Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

LIPOSOMES: A CARRIER FOR NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

There are various carriers in the field of pharmaceutical science and some of the drug carriers reached the stages of clinical trials where liposome shows the effective drug delivery to the targated site. These are vesicular concentric structures with a range in size from a nanometer to several micrometers a phospholipids bilayer and are biocompatible, biodegradable and non immunogenic. Drug enclosed in liposomes include Doxorubin, Cisplatin, Vincristin, Melphalan, Sarcolycin, Daunorubicin, Etoposide etc. The liposomes loaded drugs can be administrated by various routes like i.v, oral, in local application, ophthalmic etc. And are used for treatment of various disease cancer, rheumatoid arthritis, Fungal infections, tropical parasites, bacterial infections, Cardiovascular diseases, Darmetology, gene therapy etc. Now a days pharmaceutical science have vary demand of liposomes to reduce various problems like toxicity, poor solubility, short half life and poor bioavailability and other strong side effect of various important drugs can be over thrown by employing the idea of liposomes in various diseases like cancer etc. Liposomes offer ample opportunities for the explorer to explore the unidentified development in the field of pharmaceutical technology.

KEYWORDS

Drug Carrier, Liposomes, Biocompatible, Biodegradable, Etoposide, Phospholipids and Bilayer.

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INTRODUCTION

Liposomes were defined as an artificial microscopic vesicle consisting of a central aqueous compartment surrounded by one or more concentric phospholipid layers (lamellas). Furthermore, hydrophilic (in the aqueous cavity), hydrophobic (enclosed in lipidic membrane) and amphiphilic substances can be incorporated within these vesicles developing large potential applications[1]. Numerous researchers have worked with these structures making of liposomes the most popular nanocarrier systems. Liposomes

were first produced in England in the 60's, by Bangham.

Drug carriers are usually required in pharmaceutical field for many reasons: firstly, most of the drugs are scarcely soluble in aqueous environments, like body fluids or the cell; secondly, many of the drugs, as well as proteins or DNA, need to be protected from unwanted interactions which could yield enzymatic degradation or loss of the native structure, hydrolysis and consequently of their activity[2]. Carriers can be arrange to include surface functionalities, such as to improve the selectivity of delivery, targeting ligands. Moreover, both vectors and their load may undergo chemical and physical modifications so that it affect the structure of the system, its loading and release capacity, interfacial properties and bio distribution. In some cases, the drug itself activate these modifications and may also unstable the starting system. So that a physical and chemical depiction of loaded vector is necessary, to fully understand the biological efficiency.

Classification of liposomes

1. Based on structural parameter -
   a) MLV (multilamillar vesicles) (>0.5 µm)
   b) OLV (oligolamillar vesicles) (0.1-1 µm)
   c) UV(unilamillar vesicles) (all size ranges)
   d) SUV-small unilamillar vesicles(20-100 nm)
   e) MUV -medium unilamillar vesicles
   f) GUV -gaint unilamillar vesicles(>1µm)
   g) LUV -large unilamillar vesicles(>100 nm)
   h) MVV/MV (multivesicullar vesicles)(>1µm)
2. Based on method of preparation-
   a) REV SUVs/OLVs made by reverse phase evaporation method
   b) MLV-REV MLVs made by reverse phase evaporation method
   c) SPLV stable plurilamillar vesicles
   d) FATMLV Frozen and Thawed MLVs
   e) VET vesicles prepared by extrusion method
   f) DRV Dehydration rehydration method
3. Based on composition and application –
   a) CL (Conventional liposomes)
   b) Fusogenic liposomes
   c) P^H sensitive liposomes
   d) Cationic liposomes
   e) Long circulatory (stealth) liposomes (LCL)
   f) Immuno liposomes

LIPOSOMES PREPARATION METHODS[3,4]

Lipid Hydration Method

This is the most widely used method for the preparation of MLV. In this method a solution of lipid is dried at round bottom flask and formed a thin layer at the bottom and then hydrating the film by adding some aqueous buffer and for some time vortexing the dispersion is done. The hydration step is done at a temperature higher than the gel-liquid crystalline transition temperature (Tc) of lipid or above the Tc of the greater melting point component in the lipid mixture. The encapsulated compounds are added either to aqueous buffer or to organic solvent with lipids according to their solubilities. This is a simple method and a variety of substances can be enclosed in these liposomes. The disadvantage of the method are low internal volume, encapsulation efficiency is low and heterogeneous size distribution.

Solvent Spherule Method

Kim *et al*. (1985) was proposed a method for prepare a homogeneous size distribution of MLVs. The process involved the small spherules of volatile hydrophobic solvent was dispersed in aqueous solution in which lipids had been dissolved. Then in a water bath the evaporation of organic solvent was occurred and then it was controlled and MLVs were formed.

Sanitation Method

Here MLVs were form by sonicated either with a bath type sonicator or a probe sonicator at a pleasant atmosphere. The main disadvantages of this method are internal volume are very low /encapsulation efficiency, possibly degradation of phospholipids and compounds to be enclosed, exclusion of large molecules, contamination of metal from tip of probe and presence of MLV along with SUV.

French Pressure Cell Method

This method involves the extrusion of MLV at 20,000 psi at 4°C through a small orifice. The method has several advantages than sonication method. The method is simple, rapid, reproducible

and involves gentle handling of unstable materials (Hamilton and Guo, 1984). The liposomes are somewhat larger than sonicated SUVs. The drawbacks of the method are that difficult to achieve the temperature and the working volumes are relatively small (about 50 mL maximum).

Ether Infusion Method

A lipids solution is dissolved in diethyl ether or ether/methanol mixture is injected slowly to an aqueous solution of material to be encapsulated at 55-65°C. The liposomes were formed by subsequent removal of ether under vacuum[5,6]. The main drawbacks of the method are that the heterogeneous (70-190 nm) population and the exposure of encapsulated compounds to organic solvents or high temperature (Dcamcr and Bangham, 1976; Schieren *et al*, 1978).

Ethanol Injection Method

The MLVs are immediately formed after introduce a rapid injection of a lipid solution of ethanol to a vast excess of buffer. The drawbacks of the method are that heterogeneous population is (30-110 nm), very dilute liposomes, it is difficult to remove all ethanol because it forms azeotrope with water, the possibility of inactivation of various biologically active macromolecules in the presence of low amounts of ethanol (Batzri and Korn, 1973).

Detergent Removal Methods

The detergents have been used at their critical micelles concentrations to solubilise lipids. After removel of the detergent the micelles become progressively richer in phospholipid and finally combine to form LUVs. By dialysis method the detergents were removed (Kagawa and Rocker, 1971; Milsmann *et al*, 1978, Alpes *et al*, 1986). The advantages of this method are excellent reproducibility and production of liposome populations which are homogenous in size. The main disadvantages of the method is the retention of traces of detergent(s) within the liposomes[7]. A commercial device called "LIPOPREP" (Diachema A G, Switzerland) which is a version of dialysis system is available for the removal of detergents. Different techniques have been used for the removal of detergents: (a) by using Gel Chromatography involving a column made up of Sephadex G-25 (Enoch and Suitt matter, 1979); (b) by adsorption or binding of Triton X-100 (a detergent) with Bio-Beads SM-2 (Gerristen *et al*, 1978) (c) by binding of octyl glucoside (a detergent) to Amberlite XAD-2 beads (Philippot *et al*, 1985).

Reserves Phase Evaporation Method

First water in oil emulsion is formed by brief sonication of a two phase containing phospholipids in organic solvent (diethylether or isopropylether or mixture of both) and aqueous buffers. The organic solvents are removed under reduced pressure, resulting in the formation of a viscous gel. The liposomes are formed when rest of the solvent is removed by continued rotary evaporation under reduced pressure. In this method high encapsulation efficiency up to 65% can be obtained in a medium of low ionic strength for example 0.01 M NaCl. This method is used to encapsulate small, large and macromolecules. The main disadvantage of the method is that the exposure of the materials which is encapsulated to organic solvents and to brief periods of sonication[8]. These conditions result in the denaturation of some proteins or breakage of DNA strands (Szoka and Papahadjopoulos, 1978). By this method a heterogeneous sized dispersion of vesicles are obtain. Handa *et al*. (1987) was presented Modified Reverse Phase Evaporation Method and the main advantage of the method is that the liposomes had high encapsulation efficiency (about 80%). This Method of Szoka and Papahadjopoulos (1978) has also been modified by Haga and Yogi, 1989 to entrap plasmids without damaging DNA strands.

Calcium-Induced Fusion Method

This method is used to prepare LUV. The procedure is based on the observation of calcium addition to SUV induces fusion and results in formation of multilamellar structures. The addition of EDTA in this preparations results in the formation of LUVs. The advantage of this method is that macromolecules can be encapsulated under gentle conditions and results a largely unilamellar with heterogeneous size range liposomes formed. The chief disadvantage is that LUVs can only be obtained from acidic phospholipids.

Freeze-Thaw Method

SUVs are rapidly frozen and followed by slow thawing. The aggregated materials are disperses through sonication to LUV. In the processes of freezing and thawing (Pick, 1981, Ohsawa *et al*, 1985, Liu and Yonethani, 1994) the formation of unilamellar vesiclesis due to the fusion of SUV. This fusion is inhibited by increasing the ionic strength of the medium and by increasing the phospholipid concentration. The encapsulation efficiencies obtained by this method from 20 to 30% (Pick, 1981).

Microfluldization Method

Mayhew *et al*. (1984) developed a technique of micro fluidization/ micro emulsification/ homogenization for the large scale manufacture of liposomes. The reduced size range can be achieved by recycling of the sample. The process is reproducible and yields liposomes with aqueous phase encapsulation. Riaz and Weiner in 1995 prepared liposomes consisting in the ratio 10:33:57 of brain phosphatidylserin diasodium salt, cholesterol and egg yolk by this method. Liposomes were prepared by these were passed through a Microluidizer at 40 psi. The size range was 150-160 nm after 25 recylces[9,10]. The interaction of fluid streams takes place in a precisely defined micro channels at high velocities (pressures) which are present in an interaction chamber in the micro luidezer. In the chamber pressure reaches up to 10,000 psi and cause partial degradation of lipids.

The procedure for the formation of giant liposomes are the dialysis of a methanol solution of phosphatidylcholine with methylglucoside (detergent) against an aqueous solution of up to 1 M NaCl[12]. The liposomes range in diameter from 10 to 100 mm (Oku *et al*, 1982).

The formation of multi vesicular liposomes has been reported by Kim *et al*. In 1983. The w/o emulsion was converted in to spherules of organic solvent by the addition of the emulsion to across solution. Multi vesicular vesicles were formed by the evaporation of organic solvent. The diameter of liposomes ranges from 5.6 to 29 pm[13]. The liposomes have very high encapsulation efficiency (up to 89%) when materials are encapsulated in glucose, EDTA, human DNA.

Cestaro *et al*, 1982 reported a procedure for preparing a asymmetric liposomes of cerebroside sulfate at their outer phospholipid bilayer. Cerebroside sulfate was adsorbed on to a support of filter paper (cellulose) and the support was incubated with small or large fused unilamellar liposomes. After six hours sulfatide contents reached upto 6 mole percentage of the total quantity of phospholipid, corresponding to about 10 mole % of phospholipid present in the outer layer[14]. The sulfatide could not be removed by washing with 1M NaCl or 1M urea.

CHARACTERIZATION OF LIPOSOMES

Apart from the concentrations of the drug and lipids in the vesicles, size distribution, measurements of captured volume and *lamellarity* (the number of layers making up the shell of the bubble or vesicle) characterize lipid vesicles. The size is considered an important factor in measuring liposome-complement interactions[15,16]. Yamada *et al*, reported the release of carboxyfluorescein (CF) from liposomes was measured for three different diameters (800, 400, and 200 nm) by changing the concentration of liposomes from 1 to 1,000 nmol/ mL. At a low liposome concentration range i.e.1-10 nmol/mL, small liposomes (200 nm) were released CF to a similar extent (about 35%) as medium (400 nm) and large (800 nm) liposomes.

Mean vesicle size and size distribution

These essential parameters describe the quality of liposome suspensions. These are the important parameters for the physical properties and biological fate of liposomes and their entrapped substances *in vivo*. A number of methods are used to determine size and size distribution, but among these light-scattering analysis is most commonly used methods. Light scattering is popular because of the ease of operation and the speed through which data can obtain. Newer instruments are based on laser light scattering. For analyzing the monodisperse liposomes, light-scattering analysis is the best method of choice; unfortunately, most liposomes are heterogeneous preparations so they

require an accurate estimate of their size-frequency distributions. Most important, it is necessary to separate out all micron-sized particles that are present in such masses before analysis.

Stability

The stability is usually defined as the capacity of its formulation to remain within defined limits during the shelf life of the product[8]. Different colloidal models from colloid science can be used to describe liposome stability. Colloidal systems are stabilized electro statically, electro sterically or sterically, Liposome dispersions exhibit both physical and chemical stability. Generally, the physical characteristic describes the preservation of liposome structure and the chemical characteristic describes the molecular structure. Physically stable formulations covered both liposome size distribution and amount of the material encapsulated. Stability depends on the mechanical properties of liposome membranes and on the thermodynamic properties and colloidal properties of the system.

Temperature studies

High-temperature testing (>25ºC) is almost universally used for heterogeneous products. For liposomes, elevated temperatures may dramatically alter the nature of the interfacial film, especially if the phase-transition temperature is reached. If temperatures higher than the system will ever encounter are used-even in short term heat-cool cycling - one risks irreversibly damaging the bilayers such that the membrane cannot heal when brought back to room temperature. If a liposomal dispersion is partially frozen and then melt, ice crystals nucleate and grow at the expense of water. Liposomes then may press together against the ice crystals under great pressure. If crystals grow to sizes greater than the void spaces, instability is more likely. That phenomenon is well noted with a slower rate of cooling, causing formation of larger ice crystals, which leads to greater instability. Certain polymers are known to retard ice crystal growth.

Time studies

The zeta potential (ZP) and the dielectric constant (€) of liposomes are measured to study the effects of in vitro aging. Aging studies show an increase in the € and the ZP potential for liposomes at various storage temperatures. Both electrical parameters are useful in the study of structural alterations in liposomal vesicles and systems as a function of various conditions. It is critical that stability-testing protocols for liposomal products be developed case by case. Be certain that studies are performed using various types and sizes of containers. Under each test condition, the following data can be collected: visual and microscopic observations (flocculation, for example), particle size-profiles, rheological profiles, chemical stability, and extent of leakage.

Drug entrapment efficiency

In this method liposome suspension was ultra centrifuged at 4°C temperature at 5000 rpm for 15 minutes by using remi cooling centrifuge to separate the free drug. A supernant contains liposomes in suspended stage and free drug at the wall of centrifugation tube. The supernant was collected and centrifuged at 15000 rpm at 4°C temperature for 30 minutes. A clear supernant solution and liposomes pellets were obtained. The pellet containing only liposomes was re suspended in distilled water for further study. In 10 ml of methanol the drug loaded liposomes were soaked and sonicated for 10 min. The vesicles were broken for releasing the drug and then estimated for the drug content. The absorbance of the drug was observed at 222 nm. The entrapment efficiency was then calculated using following equation,

% Entrapment efficiency =Entraped drug / Total drug added X 100

APPLICATION OF LIPOSOMES

Applications of liposomes in sciences

The membranes of Lipid are two dimensional surfaces floating in three dimensional space. In the simple mode, they can be characterised only by their flexibility which is related to their bending elasticity. Various concepts were developed to understand their conformational behaviour. They can also be used as a model in order to understand the topology, permeability, shape fluctuations, phase behaviour, fission and fusion of biological membranes. Their aggregation leads to

fractal clusters. Apart from this they also serve as a model to study vesiculation including vesicle shedding and endo and exo-cytosis of living cell.

Despite their application, the mechanism of liposome formation is not yet well understood. The equilibrium calculations of the shapes of giant unilamellar vesicles and their observation, however, offer a qualitative guidance in the modeling of structural transformations in the various processes of vesiculation. Some liposomes shows that similar shapes occur also in multilamellar aggregates and it is can be assume that the gradient of hydration across the stack of concentric lamellae causes also the gradient of polar heads surface areas in the consecutive monolayers because the area of polar head is proportional to hydration. As a result of this, the curvature is induced. On the other hand the mechanism of bending, budding off and curving were observed in giant unilamellar vesicles, and can be qualitatively explain the method of formation of large multilamellar vesicles from lipid films. Moreover, vesiculation is an essential process in communication and cell function. These processes are made by laboratory preparations in which smaller vesicles are formed by high energy fragmentation of the bilayers. It is not unreasonable to assume that similar budding and pinching off mechanisms, operate *in vivo* in exocytosis and form synaptic vesicles, and in Golgi apparatus, respectively. Of course, there are several enzymatic processes which gives the driving force for these transformations (fusion and fission) but the role of the lipid bilayer is important in these processes. The Physico-chemical studies of cholesterol and other sterols containing membranes may offer some clues on the evolution of life. It represent the presence of cholesterol, which is synthetised only in certain geological time with the fully oxygeneted atmosphere and renders membrane more cohesive at increased bilayer fluidity, this was the cause which enabled endo- and exo-cytosis and therefore the development of the eukaryotic cell from multi-organelle prokaryotic cells, which contain no cholesterol and also no internal organelles. Living species contain a large number of different polar and bipolar lipids and sterols, and their occurrence and function in different species improve the understanding of evolution of plant and animal life. One of the major research aim is to duplicate photosynthesis and harvest the abundant light energy either by artificial photosynthesis or by splitting water into its reactive materials. These systems are rather complex involving precisely tuned electron relay mechanisms, photo sensitisers and catalysts embedded in lipid bilayers. Artificial systems use liposomes to simulate the organization, activity and orientation of the embedded compounds and their reactivity[9]. Although these are very complex problems, many artificial systems have already photolysed water, even though the yields are still very low. The structure of liposomes offers also a system to compart mentalise chemical reactions. This can be used in catalysis, in bio mineralisation studies or in the synthesis of colloid particles. One of the most prolific areas of liposome applications is - conformatory biochemical investigations and function of membrane proteins. Various proteins regulate docking, directions, addresses, internalization or fusion of these vesicles with a great efficacy. Cells secrete and engulf macromolecules via exo and endocytosis, respectively as well as transport molecules to within Golgi apparatus by the use of vesicles. the increasing knowledge of these processes will give importance on the function of living cells and offer some solutions in the case of its disfunction.

Applications of liposomes in medicine

Liposomes applications in pharmacology and medicine can be divided into two parts i.e. therapeutic and diagnostic applications containing drugs or various markers, and their use as a model, tool, reagent in the studies of cell interactions, recognition processes, and mode of action of certain substances. But many drugs have a very narrow therapeutic window (the therapeutic concentration is nearer to the toxic one). In most of the cases we can reduce the toxicity or the efficacy enhanced by the use of an appropriate drug with appropriate carrier which changes the secular and spatial distribution of the drug, i.e. its pharmacokinetics and bio distribution.

Modes of liposome action

Liposomes as a drug delivery systems can offer several advantages over conventional dosage forms particularly for parenteral (i.e. local or systemic injection or infusion), topical, and pulmonary route of administration. The following discussion shows that liposomes exhibit different bio distribution and pharmacokinetics than a free drug molecules. In most of the cases this can be used to improve the therapeutic efficacy of the encapsulated drug molecules. The limitations may reduced bioavailability of the drug, saturation of the cells of the immune system with lipids and respectively increased toxicity of drugs due to their increased interactions with particular cells. The benefits of drug loaded liposomes, which can applied as (colloidal) solution, aerosol, or in (semi) solid forms, such as creams and gels.

In parasitic diseases and infections

As conventional liposomes are digested by phagocytic cells in the body after intravenous administration, they are the vehicles for the targetting of drug molecules into these macrophages. The best known example is 'Trojan horse-like' mechanism are several parasitic diseases which normally reside in the cell of mononuclear phagocytic system[16]. This include leishmaniasis and several fungal infections. The efficacious dose of drugs, is nearer the toxic one. Liposomes accumulate in the very same cell which is infected and offer an ideal drug delivery vehicle.

The best results reported so far in human therapy are probably liposomes as carriers for the drug Amphotericin B in the treatment antifungal therapies. This drug is the drug of choice in fungal infections, chemotherapy, or AIDS and are frequently fatal. But the drug itself is very toxic and its dosage is limited due to its nephro- and neuro-toxicity. Toxicities are correlated with the size of drug molecule or its complex with liposome encapsulation which prevents accumulation of drug in these organs and drastically reduces toxicity. Liposome encapsulated antivirals like ribavarin, acyclovir, azide thymidine (AZT) etc have also shown reduced toxicity and detailed experiments are being performed with respect to their efficacy.

In Macrophage activation and vaccination

Automatic targetting of liposomes to macrophages can be utilized in several ways, including vaccination and macrophage activation. Some natural toxins induce strong macrophage response which results in activation of macrophage. This can be duplicated and improved by the use of liposomes because small molecules having immunogenic properties (haptens) cannot induce immune response without being attached to a larger particle. Activated macrophages are larger and contain more granulomae and lysosome material. In cancer therapy, surgery or radiotherapy often does not remove all the tumor cells and in these cases, when tumour load is low, this therapy is very useful for complete removal of malignant cells. Activation of macrophages was useful in the treatment of bacterial infection, viral infection, and fungal infections as well. Indeed, liposomes are used in animal vaccination since 1988, where as human vaccinations for malaria are now in the stage of clinical trials.

In anticancer therapy

Many liposomel formulations with various anticancer agents were shown less toxic than the free drug. Anthracyclines are drugs which stop the growth of dividing cells by killing of these cells. These cells are in tumours, but these are also present in gastrointestinal mucosa, hair, and blood cells, hence this class of drugs is very toxic. In addition to acute toxicities its dosage is limited to its cumulative cardiotoxicity. Most of the formulations were tried but in most cases the toxicity was reduced upto 50%[13]. This toxicity includes both short term and chronic toxicities because liposome encapsulation were reduces the distribution of the drug molecules towards those tissues. In some cases like systemic lymphoma, the effect of liposome encapsulation shows the efficacy was enhanced because of the sustained release effect. Applications showed reduced toxicity, better tolerability of administration with not much encouraging efficacy. Many different formulations are in different stage of clinical studies and show mixed results.

Other applications

Small liposomes composed of lipids with long and saturated hydrocarbon chains and mixtured with cholesterol. Such liposomes were used for diagnostic purposes. They can also deliver anti inflammatory drugs. Additionally, the contamination of healthy tissues with drug molecules was reduced. And also used to deliver drugs into the lung. This is most often done by inhalation of liposome aerosol and are used for the treatment of various lung disorders, infections, asthma etc. The application of free and liposomal metalloporphyrins which inhibit enzyme and breaks down haemoglobin into toxic bilirubin, however, did not result in statistically significant reduction of the enzyme activity. Liposomes can be applied also as a thick cream, gel, or tincture. Apart from this, subcutaneous or intramuscular drug depot, the formulations can be applied topically. Several researchers claim as the penetration of lipid and drug molecules increased into the skin.

Oral applications of liposomes are at present limited because of very liposomicidal environment in stomach and duodenum and normally the administration of free or liposome loaded drug exhibits usually no differences. Intragastrical administration, however, shows that liposomes increase the systemic bioavailability of certain water insoluble drugs and vitamins. Several designs to make a stable liposomes at low pH, degradative enzyme, and bile salts containing environments are being studied. They include liposomes made of many bilayers with different chemical stability and with programmable degradation kinetics, liposome with biodegradable gels or capsules, polymer coated liposomes, and similar.

Application in bioengineering

Modern genetic engineering and gene recombinant technology is based on the delivery of genetic material into various cells, i.e. fragments of DNA, and microorganisms in order to alter their genetic code and force them to produce particular proteins or polypeptide. Nucleic acids used in gene transfer are large molecular weights up to several million Daltons, hydrophilic and highly charged and therefore not easy to transfer across cell membranes. Liposomes can deliver the loaded or bound nucleic acid into cells predominantly in two ways: the classical approach is to loaded the genetic material into liposomes and liposomes act as an endocytosis enhancer while recently the phosphate or DEAEmprecipitation was simulated by liposomes[11]. In these cases the nucleic acid forms a complex with cationic liposomes and the size of the complex and its adsorption on the cell surface catalyses endocytosis or fusion. The third is still unexplored way which would be use fusogenic liposomes or cause fusion upon adsorption of the liposome on the cell surface. Recently, transfection was successfully performed using SUV made from positively charged lipids. First studies used cationic lipid dioleoyl-propyl-trimethylammonium (DOTMA). Better transfection efficiencies were found at reduced toxicity by using liposomes enclosed positively charged cholesterol. Many new cationic lipids are being synthetised in order to improve transfection. This methods can also used in gene therapy. The idea is to deliver the healthy gene into the appropriate cells and hope that they will respond.

Application in cosmetics

In general the rules for topical drug delivery of compounds are less stringent than the ones for parenteral administration and several cosmetic preparations are commercially available since Capture (C. Dior) and Niosomes (L'Or´eal) were introduced in 1987[15]. They range from simple pastes of liposome which are used as a replacement for creams, gels and ointments contains various plant extracts, antibiotics and to complex products contains recombinant proteins for healing wound or sunburn. Most of the products are anti-ageing skin creams. Sunscreens, long lasting perfumes, hair conditioners, aftershaves product and similar products are also gaining large fractions of the market. Liposomal skin creams already takes share more than 10% of the over $10 billion market. Bellow Table shows some of the liposomal products. These liposomes are more stable than their natural analogues and can be easily produced in large quantities and are very inexpensive.

Application in agro-food industry

The ability of liposomes to solubilize compounds with demanding solubility properties, segregate compounds from potentially harmful milieu, and release incorporated molecules in a sustained and predictable fashion can be used in the food processing industry. Lipid molecules, from fats to polar lipids, are one of the primary ingredients in almost any food. For example, lecithin and some other polar lipids are routinely extracted from nutrients. Traditionally polar lipids were used to stabilize w/o and o/w emulsions and creams, or to improve dispersal of various insistent powders in water. With the onset of microencapsulation technology, liposomes have become an attractive system because they are composed perfectely from food acceptable compounds[17]. The sustained release system concept can be used in various fermentation processes in which shorten fermentation times and improve the quality of the product by the encapsulated enzymes. This is due to improved spatial and temporal release of the ingredient(s) as well as to their protection in particular phases of the process against chemical degradation.

In addition to improved agitation, liposomes are being tried in the preservation process of cheeses. Nitrates were added to cheese milk to suppress the growth of spore-forming bacteria is now a questionery due to health concerns and natural alternatives are under study. Liposome encapsulation can both preserve potency and increase effectivenes because it become localized in the water spaces between the casein matrix and fat globules of curd and cheese.

These applications of enhancing natural preservatives, antioxidants like vitamins E, C will undoubtedly become very important due to recent dietary trends which reduce the addition of artificial preservatives and ever larger portion of unsaturated fats in the diet.

In the other areas of agro-food industry, liposomes encapsulated biocides have shown superior action due to extended presence of the fungicides, herbicides or pesticides. Liposome surface can be made sticky so that they stick on the leafs for longer times and do not wash into the ground. In these applications synthetic lipids are used to produce inexpensive liposomes.

Other applications of liposomes

The potential of making large quantities of inexpensive and stable liposomes may further used in several other applications. They range from water based paints, self healing paints, and similar products. They are based mostly on the dissolving potential and their ability to protect the encapsulated substance until an external stimulus such as the presence of oxygen, light, or change in hydration[14]. Critical evaluation of these applications is difficult, however, because the information is concentrated in progress reports, business analyses or prospectuses of various producers. In bionomics, liposomes offer improvements in bio reclamation and various monitoring and analytical diagnostic applications. Because liposomes have the surfactant action it also improve the coagulation and sinking of oil spread on the water surface or its cleaning up with floating booms . Some of the Environmental Protection Agency is testing liposomes' ability to deliver nutrients to oil spills to speed up the degradation. In addition to the above mentioned liposome applications there are many others which were not mention.

Table No.1: Advantages and disadvantages of liposomes

Advantages	Disadvantages
-Relatively easy to prepare -Can be loaded in high yield with shorter-lived as well as longer-lived alpha emitters -Good resistance against radiolysis -Passive targeting of solid tumors -Can be conjugated with receptor binding molecules including antibodies to target cellular receptors.	-Relatively slow penetration into tumors -Various degree of accumulation in the RES -Variable stability *in vivo*.

Table No.2: Application of liposomes in the sciences

S.No	Discipline	Application
1	Mathematics	Topology of two dimentional surfaces in three dimentional space governed only by bilayer elasticity
2	Physics	Aggregation behaviour, fractals, soft and high- strength materials.
3	Biophysics	Permeability, phase transitions in two-dimensions, photophysics.
4	Physical Chemistry	Colloid behaviour in a system of well-defined physical characteristics, inter and intra-aggregate forces, DLVO Chemistry Photochemistry, artificial photosynthesis, catalysis, micro compartmentalization
5	Biochemistry	Reconstitution of membrane proteins into artificial membranes
6	Biology	Model biological membranes, cell function, fusion, recognition.
7	Pharmaceutics	Studies of drug action
8	Medicine	Drug-delivery and medical diagnostics, gene therapy.

Table No.3: Liposomes in the pharmaceutical industry

S.No	Liposome Utility	Current Applications	Disease States Treated
1	Solubilization	Amphotericin B, minoxidil	Fungal infections
2	Site-Avoidance	Amphotericin B - reduced nephrotoxicity, doxorubicin-decreased cardiotoxicity;	Fungal infections, cancer
3	Sustained-Release	Systemic antineoplastic drugs, hormones, corticosteroids, drug depot in the lungs	Cancer, biotherapeutics
4	Drug protection RES Targeting	Cytosine arabinoside, interleukins. Immuno modulators, vaccines, antimalarials, macophage-located diseases	Cancer, etc Cancer, MAI, tropical parasites.
5	Specific Targeting Extra vasation	Cells bearing specific antigens. Leaky vasculature of tumours, inflammations infections	Wide therapeutic applicability, Cancer, bacterial infections.
6	Accumulation	Prostaglandins	Cardiovascular diseases
7	Enhence preparation Drug depot	Topical vehicles, Lungs, sub cutaneous, intra mascular, ocular	Darmetology , Wide therapeutic applicability

Table No.4: Some liposomal cosmetic formulations currently on the market

S.No	Product	Manufacturer	Liposomes and key ingradient
1	Capture	Cristian Dior	Liposomes in gel with ingredients
2	Effect du Soleil	L'Or´eal	Tanning agents in liposomes
3	Nactosomes	Lancome (L'Or´eal	Vitamins
4	Formule Liposome Gel	Payot (Ferdinand Muehlens)	Thymoxin, hyaluronic acid
5	Future Perfect Skin Gel	Estee Lauder	TMF, vitamins E, A palmitate, cerebroside ceramide, phospholipid
6	Symphatic 2000	Biopharm GmbH	Thymus extract, vitamin A palmitate
7	Natipide II	Nattermann PL	Liposomal gel for do-it-yourself cosmetics
8	Flawless finish	Elizabeth Arden	Liquid make-up
9	Inovita	Pharm/Apotheke	Thymus extract, hyaluronic acid, vitamin E
10	Eye Perfector	Avon	Soothing cream to reduce eye irritation
11	Aquasome LA	Nikko Chemical Co.	Liposomes with humectant

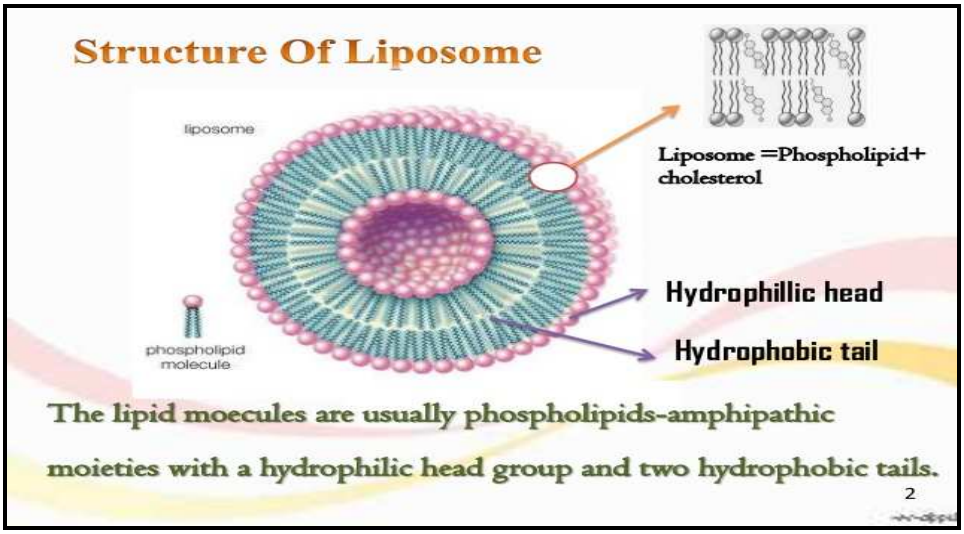

Figure No.1: Structure of Liposome

CONCLUSION

In conclusion, it seems that liposomes established an important model system in several different sciences and as a possible alternative in several applications. Despite over cosmetic industry, liposomes have the real future in anticancer and other chemotherapies, gene therapy and some other medical applications like artificial blood.

ACKNOWLEDGEMENT

I am very thankful to the Department of pharmacy, Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS) and all other persons who help me during the writing of this articles.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Juti Rani Devi and Bidyut Das. Liposomes: A carrier for novel drug delivery system, *International Journal* of *Research in Pharmaceutical and Nano Sciences*, 5(4), 2016, 212-223.