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A BRIEF REVIEW ON LIPOSOME – AS DRUG CARRIER

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ABSTRACT: Liposomes have received a lot of attention during the last three decades as pharmaceutical carriers of great potential. Their merit lies in their composition, which makes them biocompatible and biodegradable. They have an aqueous core entrapped by one or more layers composed of natural or synthetic lipids. Liposomes composed of natural phospholipids are biologically inert and non-immunogenic. Moreover, drugs with different HLB value can be incorporated into liposomes: strongly lipophilic drugs are entrapped almost completely in the lipid bilayer, strongly hydrophilic drugs are located exclusively in the aqueous compartment, and drugs with intermediate lipophilicity easily partition between the lipid and aqueous phases, both in the bilayer and in the aqueous core. Liposomes are now used to deliver certain vaccines, enzymes and drugs to the body. When used in cancer therapy liposomes helps in protecting healthy cells from the drug toxicity and prevent their concentration in vulnerable tissue. Gene delivery and cancer therapy are still being the principal areas of interest. Liposomes sensitivity to pH, light, magnetism, temperature and ultrasonic waves can be used to enhance therapeutic efficacy. Targeted liposome formulations having antibodies, peptides, glycoproteins, polysaccharide, growth factors and carbohydrates may increase liposomal drug accumulation in the cells and tissues by over expressed receptors and antigens. Promising trends must be identified and exploited for further successful development of liposomal drug delivery.

Introduction:

One of the main goals of any treatment employing medicine is to increase the therapeutic index of the drug while minimizing its side-effects. The method by which a drug is delivered can have a significant effect on its efficacy. Drugs have an optimum concentration range in which maximum benefit is derived, and concentrations above or below this can leads to toxicity or there is no therapeutic effect at all. So there is a growing need for a multidisciplinary approach to the delivery of therapeutics to site of action. So there is an idea to control the pharmacokinetics,

pharmacodynamics, toxicity, immunogenicity, biorecognition, and efficacy of drugs. These new strategies, often called novel drug delivery systems (NDDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry and molecular biology. Molecular conjugates and colloidal particulates can be used for this purpose. Colloidal particulates result from physical incorporation of the drug into a particulate colloidal system such as liposomes, niosomes, microspheres, nanospheres, erythrocytes, polymeric and reverse micelles. Among these carriers, liposomes have received a lot of attention during the past 30 years as pharmaceutical carriers of great potential. Their merit lies in their composition, which makes them biocompatible and biodegradable. They have an aqueous core entrapped by one or more layers composed of natural or synthetic lipids. Liposomes composed of natural phospholipids are biologically inert and non-immunogenic. Moreover, drugs with different HLB value can be incorporated into liposomes: strongly lipophilic drugs are entrapped almost completely in the lipid bilayer, strongly hydrophilic drugs are located exclusively in the aqueous compartment, and drugs with intermediate lipophilicity easily partition between the lipid and aqueous phases, both in the bilayer and in the aqueous core. More recently, many new developments have been seen in the area of liposomal drug delivery from clinically approved products to new experimental applications, Liposomes are now used to deliver certain vaccines, enzymes and drugs to the body. When used in cancer therapy liposomes helps in protecting healthy cells from the drug toxicity and prevent their concentration in vulnerable tissue. Gene delivery and cancer therapy are still being the principal areas of interest. Promising trends must be identified and exploited for further successful development of liposomal drug delivery.

ADVANTAGES

1. Liposomes can carry both water and lipid soluble drugs, drug having intermediate lipophilicity may partition itself into both mediums
2. Drugs can be protected from oxidation by phospholipids bilayer
3. Protein stabilization is possible by liposome drug delivery
4. Targeted drug delivery or site-specific drug delivery can be achieved and very useful in cancer treatment.
5. Stabilization of entrapped drug from hostile environment i.e. extreme pH, ionic concentration and enzymes.
6. Controlled hydration is possible
7. Naturally provide sustained release
8. Alteration in pharmacokinetics and pharmacodynamics of drugs is possible
9. Liposomes can be administered through various routes
10. Both micromolecules and macromolecules can be incorporated
11. Liposomes acts as reservoir of drugs
12. Therapeutic index of drugs is increased
13. Site avoidance therapy is possible
14. Liposomes can modulate the distribution of drug in body
15. Direct interaction of the drug with cell is possible
16. Liposomes provide controlled drug delivery
17. Liposomes are biodegradable, biocompatible, flexible and non-ionic.

LIMITATIONS

1) Phospholipids undergoes oxidation and hydrolysis which may leads to incomplete protection, leakage and fusion
2) High production cost in comparison to conventional dosage forms
3) Quick uptake by cells of R.E.S although it may be utilized for drug targeting
4) Few people show allergic reactions to liposomal constituents
5) Large size poses problem in targeting to various tissue
6) Low solubility and short half life

Classification

Table 1: Types of liposomes based on pharmaceutical aspects and sizes:

UV	Unilamellar vesicles	All size range
SUV	Small Unilamellar vesicles	20-100nm
MUV	Medium sized Unilamellar vesicles	--
LUV	Large Unilamellar vesicles	>100μm
GUV	Giant Unilamellar vesicles	>1μm
MVV	Multivesicular vesicles	1μm
MLV	Multilamellar large vesicles	>0.5μm
OLV	Oligolamellar vesicles	0.1-1μm

Table 2: Types of Liposomes based on method of Preparation

REV	Single or oligolamellar vesicle made by reverse phase evaporation method.
MLV	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

RAW MATERIALS FOR FORMATION OF LIPOSOMES

A) Phospholipids

Phospholipids are most common used component of liposome formulation. These are derived from Phosphatidic acid, having glycerol moiety as back bone of the molecule. Fatty acid is responsible for lipidic nature. OH group of phosphoric acid may be further esterified to a wide range of organic alcohols including glycerol, choline, ethanolamine, serine and inositol. Unsaturated fatty acids may cause instability so saturated fatty acids are more preferred.

Types of phospholipids:

- Phosphatidyl Glycerol (PG)
- Phosphatidyl choline (Lecithin) – PC
- Phosphatidyl ethanolamine (cephalin) – PE
- Phosphatidyl serine (PS)
- Phosphatidyl inositol (PI)

Synthetic phospholipids:

- Dioleoyl phosphatidyl choline (DOPC)
- Dioleoyl phosphatidyl glycerol (DOPG)
- Dipalmitoyl phosphatidyl serine (DPPS)
- Dipalmitoyl phosphatidic acid (DPPA)
- Dipalmitoyl phosphatidyl glycerol (DPPG)
- Dipalmitoyl phosphatidyl choline (DPPC)
- Distearoyl phosphatidyl choline (DSPC)
- Dipalmitoyl phosphatidyl ethanolamine (DPPE)

B) Sphingolipids

As there name suggests backbone is sphingosine or a related base. These are important constituents of plant and animal cells. These contain three characteristic building blocks, a molecule of fatty acid, sphingosine and a head group that can vary from simple alcohols such as choline to very complex carbohydrates.

C) Sterols

Sterols are included in liposomes for decreasing the fluidity of the bilayer, reducing the permeability of the membrane to hydrophilic molecules or to stabilizing the membrane of i.v. liposomes in the presence of biological fluids such as plasma. If cholesterol is not used Liposomes will interact rapidly with plasma protein such as albumin, transferrin, and macroglobulin which will leads to physical instability. Cholesterol substantially reduce this type of interactions.

D) Polymeric materials

Synthetic phospholipids polymerizes when exposed to U.V. radiations, leading to formation of polymerized liposomes having higher permeability barriers to entrapped hydrophilic drugs. Lipids containing conjugated diene, methacrylate and there are also surfactants which can be polymerized.

E) Other Substances

Other substances used to form liposomes are:

- In cosmetic preparations there is use of variety of Polyglycerol and Polyethoxylated mono and dialkyl amphiphiles.
- Stable liposomes can be prepared by using single and double chain lipids having fluoro carbon chains.
- Sterylamine and Dicetyl phosphate can impart either a negative or positive surface charge to liposomes.
- Compounds having a single long chain hydrocarbon and an ionic head group are capable of forming vesicles. E.g. quaternary ammonium salts of dialkyl phosphates.
- Single chain surfactants on mixing with cholesterol can form liposomes.

TECHNIQUES FOR PREPARATION AND DRUG LOADING OF LIPOSOMES:

In all techniques there are four basic steps:

A. Drying down lipids from organic solvent.
B. Dispersion of lipid in aqueous media.

C. Purification of resultant liposome.
D. Analysis of final product.

Drug loading in liposomes:

1. Passive loading techniques: This includes three different methods:

   a) Mechanical dispersion method
   - Ultrasonification
   - Micro-emulsification
   - Lipid film hydration by shaking or freeze drying
   - Dried reconstituted vesicles
   - Freeze-thawed liposomes
   - French pressure cell
   - Membrane extrusion

   b) Solvent dispersion method
   - Reverse phase evaporation vesicles
   - Stable plurilamellar vesicles
   - Double emulsion vesicles
   - Ether injection
   - Ethanol injection

   c) Detergent removal method
   - Dialysis
   - Dilution
   - Column chromatography
   - Reconstituted sendai virus enveloped vesicles
   - Detergent removal form mixed micelles

2. Active loading techniques: These techniques are used for industrial production of liposomes. The main problem faced is the presence of organic solvent residues, physical and chemical stability, pyrogen control, sterility, size and size distribution and batch to batch reproducibility. Liposomes for parenteral use should be sterile and pyrogen free. The liposomes based on crude egg yolk phospholipids are not very stable. The cost of purified lipids is very high. So it is better to use synthetic and polymerizable lipids. The liposomes prepared from polymerizable phospholipids are exposed to UV radiations. Such liposomes have better storage stability. These materials are phospholipid analogues and their metabolic fates are uncertain. E.g.: Detergent dialysis, microlluidization.

CHARACTERIZATION OF LIPOSOMES

Liposome characterization should be performed immediately after preparation. The most important parameters of liposome characterization are followings:

A) Visual Appearance

In homogeneous sample turbidity has a bluish shade; gray color indicates the presence of a non-liposomal dispersion. An optical microscope (phase contrast) can detect liposome of more than 0.3 μm and contamination with larger particles.

B) Size Distribution

Size distribution is measured by light scattering method. This method is reliable for liposomes having relatively homogeneous size distribution. In gel exclusion chromatography a truly hydrodynamic radius can be detected.

C) Surface Charge

Liposomes are usually prepared using charged lipids and hence it is imparting to study the charge on the vesicle surface. Electrophoresis and zeta potential measurement can be used to assess the charge.

D) Lamillarity

It can be measured by electron microscopy and by spectroscopic techniques. The NMR spectrum of liposome is recorded with and without the addition of a paramagnetic agent that shifts the signal of the observed nuclei on the outer surface of liposome. Encapsulation efficiency can be measured by encapsulating a hydrophilic marker.

E) Entrapped Volume

The entrapped volume of a liposome can be deduced from measurements of the total quantity of solute entrapped inside liposome assuring that the concentration of solute in the aqueous medium inside liposomes is the same after separation from unentrapped material.

F) **Stability**

The stability of a pharmaceutical product is defined as the capacity of the delivery system to remain within defined limits during the selflife of the product. There is no established protocol for either accelerated or long–term stability studies

for the liposomal formulation. Liposome stability is consisting of physical, chemical, and biological stability. In drug delivery shelf-life stability is also important. Physical stability includes mainly the constancy of the size and the ratio of lipid to active agent. The stability problems can be overcomes by using appropriate techniques like freezing, lyophilization and osmification. It is also prevented by using fresh solvents and purified lipid, using nitrogen gas and to avoid high temperature. Liposomes resembles biomembranes, they still are foreign objects for the body cells. Therefore, they are recognized by the mononuclear phagocytic system after interaction with plasma proteins. As a result, liposomes are cleared from the body. These types of stability problems can be solved by using synthetic phospholipids, microencapsulation, polymerization, coating liposomes with chitin derivatives or with polyethylene glycol and freeze drying. Liposome meant to be administered via the parenteral route or in the eyes must be sterile. Sterilization can be done by autoclaving or by γ-radiation. Aseptic production procedures have been used to produce sterile products. Large liposome cannot be sterilized by heat therefore, need to be manufactured aseptically. Pyrogen testing in liposome dispersions is quite difficult. There is uncertainty whether LAL test can be used for pyrogen detection or not.

FUTURE TRENDS

Integration of the more advanced types of liposome-based technologies such as targeted or stimuli-sensitive liposomes in this system will enhance therapeutic efficacy. Targeted liposome formulations having antibodies, peptides, glycoproteins, polysaccharide, growth factors and carbohydrates may increase liposomal drug accumulation in the cells and tissues by over expressed receptors, antigen, and unregulated selectins. Liposomes sensitivity to pH, light, magnetism, temperature and ultrasonic waves can be used to enhance therapeutic efficacy. Polymeric systems may results in insufficient drug release due to their non degradability. On the other hand biodegradable or non-biodegradable polymers may be used to increase strength of depot while improving liposomal release profile. Considering the Liposomes and also its modifications or upgraded versions like Enzymosomes, Hemosomes,Virosomes, Erythrosomes and Virosomes. Liposomes have emerged as a dynamic mode for Targeted Drug Delivery.

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