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Review Article

LIPOSOMAL GEL FOR TRANSDERMAL APPLICATION FOR THE TREATMENT OF TOPICAL INFECTIONS

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ABSTRACT

Liposomes as artificial colloidal vesicular structure having hydrophilic core in a lipid bilayer membrane became one of the most tremendously explored drug delivery system. These spherical vesicles consist of amphiphilic molecule like cholesterol, sterols and can be used to deliver both hydrophilic drugs as well as lipophilic drug. These vesicles are differentiated on the basis of size, composition, method of preparation and application. Liposomes are biodegradable, non-immunogenic, biocompatible, provide targeted and prolonged release, change pharmacokinetic and pharmacodynamics attribute of drug, they find wide clinical application as diagnostic, antimicrobial, anticancer, vaccine adjuvant and cosmetics. Topical liposome formulations could be more effective and less toxic than conventional formulations. The liposome gel formulations could perform therapeutically better effects than the conventional formulations, as prolonged and controlled release topical dosage forms, may lead to improved efficiency and better patient compliance.

Keywords: *Liposomes, Topical, Amphiphilic, Non-immunogenic, Biocompatible*

INTRODUCTION

Liposomes consist of vesicles composed of bilayers or multilayers that contain or have phospholipids and cholesterol surrounding an aqueous compartment. Drug is entrapped within the liposome and is released from the liposome for absorption at the intestinal membrane surface. This dosage form received considerable and this may well relate to their absorption enhancing ability, the feasibility of their use to promote drug absorption is uncertain drugs or chemical entities. Advances in combinatorial chemistry have led to the discovery of a wide number of new chemical entities (NCE) or drugs that have a potential therapeutic action on the biological systems. But most of the NCEs or drugs being discovered provide a challenge or produce most difficulties to the formulation scientist because of their physicochemical properties like poor solubility and 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 targeted to a specific site (diseased site) in order to reduce their toxic 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 sites. Various carriers like nanoparticles, micro particles, polysaccharides, lectins and liposomes can be used to target the drug to a specific site. Liposomal drug delivery is gaining interest due to its contribution to varied areas like drug delivery, cosmetics, and structure of biological membrane. Liposomes very useful because act as a carrier for a variety of drugs, having a potential therapeutic action or other properties. Liposomes are colloidal carriers, having a size range of 0.01–5.0μm in diameter. Indeed these are bilayer vesicles that are formed when

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phospholipids are hydrated in excess of aqueous medium or aqueous solution. Liposomes have got a potential advantage of encapsulating hydrophilic as well as hydrophobic drugs and targeting them to the phospholipidsare hydrated in excess of aqueous medium. Liposomes have got a potential advantage of encapsulating hydrophilic as well as hydrophobic drugs and targeting them to the required diseased site in the body.

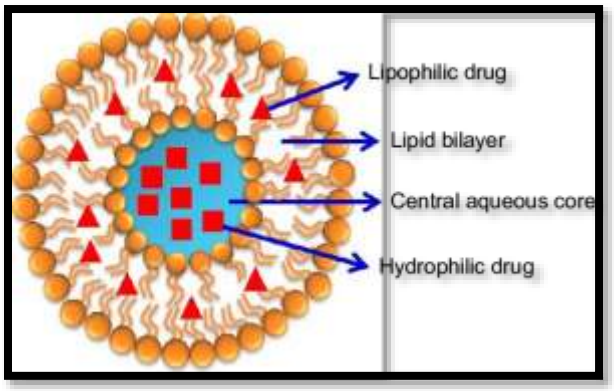

Fig 1: Structure of liposome

Mechanism of liposome formation:

The basic or important part of liposome is formed by phospholipids, which are amphiphilic molecules (having a hydrophilic head and hydrophobic tail). The hydrophilic part is important it is mainly phosphoric acid bound to a water soluble molecule, whereas, the hydrophobic part consists of two fatty acid chains with 10-24 carbon atoms and 0-6 double bonds in each chain. When these phospholipids are disseminate or dispersed in aqueous medium, they form lamellar sheets by organizing in such a way that, the polar head group faces outwards to the aqueous region while the fatty acid groups face each other and finally form spherical/vesicle like structures called as liposomes. The polar portion remains or residue part in contact or touch with aqueous region along with shielding or keep safe of the non-polar part (which is oriented at an angle to the membrane surface). When phospholipids are hydrated in water, along with the input of energy like Sonication, shaking, heating, homogenization, etc. it is the hydrophilic/ hydrophobic interactions between lipid–lipid, lipid–water molecules that lead or show to the formation of bilayer vesicles in order to achieve or arrive at a thermodynamic equilibrium in the aqueous phase.

Advantages of liposome

• Stability increased if liposome prepared via encapsulation

• Liposomes increased efficacy and therapeutic index of drug (actinomycin-D)

• Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol)

• Liposomes help reduce the exposure of sensitive tissues totoxic drugs

• Site avoidance effect

• Liposomes are flexible, non-toxic, biocompatible, completely biodegradable, and non-immunogenic for systemic and no systemic administrations

• Flexibility to couple with site-specific ligands to achieve active targeting

Disadvantages of liposome

• Short half-life

• Low solubility

• Leakage and fusion of encapsulated drug/molecules

• Production cost is high

• Fewer stables

• Sometimes phospholipids undergoes oxidation and hydrolysis-like reaction1

Classification of liposomes based on structure parameters

1. Multilamellar Large vesicles > 0.5um
2. Oligolamellar vesicles 0.1-1um
3. Unilamellar vesicles (All size range)

a) Small unilamellar vesicles 20-100nm
b) Medium sized unilamellar vesicles
c) Large unilamellar vesicles >100nm
d) Giant unilamellar vesicles >1um

4. Multivesicular vesicles >1um

Methods of preparation of liposomes

A) Multilamellar Liposomes (MLV)

1. Lipid hydration method

This is the most widely used method for the preparation of MLV. The method involves drying a solution of lipids so that a thin film is formed at the bottom of round bottom flask and then hydrating the film by adding aqueous buffer and vortexing the dispersion for some time. The hydration step is done at a temperature above the gel-liquid crystalline transition temperature Tc of the lipid or above the Tc of the highest melting component in the lipid mixture. The compounds to be encapsulated are added either to aqueous buffer or to organic solvent containing lipids depending upon their solubilities. MLV are simple to prepare by this method and a variety of substances can

been capsulated in these liposomes. The drawbacks of the method are low internal volume, low encapsulation efficiency and the size distribution is heterogeneous.

2. Solvent Spherule Method

A method for the preparation of MLVs of homogeneous size distribution .The process involved dispersing in aqueous solution the small spherules of volatile hydrophobic solvent in which lipids had been dissolved. MLVs were formed when controlled evaporation of organics solvent occurred in a water bath.

B) Small Unilamellar Liposomes (SUV)

1. Sanitation Method

Here MLVs are sonicated either with a bath type sonicator or a probe sonicator under an inert atmosphere. The main drawbacks of this method are very low internal volume/encapsulation efficiency, possibly degradation of phospholipids and compounds to be encapsulated, exclusion of large molecules, metal contamination from probe tip and presence of MLV along with SUV.

2. French Pressure Cell Method

The method involves the extrusion of MLV at 20,000 psi at 4°C through a small orifice. The method has several advantages over sonication method. The method is simple rapid, reproducible and involves gentle handling of unstable materials. The resulting liposomes are somewhat larger than sonicated SUVs. The drawbacks of the method are that the temperature is difficult to achieve and the working volumes are relatively small (about 50 mL maximum).

C) Large Unilamellar Liposomes (LUV)

They have high internal volume/encapsulation efficiency and are now days being used for the encapsulation of drugs and macromolecules.

1. Solvent Injection Methods

a) Ether Infusion Method

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous solution of the material to be encapsulated at 55-65°C or under reduced pressure. The subsequent removal of ether under vacuum leads to the formation of liposomes. The main drawbacks of the method are that the population is heterogeneous (70- 190 nm) and the exposure of compounds to be encapsulated to organic solvents or high temperature.

b) Ethanol Injection Method

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

c) Reserves Phase Evaporation Method

First water in oil emulsion is formed by brief sonication of a two phase system containing phospholipids in organic solvent (diethylether or isopropylether or mixture of isopropyl ether 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 for example 0.01 M NaCl. The method has been used to encapsulate small, large and macromolecules. The main disadvantage of the method is the exposure of the materials to be encapsulated to organic solvents and to brief periods of sonication. These conditions may possibly result in the denaturation of some proteins or breakage of DNA strands. We get a heterogeneous sized dispersion of vesicles by this method. Modified Reverse Phase Evaporation Method was presented and the main advantage of the method is that the liposomes had high encapsulation efficiency (about 80%). The Reverse Phase Evaporation has also been modified to entrap plasmids without damaging DNA strands.

d) Calcium-Induced Fusion Method

This method is used to prepare LUV from acidic phospholipids. The procedure is based on the observation that calcium addition to SUV induces fusion and results in the formation of multilamellar structures in spiral configuration (Cochleate cylinders). The addition of EDTA to these preparations results in the formation of LUVs. The main advantage of this method is that macromolecules can he encapsulated under gentle conditions. The resulting liposomes are largely unilamellar, although of a heterogeneous size range. The chief disadvantage of this method is that LUVs can only be obtained from acidic phospholipids.

e) Freeze-Thaw 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 processes of freezing and thawing. This type of fusion is strongly inhibited by increasing the ionic strength of the medium and by

increasing the phospholipid concentration. The encapsulation efficiencies from 20 to 30% were obtained.

(D) Giant Liposomes

The procedure for the formation of giant liposomes involves the dialysis, of a methanol solution of phosphatidylcholine in the presence of methylglucoside detergent against an aqueous solution containing up to 1 M NaCl. The liposomes range in diameter from 10 to 100 mm.[2]

Modes of liposome action

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

(i) Improved solubility of lipophilic and amphiphilic drugs. Examples include Porphyrins, Amphotericin B, Minoxidil, some peptides, and anthracyclines, respectively; furthermore, in some cases hydrophilic drugs, such as anticancer agent Doxorubicin or Acyclovir can be encapsulateded in the liposome interior at concentrations several fold above their aqueous solubility. This is possible due to precipitation of the drug or gel formation inside the liposome with appropriate substances encapsulated;

(ii) Passive targeting to the cells of the immune system, especially cells of the mononuclear phagocytic system (in older literature reticuloendothelial system). Examples are antimonials, Amphotericin B, porphyrins and also vaccines, immunomodulators or (immuno) supressors;

(iii) Sustained release system of systemically or locally administered liposomes. Examples are doxorubicin, cytosine arabinose, cortisones, biological proteins or peptides such as vasopressin;

(iv) Site-avoidance mechanism: liposomes do not dispose in certain organs, such as heart, kidneys, brain, and nervous system and this reduces cardio-, nephro-, and neuro-toxicity. Typical examples are reduced nephrotoxicity of Amphotericin B, and reduced cardiotoxicity of Doxorubicin liposomes;

(v) Site specific targeting: in certain cases liposomes with surface attached ligands can bind to target cells („key and lock" mechanism), or can be delivered into the target tissue by local anatomical conditions such as leaky and badly formed blood vessels, their basal lamina, and capillaries. Examples include anticancer, anti-infection and anti-inflammatory drugs;

(vi) Improved transfer of hydrophilic, charged molecules such as chelators, antibiotics, plasmids, and genes into cells.[3]

Targeting liposomes to specific organelles

Related to active targeting discussed in the section on stealth liposomes, a sub-area of growing interest is the ability to target drugs to specific organelles. While specific subcellular targeting is still a significant challenge, efforts have so far been most successful with targeting drugs to lysosomes or mitochondria. Most of these systems are still at the in vitro research phase. In one such in vitro demonstration, drugs encapsulated in liposomes modified with various lysosomotropic ligands, such as octadecyl-rhodamine B (RhB), were successfully delivered to lysosomes. Elsewhere, mitochondria-targeting was achieved in vitro with the polymer (Rh123) - PEG-DOPE (Rhodamine 123- Polyethylene glycol-1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine) which contains mitochondriotropic dye rhodamine. The polymer, incorporated into the lipid bilayer of the liposomes, showed good uptake by cells (HeLa, B16F10) with a high degree of accumulation in the mitochondria. When these mitochondrial- targeted liposomes were loaded with paclitaxel (PCL), they showed enhanced cytotoxicity toward cancer cells compared with non-targeted liposomes or free PCL. Such subcellular targeting is highly pharmaceutically desirable and efficiently developing new delivery systems that can successfully achieve such targeting will require understanding the microenvironment of the diseased site inorder to design drugs and delivery vehicles with robust stability, pharmacokinetic and pharmacodynamics profiles, and good biocompatibility and biodegradability.

Liposomes in clinical use

The function of liposomes in vivo is directly related to their composition. Liposomes can be classified according to their lamellarity (unilamellar liposomes contain a single phospholipid bilayer, while multilamellar liposomes are composed of multiple liposomal membranes), size (liposomes are defined as small [100 nm], intermediate [100–250 nm], large [250 nm] or giant [41 um]), and surface charge (anionic, cationic, or neutral). Generally, assembly methods can be used to control the physical characteristics of liposomes. For instance, hydration of a thin lipid film generates liposomes that are largely oligolamellar, while extrusion is used to further size these liposomes and obtain monodisperse populations of

unilamellar structures. Practically, a population of monodisperse, unilamellar liposomes is always preferred. Such liposomes behave more uniformly in a way that can be aligned with the behavior of cellular systems and exhibit physical characteristics that are more predictable and statistically comparable. It is important to mention that cellular organelles with a high number of bilayers exist (mitochondria and the nucleus are two examples of double-bilayer systems), and synthetic systems mimicking their behavior need to account for such structural specificities. Such structural specificities are critical and should not be understated: in mitochondria, for instance, the two membranes create distinct compartments within the organelle, and differ significantly in structure and in function. The outer membrane contain sporins, while the inner membrane's structure is highly complex with multiple transport membrane proteins. Mimicking such complexity on liposomes is not simple. Clinically, liposomes are used as carriers for biologically active molecules and are nontoxic to humans. Two delivery areas where liposomes have shown most promise are drug delivery and gene therapy, owing to the advantages that their use brings over traditional methods. Their unique chemical composition allows them to encapsulate hydrophilic biomolecules or drugs in the aqueous core and increase penetration through lipophilic membranes. On the other hand, the lipid bilayer can entrap lipophilic drugs and thus increase their solubility in aqueous body fluids. In immunotherapy, for instance, the use of liposomes is preferred to viral gene delivery methods for mesenchymal stem cell-based cell therapy due to its safety, lack of immunogenicity, negligible toxicity, and the ability to carry larger therapeutic genes. As a result, an increased number of studies have focused on developing improved liposomal transfection agents. Drug delivery has been the area where the use of liposomes have shown most promise. These efforts are well documented in the scientific literature. In clinical studies, liposomes have shown improved pharmacokinetics and bio distribution of therapeutic agents which minimizes toxicity by their accumulation at the target tissue. Currently, there are approximately a dozen liposome- based drugs approved for clinical use with more in various stages of clinical trials. While most liposomal drug formulations are approved for intravenous application, intramuscular and oral delivery have also been examined. Although the mechanism of drug release in tumors from liposomes is not fully understood, it is thought to depend on three main factors: the mechanism of drug loading, lipid composition of the membrane, and the tumor microenvironment. All of the systems currently approved are based on either simple liposomes or PEGylated variants to improve circulation time. New, higher complexity systems – as discussed at length in this review and which include transferosomes and ethosomes – that have emerged in the past few years, have not been met with the same kind of success in the clinic and in the commercial space. In line with this, a significant hurdle in developing liposomal systems for delivery of active biomaterials has been the development of robust formulations that overcome the traditional limitations associated with traditional liposomal delivery systems. The complexity of some of these systems is increased because of the physicochemical changes to the liposomes that are brought about by the addition of components that interact with the membrane, such as ethanol or covalent complexing agents. Moreover, the development of most new liposomal drug products is challenged by a lack of biologically relevant in vitro release methods. For those reasons, regulatory bodies rely on various academic and industry developers to provide timely and thorough information on these new systems to support and advance the regulatory process. The issues that are the core of development studies to achieve robust liposome-based drug delivery systems can be broadly summarized as having to achieve the following:

(a) Controlled release rate of encapsulated material,
(b) Prolonged lifetime/reduced clearance of liposomes,
(c) Intracellular delivery of encapsulated material to the target site.

This is part of the reason why more complex systems, which are based on agents other than lipids to achieve the delivery system's biophysical function, still face significant hurdles to regulatory acceptance. In the cell therapy space, liposomes were shown to be efficient for the targeted delivery of growth factors such as vascular endothelial growth factor recently developed VEGF-encapsulated immunoliposomes targeting myocardial infarction (MI). By injecting the VEGF-immunoliposomes together with mesenchymal stem cells (MSCs) into a rat immediately following MI, the authors observed a remarkably high attenuation in cardiac function loss, together with an 80% increase in blood vessel density.[4]

Topical preparations are applied to the skin for surface, local, or systemic effects. In some cases the base may be used alone for its beneficial properties, such as emollient, soothing, or protective action. Many topical preparations, however, contain a therapeutically active ingredient which is dispersed or dissolved in the base. The combination of active ingredient and base provides the opportunity for a wide range of topical preparations, appropriate for many types of drug delivery and therapy. Terms used to classify the bases of topical preparations in which therapeutically active ingredients may be incorporated, may be based on their physical properties or on their intended use or on their composition.

Novel Topical Drug Delivery Systems

There are two ways to improve therapeutics: to discover new and better drugs and / or to develop novel controlled, site specific drug delivery systems. The goal of any drug delivery system involves altering of the pharmacokinetics and physiological disposition of the drug in question in

order to obtain a higher therapeutic index. This can be accomplished either by decreasing the toxicity of the drug or by increasing its efficiency. Attempts are being made to develop novel topical delivery systems and techniques which could provide controlled and selective topical drug delivery with minimal toxicity and maximum therapeutic index. Until recently, topical formulations were essentially only able to control the release of a drug but not its penetration rate or residence time in the different layers. However, over the past few years, with the advent of particulate and vesicular carriers and techniques for site specific drug delivery via parenteral administration, some research groups have focused on their potential topical applications in dermal or even transdermal therapy. Promising results show that these carriers and techniques may improve the penetration of some drugs, by targeting either to the stratum corneum or to the hair follicles, and control the release of drugs. Drug targeting is one of the most exciting areas of pharmaceutical research and perhaps the most challenging. The aim is to deliver the drug to the target organ i.e. the site of action, and minimize the distribution of the drug to non-target tissues. However, there is a need for novel drug delivery systems for the therapy of skin disorders that can precisely target the drug to the site if the disease. In the past decades, Novel drug delivery systems and techniques have been extensively investigated for delivering drugs to specific skin sites. Topical delivery carriers including liposomes, niosomes and microspheres may increase or regulate drug transport into the skin and consequently reduce variability in drug bioavailability from one patient to another. They can also reduce toxic side effects that may arise from undesirable high systemic drug absorption and target the drugs to definite skin compartments. Besides, these systems and techniques are generally nontoxic, non-immunogenic, non-irritant, biodegradable, and they are able to incorporate a wide range of hydrophilic and hydrophobic drugs. On the contrary ethosomes, transfersomes (ultra-deformable vesicles) and techniques such as iontophoresis, sonophoresis and electroporation can be used to enhance the drug absorption to the systemic circulation. Novel topical drug delivery systems have evolved from the research phase to the industrial scale. Topical anticancer, local anesthetic and antifungal liposomal formulations are available in the market. Also, Liposomal-like formulations are now in the industrial phase, such as Transfersomes (IDEA AG) and Ethosomes (Therapeutic Technology Inc. (NTT)).[5]

Application of liposomes:

- In gene delivery.
- As drug delivery carriers.
- Enzyme replacement therapy.
- Liposomes in anti-viral / anti-microbial therapy.
- In multidrug resistance.
- In Tumour therapy.
- In Immunology.
- In Cosmetology.
- Liposomes as vaccine carriers.
- Liposomes as artificial blood Surrogates.
- Liposomes as radiopharmaceuticals and radio diagnostic carriers.[6]

Drug Criteria for Topical Liposomal Drug Delivery System:

Which groups of substances are considered to be especially interesting for liposomal encapsulation in the field of dermatology?

1. There are drugs which are known to have severe side-effects by the conventional way of topical administration, e.g. topical glucocorticosteroids.

2. There are substances which normally are effective by systemic application but not by topical application, e.g. interferon.

3. There are drugs which only show insufficient effects when applied topically. E.g. hamamelisdistillate.

Conclusion:

Liposomes have some advantages which make them look interesting as drug carriers for topically applied drugs. First, they are variable concerning size and surface properties and Second, They can act as sustained release depots, releasing encapsulated drugs of half-lives ranging from 0.6 to 11 days. Moreover a new generation of liposomes, the so called “collagen modified liposomes” can moderate the liposome- liposome and the liposome-cell interaction due to their collagen surface properties. This indeed might mean a greater possibility to control the drug release. The topically applied liposomal formulations, particularly those prepared from lipid mixtures of composition similar to the stratum corneum, would be an effective delivery system for the treatment of skin diseases. Since these liposomal formulations provide sustained, enhanced levels in deeper strata of the skin, they have the capacity to meter a sufficient quantity of drug into deeper tissue to treat the skin symptomology. Such metering should also reduce the incidence of undesirable side effects arising from systemic administration, or enhanced systemic absorption of drug.[7]

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