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Pharmaceutical Sciences **Review Article……!!!**

LIPOSOMES: APPLICATIONS IN DRUG DELIVERY STSTEM

Sharma Anjali[1],Dev Dhruv[1],Prasad Dn[1]

Shivalik College of Pharmacy Punjab, Dist. Rupnagar.

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FOR CORRESPONDENCE:

Sharma Anjali *

ADDRESS:

Shivalik College of Pharmacy Punjab, Dist. Rupnagar, India.

ABSTRACT

In this current review article, new drug development in liposomes with aim to provide desired therapeutic effect. There is various drug delivery system used to target the particular tissue by using drug. Now we discussed about liposomes. In the mid-60s, liposomes are sphere shaped vesicles enclosed by 1 or more phospholipid bi-layers. The size of liposomes from 20 nm up to several micrometres. Now a day, they are very useful tool in reproduction, reagent, and also used in various mathematical and theoretical physics, biophysics, chemistry, biochemistry and biology. Liposomes are advanced drug delivery system deliver active molecule of the drug to the site of action and also several formulations are in clinical use. Liposomes proved that a promising drug carriers by reduced side effects, toxicity with no adverse effects and increased the therapeutically effect at site of action. The latest advancement in field of medicines having better biocompatibility, efficiency, targeting ability and improve in-vivo performance. They also having lower systemic toxicity and improve pharmacokinetic and pharmaco-dynamics properties of drugs of liposomal drug delivery system. Recent development in the delivery of antifungal, antibiotic, antiinflamatory and anticancer drugs through liposomal drug delivery system. This review article shown that the structure of liposomes, advantages, disadvantages and factor affects method of preparation and its applications or use as NDDS.

INTRODUCTION:

In earlier 1960s liposomes were first reported by A.D Bangham who discovered the spherical structure when phospholipid comes in contact with water. They investigate that various categories of drugs enclosed in the phospholipid bilayer for increasing therapeutically effect by reduce side effects[(1)]. There are many pharmaceutical dosage forms, tablets, capsules, pills, creams, oientments, aerosols, injectable and suppositories as carriers for delivering drugs to the patient body but they provide some toxicity to patient body and poor efficiency. To reduce these toxicity or fluctuation novel drug delivery system like Niosomes, Liposomes, Nanoparticles, Microemulsions and Magnetic micro capsule.

The ability of advanced technique in drug delivery system discovery and research of a wide number of therapeutically molecules but more of them are unsuccessful in this process due to poor correlation between in-vitro and in-vivo result. Liposome is a novel drug delivery system with size range of 0.01 to 5.0 micrometer.Liposome used as drug carrier for better therapeutic effect at target site of action. In liposome drug is encapsulated in the phospholipid bilayer. Phospholipid is amphiphilic molecules which contain hydrophilic and hydrophobic nature. On polar part is shielded with polar part[(9-11)]. Liposomes can be classified based on number of bilayers, size, composition and method of preparation but mainly classified based on size. In this aqueous, drug can be enclosed in aqueous phase and poorly soluble drug enclosed in phospholipid bilayer[(13)]. Phospholipid bilayer is safe and effective for the delivery of drug to the target site of action that showed the path to the development of liposomal novel drug delivery system. Liposomes are colloidal, concentric-bilayer vesicle where aqueous compartment is entirely enclosed by a bilayer membrane composed of natural and synthetic lipids.

Salient features of liposomes

A liposome is a spherical vesicle containing a bilayer of at least one lipid. The liposome may be used as a medium for the nutrient and prescription drug administration. The preparation of liposomes can be achieved by destroying biological membranes (such as sonication)[34].

Liposomes are most often composed of phospholipids, especially phosphatidylcholine, but may also include other lipids, such as egg phosphatidylethanolamine, as long as they are consistent with the lipid bilayer structure. A liposome design may use surface ligands to bind to the unhealthy tissues[35].

Multilamellar vesicle (MLV, with several lamellar phase lipid bilayers), small unilamellar liposome vesicle (SUV, with one lipid bilayer), large unilamellar vesicle (LUV), and cochleate vesicle are the major types of liposomes[36]. Multivarsicular liposomes are a less desirable type in which one vesicle comprises one or more smaller vesicles.

Liposomes should not be confused with monolayers consisting of lysosomes, or with micelles and reverse micelles.

Mechanism of liposomes formation

Phospholipids, which are amphiphilic molecules (with a hydrophilic head and hydrophobic tail) form the basic part of liposome. The hydrophilic part is primarily phosphoric acid bound to a water-soluble molecule whereas the hydrophobic portion consists of two fatty acid chains with 10–24 carbon atoms and 0–6 double bonds in each chain.When these phospholipids are distributed in aqueous medium, they form lamellar sheets by arranging in such a way that the polar head group faces the aqueous area outwards while the fatty acid groups face each other and eventually form spherical / vesicle structures called liposomes.When phospholipids are hydrated in water, together with the input of energy such as sonication, shaking, heating, homogenisation, etc., it is the hydrophilic / hydrophobic interactions between lipid – lipid, lipid – water molecules that lead to the formation of bilayered vesicles to achieve a thermodynamic equilibrium in the aqueous phase.The reasons for bilayered formation include:

By folding into closed concentric vesicles, unfavorable interactions produced between the hydrophilic and hydrophobic phases can be minimized.

Broad bilayered vesicle formation facilitates the reduction of the substantial free energy gap between the hydrophilic and hydrophobic conditions.Maximum stability can be achieved by shaping into vesicles to the supramolecular self-assembled structure.

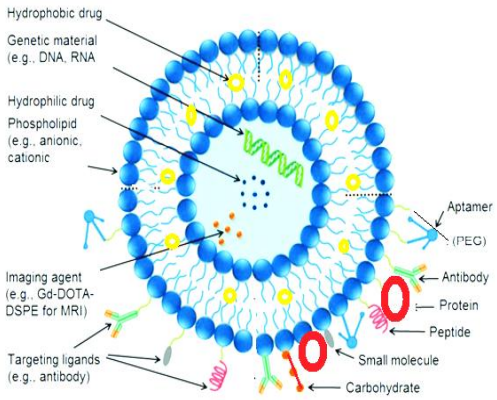
ADVANTAGES

1. Liposomes increase the efficiency and therapeutically index of drug.
2. Liposomes reduce the toxicity of the enclosed molecules and improve pharmacokinetic effects.
3. Liposomes used as drug carrier for control and sustain drug delivery system.[14]
4. Liposomes can be made in various numbers of sizes.
5. Liposomes provide selective passage targeting to tumour tissues in body of patient.

DISADVANTAGES

1. There is a possibility of leakage of enclosed drugs during storage.
2. Liposomes cannot be removed after administration.
3. There is variations occur batch to batch.
4. Liposomes having low solubility.
5. There is difficulty in large scale sterilization and manufacturing in liposome.

STRUCTURE OF LIPOSOMES



CLASSIFICATION OF LIPOSOMES

Liposomes can be classified on the basis of

1. Composition of liposomes
2. Method of preparation
3. Applications Advance techniques in liposome

1. Composition of liposomes

There are main 2 components of *liposomes*;

1. Phospholipid
2. Cholesterol

1. Phosphilipid Phospholipid are the basic molecular building block of the liposome and they are amphipathic in nature consist of-[17-18]

-hydrophilic polar head

-hydrophobic tale

Phosphatidylcholine is the main phospholipid component used in the preparation of liposomesvarious phospholipids like;

-saturated synthetic phospholipid is

1.Dipamitoyl phosphatidic acid

2.Dipalmitoyl phosphatidyl glycerol

-unsaturated phospholipid[18]

1.Dioleoyl phosphatidyl choline

2.Dioleolyl phosphatidyl glycerol

-synthetic phospholipid

1.phosphatidyl alkanolamide

2.Cholesterol

There are steroid derivatives cholesterol incorporated in concentration range 1:1 or 1:2 but not in bilayer form hydroxyl group of cholesterol towards aqueous phase and in centre of phospholipid bilayer acyl chain parallel to aliphatic chain. They minimize the leakage from liposome and make tight fluid bilayer.[27-28]

Structural parameters

There are 4 structural parameters[29]

1. MLV (Multilamellar vesicles) (>0.5)
2. OLV (oligolamellar vesicles) (0.1-1.0)
3. ULV (unilamellar vesicles) (all size ranges)

-MUV (medium unilamellar vesicles)

-SUV (small unilamellar vesicles) (20-100nanometer)

-GUV (gaint unilamellar vesicles) (>1.0)

-LUV (large unilamellar vesicles) (>100nanometer)

Method of preparation

A.Passive loading technique

B.Active loading technique

Passive loading techniques

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

1. Mechanical dispersion method

Liquid film hydration by hand shaking, on hand shaking or freeze dryer

b.microemulsification

c.sonication

D.french pressure cell

Membrane extraction

F.dried reconstituted vesicles

G.freeze thawed liposomes

2. Solventdispersion method

A.ethanol injection

Double emulsion vesicles

C.reverse phase evaporation vesicles

D.stable plurilamellar vesicles

3. Detergent removal method

A.detergent removal from mixed micelles

Dialysis

Column chromatography

Dilution

Reconstituted sendal virus enveloped vesicles

General method of liposome preparation:

All method of preparationhas 4 basic steps(25-27)

Step1: lipids are drying from organic solvent

Step2: dissolve the lipid in aqueous solvent

Step3: the solvent is evaporated form a small film of lipids on a wall of container

Step4: purify the formed liposome and analyse it.

1. Mechanicaldispersion method

It is also called physical dispersion method. In this method MLV type of lipids are formed[29-30].Take different mixture of phospholipid and charged molecules are added to the solvent (chloroform: methanol).Then this mixture is transfer to round bottom flask attach to the rotating evaporator (rotate at 60rpm).Then formation of thin film by the evaporation of organic solvent(Dried film is formed).

Disadvantages: Large amount of water soluble drug is waste.

A.Hand shaking method

Take different mixture of phospholipid and charged molecules are added to the solvent (chloroform: methanol)Then, this mixture is transfer to round bottom flask attach to rotating evaporator (rotate at 60rpm)Then, formation of thin film by evaporation of organic solvent.Then dried film is formed.Again rotating for 15 mins until dry film is formed (remove evaporator)**.**Attach vacuum source to fill with nitrogen gas.Then, round bottom flak is transfer to the lyophilizer to separate organic solvent.Then again add nitrogen gas in the round bottom flask+5ml saline phosphate buffer solution**.**Again rotate at 60rpm speed for 30 mins to remove all lipids from wall of flask.Finally milky white suspension is formed rest for 2hrs and MLV liposomes are formed.

B.NON hand shaking method

(By swelling procedure)

In this method add mixture of lipids in organic solvent (chloroform: methanol) in round bottom flask (spread over the flat bottom of flask).Then solution evaporate by flow of nitrogen gas without disturbing room temp (after drying).Saturated nitrogen gas passed through round bottom flask until dry

film is obtained.Make solution of 10-20ml 0.2m sucrose in distilled water is added to the side of flask and return to upright portion slowly.Round bottom flask is sealed with nitrogen and Stand for 2hrs for swelling process.Formation of milky white suspension and this suspension centrifuged at 1200rpm for 10mins.Formation of LUV liposome is formed.

c.Ethanol injection

This method is simplest and widely used method.In this method add amount of lipid in ethanol solution inject to a fine needle to other aqueous media directly.Then phospholipid molecules separate through the medium and ethanol is dissolved in aqueous medium.Formation of SUV liposomes.

d.Ether injection

This method is very simple than the ethanol injection method.In this inject the organic solution media to aqueous media through a fine needle at vaporation temp of organic solvent.In this method very less risk of oxidation degradation.Formation of liposome.

Disadvantages: They take long time for the process.

e.Microemulsification method

This method also called microfludization method.Micro fluidizer is equipment used for the formation of SUV for lipid suspension.Add suspension of lipids to the fluidizer equipment pump the fluid through 5micrometer screen at high pressure.2 streams of fluid colloid to each other at high speed.Collect fluid and intraction until spherical size liposomes are formed.

f.Freeze drying: Freeze drying is another technique for scattering the lipid in an at last isolated structure preceding expansion of fuild media.Generally tertiary butanol is utilized as a dissolvable.All the above techniques procedure MLVs.So as to change the size, the readied MLVs are additionaly handled utilizing the accompying system.

g.Sonication

It is most widely used method of prepration of liposomes.

Some drawbacks of this method-

-low interal volume

-removal of large molecules from probe tip.

2 techniques of sonication-

Probe sonication-This includes handling vesicles for several minutes with titanium dipped probe sonication.Dissolve mixture of phospholipid with cholesterol in chloroform with ratio 2:1 v/v.filter the mixture to seprate the insoluble ingredient rotary evaporator is used to remove the solvents. (Vacuum pump is used to remove organic solvent).Small quantity of glass beads and addition of aqueos phase like(And drug to be encapsulated).MLV type of liposomes is created.

Bath sonicato: Dissolve mixture of phospholipid with cholesterol in chloroform with ratio 2:1v/v.filter the mixture to seprate the insoluble ingredient rotary evaporator is used to remove the solvents.Vacuum pump is used to remove organic solvent.Small quantity of glass beads and addition of aq phase and drug to be encapsulated.MLV type of liposomes is created.bath sonicator with water mixed with drop of liquid detergent and suspends the MLV flask in the bath sonicator sonicate for 30-45min.

3. Detergent removal method

At critical micelles conc. Detergents are used to solubilize lipids. Detergent is removed micelles progressively richer in phospholipid and combines to form LUVs.Detergent can be removed by dialysis.Detergent dialysis method have excellent reproductibility and production of liposome is homogenous in size.Main disadvantage of this method retention of traces of detergent within liposome.

Techniqe used to remove detergents.

a) Using gel chromatography

b) Binding of triton X-100

c) Binding of octyl glucoside to amberlite XAD-2beads.

Applications of liposomes

Liposome exemplification can modify the spatial and worldly dissemination of the epitomized medication atoms in the body,which may altogether diminish undesirable harmful reactions and increment the adequancy of the treatment.Uses of liposomes in pharmacology and medication can be isolated into remedial and demonstrative uses of liposomes containing drugs and their usage as a structure,apparatus or reagent in the major investigations of cells interfaces,acknowledgement methodology and the instrument of specific materials.The advantages and restrictions of liposomal basically conc of liposomes with cells and their destiny in vivo after organisation.In vitro and in vivo investigations of their communications with cells have indicated that the transcendent collaboration of liposomes with cell is either straight forward absorption or resulting endocytosis.comination with cell films is lot rarer.The fourth conceivable co-operation is the trading of bilayer fixing,eg:-cholesterol and lipid layer bound particles with segments of cell layers.

The body ensures itself with a perplexing guard framework.After entering the body bigger items cause thrombus arrangement and their surface is inevitably passivated by covering with biomolecules.They are immediately expelled from the flow by the macrophages which are found essentially in spleen,liver and bone marrow.[30-33]

1) Recent applications of liposiomes in ophthalmic drug delivery

Recently liposomes are investigated for ophthalmic drug delivery system.It is used as carrier system.It is biodegradable and biocompatible in nature.It can enhance the permeation of poorly soluble drug

molecules binding to corneal surface and impoving residence time.Liposomes can encapsulate both hydrophilic and hydrophobic drug molecule.Liposome decrease toxicity and enhance pharmacokinetic profile and therapeutic effect.Liposomes are used to treat both anterior and posterior segment eye disorders.Recent approaches for anterior drug delivery are focused on enhancing corneal adhesion.In case of posterior segment enhancement of intravitreal half-life[9].

Recently verteprofin is used in photodynamic therapy to tre neoat CNV(chorodial neovasculation),ocular histoplasmosis.verteprofin is administered by i.v infusion.To activate verteprofin,drug is injected low energy laser is applied to retina with thehelp of contact lens that result inclosure of abnormal vesicles.But this photodynamic therapy is not permanent close of abnormal vessles reappear after several months.Another recently investigated ophthalmic drug delivery system rostaporfin used to cure age related macular degeneration.

Disadvantage:-storage of liposomes is very difficult.

-cause long term side effects.

2) Topical applications:-several strategies in improve absorption of drug having poor physiochemical properties.

In vitro investigation of corneal flux from penicillin-G loaded SUVs.order of corneal permeation

SUV+MLV->SUV->MLV free drug.

Recent studies investigated SUVs with positive charge improved the corneal retention by intracting with negative charged corneal surface.

3)Intraviteral application:-Recently liposomes are the first injectable system for intraviteral administration.Liposomes are sustained release drug delivery system for prolonged time.liposome decreased tisse toxicity and improves intraviteral half life.

Recently ocular pharmacologists used liposomal hydrogel and sterically stabalized liposomes to find the disadvantages related to intravitral administration of liposomes.Fluconazole liposomes used to treat candida endophthalmitis.Fluconazole sol caused photoreceptor disorientation changes of retina.

Subconjunctival applications:-This administration system has gained new momentum in delivering the drug to both anterior and posterior segments.This system providessteady state release at site of injection.This system is better than topical application it improve patient compliance.Low molecular weight heparin is used to treat subconjunctival haemorrhage.clodronate liposomes used to inhibit infiltration of microphages in the conjunctive in case of blepharo conjunctivitis.

5) Topical drug delivery:-In this liposomes are applied on skin surface.It is effective drug delivery system into skin.This system having less side effects because lower doses are required.

6) Treatment[of] human immunodeficiency virus (HIV) infections:-Many antiretroviral nucleotides are used to treat AIDs.Newly investigated antiretroviral agent antisense oligonucleotide is used to cure HIV-1.

7) Antimicrobial agents are encapsulated in liposomes.Liposomes protect intraped drug from againt enzymatic degradation.

8) Lipid nature of vesicles improves cellular uptake of antibiotics into microorganisms.

Conclusion

Liposomes are used as a carrier system for targeted drug delivey.Liposomes is used in broad range of pharmaceutical applications. Liposomal drug delivery system reduced toxicities and improve efficacy compared with free complements. Liposomes can be administered by following routes such as dermal,ocular,oral,parenteral.liposomal encapsulated drugs have altered pharmacokinetics. Recently liposomes are used as carriers of drug delivery to target site. Liposomal formulations are also used to treat bacterial conjunctivitis and glaucoma.

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