Liposomal Drug Delivery System-A Review

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ABSTRACT

Purpose of this paper: Liposomes have received a lot of attention during the past 30 years as pharmaceutical carriers of great potential. More recently, many developments have been seen in the area of liposomal drugs—from clinically approved products to new experimental applications. For further successful development of this field, promising trends must be identified and exploited, with a clear understanding of the limitations of these approaches.

Design/methodology/approach: This review presents a panoramic view of current status of research in this field to serve as a ready reference for future researchers.

Practical implications: The treasure of information provided in this review find wide utility by future researchers and will serve as basis for further improvement in methodology and design of better formulations as well as evaluation methods.

What is original/value of paper: In this article, basic characteristics, method of preparation and marketed formulations of liposomes are discussed. The success of liposomes as drug carriers has been reflected in a number of liposome based formulations, which are commercially available, or are currently undergoing clinical trials.

Keywords: Lipoidal vesicles, Hydrophillic and Hydrophobic drugs, Drug carriers.

INTRODUCTION

The name liposome is derived from two Greek words: ‘Lipos’ meaning fat and ‘Soma’ meaning body. A liposome can be formed in variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. Liposomes were first described by British hematologist Dr. Alec D Bangham in 1961 (Published 1964), at the Babraham Institute, when he and R.W. Horne were testing the institute’s new electron microscope by adding negative stain to dry phospholipids.1,2

Liposomes are simple microscopic vesicles in which lipid bilayer structure is present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecules. There are number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, together with their hydrolysis products. Classification of liposomes is based on number of lamellae, composition, method of preparation and its size (Table 1 and 2). Liposomes can exhibit a range of sizes and morphologies upon the assembly of pure lipids or lipoidal mixtures suspended in an aqueous medium. A common morphology which is analogous to the eukaryotic cellular membrane is the unilamellar vesicles. This is characterized by a single bilayer membrane which encapsulates an internal aqueous solution, thus separating it from the external solution. Both cationic amine head groups and anionic phospholipid head groups can form this single walled vesicle.3 Vesicle size falls into nanometer to micrometer range: small unilamellar vesicles are 20–200 nm, unilamellar vesicles are 200 nm-1 µm, and giant unilamel lar vesicles are larger than 1 µm. In this article, basic characteristics, method of preparation and marketed formulations of liposomes are discussed.

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Table 1: Classification of liposomes based on size and lamellarity

<table>
<thead>
<tr>
<th>SL. NO</th>
<th>TYPES</th>
<th>SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Multilamellar large vesicles (MLV)</td>
<td>(&gt;0.5µm)</td>
</tr>
<tr>
<td>2.</td>
<td>Oligolamellar vesicles (OLV)</td>
<td>0.1-1 µm</td>
</tr>
<tr>
<td>3.</td>
<td>Unilamellar vesicles (UV)</td>
<td>All sizes</td>
</tr>
<tr>
<td>4.</td>
<td>Small unilamellar vesicles (SUV)</td>
<td>20-100 nm</td>
</tr>
<tr>
<td>5.</td>
<td>Medium sized unilamellar vesicles (MUV)</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Large unilamellar vesicles (LUV)</td>
<td>&gt;100 nm</td>
</tr>
<tr>
<td>7.</td>
<td>Giant unilamellar vesicles (GU)</td>
<td>&gt;1 µm</td>
</tr>
<tr>
<td>8.</td>
<td>Multivesicular vesicles (MVV)</td>
<td>usually &gt;1 µm</td>
</tr>
</tbody>
</table>

Table 2: Classification of liposomes based on the method of preparation

<table>
<thead>
<tr>
<th>SL. NO.</th>
<th>TYPES OF LIPOSOMES</th>
<th>METHOD OF PREPARATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>REV (Reverse Evaporation vesicles)</td>
<td>Single or Oligolamellar vesicles made by reverse osmosis</td>
</tr>
<tr>
<td>2.</td>
<td>MLV-REV</td>
<td>Multilamellar vesicles made by Reverse Phase Evaporation method</td>
</tr>
<tr>
<td>3.</td>
<td>SPLV</td>
<td>Stable Plurilamellar vesicles</td>
</tr>
<tr>
<td>4.</td>
<td>FATMLV</td>
<td>Frozen and Thawed MLV</td>
</tr>
<tr>
<td>5.</td>
<td>VET</td>
<td>Vesicles prepared by Extrusion method</td>
</tr>
<tr>
<td>6.</td>
<td>DRV</td>
<td>Vesicles prepared by Dehydration-Rehydration method</td>
</tr>
</tbody>
</table>

CLASSIFICATION OF LIPOSOMES

ADVANTAGES
1. Liposomes are biocompatible, completely biodegradable, non-toxic in nature.
2. They are suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs.
3. They protect the encapsulated drug from external environment.
4. They reduce toxicity and increase stability. Since therapeutic activity of chemotherapeutic agent can be improved through liposome encapsulation. This reduces deleterious effects that are observed at concentration similar to or lower than those required for maximum therapeutic activity.
5. It reduces exposure of sensitive tissue to toxic drugs.

DISADVANTAGES
1. The production cost is high.
2. Leakage and fusion of encapsulated drug/molecules can occur.
3. It has short half-life. In reticuloendothelial system, particularly the Kupffer cells in the liver remove liposomes from the circulation.

METHODS OF LIPOSOME PREPARATION

Passive Loading Techniques
a. Mechanical dispersion methods:
   - Lipid film hydration by hand shaking, non hand shaking or freeze drying
   - Micro emulsification
   - Sonication
   - French pressure cell
   - Membrane extrusion
   - Dried reconstituted vesicles
   - Freeze thawed liposomes
b. Solvent dispersion methods:
   - Ethanol injection
   - Ether injection
• Double emulsion
• Reverse phase evaporation vesicles
• Stable pluri lamellar vesicles

c. Detergent removal methods:
• Dialysis
• Column chromatography
• Dilution
• Reconstituted Sendai virus enveloped

Active loading technique

GENERAL METHOD OF PREPARATION\textsuperscript{5,7,8}

Liposomes are mainly manufactured using various procedures in which the 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 manufacture of liposomes. The lipid soluble (lipophilic) materials are solubilized in the organic solution of the constituent lipid and then evaporated to a dry drug containing lipid film followed by its hydration. These methods involve loading of the entrapped agents before or during the manufacturing procedure (Passive loading). However, certain type of 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 (remote loading).

MECHANICAL DISPERSION METHODS

Preparation of liposomes by lipid film hydration

When preparing liposomes with mixed lipid composition, the lipids must be dissolved and mixed in organic solvent to assure a homogeneous mixture of lipids. Usually this process is carried out using chloroform or chloroform: methanol mixture. The purpose is to obtain a clear lipid solution for complete mixing of lipids. Typically lipid solutions are prepared at 10–20 mg lipid/ml of organic solvent, although higher concentrations may be used if the lipid solubility and mixing are acceptable. Once the lipids are thoroughly mixed in the organic solvent, the solvent is removed to yield a lipid film. For small volumes of organic solvent (<1ml), the solvent is evaporated by using dry nitrogen or argon stream in a fume hood. For larger volumes, the organic solvent should be removed by rotary evaporation yielding a thin lipid film on the sides of round bottom flask. The lipid film is thoroughly dried to remove residual organic solvent by placing the vial or flask on a vacuum pump overnight. If the use of chloroform is objectionable, an alternative is to dissolve the lipids in tertiary butanol or cyclohexane. The lipid solution is transferred to containers and frozen by placing the containers on a block of dry ice or swirling the container in a dry ice-acetone or alcohol (ethanol or methanol) bath. Care should be taken when using the bath procedure that, the container can withstand sudden temperature changes without cracking. After complete freezing, the frozen lipid cake is placed on a vacuum pump and lyophilized until dry (1–3 days depending on volume). The thickness of the lipid cake should not be more than the diameter of the container being used for lyophilization. Dry lipid films or cake can be removed from the vacuum pump; the container should be closed tightly, tapped and stored frozen until ready to hydrate.

Hydration of Lipid Film/Cake

Hydration of the dry lipid film/cake is accomplished by adding an aqueous medium to the container of dry lipid and agitating. The temperature of the hydrating medium should be above the gel liquid crystal transition temperature ($T_g$ or $T_m$) of the lipid. After addition of the hydrating medium, the lipid suspension should be maintained above the $T_g$ during the hydration period. For high transition lipids, this is easily accomplished by transferring the lipid suspension to a round bottom flask and placing the flask on a rotary evaporation system without a vacuum. Spinning of round bottom flask in warm water bath maintained at a temperature above the $T_g$ of the lipid suspension allows the lipid to hydrate in its fluid phase with adequate agitation. Hydration time may differ slightly among lipid species and structure, however, a hydration time of 1hr with vigorous shaking, mixing, or stirring is highly recommended. It is also believed that allowing the vesicle suspension to stand overnight prior to downsizing makes the sizing process easier and improves the homogeneity of the size distribution. Aging is not recommended for high transition lipids as lipid hydrolysis increases with elevated temperatures. The hydration medium is generally determined by the application of the lipid vesicles. Suitable hydration media include distilled water, buffer solutions, saline, and non-electrolytes such as sugar solutions. Generally accepted solutions which meet these conditions are 0.9% saline, 5% dextrose and 10% sucrose. During hydration some lipids form complexes unique to their structure. Highly charged lipids have been observed to form a viscous gel when hydrated with low ionic strength solutions. The problem can be alleviated by addition of salt or by downsizing the lipid suspension. Poorly hydrating lipids such as phosphatidylethanolamine have a tendency to self aggregate upon hydration. Lipid vesicles containing more than 60% phosphatidylethanolamine form particles having a small hydration layer surrounding the vesicle. As particles approach one another there is no
hydration repulsion to repel the approaching particle and the two membranes fall into an energy well where they adhere and form aggregates. The aggregates settle out of solution as large flocculates which will disperse on agitation but reform upon settling. The product of hydration is a large multilamellar vesicle (LMV) analogous in structure, with each lipid bilayer separated by a water layer. The spacing between lipid layers is dictated by composition with poly-hydrating layers being closer together than highly charged layers which separate on electrostatic repulsion. Once a stable, hydrated LMV suspension has been produced, the particles can be downsized by a variety of techniques, including sonication or extrusion.

**Sizing of Lipid Suspension**

**Sonication**

Disruption of LMV suspensions using sonic energy (sonication) typically produces small, unilamellar vesicles (SUV) with diameters in the range of 15-50nm. The most common instrumentation for preparation of sonicated particle is bath and probe tip sonicators. Cuphorn sonicators, although less widely used, but they have successfully produced SUV. Probe tip sonicators deliver high energy input to the lipid suspension but suffer from overheating of the lipid suspension causing degradation. Sonication tips also tend to release titanium particles into the lipid suspension which must be removed by centrifugation prior to use. For these reasons, bath sonicators are the most widely used instrument for preparation of SUV. 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 above the Tc of the lipid. The lipid suspension should begin to clarify to yield a slightly hazy transparent solution. The haziness is due to light scattering induced by residual large particles remaining in the suspension. These particles can be removed by centrifugation to yield a clear suspension of SUV. Mean size and distribution is influenced by composition and concentration, temperature, sonication time and power, volume, and sonicator tuning. Since it is nearly impossible to reproduce the conditions of sonication, size variation between batches produced at different times is not uncommon. Also, due to the high degree of curvature of these membranes, SUV are inherently unstable and will spontaneously fuse to form larger vesicles when stored below their phase transition temperature (Figure 1).

**French Pressure Cell Method**

The method involves the extrusion of MLV at 20,000 psi at 4°C through a small orifice. The method has several advantages over sonication method. The method is simple, rapid, and reproducible and involves gentle handling of unstable materials (Figure 2). The resulting liposomes are somewhat larger than sonicated SUVs. The drawbacks of the method are that the required temperature is difficult to achieve and the working volumes are relatively small.
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Dried Reconstituted Vesicles (DRVs)

In dried reconstituted vesicles method preformed liposomes are added to an aqueous solution containing an active agent or are mixed with a lyophilized protein, followed by rehydration of mixture. This leads to a dispersion of solid lipids in finely subdivided form (Figure 3). However, this method is suitable only for unilamellar vesicles, as the incorporation rates with multi lamellar vesicles are quite low.

Freeze thaw method

In this method, SUVs are rapidly frozen and followed by slow thawing. The brief sonication disperses aggregated materials to LUV. The formation of unilamellar vesicles is due to the fusion of SUV during the process of freezing or thawing. This type of fusion is strongly inhibited by increasing the ionic strength of the medium and by increasing the phospholipids concentration (Figure 3). The encapsulation efficiencies from 20–30% were obtained. The disadvantages with the method are divalent metal ions; sucrose and high ionic strength salt solutions cannot be entrapped efficiently.

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. The subsequent removal of ether under vacuum leads to the formation of liposomes. The main disadvantage with the method is liposomes produced are heterogeneous in nature (70–190 nm) and the material to be encapsulated will be exposed to higher temperature (Figure 4).

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 residual 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 (Figure 4).

**Reverse Phase Evaporation Method**

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

**Detergent Removal Method**

The detergents at their critical micelle concentrations have been used to solubilize lipids. As detergent is removed the micelles become progressively rich 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 liposomes which are homogenous in size. The main drawback of the method is the retention of traces of detergent within the liposomes. A commercial device called LIPOPREP which is a version of dialysis system available for the removal of detergents. Other techniques have been used for the removal of detergents: (a) by using Gel Chromatography involving a column of Sephadex G-259 (b) by adsorption or binding of Triton X-100 (detergent) to Bio-Beads SM-210 (c) by binding of octylglucoside (detergent) to Amberlite XAD-2beads.

**MARKETED PRODUCTS**

In clinical applications, liposomal drugs have been proven to be most useful for their ability to passively accumulate at site of increased vasculature permeability, when their average diameter is in the ultra filterable range, and for their ability to reduce the side effects of the encapsulated drugs relative to free drugs. This has resulted in an overall increase in therapeutic index, which measures efficacy over toxicity. However, the gains in the rapeutic index have been more on the side of reduced toxicity than on the side of increased efficacy. Liposomes have diverse applications in the treatment of infections, vaccine and gene delivery, cancer treatment, lung diseases and skin conditions (Table 3).
CHARACTERIZATION OF LIPOSOMES

- **Vesicle shape and lamellarity**: The shape and lamellarity of liposome is measured by electron microscopy or by spectroscopic techniques. Most frequently the nuclear magnetic resonance spectrum of liposome is recorded with and without the addition of a paramagnetic agent that shifts or bleaches the signal of the observed nuclei on the outer surface of liposomes.

- **Vesicle size and size distribution**: The size distribution is normally measured by dynamic light scattering. This method is reliable for liposomes with relatively homogenous size distribution. A simple but powerful method is gel exclusion chromatography, in which a truly hydrodynamic radius can be detected. Sephacryl-S100 can separate liposome in size range of 30-300nm. Sepharose -4B and -2B columns can separate SUV from micelles.

- **Surface charge determination**: Liposomes are usually prepared using charge imparting constituting lipids and hence it is imperative to study the charge on the vesicle surface. The free flow electrophoresis and zeta potential measurement will be done to determine the charge on the surface of vesicles.

- **Encapsulation efficiency**: It describes the percent of drug in aqueous phase and hence percent of water soluble drug ultimately entrapped during preparation of liposomes and is usually expressed as % entrapment/mg lipid. Encapsulation efficiency is assessed using two techniques including mini column centrifugation method and protamine aggregation method. In mini column centrifugation method, the hydrated gel is filled in a barrel of 1 ml syringe without plunger which is plugged with Whatman GF/B filter pad. This barrel is rested in a centrifuge tube. This tube is spun at 2000 rpm for 3 min to remove excess saline solution from gel. After centrifugation the gel column should be dried and the eluted saline is removed from collection tube. Liposome suspension of 0.2 ml is applied drop wise to top gel bed, and the column is spun at 2000 rpm for 3 min to expel the void volume containing the liposomes into centrifugation tube. The elution is then removed and set aside for assay.

\[
\% \text{ Entrapment Efficiency} = \left( \frac{\text{Entrapped Drug (mg)}}{\text{Total Drug added (mg)}} \right) \times 100
\]

- **Entrapped volume**: The entrapped volume of a population of liposomes (in µl/mg phospho-
lipids) can often be deduced from measurements of total quantity of solute entrapped inside liposome assuring that the concentration of solute in the aqueous medium inside liposome is the same after separation from entrapped material.

- **Phase Response and transitional behavior:** Liposome and lipid bilayer exhibit various phase transition that are studied for their role in triggered drug release or stimulus mediated fusion of liposomal constituent with target cell. An understanding of phase transition and fluidity of phospholipids membrane is important both in manufacture and exploitation of liposomes since phase behavior of liposomal membrane determine such properties such as permeability, fusion, aggregation and protein binding. The phase transition has been evaluated using freeze fracture electron microscopy. They are more comprehensive verified by differential scanning calorimeter analysis.

- **Stability of liposomes:** Liposomal stability includes physical, chemical and biological stability. The physical stability indicates mostly the constancy of the size and the ratio of lipid to active agent. The cationic liposomes can be stable at 4°C for long period of time, if properly sterilized. The chemical instability mainly concerns two degradation pathways, oxidative and hydrolytic. Oxidation of phospholipids in liposomes mainly takes place in unsaturated fatty acyl chain-carrying phospholipids. These chains are oxidized via a free radical chain mechanism in the absence of particular oxidants. Storage at low temperatures and protection from light and oxygen will reduce the chance of oxidation. Further protection could be enhanced with the addition of antioxidants such as α-tocopherol and butyl hydroxyl toluene. Working under nitrogen or argon also minimizes the oxidation of lipids during preparation. The hydrolysis of ester bonds can also be reduced by optimizing pH, temperature, ionic strength, chain length and head group and the amount of cholesterol incorporated into the bilayer.

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

**APPLICATIONS**

- **Cancer chemotherapy:** The long term therapy of anticancer drug leads to several toxic side effects. The liposomal therapy to the tumour cell has revolutionized the world of cancer therapy with least side effects. It has been said that the small and stable liposomes are passively targeted to different tumor because they can circulate for longer time and they can extra vasate in tissue with enhanced vascular permeability. The light sensitive liposomes have been prepared, where light triggers the release of anticancer drugs, like doxorubicin. The light triggered system will reduce the potential toxicity and lead to more effective therapy.

- **Gene delivery:** Negatively charged or classical liposomes have been used as vehicles for gene transfer into cell in culture. The cationic lipids are able to interact spontaneously with negatively charged DNA to form cluster or aggregated vesicles along the nucleic acid. At a critical liposome density the DNA is condensed and becomes encapsulated with in a lipid bilayer.

- **Liposomes for topical applications:** Liposomes are proved to be effective in delivering drugs in to the skin. Liposomes increase the permeability of skin for various entrapped drugs. Liposomes can exert different functions after topical application. They can improve drug deposition within the skin at the site of action where the goal is to reduce systemic absorption and thus minimize side effects. They can provide targeted delivery to skin appendages in addition to their potential for transdermal delivery. In the recent studies, it is shown that liposomes penetrate effectively into hair follicles and thus hair follicle penetration can be increased by
massaging the skin, which stimulates the in vivo movement of hairs in the hair follicles.

- **Liposomes for pulmonary delivery**: Targeted drug delivery to the lungs, has evolved to be one of the most widely investigated systemic or local drug delivery approaches. The use of drug delivery system for the treatment of pulmonary diseases is increasing because of their potential for localized topical therapy in the lungs. This route also makes it possible to deposit drugs more site specific at high concentrations within the diseased lung thereby reducing the overall amount of drug given to patients, as well as increasing local drug activity while reducing systemic side effects and first pass metabolism.

- **Liposome for Nasal administration**: For nasally administered products good penetration, is of little use if the formulation is not able to remain in contact with the mucosal surface for a long enough time to enable penetration to occur. Therefore mucoadhesion is a key characteristic of nasally administered formulations.

  The liposomes coated with alginites, chitosan or trimethyl chitosan, which are able to penetrate through the nasal mucosa and offer enhanced penetration over uncoated liposomes when delivered as dry powders. The coating of liposomes may result in some reduction in encapsulation efficiency, still maintained between 60–69% and the structural integrity of the entrapped protein and its release characteristics were maintained.

- **Liposomes in parasitic diseases**: The conventional liposomes are digested by phagocytic cells in the body after intravenous management; they are ideal vehicles for the targeting drug molecules into these macrophages. Leishmaniasis is a parasitic infection of macrophages which affects over 100 million people in tropical regions and is often deadly. The effectual dose of drugs, mostly different antimonials, is not much lower than the toxic one. Liposomes accumulate in the very same cell population which is infected. The best results reported so far in human therapy are probably liposomes as carriers for Amphotericin B in antifungal therapies. This is the drug of choice in dispersed fungal infections.

- **Ophtalmic delivery of drugs**: Liposomes has been investigated for ophthalmic drug delivery since it offers advantages as a carrier system. It is biodegradable and biocompatible nano carrier. It can enhance the permeation of poorly absorbed drug molecules by binding to the corneal surface and improving residence time.

To reduce the drug loss and side effects associated with conventional eye drops, a novel approach was introduced, where the liposomes made up of dimyristoylphosphatidylcholine are dispersed in contact lens hydrogels made up of poly-2-hydroxyethyl methacrylate. The contact lens loaded with hydrogels is transparent in nature and deliver drugs at therapeutic level for few days.

- **Liposomes for Brain targeting**: The liposomal technology is quite advanced to design with better site specific action. The basic reason for the acceptance of liposomal carrier is due to their controlled profile or drug release nature as well as due to their selected targeting mechanism. The surface modified liposomes can be used to directly encapsulate drug molecules to diseased tissues or organs.

  The brain distribution of liposomes can be modulated by conjugation of appropriate targeting vectors, like monoclonal antibody. The mechanism involved in the concentration of liposomes in brain by crossing blood brain barrier—coupling of liposomes with brain drug transport vector through absorptive mediated transcytosis or by receptor mediated transcytosis.

**CONCLUSION**

Liposomes are extremely useful carrier systems for targeted drug delivery. The flexibility of their behavior can be exploited for the drug delivery through any route of administration and for any drug material irrespective of their solubility properties. There is even greater promise in future for marketing of more sophisticated and highly stabilized liposomal formulations. The use of liposomes in the delivery of the drugs and genes are promising and is sure to undergo further development in future. The liposomal drug delivery system will revolutionize the vesicular systems with wide application especially in the treatment of cancer.

**REFERENCES**