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A Review on: Liposemes

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ABSTRACT

Liposomes derived from two Greek words: Lipo (FAT) and soma(BODY).It is so named becauseof its composition is primarily of phopholipid. Liposomes are microparticulate lipoidal vesicales which are under extensive investigation as drug carriers for improving the drug delivery of therapeutic agents,relatively composed of biocompatible and bio degradable materials,and they consists of an aqueous volume entrapped by one or more bilayers of natural or synthetic lipids.A liposome is a spherical veicle having at least one lipid bilayer.the liposomes can be used as a vehicle for administration of nutrients and pharmaceutical drugs.liposomes can be prepared by disrupting biological membranes(such as by sonication).Size range:25-5000nm.

Introduction

LIPOSOMES AND HYDROPHILIC, AMPHIPHILIC ANDLIPOPHILIC SUBSTANCES

Liposomes which are used as delivery systems, may encapsulate hydrophilic substancesin their aqueous core.Amphiphilic and lipophilic substances, e.g. oil soluble UV filters, can be incorporatedinto the lipid bilayer.Loaded liposomes as well as non-loaded, empty liposomes, are used in cosmetics.The major effect of empty liposomes is an increase in skin humidity.

BENEFITS OF USING LIPOSOMES IN SKINCAREPRODUCTS

Liposomes frequently favor the disposition of encapsulated active ingredientsin theepidermis and dermis, while the permeation rate is decreased. This helps to fix active ingredients to the outermost skin layers as desired for cosmetic products. Simultaneously, the washing out may be delayed so that, for example, aqueoussun care products containing liposome-encapsulated UVfilters are water-resistant.

THE SIZE, COMPOSITION AND THE NUMBER OF LIPOSOMES USED DETERMINES THEIR SUCCESS INCOSMETIC PRODUCTS

However, these positive effects mentioned above depend on the composition, size, andthe amount of liposomes.As far as empty liposomes are concerned, it has recently been discussed that the positiveeffects are not strongly related to the vesicular nature.The presence of the appropriate lipids (phospholipids, sphingolipids) sufficesforcosmetic efficacy.

RISK ASSESSMENT AND REGULATIONS CONCERNING THE USE OF APPLIED PHOSPHOLIPIDS IN FOOD ANDCOSMETICS

The skin compatibility of topically applied phospholipids is very high.There are no restrictions concerning their use in foodstuff and cosmetics, neither in the EU nor for regulations of the US Food and Drug Administration; lecithins are generallyaccepted as safe (GRAS status - Generally Recognized As Safe).

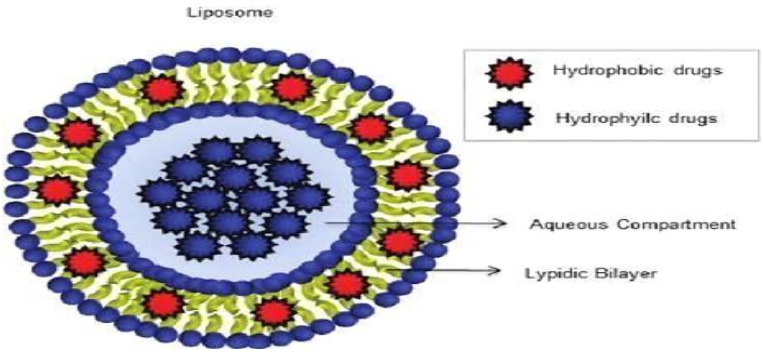
However, it is known that high doses of phospholipids which are applied topically over alonger period may lead to irritations on dry and normal skin. Likewise, it has been mentioned that due to a biochemical feedback mechanism, a long-term application of phospholipids may have an impact on the dermal lipid metabolism.

CHARACTERISTICS OF LIPOSOME USED FOR DRUGDELIVERY SYSTEM

Liposome as a drug delivery system is emerges as a one of the potential in pharmaceutical industries.The properties of nano-medicines such as release from dosage forms at specific sites as well as drug circulation and absorption into body membranes are dramatically affected by some physical and chemical characteristics of liposome as a drug delivery system.Zeta potential is a scientific term used for electro kinetic potential in colloidalsystemswhich has a major effect on the various properties of liposome.There are various challenges in the field of drug delivery system, including poorsolubility and stability.
Particle size and charge are two major factors which could play key roles in this regard.In this paper synthesis of liposome by extrusion method and the effect of zeta potentialand particle size are considered.

COMPONENTS OF LIPOSOMES;

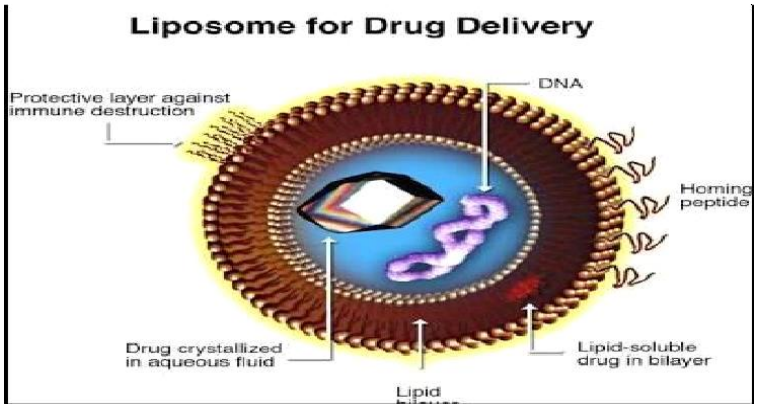
The structural components ofliposomes include:phospholipids, especially phosphatidyl choline. Cholesterol And drug molecule



LIST OF SOME CLINICALLY APPROVED LIPOSOMALDRUGS:

MECHANISM OF OF LIPOSOMAL DRUGS:

They typically form after supplying enough energy to a dispersion of phosphor lipids in a polar solvants such as,water to break multiamellar aggregates into oligo-or uniamellar bilayer vesicles.



- A liposome encapsulates a region of aqueous solution inside ahydrophobic membrane
- Dissolved hydrophilic solutes can not pass through thelipids.hydrophobic chemicals can bemembrane.
- In this way, liposomes carry both hydrophobic and hydrophilicmolecules to deliver themolecules to sit of action.
- The lipid bilayer can fuse with each other bilayer such as the cellmember, thus deliveringthe liposome contents.

CLASSIFICATION OF LIPOSOME

Liposomes are often distinguished according to their number of lamellae and size. Smallunilamellar vesicles (SUV), large unilamellar vesicles (LUV) andlarge multilamellar vesicles (MLV) or multivesicular vesicles (MVV) are differentiated (see figure 2).
SUVs show a diameter of 20 to approximately 100 nm. LUVs, MLVs, andMVVs rangein size from a few hundred nanometers to several microns. The thickness of the membrane (phospholipid bilayer) measuresapproximately 5 to 6nm.

PROCESSING METHODS FOR FORMING LARGELIPOSOMES

Large liposomes form spontaneously when phospholipids are dispersed inwater abovetheir phase transition temperature.
The preparation of SUVs starts usually with MLVs, which then aretransformed intosmall vesicles using an appropriate manufacturing technique, e.g. high-pressure homogenization.

NIOSOMES AND SPHINGOSOMES

Niosomes and sphingosomes are vesicles with a similar structure. In contrast to liposomes,nonionic surfactants, e.g. polyglyceryl alkyl ethers, or sphingolipids make up the bilayer ofniosomes and sphingosome

CHARACTERISTICS AND BEHAVIOUR OF LIPOSOMESWHEN INCUBATED WITH NATURAL BILE SALT EXTRACT: IMPLICATIONS FOR THEIR USE AS ORAL DRUGDELIVERY SYSTEMS

The use of liposomes for oral administration of drugs and for food applications is basedon their ability to preserve entrapped substances and to increase their bioavailability.
Bile salts are one of the agents that affect the liposome structure during intestinal digestion and the main reported studies on liposome/bile salt systemsused only one bilesalt.
The aim of this work is to characterise the interaction of liposomes with a natural bile saltextract (BSE) at physiological pH and temperature.
Three types of liposomes (fluid, gel-state and liquid-ordered bilayers) were studied.
Fluid bilayers were completely permeable to an entrapped dye with partial or completedisruption of vesicles (final size 10 nm).
Gel-state bilayers released their content but BSE led to the formation of largemixedstructures (2000 nm).
Liquid-ordered bilayers formed mixed vesicles (1000 nm) and, surprisingly, retained a high percentage of their aqueous content (about 50%). As a consequence, each type ofliposome offers singular features to be used in oral applications due to their specific interaction with bile salts.

STABILITY OF LIPOSOMES:

During the development of liposomal drug products, the stability of thedeveloped formulation isof major consideration. The therapeutic activity of the drug is governed by the stability of the liposomes right from the manufacturing steps to storage to delivery. A stable dosage forms is the one which maintains the physical stability and chemical integrity of the active molecule during its developmental procedure and storage. A well designed stability study includesthe evaluation of its physical, chemical and microbial parameters along with the assurance of product's integrated .throughout its storage period. Hence a stability protocol is essential to study the physical andchemical integrity of thedrug product in its storage.

PHYSICAL STABILITY

Liposomes are bilayered vesicles that are formed when phospholipids are hydrated in water. The vesicles obtained during this process are of different sizes. During its storage, the vesicles tend toaggregate and increase in size to attain thermodynamically favorable state. During storage, drug leakage from the vesicles can occur due to fusion and breaking of vesicles, which deteriorates the physical stability of the liposomal drug product. Hence morphology, size and size distribution of the vesicles are important parametersto assess the physical stability

. In order to monitor this, a variety of techniques like light scattering and electron microscopy can be used to estimate the visual appearance (morphology) and size of the vesicles.

CHEMICAL STABILITY

Phospholipids are chemically unsaturated fatty acids that are prone to oxidation and hydrolysis,which may alter the stability of the drug product. Along with this, pH, ionic strength, solvent system and buffered species also play a major role in maintaining a liposomal formulation.
Indeed chemical reaction can be induced even by light, oxygen, temperature and heavy metal ions. Oxidation deterioration involves the formation of cyclicperoxides and hydroxyperoxidasesdue to the result of free radical generation in the oxidation process.

IN VIVO BEHAVIOR OF LIPOSOMES

During the optimization of liposomal formulation, various physico-chemical parameters are altered in order to achieve a desired bio-distribution and cellularuptake of drugs. Those parameters which affect the in vivo (biological)performance of liposomes are described below:

LIPOSOME SIZE

The size of the vesicle governs the in vivo fate of liposomes, because it determines the fractioncleared by RES. The rate of uptake of liposome by RES increases with the vesicle size. Liposomes larger than 0.1 μm are takenup (opsonized) more rapidly by RES, when compared to liposomes smaller than 0.1 μm. The size of the vesicle also determines the extravasation of liposomes. Tumor capillaries are more permeable than normal capillaries.

SURFACE CHARGE

The lipid – cell interaction can be governed by the nature and density of chargeon the liposomesurface. Charging the lipid composition can alter the nature and charge on the liposome. Lack ofcharge in the SUV liposomes can lead to their aggregation and thereby reducing the stability of the liposome; whereas,the interaction of neutrally charged liposome
with the cell is almost negligible . High electrostatic surface charge on the liposome may provideuseful results in promoting lipid – cell interaction.

SURFACE HYDRATION

Liposomes with hydrophilic surface coatings are less prone to opsonization, hence reducing its uptake by RES cells. This can be attributed to the hydrophilic surface coating, which reduces theinteraction of liposomes with cell and blood components.These sterically stabilized liposomes are more stable in the biological environment and exhibit high circulation half lives.

BILAYER FLUIDITY

Lipid exists in different physical states above and below the phase transition temperature. Theyare rigid and well ordered below Tc but are in fluid like liquid – crystalline state above. Table inidcates the phase transition temperatures of various phospholipids.Liposomes with low (less than 37°C) are fluid like and are prone to leakage of the drug content at physiological temperature. But, the liposomes with high (greater than 37°C) are rigid and less leaky at physiological temperature.

ADVANTAGES OF LDDS

Suitable for delivery of hydrophobic, hydrophilic and amphipatic drugs and agents
Chemically and physically well characterized entities Biocompatible Use as carrierfor suitable for controlled release drug delivery.
Suitable to give localized action in particular tissues. Suitable to administer viavariousroutes. Increased efficacy and therapeutic index. Reduction on toxicityof the encapsulation agent.
Improved pharmacokinetic properties. Can be made into Varity of drug.Minimum antigenicity.

DISADVANTAGE OF LDDS

Their rapid clearance from circulation due to uptake.By the reticuloendothelial system(RES), primarily in the liver.Leakage of encaptulation drug delivery during storage.Batch to batch variation. Once administered, can't removed. Difficult in large scale manufacture and sterilization.Physical /chemical stabilityVery high production cost.Possibility of dumping due to faulty administration.

LIPOSOMES IN ANTICANCER THERAPY

Numerous different liposome formulations of numerous anticancer agents were shown to be lesstoxic than the free drug .Anthracyclines are drugs which stop the growth of dividing cells by intercalating into the DNA and, thus, kill mainly rapidly dividing cells. These cells are not only in tumors but are also inhair, gastrointestinal mucosa, and blood cells; therefore, this class of drug is very toxic. In most cases, the toxicity was reduced to about 50%. These includeboth acute and chronic toxicities because liposome encapsulation reduces the delivery of the drug molecules towards those tissues. For the same reason, theefficiency was in many cases compromised due to the reduced bioavailabilityof the drug, especially if the tumor was not phagocytic or located in the organsof mononuclear phagocytic system. In some cases, such as systemic lymphoma, the effect of liposome encapsulation showed enhanced efficacy due to the continued release effect, i.e., longer presence of therapeutic concentrations in the circulation.

APPLICATIONS OF LIPOSOMES INMEDICINE ANDPHARMACOLOGY

FORMULATION AID

Hydrophobic drugs such as cyclosporin and paclitaxel are usually formulated in surfactants and organic co- solvents for systemic administration in humans. These solubilizers may cause toxicity at the doses needed to deliver the drug. In contrast, liposomes are made up of lipids which are relatively non-toxic, non-immunogenic, biocompatible and biodegradable molecules, and can encapsulate a broad range of water-insoluble (lipophilic) drugs.Currently, liposomes or phospholipid mixtures are being used as excipients for preparing better-tolerated preclinical and clinical formulations of several lipophilic, poorly water soluble drugs such as amphotericin B. In preclinical studies, liposomes have been evaluated as a vehicle for the delivery of paclitaxel and its analogs as an alternative to the cremophor/ ethanol vehicle.Paclitaxel liposomes were able to deliver the drug systemically and increase the therapeutic index of paclitaxel in human ovarian tumor models.

INTRACELLULARDRUGDELIVERY

Drugs with intracellular targets/receptors are required to cross the plasma membrane for pharmacological activity. Liposomes can be used to increase cytosolic delivery of certain drugs such as N- (phosphonacetyl)-L-aspartate (PALA) which are normally poorly taken up into cells.PALA is taken up intothe tumor cells through fluid-phase endocytosis (pinocytosis) and it diffuses out into the cytoplasm as the endosome pH drops . However, pinocytosis is very limitedin its efficiency.Liposomal delivery of drugs which normally enter the cells by pinocytosis canbevery effective because liposomes can contain greater concentrations of drug compared to the extracellular fluid and the endocytosis process by which negatively charged liposomes are predominantlytaken up by the cells, is more efficient than pinocytosis.

SUSTAINED RELEASE DRUG DELIVERY

Sustained release systems are required for drugs such as cytosine arabinoside (Ara-C) that are rapidly cleared in vivo and require plasma concentrations at therapeutic levels for a prolonged period for optimum pharmacological effects. It is now possible to design sustained release liposome formulations with an extended circulation half-life and an optimized drug release ratein vivo.

GENE THERAPY

A number of systemic diseases are caused by lack of enzymes/factors which are due to missingor defective genes. In recent years, several attempts have been made to restore gene expressionby delivery of the relevant exogenous DNA or genes to cells.

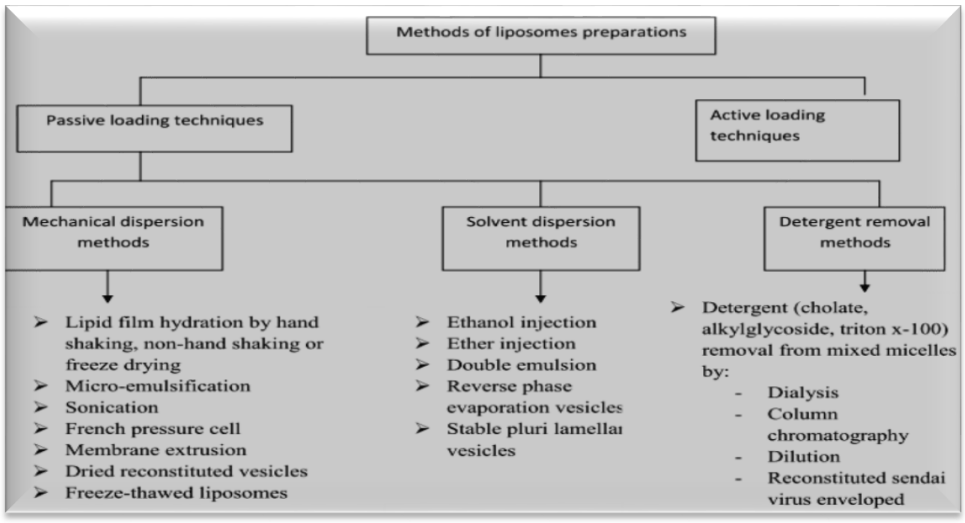
SITE-AVOIDANCE DELIVERY:

Drugs used in the treatment of diseases like cancer usually have a narrow therapeutic index (TI)and can be highly toxic to normal tissues. The toxicity of these drugs may be minimized by decreasing delivery to critical normal organs.It has been shown that even a small reduction in distribution of the drugto critical organs by encapsulation in liposomes can significantly reduce the drug toxicity. Liposomes are taken up poorly

by tissues such as heart, kidney, and GI tract, which are major sites for toxic side-effects of a variety of antineoplastic drugs.Thus, liposome formulation may improve the TI by altering the biodistribution of drug away from drug sensitivenormal tissues.

SITE-SPECIFIC TARGETING

Site-specific delivery, the concept first proposed by Paul Ehrlich >involves thedelivery of alarger fraction of drug to the target site and therefore, reducing exposure to normal.



METHODS OF PREPERATIONS OF LIPOSOMALDELIVERY SYSTEM

GENERAL METHOD OF LOADING

water soluble (hydrophilic) materials are entrapped by using aqueous solution of these materials as hydrating fluid or by the addition of drug/drug solution atsome stage during manufacturing ofthe liposomes.lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid andthen evaporated to a dry drug containing lipid film followed by its hydration. Passive Loading : involve the loading of the entrapped agents before or duringthemanufacturing procedure .
Active Loading: compounds with ionizable groups, and those which display both lipid andwater solubility, can be introduced into the liposomes after the formation of intact vesicles.

MECHANICAL DISPERSION METHODS

PREPARATION OF LIPOSOMES BY LIPID FILMHYDRATION

For preparing liposomes with mixed lipid composition, the lipids must first bedissolved and mixed in an organic solvent to assure a homogeneous mixture of lipids. Organic solvents used are chloroform or chloroform: methanol mixtures. Once the lipids are thoroughly mixed in the organic solvent, the solvent is removed to yield a lipid film.For removal of small volume of organicsolvents, dry nitrogen is used, for large volumes, rotary evaporator is used.Thelipid filmis thoroughly dried to remove residual organic solvent by placing thevial or flask on a vacuum pump overnight.Lipid solution frozen by placing thecontainers on a block of dry ice or swirling the container in a dry ice-acetone or alcohol.

SIZING OF LIPID SUSPENSION SONICATION

Disruption of LMV suspensions using sonic energy (sonication) typically produces small, unilamellar vesicles (SUV) with diameters in the range of 15-50nm. The most common instrumentation for preparation of sonicated particles are bath and probe tip sonicators.Sonication of an LMV dispersion isaccomplished by placing a test tube containing the suspension in a bathsonicator (or placing the tip of the sonicator in the test tube) and sonicating for5-10 minutes.

FRENCH PRESSURE CELL METHOD

The method involves the extrusion of MLV at 20,000 psi at 4°C through a small orifice. The method has several advantages over sonication method. The method is simple, rapid, reproducible and involves gentle handling of unstable materials. Drawbacks of this method arethat the temperature is difficult to achieve and the working volumes are relatively small (about50 mL maximum).

SOLVENT DISPERSION METHODSETHERINJECTIONMETHOD

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to anaqueous solution of the material to be encapsulated at 55-65°C or under reduced pressure. 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

A lipid solution of ethanol is rapidly injected to a vast excess of buffer. The MLVs are immediately formed. The drawbacks of the 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 thepresence of even low amounts of ethanol.

REVERSE PHASE EVAPORATION METHOD

First water in oil emulsion is formed by brief sonication of a two phase system containing phospholipids in organic solvent (diethylether or isopropylether or mixture of isopropyl ether andchloroform) and aqueous buffer. The organic solvents are removed under reduced pressure, resulting in the formation of a viscous gel. The liposomes are formed when residual solvent is removed by continued rotary evaporation under reduced pressure. With this method high encapsulation efficiency up to 65% can be obtained in a medium of low ionic strength for example 0.01M NaCl. The method has been used to encapsulate small and large macromolecules. The main disadvantage of the method is the exposure of the materials to be encapsulated to organic solvents and to brief periods of sonication.

DETERGENTREMOVALMETHOD

The detergents at their critical micelles concentrations have been used to solubilize lipids. As the detergent is removed the micelles become progressively richer in phospholipid and finally combine to form LUVs. The detergents can be removed by dialysis. The advantages of detergent dialysis method are excellent reproducibility and production of liposome populations which are homogenous in size. The main drawback of the method is the retention of traces of detergent(s) within the liposomes.

Conclusion

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 delivery system. Liposomes have been
used in a broad range of pharmaceutical applications. Drugs encapsulated in liposomes can have a significantly altered pharmacokinetics. The efficacy of the liposomal formulation depends on its ability to deliver the drug molecule to the targeted site over a prolonged period of time, simultaneously reducing its (drug's) toxic effects. The drugs are encapsulated within the phospholipidsbilayer and are expected to diffuse out from the bilayer slowly. Various factors like drug concentration, drug to lipid ratio, encapsulation efficiency and in vivo drug release must be considered during the formulation of liposomal drug delivery systems. Finally, liposomal drugs exhibit reduced toxicities and retain enhanced efficacy compared with free complements.

The development of deformable liposomes and ethosomes along with the administration of drug loaded liposomes through inhalation and ocular route are some of the advances in the technology and very useful in pharma Industries. Thus liposomal approach can be successfully utilized to improve the pharmacokinetics and therapeutic efficacy, 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 definitely but surely most acquire space in pharma Industries and also established their position in modern delivery systems.

Declaration of Interest: The authors declare no conflict of interest.Acknowledgement:

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