

LIPOSOMES: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Liposomes derived from two Greek words: Lipo (FAT) and soma (BODY). It is so named because of its composition is primarily of phospholipid. Liposomes are microparticulate lipoidal vesicles 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 consist of an aqueous volume entrapped by one or more bilayers of natural or synthetic lipids. A liposome is a spherical vehicle 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.

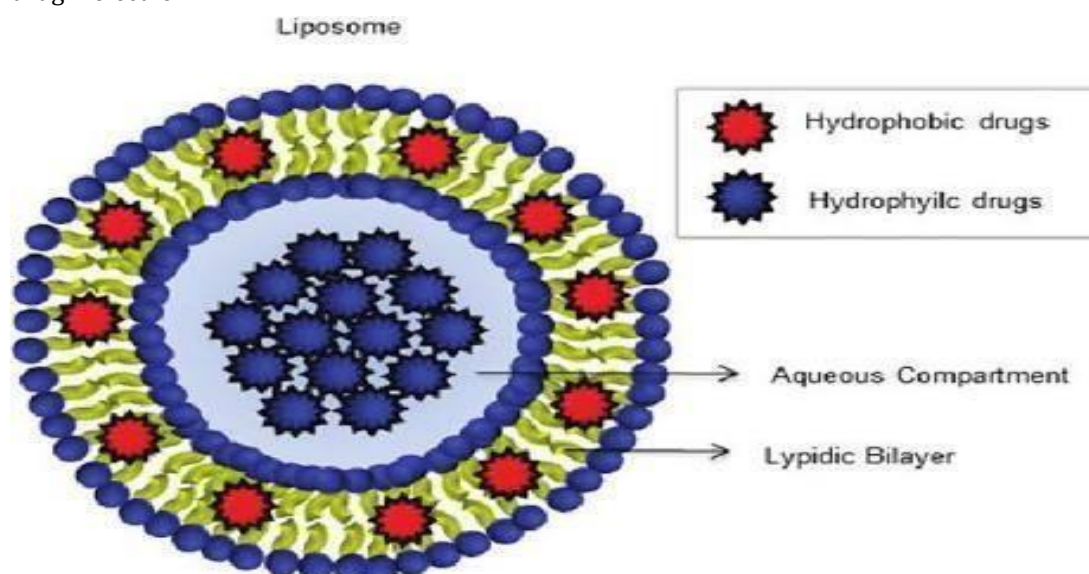
I. INTRODUCTION

Liposomes are self-assembled (phospho)lipid-based drug vesicles that form a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multilamellar) enclosing a central aqueous compartment. The size of liposomes ranges from 30 nm to the micrometer scale, with the phospholipid bilayer being 4-5 nm thick. The field of liposomology was launched by the British scientist Alec Bangham and colleagues at Babraham Cambridge in the mid-1960s, and they first published the structure of liposomes in 1964. Since then, liposomes have been widely investigated as delivery vehicles for small molecular drugs, protein, nucleic acid, and imaging agents. Different administration routes, such as parenteral, pulmonary, oral, transdermal, ophthalmic, and nasal routes, have been developed to improve therapeutic efficacy and patient compliance. In addition, liposomes have been widely applied in the fields of food and cosmetics.

COMPONENTS OF LIPOSOMES:

The structural components of liposomes include:

- Phospholipids, especially phosphatidylcholin.
- Cholesterol
- And drug molecule

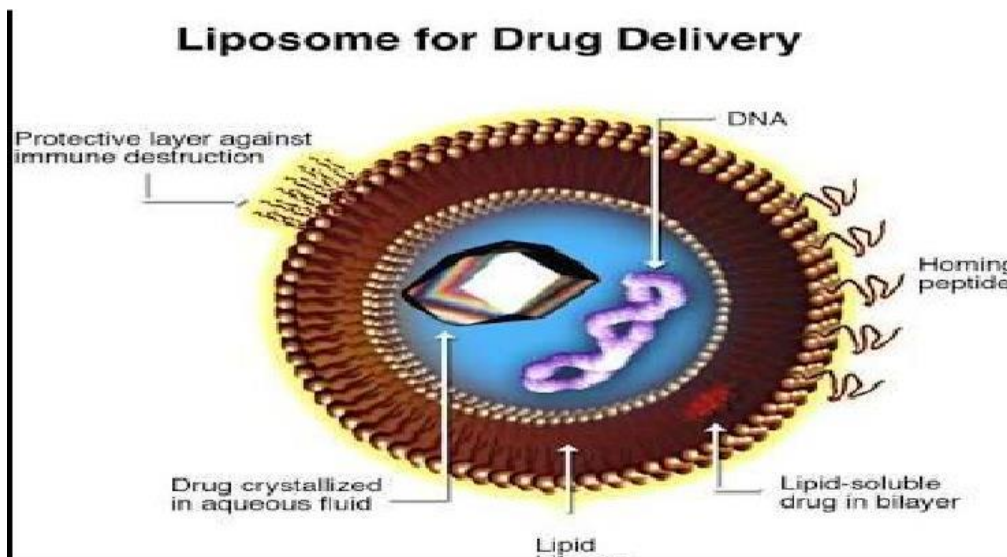


Therapeutic agent	Disease treated	Liposomal Product name	Company Name	FDA approval year
Amphotericin- B	Systemic Fungal Infections	Ambelcet®	Enzon	1995/1996
		Ambiosome®	Gilead Sciences	1997
		Amphotec®	Alza Corp.	1997
Cytarabine	Lymphomatous Meningitis	DepoCyt®	SkyePharma/Enzon	1999
Daunorubicin	AIDS-related Kaposi's Sarcoma	DaunoSome®	Gilead Sciences	1996
Doxorubicin	Ovarian and Breast Cancer	Caelyx®*	Schering-Plough	1999
	AIDS-related Kaposi's	Doxil®*	Alza Corp.	1995

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 solvents such as,water to break multiamellar aggregates into oligo-or uniamellar bilayer vesicles.



1. A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane:
2. Dissolved hydrophilic solutes can not pass through the lipids. hydrophobic chemicals can pass through the membrane.
3. In this way, liposomes carry both hydrophobic and hydrophilic molecules to deliver the molecules to site of action.
4. The lipid bilayer can fuse with each other bilayer such as the cell membrane, thus delivering the liposome contents.

CLASSIFICATION OF LIPOSOME

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

PROCESSING METHODS FOR FORMING LARGE LIPOSOMES

1. Large liposomes form spontaneously when phospholipids are dispersed in water above their phase transition temperature.
2. The preparation of SUVs starts usually with MLVs, which then are transformed into small 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 of niosomes and sphingosomes, respectively.

LIPOSOMES AND HYDROPHILIC, AMPHIPHILIC AND LIPOPHILIC SUBSTANCES

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

BENEFITS OF USING LIPOSOMES IN SKINCARE PRODUCTS

1. Liposomes frequently favor the disposition of encapsulated active ingredients in the epidermis and dermis, while the permeation rate is decreased.
2. 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, aqueous sun care products containing liposome-encapsulated UV filters are water-resistant.

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

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

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

1. The skin compatibility of topically applied phospholipids is very high.
2. 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 generally accepted as safe (GRAS status - Generally Recognized As Safe).
3. However, it is known that high doses of phospholipids which are applied topically over a longer 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 DRUG DELIVERY SYSTEM

1. Liposome as a drug delivery system emerges as one of the potential in pharmaceutical industries.
2. 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.
3. Zeta potential is a scientific term used for electro kinetic potential in colloidal systems which has a major effect on the various properties of liposome.
4. There are various challenges in the field of drug delivery system, including poor solubility and stability.
5. 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 potential and particle size are considered.

CHARACTERISTICS AND BEHAVIOUR OF LIPOSOMES WHEN INCUBATED WITH NATURAL BILE SALT

EXTRACT: IMPLICATIONS FOR THEIR USE AS ORAL DRUG DELIVERY SYSTEMS

1. The use of liposomes for oral administration of drugs and for food applications is based on their ability to preserve entrapped substances and to increase their bioavailability.
2. Bile salts are one of the agents that affect the liposome structure during intestinal digestion and the main reported studies on liposome/bile salt systems used only one bile salt.
3. The aim of this work is to characterise the interaction of liposomes with a natural bile salt extract (BSE) at physiological pH and temperature.
4. Three types of liposomes (fluid, gel-state and liquid-ordered bilayers) were studied.
5. Fluid bilayers were completely permeable to an entrapped dye with partial or complete disruption of vesicles (final size 10 nm).
6. Gel-state bilayers released their content but BSE led to the formation of large mixed structures (2000 nm).
7. 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 of liposome 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 the developed formulation is of 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 form 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 includes the evaluation of its physical, chemical and microbial parameters along with the assurance of product's integrity throughout its storage period. Hence a stability protocol is essential to study the physical and chemical integrity of the drug 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 to aggregate 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 parameters to 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 cyclic peroxides and hydroxyperoxides due to the result of free radical generation in the oxidation process.

IN VIVO BEHAVIOR OF LIPOSOMES (EVALUATION)

During the optimization of liposomal formulation, various physico-chemical parameters are altered in order to achieve a desired bio-distribution and cellular uptake 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 fraction cleared by RES. The rate of uptake of liposome by RES increases with the vesicle size. Liposomes larger than 0.1 μm are taken up (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 charge on the liposome surface. Charging the lipid composition can alter the nature and charge on the liposome. Lack of charge 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 provide useful 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 the interaction 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. They are rigid and well ordered below T_c but are in fluid like liquid – crystalline state above. Table indicates 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

1. Suitable for delivery of hydrophobic, hydrophilic and amphipatic drugs and \square agents.
2. Chemically and physically well characterized entities Biocompatible Use as carrier for suitable for controlled release drug delivery.
3. Suitable to give localized action in particular tissues. Suitable to administer via various routes. Increased efficacy and therapeutic index. Reduction on toxicity of the encapsulation agent.
4. Improved pharmacokinetic properties. Can be made into Variety of drug.
5. Minimum antigenicity.

DISADVANTAGE OF LDDS

1. Their rapid clearance from circulation due to uptake.
2. By the reticuloendothelial system (RES), primarily in the liver.
3. Leakage of encapsulation drug delivery during storage
4. Batch to batch variation. Once administered, can't removed.
5. Difficult in large scale manufacture and sterilization.
6. Physical /chemical stability
7. Very high production cost.
8. Possibility of dumping due to faulty administration

LIPOSOMES IN ANTICANCER THERAPY

Numerous different liposome formulations of numerous anticancer agents were shown to be less toxic 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 in hair, gastrointestinal mucosa, and blood cells; therefore, this class of drug is very toxic. In most cases, the toxicity was reduced to about 50%. These include both acute and chronic toxicities because liposome encapsulation reduces the delivery of the drug molecules towards those tissues. For the same reason, the efficiency was in many cases compromised due to the reduced bioavailability of the drug, especially if the tumor was not phagocytic or located in the organs of 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 IN MEDICINE AND PHARMACOLOGY

FORMULATION AID

Hydrophobic drugs such as cyclosporin and paclitaxel are usually formulated in surfactants and organic 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.

INTRACELLULAR DRUG DELIVERY

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 into the tumor cells through fluid-phase endocytosis (pinocytosis) and it diffuses out into the cytoplasm as the endosome pH drops. However, pinocytosis is very limited in its efficiency. Liposomal delivery of drugs which normally enter the cells by pinocytosis can be very effective because liposomes can contain greater concentrations of drug compared to the extracellular fluid and the endocytosis process by which negatively charged liposomes are predominantly taken 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 rate in vivo.

GENE THERAPY

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

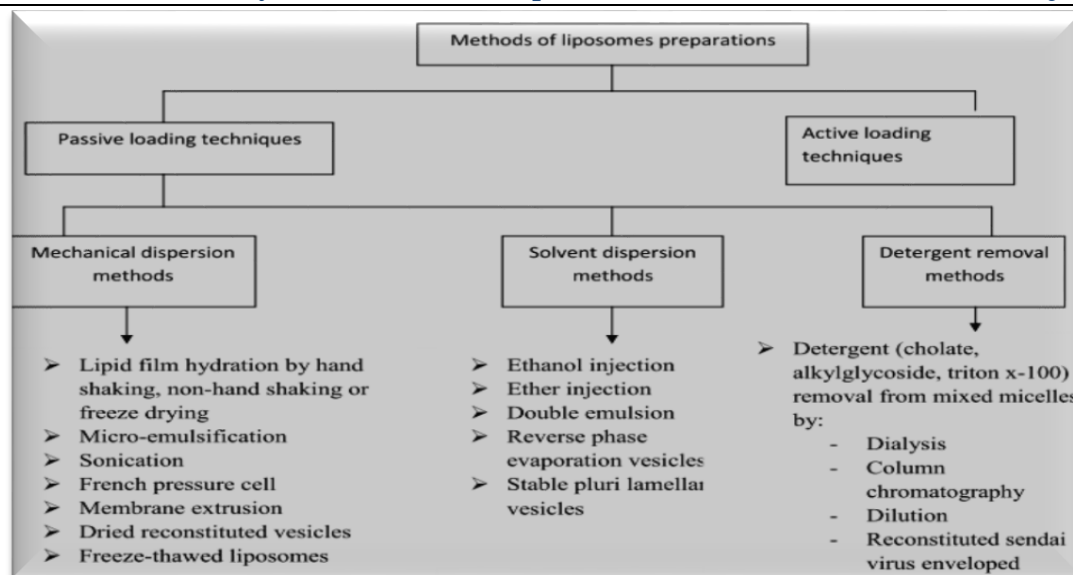
SITE-AVOIDANCE DELIVERY:

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 drug to 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 sensitive normal tissues.

SITE-SPECIFIC TARGETING

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

II. METHODS OF PREPARATIONS OF LIPOSOMAL DELIVERY 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 at some stage during manufacturing of the liposomes. Lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid and then evaporated to a dry drug containing lipid film followed by its hydration.

Passive Loading: involve the loading of the entrapped agents before or during the manufacturing procedure.

Active Loading: compounds with ionizable groups, and those which display both lipid and water solubility, can be introduced into the liposomes after the formation of intact vesicles.

MECHANICAL DISPERSION METHODS:

PREPARATION OF LIPOSOMES BY LIPID FILM HYDRATION

For preparing liposomes with mixed lipid composition, the lipids must first be dissolved 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 organic solvents, dry nitrogen is used, for large volumes, rotary evaporator is used. The lipid film is thoroughly dried to remove residual organic solvent by placing the vial or flask on a vacuum pump overnight. Lipid solution is frozen by placing the containers on a block of dry ice or swirling the container in a dry ice-acetone or alcohol.

SIZING OF LIPO-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 is accomplished by placing a test tube containing the suspension in a bath sonicator (or placing the tip of the sonicator in the test tube) and sonicating for 5-10 minutes.

SOLVENT DISPERSION METHODS

ETHER INJECTION METHOD

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous 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 the presence of even low amounts of ethanol.

DETERGENT REMOVAL METHOD

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.

III. FUTURE ASPECT

Liposome-based formulations can be an ideal technique to deliver lipophilic bioactive, vitamins, minerals, and phytochemicals.

Research into the targeted delivery of liposomes to a tumour or cancer cells has reported this as a potential application of liposomal drug delivery systems.

IV. CONCLUSION

It was concluded from the review that liposomes can be a promising carrier for improving targeted delivery of a large number of drugs: Antimicrobial agents, drugs against cancer, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials. Liposomes are administered orally, parenterally and topically as well as employed in a broad range of pharmaceutical and pharmacology applications with therapeutic and diagnostic purposes and as good carriers in gene delivery various drugs. Liposomal delivery systems have been approved as a suitable carrier for therapeutic effectiveness in terms of duration of action and decrease in dose frequency and delivering drugs at higher efficiency and lower toxicity

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