Liposomes a drug carrier

Rutuja N. Mohite*[1], Sameer shafi[2], Suraj G. Malpani[2] , Sushil S. Kore[3], Nilesh N. Shinde[3], Ankita A. Shinde[3]

[1*,3]Students, [2]Assistant Professor
Shivlingeshwar College of Pharmacy,
Almala, tq. Ausa, district. Latur [M.S.] India.

***Abstract*: Liposomes are upmost placed acquiring in pharma industries and very useful in the several drug delivery systems used to target the drug to specific tissue. Because of structural similarity between lipid bilayer [two layers] and cell membrane, liposome can easily penetrate effectively deliver drug to such that a free drug would not easily penetrate. Liposomes can be also encapsulated in both hydrophilic and hydrophobic materials, and are utilized as drug carriers in drug delivery. This technology is very useful for the treatment of certain diseases. Now a day's maximum of the researcher desirability and interest will increase for that knowledge i.e. Liposomes. Main object of this review this technology i.e. Liposomes very valuable in certain disease and easily formulate and also give various advantages except. Liposomes are mostly biocompatible, with applications ranging from delivering enzymes, antibacterial, antiviral drugs, antiparasitic drugs, transdermal transporters, fungicides, diagnostic tools and adjuvant for vaccines. This paper mainly focuses on exclusively scalable techniques and also focus on strength, respectively, limitations in respect to industrial applicability and regulatory requirements concerning liposomal drug formulations based on FDA and EMEA documents.**

***Keywords*: Liposomes, Method of preparation, Liposome stability, Clinical application.**

INTRODUCTION:

Liposomes

Liposomes consist of vesicles composed of bilayers or multilayers that contain or have phospholipids and cholesterol surrounding an aqueous compartment. Drug is ensnared with-in the liposome and is unrestricted from the liposome for absorption on the intestinal membrane surface. This dosage forms usual considerable and this may well-relate to their absorption enhancing ability, the possibility of their use to sponsor drug absorption is uncertain drugs otherwise chemical entities. Advances in combinational chemistry have led to the detection of a wide number of new chemical entities [NCE] or drugs that have a potential healing action on the biological systems. But most of the NCEs or drugs being discovered provide a contest or create most difficulties to the formulation scientist because of their physicochemical goods like meagre solubility as well as permeability. Even though, above problems or difficulties could be addressed, but most of the molecules do not show or they fail their desired therapeutic action in vivo, which leads to lack of in vitro – in vivo correlation. A majority of antineoplastic agents, which are highly cytotoxicity to tumor cells in vitro, affect the normal cells also. This is due to their low therapeutic index [TI], i.e., the dose required to produce anti-tumor effect is toxic to normal cells. Such drugs have to be embattled to a exact site [diseased site] in order to decrease their poisonous effects to normal tissues. Hence, an efficient drug delivery system is required to present the maximum fraction of administered dose at the target site or valuable for targeted site.

Various carriers like nanoparticles, microparticles, polysaccharides, lectins and liposomes can be used to target the drug to a specific site. Liposomal drug delivery is achieving interest due to its input to diverse areas like drug delivery, cosmetics, and construction of biological membrane. Liposomes are very valuable because they act as a carrier for a variety of drugs, having a potential therapeutic action or other belongings. Liposomes are colloidal carriers, having a size range of 0.01–5.0 m in diameter. Indeed, these are bilayer vesicles that are formed when phospholipids are hydrated in excess of aqueous medium or aqueous solution. Liposomes have got a possible benefit of encapsulating hydrophilic along with hydrophobic drugs and targeting them to the phospholipids.

STRUCTURE OF LIPOSOMES

There are number of the structural as well as non-structural components of liposomes, major structural components of liposomes.

1. Phospholipid

Phospholipids are the main structural constituent of biological membranes, where two type of phospholipids exit-PHOSPHODIGLYCERIDES also SPHINGOLIPIDS. The most mutual phospholipid is phosphatidylcholine [PC] particle. Molecule of phosphatidylcholine are not soluble in water and in aqueous media they align themselves closely in planner bilayer sheets in order to minimize the unfavorable action between the bulk aqueous phase and long hydrocarbon fatty chain.

The Glycerol holding phospholipids are most common used component of liposome preparation and re-present more than 50% of weight of lipid in cutting-edge of biological membranes. These are derived from Phosphatidic acid.

Examples of phospholipids are:

1. Phosphatidyl choline [Lecithin] – [PC]
2. Phosphatidyl ethanolamine[cephalin] – [PE]
3. Phosphatidyl inositol [PI]
4. Phosphatidyl Glycerol [PG].

2. Cholesterol's

Cholesterol doesn't by itself form bilayer assembly, but can be combined into phospholipid membranes in very high concentration up to 1:1 or even 2:1 molar ratio of cholesterol to phosphatidylcholine. Cholesterol additions into the membrane with its hydroxyl group concerned with the aqueous surface as well as aliphatic chain aligent similar to the acyl chains in the midpoint of the bilayer. The most common usual polar phospholipids are phosphatidylcholine. These are amphipathic molecules in which a glycerol bridge relates to a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar head group, phosphocholine. The amphipathic flora of phospholipids and their equivalents reduce them the capability to form closed concentric bilayers in presence of water. Liposomes are formed when reedy lipid films or lipid cakes are hydrated and stacks of lipid crystalline bilayers become fluid also swell.

TECHNIQUES OF LIPOSOME PREPARATION

In different preparation procedures a general pattern can be discerned.[1]

GENERAL METHODS OF PREPRATION

All the methods of formulating the liposomes involve four basic stages:

A. Drying down lipids from organic solvent.

B. Dispersing the lipid in aqueous media.

C. Purifying the resultant liposome.

D. Analyzing the final product.

1] Hydration stage

A] Mechanical Methods: MLVs were by tradition produced by hydrating thin lipids films placed from an organic solution on a glass wall by shaking at temperatures above the phase transition temperature of the phospholipid with the uppermost Tc. The wide size distributions of the formed liposome dispersions were usually tapering down by small pressure extrusion or else ultrasonication.[2]

B] Methods based on detergent removal: Phospholipids, lipophilic compounds and amphipathic proteins can be solubilized by detergents forming mixed micelles. Upon elimination of the detergent, vesicle formation can occur. This technique is well established for preparation of reconstituted virus envelopes [3] or reconstituted tumor membrane material.[4] Schreier and coworkers described a two-step strategy for insertion of proteins into the outer layer of liposomes. First liposomes were formed by detergent dialysis method and subsequently proteins were inserted by partial re-solubilization of the membrane by the detergent (deoxycholate) in the presence of protein. [5]

C] Method based on size transformation and fusion: Sonication of phospholipids below their phase transition temperature [Tc] results in vesicles with defects in the bilayers. Heating the dispersion to Tc eliminates these structural defects and causes fusion resulting in large unilamellar liposomes with a wide size distribution.[6] Main disadvantage of this process is the limited number of bilayer composition that reacts and the poor reproducibility of the particle size distribution of the liposome dispersion that is formed.

2] Sizing stage

There are two approaches, one without a special sizing step [A] and one with a special sizing step [B]

[A]In liposome formation process, circumstances are selected and controlled in such a way that particle size distributions with an acceptable width are produced. High shear homogenization produces a size distribution which depends on operational pressure. [7,8,9]

[B] Removal of nonencapsulated material

Many lipophilic drugs show a max affinity to the bilayer and are completely liposome related. Though, for other compounds, the encapsulation efficacy is fewer than 100 percent. The non-encapsulated fraction of the lively compound can create unacceptable side effects or physical instability.[3] For removal of nonencapsulated material, the subsequent methods are used:

a) dialysis and ultra-centrifugation.

b) Gel permeation chromatography.

c) Ion exchange reactions.

STABILITY OF LIPOSOMES [10-11]

1. Physical stability

The stability of a pharmaceutical product typically is well-defined as the capacity of the delivery system to persist within defined or pre-established limits during the self-life of the product. There is no recognized procedure for either accelerated or long–term stability studies for the liposomal preparation. Classical models from colloidal science can be used to designate liposome stability. Colloidal systems are stabilized electrostatically, sterically or electro-sterically. In addition, the self-assembling colloids can undergo fusion or phase change after aggregation. Liposome exhibit both physical and chemical stability characteristics. Usually, the physical characteristic defines the protection of liposome structure also the chemical characteristic refers to molecular structure of liposomal mechanisms. [hydrolysis as well as oxidation of phospholipid] Physically stable preparations reserve both liposome size distribution as well as the quantity of material encapsulated. The stability problem disables by using suitable techniques like freezing, lyophilization and osmification. It is also prohibited by using fresh solvents and freshly cleaned lipid, using inert nitrogen gas, sidestep high temperature and include anti-oxidants α, β, γ and δ-tocopherol.

2.Plasma stability

Although liposomes resemble bio-membranes, they still are foreign objects for the host. Therefore, liposomes are recognized by the mononuclear phagocytic system (MPS) after interaction with plasma proteins. As a result, liposomes are cleared from the blood

stream. These stability problems resolve by using artificial phospholipids, gangliosides, polymerization, coating liposomes by means of chitin derivatives, freeze drying, microencapsulation and particle coated with amphipathic polyethylene glycol.

CHARACTERIZATION OF LIPOSOMES

Both physical and chemical characteristics of liposomes influence their behavior in vivo and in vitro. [12] Liposome characterization should be performed immediately after preparation. Various kinds of chromatography can be used to distinct bilayer apparatuses. One main problem is detection as well as quantitation as UV molar absorptivity of lipids is small and depends on the degree of saturation of the acyl chains. For those phospholipids with individual saturated acyl chains, alternative detection systems not founded on UV absorption are described i.e. systems based on differential refractometry, light scattering as well as flame ionization. The corporeal properties of liposomes have a direct impact on the behavior of the liposomes with its content in vivo. Size, number of lamellae, internal morphology charge, bilayer fluidity are the factors.

A. Liposomes for Gene Delivery

It is significant to dissect the overall cell uptake process into individual steps. In fact, various studies have indicated that successful gene transfer in vitro involves:

1] the packaging of DNA,
2] the adhesion of packaged DNA to the cell surface,
3] Internalization of DNA,
4] escape of DNA from endosomes if endocytosis is involved,
5] DNA expression in cell nuclei.

To do all of the above steps, liposomes have been discovered as a delivery system for DNA as early as in 1979. [13] The encapsulation of plasmid DNA into liposomes [14] and the introduction of poliovirus RNA and SV40 DNA into cells via liposomes [15,16] were reported between 1979 and 1980.

Ph - sensitive Liposome Strategy

1] Liposomes of various compositions can extensively bind to cell surfaces. For gene transfer, it was well-known that dioleylphosphatidylethanolamine [DOPE] is by far the most effective lipid for in vitro gene transfection for pH-sensitive liposomes or as lipid helper in cationic liposomes. [17,18,19,20]

2] It has been expected that the purpose of phosphatidylethanolamine [PE] is that of a membrane fusion supporter, since in fact this lipid suffers changes upon acidification. [21] Cholesterol is often essential to achieve sufficient stability of these liposomes. The arrangement of liposomes may play an chief role in their communications with cells. The size of liposomes as well as the type of cells are fundamental for an efficient capture by cells. Generally, liposomes are taken up by various endocytosis processes. Professional phagocytes such as macrophages and neutrophils can take up liposomes of various size and charge through active phagocytosis. The vesicular pathway for cellular uptake. After binding to the cell surface, liposomes are internalized into endosomes where they encounter a more acidic pH than in the external medium. Early endosomes generally have an internal pH of 6.50.[22,23]

3] The last requirement for plasmid liposomes after cell penetration is to avoid accumulation in particular cell compartments such as lysosomes. In order to prevent this degradation, pH-sensitive liposomes have been proposed.[17,18] pH-sensitive liposomes were designed based on the concept of viruses that fuse with the endosomal membrane by means of protein at pH 5-6, delivering their genetic material to the cytosol before reaching the lysosomes.[24,25] Generally, the lipid used to design pH sensitive liposomes is PE. PE represents a lass of lipids which, when dispersed in pure form, assemble into non-bilayer structures in n inverted hexagonal phase.[21]

4] A key question remains concerning the mechanism of pH-sensitive liposomes: do they react as originally intended? Ropert et al. [26,27] encapsulated antisense oligonucleotides into pH-sensitive liposomes, a short length of DNA directed against the env gene of the murine Friend retrovirus, to inhibit virus proliferation. They recommended that the greater action of oligo-nucleotides encapsulated into pH-sensitive liposomes was not due to a weakening of the DOPE liposome bilayer but to an improved association between pH-sensitive liposomes and cells. They described that the efficacy of the viral inhibition gained with oligo-nucleotides encapsulated into PH-sensitive liposomes was one twice that of oligo-nucleotides encapsulated into non-PH-sensitive liposomes. And a two-fold growth in cell connotation was also detected when pH-sensitive liposomes were compared to PH-insensitive liposomes. In fact, pH-sensitive liposomes are taken up more efficiently by cells than pH insensitive liposomes, a fact probably leading to a better activity. [28]

CATIONIC LIPID STRATEGY

The encapsulation of DNA into conventional liposomes could be a technical issue due to the plasmid size, representing a poor transfection system. On this basis, an alternative procedure based on cationic lipids and PE was developed in the late 1980s. [19] The idea was to neutralize the negative charge of plasmids with positively charged lipids to capture plasmids more efficiently and to deliver DNA into the cells. Generally, this is a simple procedure requiring mixing the cationic lipids with the DNA and adding them to the cells. This results in the formation of aggregates composed of DNA and cationic lipids. The cationic lipid DOTMA was first synthesized and described by Felgner et al. This lipid, also alone or in combination with extra neutral lipids, impulsively formulae multilamellar vesicles (MLV) which might be sonicated to form small unilamellar vesicles (SUV). DNA intermingles impulsively with DOTMA to form DNA complexes by means of 100% of the DNA becoming related. It is presumed that complex formation simply results from ionic interactions between the positively charged headgroup of DOTMA and the negatively charged phosphate groups of DNAs. DOTMA is commercialized [Lipofectin., Gibco-BRL, Gaithersburg, MD] as a one to one mixture with DOPE and has been widely used to transfect a wide variety of cells.[29,30,31,32] In an effort to reduce the cytotoxicity of DOTMA, a series of metabolizable quaternary ammonium salts have been developed whose efficiency is comparable to that of Lipofectin

when dispersed with DOPE.[33] As stated in the list of requirements, one important step for transfection is DNA compaction to improve cell penetration.

LIPOSOME FOR TARGETED DELIVERY

Usage of liposome encapsulated enzymes for delivery into cells was initial stated in 1971. At the same time, an exact receptor on hepatocytes was confirmed to mediate clearance of ß-galactose completed glycoproteins from movement. A mannoside-specific receptor was recognized on the cell surface of the RES of rats [including the liver sinusoid and macrophages]. By grafting different glycosides on the surface of liposomes, it is possible to direct the latter to different cell types of rat liver.[34] Galactosylated liposomes are mainly taken up by liver hepatocytes, while mannosylated liposomes are mostly taken up by non-parenchymal cells.[35] Grafting to specific ligands to the liposome surface eases a fusion of the liposome with target cells via endocytosis, thus releasing material to be brought. In cancer chemotherapy, the toxicity of anticancer drugs is of major concern.

LIPOSOMES IN HUMAN THERAPY

In spite of the good as well as encouraging results got using liposomes as vehicles for drugs in many diseased animal models, in human therapy; the use of liposomes is restricted to systemic fungal infections and cancer therapy, only. However, liposomes-based vaccines show great promise and a vaccine against hepatitis A is already on the market.

Liposomes in anticancer therapy

Based on the early studies that showed that encapsulation of a drug inside of liposomes reduces its toxic side effects, the liposomes were considered as attractive candidates for the delivery of anticancer agents. However, their use was hampered by the rapid uptake of conventional liposomes by MPS cells. The increase of in vivo circulation time of modified lipids [PEG polymerized lipids, gangliosides, sphingomyelin etc.] restored the initial expectation of the advantages of liposomes. Intravenously administered stealth liposomes were passive targeted to solid tumors due to their extravasation in leaky blood vessels supporting the tumor [36]. The good results obtained with liposomal-encapsulated doxorubicin and daunorubicin have led to two products licensed for use in the treatment of Kaposi' sarcoma, namely Doxil as well as Daunoxome. Doxil [commercialized by means of Sequus Pharmaceuticals, Menlo Park, USA] is a suspension of doxorubicin precipitated in 80-100 nm sterically stabilized liposomes. Daunoxome [commercialized by NeXstar Pharmaceuticals, Inc., Boulder, USA] is a small, rigid formulation of liposomes with daunorubicin. These liposomes circulate in the vasculature of patients for several days, and thus have increased chances of extravasating at sites of increased permeability. The success achieved with anthracycline anticancer agents led to the development of other liposomal formulations that are in preclinical stages (5-fluorouracil lipid analogue) [37], vincristine [38) a porphyrin derivative for use in combination with laser light irradiation, bleomycin [39], paclitaxel20, valinomycin in combination with cisplatin.[40]

Liposomes as vaccine system

Liposomes can be used as enhancers of the immunological response by incorporation of antigens 61. For this purpose, the liposomes are administered intramuscularly, a location where the encapsulated antigen is released slowly and accumulate passively within regional lymph nodes. To control the antigen release and to improve the antibody response, the liposomes encapsulating antigens are subsequently encapsulated into alginate lysine microcapsules.[41]At present, Epaxal, a liposome-based vaccine against hepatitis A was licensed for clinical use and was introduced on the market by Swiss Serum and Vaccine Institute, Bern, Switzerland.[42]This vaccine contains formalin inactivated hepatitis hepatitis A virus particles attached to phospholipid vesicles together with influenza virus haemagglutinin. Hepatitis A virus incorporated into liposomes proved to be a suitable formulation in term of rapid seroconversion, high level of mean antibody content and low reactogenicity.[43] Also, there is in clinical trial vaccines against influenza, hepatitis B, diphtheria, tetanus, E-coli infection.

THERAPEUTIC APPLICATIONS

1. Ocular Application

The eye is protected by means of three highly effective mechanisms [a] an epithelial layer that is a difficult barrier to penetration [b] tear flow[c] the blinking reflex. All three mechanisms are responsible for poor drug penetration into the deeper layers of the cornea and the aqueous humor and for the rapid wash out of drugs from the corneal surface. Enhanced efficacy of liposomes encapsulated idoxuridine in herpes simplex infected corneal lesions in rabbits was first reported in 1981.[44] Lee in 1985 concluded that ocular delivery of drugs could be either promoted or impeded by the use of liposome carriers, depending on the physiochemical properties of the drugs and lipid mixture employed. Ganglioside-containing liposomes and wheat germ agglutinin, a lectin that has a high binding affinity for both cornea and ganglioside, were tested for corneal adhesion.[45] Corneal binding as well as accumulation and trans corneal flux of carbachol was enhanced 2.5 to 3-fold over 90 min exposure times. Davies et al. [46] proposed the use of mucoadhesive polymers, Carbopol 934P and Carbopol 1342 to retain liposomes at the cornea. While precorneal retention times were indeed significantly enhanced under appropriate conditions liposomes even in the presence of the mucoadhesive had migrated toward the conjunctival sac with very little activity remaining at the corneal surface.

2. Pulmonary Application

Pulmonary delivery of liposomes has been explored as a target selective alternative to systemic administration of antiesthetic and antiallergic compounds and for antibiotics used against pulmonary infections. Liposomes are valuable tools for pulmonary delivery of drugs due to their solubilization volume for poorly water-soluble substances interpretation them more practical for aerolisation. Their biodegradability permits for extended pulmonary residence times lacking danger of allergic or further side effects. The targeting efficacy to infected or immunologically reduced alveolar macrophages is a unique property of liposomes. The toxicity of liposomes aerosols has been investigated systematically. Gonzalez – Rothi et al. [47] found no inhibition of phagocytic activity or viability upon prolonged exposure of alveolar macrophages to liposomes. Padmanabhan et al [48] demonstrated high enzyme activity and prolonged tissue protection following pulmonary instillation of liposome in corporate superoxide dismutase and catalase

although the mechanism responsible for the observed protection remained obscure. Another promising application is the pulmonary application of liposome incorporated antimycobacterial drugs directed against Mycobacterium avium intracellular [MAI] infected alveolar macrophages. Weichert et al [49] demonstrated the superior killing efficacy of liposomal amikacin against MAI in alveolar macrophage in vitro.

CLINICAL APPLICATIONS

1. Cancer Therapy

Cytotoxic drugs can allocate non-specifically through the body, lead to death of normal and malignant cells, thus giving growth to a variety of deadly side effects. Entrapment of these drugs into liposomes caused in improved circulation lifetime, improved deposition in the infected tissues, defense from the drug metabolic degradation, altered tissue delivery of the drug, with its enhanced uptake in organs rich in mononuclear phagocytic cells [liver, spleen and bone marrow] and decreased uptake in the kidney, myocardium and brain. To target tumors, liposomes must be capable of leaving the blood and accessing the tumor. However, because of their size liposomes cannot usually undergo trans-capillary passage. In spite of this, various studies have demonstrated accumulation of liposomes in certain tumors in a higher concentration than found in normal tissues. [50,51]

Preclinical and clinical investigations have demonstrated significantly increased efficacy and decreased toxicity of liposomes containing DNR (DaunoXomeTM) in comparison with free DNR [52] in the treatment of acute leukemia.[53] However, in the treatment of hepatocellular carcinoma and liver cirrhosis liposomal DNR showed mild hematological toxicities and significant hepatic toxicity, which warns against further assessment of these liposomes in patients with hepatocellular carcinoma and liver cirrhosis.[54] However, liposomal DNR showed encouraging results in the treatment of advanced cutaneous T-cell lymphoma.[55] Furthermore, liposomal DNR and carboplatin plus etoposide, used to treat children with recurrent high-grade glioma after surgery and with progressive teratoid/rhabdoid tumor, showed encouraging results with only little and transient hematological toxicity.[56] Liposomal encapsulation of VCR resulted in increased and prolonged plasma concentration, which is associated with increased antitumor activity [murine P388 ascitic tumor] but not increased drug toxicities compared to the unencapsulated drug.[57] Guthlein et al. [58] found that VCR entrapped into a vesicular phospholipids gel consisting of densely packed liposomes was an effective delivery system with superior antitumor activity compared to conventional VCR against human small cell lung carcinoma LXFS 650 and the human mammary carcinoma MX1. Sustained release and passive tumor targeting can clarify the improved efficiency.

2. Antimicrobial Therapy

Incorporation of rifabutin in liposomes resulted in a significant enhancement of activity against Mycobacterium avium infection compared to free rifabutin.[59] Moreover, the antitubercular activity of rifampin was considerably increased when encapsulated in egg phosphatidylcholine liposomes. A further increase in the activity was observed when the macrophage activator tetrapeptide tufts in was grafted on the surface of drug-loaded liposomes. Rifampin delivered twice weekly for two weeks in tufts in-bearing liposomes was at least 2,000 times more effective than the free drug in lowering the load of lung bacilli in infected animals.[60] Liposome encapsulated clarithromycin may be more effective than the free form against Mycobacterium avium intracellular[MAI] infections in vivo, and the use of a combination therapy with ethambutol could further enhance the efficacy.[61] Furthermore, when the activity of TLC G-65 (liposomal gentamicin preparation), alone and in combination with rifapentine, clarithromycin, clofazimine and ethambutol, was evaluated in the beige mouse model of dispersed Mycobacterium avium infection displayed that the combination of rifapentine and TLC G-65 was extra active than either agent alone. The activity of clarithromycin in combination with TLC G-65 was similar to that of either agent alone. Clofazimine improved the activity of TLC G-65 with respect to the spleen, while ethambutol improved the activity with respect to the liver.[62] Entrapment of ciprofloxacin in liposomes increases the circulation half-life of the drug when given by intravenous route in mice, which is associated with enhanced delivery of the drug to the liver, spleen, kidneys, and lungs. Furthermore, liposomal entrapment was associated with increased therapeutic efficacy against the Salmonella typhimurium infection model in mice.[63] Stevenson and coworkers [64] showed enhanced activity of streptomycin and chloramphenicol against E-coli in the cells of the J774 murine macrophage line interceded by liposome delivery.

ADVANTAGES OF LIPOSOMES

· Controlled drug delivery system
· Biodegradable, non-toxic
· Carry both water soluble and oil soluble drugs
· Prevention of oxidation
· Protein stabilization
· Controlled hydration.

FIGURES AND TABLES:

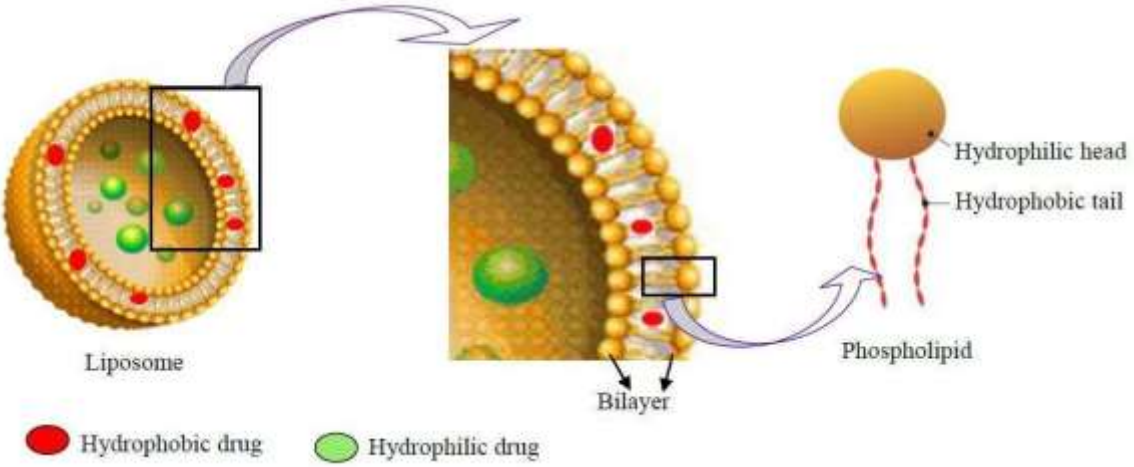

Fig.1. Structure of liposomes

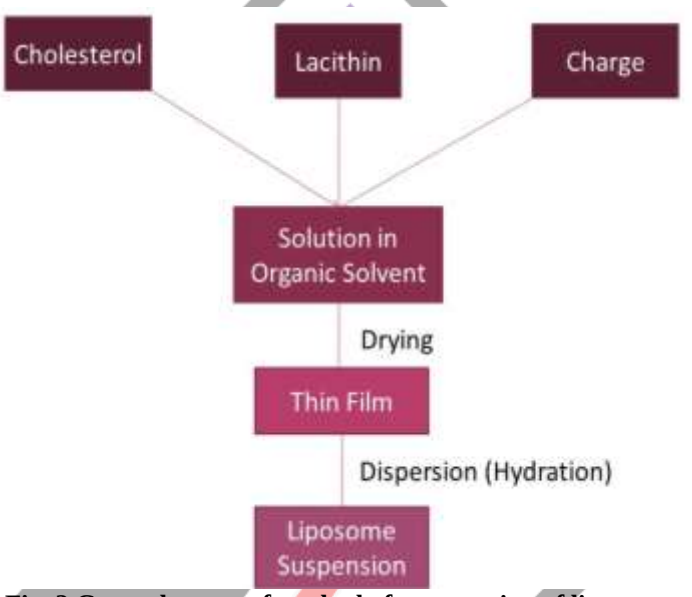

Fig. 2 General stages of method of preparation of liposomes.

Tables:

Table 1: Liposome classification based on pharmaceutical and therapeutical aspects

Type	**Specification**
MLV	Multilamellar large vesicles- >0.5µm
OLV	Oligolamellar vesicles- 0.1-1µm
UV	Unilamellar vesicles (all size range)
SUV	Small Unilamellar vesicles- 20-100nm
MUV	Medium sized Unilamellar vesicles
LUV	Large Unilamellar vesicles- >100
GUV	Giant Unilamellar vesicles- >1µm
MV	Multivesicular vesicles- 1µm

Table 2: List of clinically-approved liposomal drugs

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Depocyt	Pacira (formerly Skye Pharma)	Malignant lymphomatous meningitis
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	Skye Pharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, ScheringPlough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

CONCLUSION

Liposomes have been realized as extremely useful carrier systems, additive(s) and tools in various scientific domains. Thus, liposomes over the years have been investigated as the major drug delivery systems due to their flexibility to be tailored for varied desirable purposes. Development will continue to explore the validity of liposomes for the delivery of peptide and proteins, although progress in this particular field has been meager. Liposomes are one of the unique drug delivery system, which can be of potential use in controlling and targeting drug delivery.

ACKNOWLEDGMENT:

The author heartly thankful all subject related teaching staff, shivlingeshawar collage of pharmacy, almala, Latur, (M. S.) India.

REFERENCE

1) Ahmad et al., Antibody-Targeted Delivery of Doxorubicin Entrapped in Sterically Stabilized Liposomes Can Eradicate Lung Cancer in Mice, Cancer Res., 1993, 53, 1484–1488.
2) Lichtenberg D., Bareholz Y., "Liposomes: Preparation, Characterisation and preservation," Methods of Biological analysis 33, New york. John wiley, 1988, 337-461.
3) Nicolas K., Van der Neut R., Fok J. J., Dekruyff B., Biochim. Biophys Acta, 1985, 819, 55-65.
4) Bergers J. J., Den otter W., De groot J.W., De Blois A.W., Dullens H.F.Z., Steerenberg P.A. Crommelin D. J. A., Reconstituted membrane of tumor cellsinduce specific protection to tumor lymphoma cells., Cancer immunology and immunotherapy, 1992, 34, 233-240.
5) Chander R., Schrier H., Artificial viral envelopes containing recombinant human immunodeficiency virus (HIV) gp 120., life sciences, 1992, 50, 481-489.
6) Lawaczek R., Kainosho M., Chan S.I., Biochim Biophys Acta, 1976, 443, 313-330.
7) Brandl M., Bachmann D., Drechsler M., Bauer K. H., Liposome preparation by a new pressure homogenizer Gaulin micron Lab 40. Drug dev. Ind Pharma. 1990, 16, 2467-2191.
8) Weder H. G., Zumbuhl O., The preparation of variably sized homogeneous liposomes for laboratory, clinical and industrial use by controlled detergent dialysis. Liposome technology, Vol I. Boca Raton, Fla. CRC Press, 1984, 79-107.

9) Jiskoot W., Teerlink T., Beuvery E.C. Crommelin D. J. A., Preparation of liposomes via detergent removal from mixed micelles by dilution. The effect of bilayer composition and process parameters on liposome characteristics Pharm, 1986, 8, 259-265.
10)Lasic D. D, Papahadjopoulos D (1998). In: Medical applications of liposomes, Elsevier, New York: 9-12.
11)Zuidam N. J. and Crommelin D. J. A. (1995). J. Pharm. Science, 84:1113-1115.
12)Senior J., Fate and behaviour of liposomes in vivo: A review of controlling factors. CRC Crit. Reviews Therapeut., Drug Carrier Systems, 1987, 3, 123-1193.
13) Dimitriadis G. J., Entrapment of plasmid DNA in liposomes, Nucleic Acids Research, 1979, 6, 2697-2705.
14)Fraley R. T., Fornari C.S. Kaplan S., Entrapment of a bacterial plasmid in phospholipid vesicles: Potential for gene transfer, Proceedings of the National Academy of Sciences, USA, 1979, 76, 3348- 3352.
15)Wilson T., Papahadjopoulos D. Taber R., The introduction of poliovirus RNA into cells via lipid vesicles-liposomes, Cell, 1979, 17, 77-84.
16)Wong T.K., Nicolau C., Hofschneider P.H., Appearance of betalactamase activity in animal cells upon liposome-mediated gene transfer, Gene, 1980, 10, 87-94.
17)Wang C. Y., Huang L., Plasmid DNA adsorbed to pH-sensitive liposomes efficiently transforms the target cells, Biochemical and Biophysical Research Communications, 1987, 147, 980-985.
18)Wang C. Y., Huang L., pH-sensitive liposomes mediated target cell specific delivery and controlled expression of a foreign gene in mouse, Proceedings of the National Academy of Sciences, USA, 1987, 84, 7851-7855.
19)Felgner P. L., Gadek, T. R., Holm M., Roman R, Chan H. W., Wenz M., Northrop J.P., Ringold G.M., Danielsen, Lipofection: a highly efficient, lipid mediated DNA-transfection procedure. Proceedings of the National Academy of Sciences, 1987, 84, 7413-7417.
20)Yeoman L.C., Danels Y.J. Lynch M.J., Lipofectin enhances cellular uptake of antisense DNA while inhibiting tumor cell growth, Antisense Research and Development, 1992, 2, 51-59.
21)Litzinger D.C., Huang. L., Phosphatidylethanolamine liposomes: drug delivery, gene transfer and immunodiagnostic applications, Biochimica et Biophysica Acta, 1992, 1113, 201-227.
22).Mellman I., Fuchs R., Helenius A., Acidification of the endocytic and exocytic pathways, Annual Review of Biochemistry, 1986, 55, 663-700.
23)Schmid S. L., Fuchs R., Male P. & Mellman I., Two distinct subpopulations of endosomes involved in membrane recycling and transport to lysosomes, Cell, 1988, 52, 73-78.
17)Wang C. Y., Huang L., Plasmid DNA adsorbed to pH-sensitive liposomes efficiently transforms the target cells, Biochemical and Biophysical Research Communications, 1987, 147, 980-985.
18)Wang C. Y., Huang L., pH-sensitive liposomes mediated target cell specific delivery and controlled expression of a foreign gene in mouse, Proceedings of the National Academy of Sciences, USA, 1987, 84, 7851-7855.
24)Chu C-J, Dijkstra J, Lai M-Z, Hong K & Svoka FC., Efficiency of cytoplasmic delivery by pH-sensitive liposomes to cells in culture, Pharmaceutical Research, 1990, 7, 824-834.
25)Connor J & Huang L. pH-sensitive liposomes as efficient and target specific carriers for antitumor drugs. Cancer Research, 1986, 46, 3431-3435.
21)Litzinger D.C., Huang. L., Phosphatidylethanolamine liposomes: drug delivery, gene transfer and immunodiagnostic applications, Biochimica et Biophysica Acta, 1992, 1113, 201-227.
26)Ropert C., Malvy C., Couvreur P., Oligonucleotides in pHsensitive liposomes are efficient towards Friend retroviruses.Biochemical and Biophysical Research Communications, 1992, 183, 879-885.
27)Ropert C, Malvy C., Couvreur P., Inhibition of the Friend retrovirus by oligonucleotides encapsulated in pH-sensitive liposomes, Pharmaceutical Research, 1993, 10, 1427-1433.
28)Chu C-J, Dijkstra J, Lai M-Z, Hong K & Svoka FC., Efficiency of cytoplasmic delivery by pH-sensitive liposomes to cells in culture, Pharmaceutical Research, 1990, 7, 824-834.
19)Felgner P. L., Gadek, T. R., Holm M., Roman R, Chan H. W., Wenz M., Northrop J.P., Ringold G.M., Danielsen, Lipofection: a highly efficient, lipid mediated DNA-transfection procedure. Proceedings of the National Academy of Sciences, 1987, 84, 7413-7417.
29)Brigham K. L., Meyrick B., Christmann B., Berry L. C., King G., Expression of a prokaryotic gene in cultured lung endothelial cells after lipofection with a plasmid vector. American Journal of Respiratory Cell and Molecular Biology, 1989, 1, 95- 100.
30)Innes C.L., Smith P. B., Langenbach R., Tindall K. R., Boone L.R., Cationic liposomes (Lipofectin) mediate retroviral infection in the absence of specific receptors, Journal of Virology, 1990, 64, 957-961.
31)Brant M., Nachmansson N., Norrman K., Regnell A., Bredberg A., Schuttle vector plasmid propagation in human peripheral blood lymphocytes facilitated by liposome transfection, DNA and Cell Biology, 1991, 10, 75-79.
32)Li A.P., Myers C.A. Kaminski D.L., Gene transfer in primary cultures of human hepatocytes. In Vitro Cellular and Developmental Biology, 1992, 28, 373-375.
33)Leventis R., Silvius J.R., Interaction of mammalian cells with lipid dispersions containing novel metabolizable cationic amphiphiles. Biochimica et Biophysica Acta, 1990, 1023, 124-132.
34)Ghosh P., Bachhawat B. K., Surolia A., Synthetic Glycolipids: Interaction with Galactose-Binding Lectin and Hepatic Cells, Arch. Biochem. Biophys, 1981, 206, 454–457.
35)Ghosh P., Das P.K., Bachhawat B. K., Arch Biochem Biophys, 1982, 231, 266–270.
36)Cohen S, Bernstein H, Hewes C, Chow M, Langer R. The pharmacokinetics of and humoral responses to antigen delivered by microencapsulated liposomes. Proc. Natl. Acad. Sci. USA 1991; 88:1044010444.

37)Yoshida A Hashizakik, Yamauchi H, Sakui H. Effect of lipid with covalently attached polyethylene glycol on the surface properties of liposome bilayer membranes. Langmuir 1999; 15:2333-2337.
38)Doi K, Oku N, Toyota T, Shuto S, Sakai A, Itoh H. Therapeutic effect of reticuloendothelial system (RES) -avoiding liposomes containing a phospholipid analog of 5-fluorouracil, dipalmitoyl phosphatidyl fluorouridine, in Meth-A sarcoma-bearing mice. Biol Pharm Bull 1994; 17:1414-1416.
39)Mayer LD, Nayer R, Thies, RL, Bowman NL, Cullis, PR, Bally MB. Identification of vesicle properties that enhance the antitumour activity of liposomal vincristine against murine L1210 leukemia. CancerChemotherapy Pharmacology 1993; 33:17-24.
40)Sharma A, Mayhew E, Straubinger RM. Antitumour effect of taxol containing liposomes in a taxol resistant murine tumour model. Cancer Research 1993; 53:5877- 5881.
41)Deol P, Khuller GK, Joshi K. Therapeutic efficacies of isoniazid and rifampin encapsulated in lungspecific stealth liposomes against Mycobacterium tuberculosis infection induced in mice. Antimicrobial Agent Chemotherapy 1997; 41:1211-1214.
42)Cohen S, Bernstein H, Hewes C, Chow M, Langer R. The pharmacokinetics of and humoral responses to antigen delivered by microencapsulated liposomes. Proc. Natl. Acad. Sci. USA 1991; 88:1044010444.
43)Gregoriadis G. Engineering liposomes for drug delivery: progress and problems. Trends Biotechnol 1995; 13:527-537.
44)Smolin G., Okumoto M., Feller S., Condon D., Idoxuridine liposome therapy for herpes simplex keratitis. Am J. Opthalmol., 1981, 91, 220-225.
45)Shaeffer H. E., Brietfeller J. M. and Krohn D L., Lectin mediated attachment of liposomes to cornea. Influence od transcorneal drug flux, Invest Opthalmol Vis Sci, 1982, 23, 530-533.
46)Davies N. M., Fair S. J., Hadgraft J., and Kellaway I. W., Evaluation of mucoadhesive polymers in ocular drug delivery. II. Polymer coated vesicles. Pharm. Res. 1992, 9, 1137 – 1142.
47)Myers M. A., Thomas D. A. Straub L., Soucy D. W., Niven R. W., Kaltenbach, M. Hood, C. I. Schreier, H., Gonzalez- Rothi, R. J., Pulmonary effects of chronic exposure ti pilosome aerosols in mice., Exp. Lung Res, 1993, 19, 1-19.
48)Padmanbhan R.V., Gudapaty R., Liener I. E., Schwartz B. A., Hoidal J.R., Protection against pulmonary oxygen toxicity in rats by the intratracheal administration of liposomes encapsulated superoxide dismutase or catalse, Am. Rev. Respir. Dis., 1985, 132, 164-167.
49)Wichert B. V., Gonzlez-Rothi R. J., Straub L.E., Wichert B.M., and Schreier H. Amikacin liposomes : Characterisation, Aerolisation, and in vitro activity against Mycobacterium Avium-intracellulare in alveolar macrophages, Int. J. Pharmaceut., 1992, 78, 227-235.
50)Gregoriadis G., Overview of liposomes, J. Antimicrob. Chemother. 1991, 28, 39–48.
51)Gregoriadis G., A. T. Florence, Liposomes and cancer therapy, Cancer Cells, 1991, 4, 144–146.
52)Forssen E. A., Ross M. E., DaunoxomeTM treatment of solid tumors: Preclinical and clinical investigations, J. Liposome Res., 1994, 4, 481–512.
53)Pea F., Russo D., Michieli M., Baraldo M., Ermacora A., Damiani D., Baccarani M., Furlanut M., Liposomal daunorubicin plasmatic and renal disposition in patients with acute leukemia, Cancer Chemother. Pharmacol., 2000, 46, 279–286.
54)Daniele B., DeVivo R., Perrone F., Lastoria S., Tambaro R., Izzo F., Fiore F., Vallone P., Pignata S., Phase-I clinical trial of liposomal daunorubicin in hepatocellular carcinoma complicating liver cirrhosis, Anticancer Res., 2000, 20, 1249–1251.
55)Wollina U., Hohaus K., Schonlebe J., Haroske E., Kostler E., Liposomal daunorubicin in tumor stage cutaneous T-cell lymphoma: report of three cases, J. Cancer Res. Clin. Oncol., 2003, 129, 65–69.
56)Fiorillo A., Maggi G., Greco N., Migliorati R., Amico A. D., DeCaro M.D., Sabbatino M.S., Buffardi F., Second-line chemotherapy with the association of liposomal daunorubicin, carboplatin and etoposide in children with recurrent malignant brain tumors, J. Neurooncol., 2004, 66, 179–185.
57)Webb M.S., Logan P., Kanter P. M., St-Onge G., Gelmon K., Harasym T., Mayer L.D., Bally M. B., Preclinical pharmacology, toxicology and efficacy of sphingomyeline/cholesterol liposomal vincristine for therapeutic treatment of cancer, Cancer Chemother. Pharmacol. 1998, 42, 461– 470.
58)Guthlein F., Burger A. M., Brandl M., Fiebig H. H., Schubert R., Unger C., Massing U., Pharmacokinetics and antitumor activity of vincristine entrapped in vesicular phospholipids gels, Anticancer Drugs, 2002, 13, 797–805.
59)Gaspar M. M., Neves S., Portaels F., Pedrosa J., Silva T. M., Cruz M. E., Therapeutic efficacy of liposomal rifabutin in a Mycobacterium avium model of infection, Antimicrob. Agents Chemother. 2000, 44, 2424–2430.
60)Agarwal A., Kandpal H., Gupta H. P., Singh N. B., Gupta C. M., Tuftsin-bearing liposomes as rifampin vehicles in treatment of tuberculosis in mice, Antimicrob. Agents Chemother. 1994, 38, 588–593.
61)Onyeji C. O., Nightingale C. H., Nicolau D. P., Quintiliani R., Efficacies of liposome-encapsulated clarithromycin and ofloxacin against Mycobacterium avium-M. Intracellular complex in human macrophages, Antimicrob. Agents Chemother. 1994, 38, 523–527.
62)Cynamon M. H., Klemens S. P., Swenson C. E., TLC G-65 in combination with other agents in the therapy of Mycobacterium avium infection in beige mice, J. Antimicrob. Chemother. 1992, 29, 693–699.
63)Webb M. S., Boman N. L., Wiseman D. J., Saxon D., Sutton K., Wong K. F., Logan P., Hope M. J., Antibacterial efficacy against an in vivo Salmonella typhimurium infection model and pharmacokinetics of a liposomal ciprofloxacin formulation. Antimicrob. Agents Chemother. 1998, 42, 45–52.
64)Stevenson M., Baillie A. J., Richards R. M., Enhanced activity of streptomycin and chloramphenicol against intracellular Escherichia coli in the J774 macrophage cell line mediated by liposome delivery, Antimicrob. Agents Chemother. 1983, 24, 742–749.