods:

- Sonication.
- Micro-emulsification of liposomes.
- Membrane extrusion method.
- Freeze and thaw sonication.

2) SOLVENT DISPERSION METHOD:

In the solvent dispersion methods lipids are first dissolved in an organic solution and then brought into contact with the aqueous phase containing material to be entrapped within liposomes. At the interface between organic and the aqueous phase the phospholipids align themselves to form a monolayer, which is important step to form the bilayer of liposome.

ETHER INJECTION METHOD:

In this method a solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous solution of the material to be encapsulated at 55-65°C or under reduced pressure. In this process the subsequent removal of ether under vacuum leads to the formation of liposomes. The main drawbacks of the method are population is heterogeneous (70-190 nm) and the exposure of compounds to be encapsulated to organic solvents or high temperature.

ETHANOL INJECTION METHOD:

In this method a lipid solution of ethanol is rapidly injected to a vast excess of buffer and the MLVs are immediately formed. The main drawbacks of this method are that the population is heterogeneous (30-110 nm), liposomes are very dilute, it is difficult to remove all ethanol because it forms azeotrope with water and the possibility of various biologically active macromolecules to inactivation in the presence of even low amounts of ethanol.

3) DETERGENT REMOVAL METHODS:

Lipids, lipophilic compounds and amphiphatic proteins can be solubilized by detergents forming mixed micells. Upon removal of detergents, vesicle formation can occur. In this method phospholipids are brought into contact with aqueous phase via detergent, which is associated with phospholipid molecules. Thus the structures formed are known as micelles. Micelles composed of several hundereds of component of molecules. The concentration of detergent in water at which micelles starts to form is called CMC (critical micelle concentration). As the detergent molecules dissolves in water at concentration higher than CMC, micelles form in large amounts. As the concentration of detergent is increased, more amount of detergent is incorporated into the bilayer, until a point is reached where conversion from lamellar form to spherical micellar form takes place. As detergent concentration is further increased, the micelles are reduced in size.

STABILITY CONSIDERATION OF LIPOSOMES:

The stability of liposomes is of major concern in their development of pharmaceutical applications, includes physical, chemical and biological stability of liposomes[13,16].

PHYSICAL STABILITY:

The aggregation of liposomes may lead to fusion. This property of liposomes depends on the bilayer constituents, ionic strength of medium, particle size, encapsulated drug and temperature and the individual can monitor it by visual inspection, probe fluorescence technique and light scattering technique. To induce optimum stability Lipid composition of the bilayer & pH of aqueous solvent can be adjusted Proliposomes and lyophilization can also improve physical stability.

CHEMICAL STABILITY:

The chemical stability generally includes about the stability of phospholipids. All major factors affecting the stability of phospholipids include peroxidation and hydrolytic reactions. Temperature, bilayer rigidity and pH are parameters that strongly influence hydrolysis kinetic of phospholipids. Like for Phosphatidyl choline liposomes an optimum stability was found at pH 6.5. Peroxidation reactions can be avoided by selecting lipids with only saturated bonds, storage under inner environment, addition of antioxidants and chelating agents.

BIOLOGICAL STABILITY:

The major events which are responsible for destabilization of liposomes include membrane fusion and protein binding or simply aggregation and fusion. The stability of liposomes in blood and Plasma-destabilization is due to interaction with plasma proteins like globulin, albumin and lipoproteins. The stability of pH sensitive liposomes is also affected by the pH of the blood. Liposomes stability in GIT is affected by the Low pH of gastric environment, surfactants, and bile salts present in intestinal environment.

APPLICATIONS[17,19]

- Drug targeting.
- Gene therapy.
- Cancer chemotherapy.
- Liposomes used as carriers for vaccines and antigens.
- Liposomes are used for topical applications.
- Liposomes as drug delivery systems (oral delivery, transdermal delivery, systemic delivery, brain delivery and vaginal delivery).
- Lysosomal storage disease.
- Metal storage disease.

- Ophthalmic delivery of drugs.

CONCLUSION:

The liposomes have been realized as extremely useful carrier system for targeted drug delivery and have developed into a viable pharmaceutical storage form. The flexibility of their use in the drug delivery systems through any route of administration increases their use in the last decade. Use of the liposomes in the delivery of drugs and gene are promising and is sure to undergo further development in future. Vital progress has been made in development of long circulating liposomes that are not immediately recognized and removed by the cells of mononuclear phagocyte system. Development in the field of liposomes will continue to explore the validity of liposomes for the delivery of proteins and peptides and these developments will surely lead into another highly productive and innovative phase of liposome research.

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