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A COMPREHENSIVE REVIEW ON LIPOSOMES

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ABSTRACT

This article is intended to provide an overview of liposomal drug delievery system. In this, we focussed on the factors affecting the behaviour of the liposomes, these are one amongst the various drug delievery system is used to target the drug to particular tissue. Because of structure similarity between the lipid bilayer and cell membrane, lip[osomes can easily penetrate and show their effect and a free drug would not penetrate. Liposome were first made by A.D Bangham in early 1960. Their size range from 25 to 500nm.

KEYWORDS: liposomal drug delievery, Bangham.

INTRODUCTION

Over the past few decades, liposomes have received widespread attention as a carrier system for therapeutically active compound, due to have a specialised characteristics such as capability to incorporate both hydrophillic as well as in hydrophobic drug, low toxicity, good compatibility, lack of immune system activation and targeted delievery of bioactive compound to the site of action.[1] Although, liposomes have been extensively studied as promising carriers for therapeutically active compound, some of the drawback of liposomes.used in pharmaceutics are the rapid degradation due to reticuloendothelial system[RES] and inability to achieve a sustain release of a drug.[2]

Liposomes are colloidal vesicular structures composed of one and more than one lipid bilayers surrounding and equal numbers of aqueous compartments. the sphere like shell encapsulated a liquid interior which contains substance such as peptides and protein, hormones and enzymes, anti-fungal and anti-cancer agents. Free drug introduce in blood stream achieves a therapeutic level for a long duration as drug must first be release from liposomes before metabolism.[3]

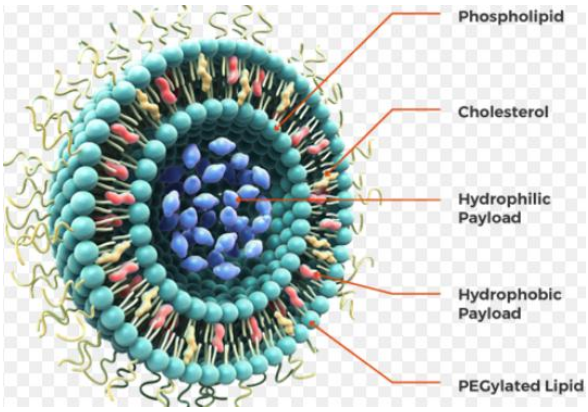

Figure 1: Liposomes.

Advantage of liposomes[4]

- Suitable for delievery of hydrophobic, amphiphatic and hydrophillic drugs.
- Liposomes are biocompatible, completely biodegradable, non-toxic and non immunogenic.
- Stability increased if liposomes prepared via encapsulation.
- Liposomes reduce the toxicity of the encapsulated agent (amphoterecin B Taxol)
- Site avoidance effect.

Disadvantages of liposomes[5]

Production cost is high
Leakage an fusion of encapsulated drug/ molecules
Short half-life

Types of liposomes

Liposomes are classified on the basis of;

A. Based on structural parameters[6]

1. Unilamellar vesicles

- Smaller unilamellar vesicles(SUV): size ranges from 20-40 nm
- Medium unilamellar vesicles(MUV): size ranges from 40-80nm
- MNLarge unilamellar vesicles(LUV): size ranges from 100-1000 nm

2. Oligolamellar vesicles(OLV): These are made up of 2-10 bilayers of lipids surrounding a large internal volume.[7]

3. Multilamellar vesicle (MLV): They have multiple bilayers. They differ according to way by which they are prepared.[8]

B. Based on method of liposomes preparation

1. REV: Single or oligolamellar vesicles made by reverse phase evaporation method.
2. MLV-REV: Multilamellar vesicles made by reverse -phase evaporation method.
3. FATMLV: Frozen and thawed MLV
4. SPLV: Stable plurilamellar vesicles
5. DRV: Dehydration -rehydration method
6. VET: Vesicles prepared by extrusion technique

C. Based upon composition and application

1. Conventional liposomes(CL): Neutral or negatively charged phopholipid and cholestrol.
2. Fusogenic liposomes(RSVE):Reconstituted sendai virus envelopes
3. Cationic liposomes: Cationic lipids with DOPE
4. PH sensitive liposomes: Phospholipids such as PE or DOPE with either CHEMS or OA.[9]

Structural components

1. Phospholipids

Glycerol containing phospholipid are most common used component of lipospome formulation and represent greater than 50% of weight of lipid in biological membranes. These are derived from phophatidic acid and backbone of the molecule is glyceryl moeity. The group C3OH is esterified to phosphoric acid and OH at C1 and C2 are esterified with long chain. The remaining OH groups of phophoric acid may be further esterified to a wide range of organic alcohols including glycerol choline, ethanolamine, serine and inositol.[9]

- Example of phopholipid are
- Phosphatidyl choline (lecithin)
- Phophatidyl serine (ps)
- Phophatidyl inositol(PI)

2. Sphingolipids

These are important constituents of plant and animal cell. It contain 3 characteristic building blocks.

- A molecule of F.A
- A molecule of sphingosine
- A head group that can vary from simple alcohols such as choline to very complex carbohydrate.[10]

3. Sterols

- Cholesterol and its derivative are often included in liposomes for :
- Decreasing the fluidity or microviscosity of the bilayer.
- Reducing the permeability of the membrane to water soluble molecule.[11]

4. Synthetic phopholipids

Example for saturated phospholipid are

- Distearoyl phosphatidyl choline (DSPC)
- Dipalmitoyl phosphatidyl choline (DPPC)
- Dipalmitoyl phosphatidyl serine (DPPS)

Example for unsaturated phospholipids

1. Dioleoyl phophatidyl choline (DOPC)
2. Dioleoyl phophatidyl glycerol(DOPG)[12]

5. Polymeric material

Synthetic phopholipid with diactylenic group in the hydrocarbon chain polymerize when exposed to U.V, leading to formation of polymerized barrier to entrapped aqeous drugs.[13]

6. Cationic lipids

Example - DODAB/C -Dioctadecyl dimethyl ammonium bromide or chloride.

DOTAP- Dioleoyl propyl trimethyl ammoniumchloride - this is an analogue of DOTAP and various others including various analogues of DOTMA and cationic derivatives of cholesterol.[14]

7. Other substances

- Many single chain surfactants can form liposomes on mixing with cholesterol.
- Sterylamine and dicetyl phosphate

Non - ionic lipids.[15]

Method of liposome preparation

General methods

Liposomes are prepared by four basic stages

1. Drying down lipid from organic solvent.
2. Dispersing the lipid in aqueous media.[16]
3. Purifying the resultant liposomes.
4. Analyzing the final produc.t

Method of liposome preparation and drug loading.

The following methods are used for the preparation of liposomes.

1. Pssive loading technique.
2. Active loading technique.

Passive loading technique include three different methods.

1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method.[17]

Mechanical dispersion method
Mechanical dispersion method are of following types:
1.1 Sonication
1.2 French pressure cell: extrusion
1.3 Freeze-thawed liposomes
1.4 Membrane extrusion.[18]
1.5 Microemulsion
1.6 Dried reconstitued vesicles.[19]

Sonication
Sonication uses an ultrasonic bath or probe to apply sound energy to a liquid containing particles. This uses sound waves to agitate particles in a solution. It converts an electrical signal into a physical vibration to break substance apart.These disruption can mix solutions, accelerate the dissolution of a solid into a liquid such as sugar into water, and remove dissolved gas from liquid.[20]

These are two sonication techniques:
a) Probe sonication
b) Bath sonication

French pressure cell: extrusion
It involves the extrusion of MLV through a small orifice. An important feature of the french pressure vesicle method is that the proteins do not seem to be significantly pretentious during the procedure as they are in sonication. An interesting comment is that french pressure vesicle appears to recall entrapped solutes significantly longer than SUVs do, produced by sonication or detergent removal.[21,22]

Freeze -thawed liposomes
SUVs are rapidly frozen and thawed slowly. The creation of unilamellar vesicles is as a result of the fusion of SUV throughout the processes of freezing and thawing.[23]

Solvent dispersion method
In these methods, lipids are first dissolved in an organic solution and then brought into contact with aqueous phase containing material to be entrapped with liposomes.[24]

Ethanol injection method : In this ethanol solution of the lipids is directly injected rapidly to an excess of saline or other aqueous medium with a fine needle and the ethanol is diluted in water and phospholipids molecules are dispersed through the medium. This procedure yield a high amount of SUVs (about 25 nm diameter).[25]

Ether injection: It involves injecting the immiscible organic solution very slowly into an aqueous phase through a narrow needle at a tem perature of vaporizing of organic solvent.

Detergent removal method (removal of non-encapsulated material).[26]

Dialysis the detergents at their critical micelle concentration (CMC) have been used to solubilize lipids. As the detergent is detached, the micelles become increasingly better -off in phospholipid and lastlly combine to form LUVs. The detergents were removed by dialysis. The dialysis can be performed in dialysis bags engrossed in large detergent free buffers (equillibrium dialysis).[27]

Evaluation of liposomes
To ensure the performance of liposome, the evaluation parameters were performed.

Physical characterisation evaluates variopus parameters including size, shape, surface featurelamellarty, phase behaviour and drug release profile.

Chemical characterisation includes those studies which establish the purity and potency of various lipophillic constituents.[28]

Some of the parametrs are
1-Vesicle shape and lamellarity: Vesicle shape can be assesed using electron microscopic techniques. Lamellarity of vesicles i.e number of bilayer present in liposomes is determined using Freeze -Fracture elecron micrpscopy.[29]

2-Vesicle size and size distribution: For the determination of size of liposomes, electron microscopy is used.[30]

Most of method used in size shape and distribution analysis can be grouped into various categories namely microscopic, diffraction, scattering and hydrodynamic technique.

a) Microscopic technique
i) Optical microscopy: The microscopic method includes use of bright- field, phase contrast microscope and flourescent microscope and is useful in evaluating vesicle size of large vesicle.[31]
ii) Negative strain TEM: Electron microscopic technique used to assess liposomes shape and size are mainly negative strain TEM and scanning electron microscopy. Negative strain electron micrposcopy visualizes bright areas against dark background.[32]
iii) Cryo- transmission electron microscopy techniques (cryo-TEM): This technique has been used to elucidate the surface morphology and size of vesicles.

b) Diffraction and scattering techniques
i. Laser light scattering: By using this techniques, we can measures particle in range about 3nm.[33]

c) Hydrodynamic technique: This technique includes gel permeation and ultracentrifuge. Exclusive chromatography on large pure gels was introduced to separate SUVs from radial MLVs.

3) Encapsulation efficiency and trapped volume: These determine amount and rate of entrapment of water soluble agents in aqueous compartment of liposomes.

a) Encapsulation efficiency: It describes the percent of the aqueous phase and hence percent of water soluble drug that become ultimately entrapped during preparation of liposomes and usually expressed as % entrapment/mg lipid.[34]

b) Trapped volume: The best way to measure internal volume is to measure quantity of water directly, by replacing external medium (water) with spetroscopically inert fluid (deuterium oxide) and then measuring water signal using NMR.

4) Drug release: The mechanism of drug release from liposomes can be assessed by use of well calibrated in vitro diffusion cell. The liposome based formulation can be assissted by employing in vitro assays to predict pharmacokinetics and bioavailability of drug before employing costly and time-consuming in vivo studies. The dilution - induced drug release in buffer and plasma was employed as predictor for pharmacokinetic performance of liposomal formulations and another assay which determined intracellular drug release induced by liposome degradation in presence of mouse-liver lyosome lysate was used to aseess the bioavailability of drug.[35]

Applications

- Cancer chempotherapy
- Gene therapy
- Liposomes as carriers for vaccine
- Liposomes as carrier of drug in oral treatment
- Metal storage disease
- Opthalmic delievery of drugs
- Against leishmaniasis
- Liposomes for topical application
- Liposomes for pulmonary delivery.[32]

CONCLUSION

Liposomes have been used in a broad range of pharmaceutical application. Liposomes have been realized as extremely useful carrier system for targeted drug delievery. A number of drug candidates or chemical molecules which are highly potent and have low therapeutic indication can be targeted to the required diseased site using the liposomal drug delievery system. The pharmacokinetic of drug is altered due to the drug encapsulated in liposomes. The drug encapsulated in with in the phospholipid bilayer diffuses out from the bilayer slowly. The release rate of drug is depend upon various factors like drug concentration, drug to lipid ratio, encapsulated efficiency. Liposomal drug exhibit reduced toxicities and enhance their efficacy compared with free complements. Thus, the liposomal approach can be succesfully utilized to improve the pharmacokinetic and therapeutic efficacy and simultaneously reducing the toxicity of various highly potent drugs. However, property of liposome based on the pharmaceutical applications and available products, we can say that liposomes have not difinitely, but surely most acquire space in pharma industries and also estabilished their position in modern delievery system.

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