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Liposome: New strategy in drug delivery

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Abstract

Liposomes are concentric bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are artificially prepared vesicles made of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membranes, for example by sonication. Liposomes have now been used for targeting of antigens to macrophages as a first step in the index of immunity. A pre requisite for targeting is the targeting agents be positioned on the liposomal surface such that the interaction with the target i.e., the receptor is tabulated such as a plug and socket device. The liposome physically prepared such that the lipophilic part of the connector is anchored into the membrane during the formation of the membrane.

Key-Words: Liposomes, Drug Delivery

Introduction

The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. A liposome does not necessarily have lipophobic contents, such as water, although it usually does.

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Liposomes are micro perticulate or colloidal carriers, usullay 0.05- 5.0 µm in diameter which form spontaneously when certain lipid are hydrated in aqueous media. Liposomes are composed of relatively biocompatable and biodegradable material, and they consist of an aqueous volume entrapped by one or more bilayer of natural and/ or synthetic lipids. Drug with widely varying lipophilicities can be encapsulated in liposomes, either in the phospholipid bilayer, in the entrapped aqueous volume or at the bilayer interface.

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Manufacturing liposome

- The correct choice of liposome preparation method depends on the following parameters
- The physicochemical characteristics of the material to be entrapped and those of the liposomal ingredients.
- The nature of the medium in which the lipid vesicles are dispersed.
- The effective concentration of the entrapped substance and its potential toxicity.
- Additional processes involved during application/delivery of the vesicles.
- Optimum size, polydispersity and shelf-life of the vesicles for the intended application.
- Batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

Classification of liposome

A. Based on Size and Number of Lamellae

(i). Multi lamellar vesicles (M.L.V)

Size □ 0.1 - 0.3 micro meter

Have more than one bilayer, moderate aqueous volume to lipid ratio 4: 1 mole lipid. Greater encapsulation of lipophilic drug, mechanically stable upon long term storage, rapidly cleared by R.E.S, useful for targeting the cells of R.E.S, simplest to prepare by thin film hydration of lipids in presence of an organic solvent.

a) Oligo lamellar vesicles or Paucilamellar vesicles
Intermediate between L.U.V & MLV

b) Multi vesicular liposome
Separate compartments are present in a single M.L.V.

c) Stable Pluri lamellar vesicles
Have unique physical and biological properties due to osmotic compression.

(ii) Large Unilamellar Vesicles (L.U.V)

Size 0.1 - 10 micro meter

Have single bilayer, high aqueous volume to lipid ratio (7: 1 mole lipid), useful for hydrophilic drugs, high capture of macro molecules rapidly cleared by R.E.S. Prepared by detergent dialysis, ether injection, reverse phase evaporation or active loading methods.

(iii) Small Unilamellar Vesicles (S.U.V)

Size 0.1 micro meters

Single bilayer, homogeneous in size, thermodynamically unstable, susceptible to aggregation and fusion at low or no charge, limited capture of macro molecules, low aqueous volume to lipid ratio (0.2 : 1.5 : 1 mole lipid) prepared by reducing the size of M.L.V or L.U.V using probe sonicator or gas extruder or by active loading or solvent injection technique.

B. Based on composition and mode of drug delivery

(i) Conventional liposome

Composed of neutral or negatively charged phospholipids and cholesterol. Subject to coated pit endocytosis, contents ultimately delivered to lysosomes if they do not fuse with the endosomes, useful for E.E.S targeting; rapid and saturable uptake by R.E.S short circulation half life, dose dependent pharmacokinetics.

(ii) pH sensitive liposomes

Composed of phospholipids such as phosphatidyl ethanolamine, dioleoyl phosphatidyl ethanolamine.Subjected to coated pit endocytosis at low pH, fuse with cell or endosomes membrane and release their contents in cytoplasm; suitable for intra cellular delivery of weak base and macromolecules. Biodistribution and pharmacokinetics similar to conventional liposomes.

(iii) Cationic Liposomes

Composed of cationic lipids fuse with cell or endosome membranes suitable for delivery of negatively charged macromolecules (DNA, RNA) ease of formation, structurally unstable; toxic at high dose, mainly restricted to local administration.

(iv) **Long circulating or stealth liposomes**

Composed of neutral high transition temperature lipid, cholesterol and 5-10% of PEG-DSPE. Hydrophilic surface coating, low opsonisation and thus low rate of uptake by RES long circulating half life (40 hrs) Dose independent Pharmacokinetics.

(v) Immuno liposomes

Conventional or stealth liposomes with attached Antibody or Recognition Sequence. Subject to receptor mediated endocytosis, cell specific binding (targeting) can release contents extra cellularly near the target tissue and drugs diffuse through plasma membrane to produce their effects.

(vi) Magnetic Liposomes

Composed of P.C, cholesterol and small amount of a linear chain aldehyde and colloidal particles of magnetic Iron oxide. These are liposomes that indigenously contain binding sites for attaching other molecules like antibodies on their exterior surface. Can be made use by an external vibrating magnetic field on their deliberate, on site, rapture and immediate release of their components.

(vii) Temperature (or) heat sensitive liposomes

Composed of Dipalmitoyl Phosphatidyl choline. These are vesicles showed maximum release at 41°, the phase transition temperature of Dipalmitoyl Phosphatidyl choline. Liposomes release the entrapped content at the target cell surface upon a brief heating to the phase transition temperature of the liposome membrane.

Method of liposome preparation and drug loading

Liposome may be prepared by two techniques:

1 Passive loading technique.
2 Active loading technique.

1 Passive loading technique

A Mechanical dispersion method
- Lipid hydration by hand shaking or freeze drying
- Micro emulsification
- Sonication
- French pressure cell
- Membrane extrusions
- Dried reconstituted vesicle
- Freeze thawed liposome

B Solvent dispersion method
- Ethanol injection
- Ether injection
- Double emulsion vesicle
- Reverse phase evaporation vesicle
- Stable plurilamellar vesicle

C Detergent removal method
- Detergent (cholate, alkylglycoside, Triton x-100) removed from mixed micelles
- Dialysis
- Column chromatography
- Dilution
- Reconstituted sendai virus enveloped vesicle

2 Active loading techniques

Advantage of liposome
- Non ionic.
- Can carry both water and lipid soluble drugs.
- Biodegradable Drugs can be stabilized from oxidation.

- Improve protein stabilization.
- Controlled hydration.
- Provide sustained release.
- Targeted drug delivery or site specific drug delivery.
- Stabilization of entrapped drug from hostile environment.
- Alter pharmacokinetics and pharmacodynamics of drugs.
- Can be administered through various routes.
- Can incorporate micro and macro molecules.
- Act as reservoir of drugs.
- Therapeutic index of drugs is increased.
- Site avoidance therapy.
- Can modulate the distribution of drug.
- Direct interaction of the drug with cell.
- Biodegredable and flexible.

Disadvantages of liposome

- Less stability.
- Low solubility.
- Short half life.
- Phospho lipid undergoes oxidation, hydrolysis.
- Leakage and fusion.
- High production cost.
- Quick uptake by cells of R.E.S.
- Allergic reactions may occur to liposomal constituents.
- Problem to targeting to various tissue due to their large size.

Therapeutic application of liposomes

(i) Liposome as drug/protein delivery vehicle:

- Controlled and sustained drug release in situ.
- Enchaned drug solubilization.
- Altered pharmacokinetic and biodistribution.
- Enzyme replacement therapy and lysosomal disorders.

(ii) Liposome in antimicrobial, antifungal and antiviral therapy:

- Liposomal drugs.
- Liposomal biological response modifier.

(iii) Liposomes in tumour therapy:

- Crrrier of small cytotoxic molecule.
- Vehicle for macromolecule as cytokines or genes.

(iv) Liposome in gene therapy:

- Gene and antisence therapy.
- Genetic (DNA) vaccination.

(v)Liposome in immunology:

- Immunoadjuvant.
- Immunomodulator.
- Immunodiagnosis.

(vi) Liposome as artificial blood surrogates.

(vii) Lipososmes as radiopharmaceutical and radiodiagnostic carrier.

(viii) Liposomes in cosmetics and dermatology.

(ix) Liposomes in enzyme immobilization and bioreactor technology.

Limitation in liposome technology

a. Stability
b. Sterilization
c. Encapsulation efficiency
d. Active targeting
e. Gene therapy
f. Lysosomal degradation

Pharmacokinetics of liposomes

- Liposomal drugs can be applied through various routes, but mainly i.v and topical administration is preferred. After reaching in the systemic circulation or in the local area, a liposome can interact with the cell by any of the following methods.
- endocytosis by Phagocytotic cells of the R.E.S such as macrophages and Neutrophils
- adsorption to the cell surface either by non specific weak hydrophobic or electrostatic forces or by specific interaction with cell surface components
- Fusion with the plasma cell membrane by insertion of lipid bilayer of liposome into plasma membrane with simultaneous release of liposomal contents into the cytoplasm.
- Transfer of liposomal lipids to cellular or sub cellular membrane or vice versa without any association of the liposome contents.
- It is often difficult to determine what mechanism is operative and more than one may operate at the same time.

Structural components

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 C_3 OH group is esterified to phosphoric acid. OH at C_1 & C_2 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.

Sphingolipids

Backbone is sphingosine or a related base. These are important constituents of plant and animal cells. This contain 3 characteristic building blocks

- A mol of Fatty acid.
- A mol of sphingosine.
- A head group that can vary from simple alcohols such as choline to very complex carbohydrates.

Most common Sphingolipids – Sphingomyelin. Glycosphingo lipids.

Gangliosides – found on grey matter, used as a minor component for liposome production.

This molecule contain complex saccharides with one or more Sialicacid residues in their polar head group & thus have one or more negative charge at neutral pH. These are included in liposomes to provide a layer of surface charged group.

Sterols

- Cholesterol & its derivatives are often included in liposomes.
- decreasing the fluidity or microviscocity of the bilayer.
- reducing the permeability of the membrane to water soluble molecules.
- Stabilizing the membrane in the presence of biological fluids such as plasma.(This effect used in formulation of i.v. liposomes).

Liposomes without cholesterol are known to interact rapidly with plasma protein such as albumin, transferrin, and macroglobulin. These proteins tend to extract bulk phospholipids from liposomes, there by depleting the outer monolayer of the vesicles leading to physical instability. Cholesterol appears to substantially reduce this type of interaction. Cholesterol has been called the mortar of bilayers, because by virtue of its molecular shape and solubility properties, it fills in empty spaces among the Phospholipid molecules, anchoring them more strongly into the structure. The OH group at 3rd position provides small Polar head group and the hydrocarbon chain at C_{17} becomes non polar end by these molecules, the cholesterol intercalates in the bilayers.

Synthetic phospholipids

E.g.: for saturated phospholipids are

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

E.g.: for unsaturated phospholipids

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

Polymeric materials

Synthetic phospholipids with diactylenic group in the hydrocarbon chain polymerizes when exposed to U.V, leading to formation of polymerized liposomes having significantly higher permeability barriers to entrapped aqueous drugs.E.g.: for other Polymerisable lipids are – lipids containing conjugated diene, Methacrylate etcAlso several Polymerisable surfactants are also synthesize.

Polymer bearing lipids

Stability of repulsive interactions with macromolecules is governed mostly by repulsive electrostatic forces. This repulsion can be induced by coating liposome surfaces with charged polymers.

Non ionic and water compatible polymers like polyethylene oxide, polyvinyl alcohol, and Polyoxazolidines confers higher solubility. But adsorption of such copolymers containing hydrophilic segments with hydrophobic part leads to liposome leakage, so best results can be achieved by covalently attaching polymers to phospholipids

E.g.: Diacyl Phosphatidyl ethanolamine with PEG polymer linked via a carbon at or succinate bond.

The degree of polymerization varies from 15-120 units. Longer polymers give rise to aqueous solubility of polymer lipids and their first removal from membranes in non equilibrium conditions. While shorter polymers do not offer enough repulsive pressure because Vanderwaal's attraction is a long range force.

Cationic lipids

E.g.: DODAB/C – Dioctadecyl dimethyl ammonium bromide or chloride

DOTAP – Dioleoyl propyl trimethyl ammonium chloride – this is an analogue of DOTAP and various others including various analogues of DOTMA and cationic derivatives of cholesterol.

Other Substances

- Variety of other lipids of surfactants are used to form liposomes.
- Many single chain surfactants can form liposomes on mixing with cholesterol.
- Non ionic lipids.

- A variety of Polyglycerol and Polyethoxylated mono and dialkyl amphiphiles used mainly in cosmetic preparations.
- Single and double chain lipids having fluoro carbon chains can form very stable liposomes.
- Sterylamine and Dicetyl phosphate.
- Incorporated into liposomes so as to impart either a negative or positive surface charge to these structures.
- A number of compounds having a single long chain hydrocarbon and an ionic head group found to be capable of forming vesicles. These include quaternary ammonium salts of dialkyl phosphates.

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