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Recent advances in various emerging vescicular systems: An overview

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ABSTRACT

Liposomes have been widely investigated since 1970 as drug carriers for improving the delivery of therapeutic agents to specific sites in the body. As a result, numerous improvements have been made to make this technology potential the treatment of certain diseases in the clinics. This review mainly focused on various aspects related to the vesicular system, including method of preparation, stabilization, drawbacks, and applications. Various types of vesicular systems such as liposomes, niosomes, transfersomes, pharmacosomes, and nanoparticle have been discussed briefly along with some other emerging vescicular systems (photosomes, archaesomes, genosomes, cryptosomes, discomes) focusing on cell specific gene transfer, photodynamic therapy and ligand mediated drug targeting. Present applications of the liposomes are in the immunology, dermatology, vaccine adjuvant, eye disorders, brain targeting, infective disease and in tumour therapy. The new developments in this field are of specific binding properties of a drug-carrying liposome to a target cell such as a tumor cell and specific molecules in the body (antibodies, proteins, peptides *etc*), stealth liposomes which are especially used as carriers for hydrophilic (water soluble) anticancer drugs like doxorubicin, mitoxantrone and bisphosphonate-liposome mediated depletion of macrophages. This review would help researchers working in the area of liposomal drug delivery.

1. Introduction

An ideal controlled drug-delivery system should possess two characteristics: the ability to reach its therapeutic target and the ability to release the active pharamceutical ingredient in a controlled manner. One way to modify the original biodistribution of substances is to entrap them in submicroscopic drug carriers such as liposomes, transferosomes, niosomes, polymeric nanoparticles serum proteins, immunoglobulins, microspheres, erythrocytes, reverse micelles, monoclonal antibodies, and pharmacosomes[1].

Different types of pharmaceutical carriers are present (Figure 1). They are particulate, polymeric, macromolecular, and cellular carrier. Particulate type carrier also known as a colloidal carrier system, includes lipid particles (low and high density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicular like liposomes, noisome[2-4], pharmacosomes[5], virosomes[6] and sphingosomes[7]. The vesicular systems

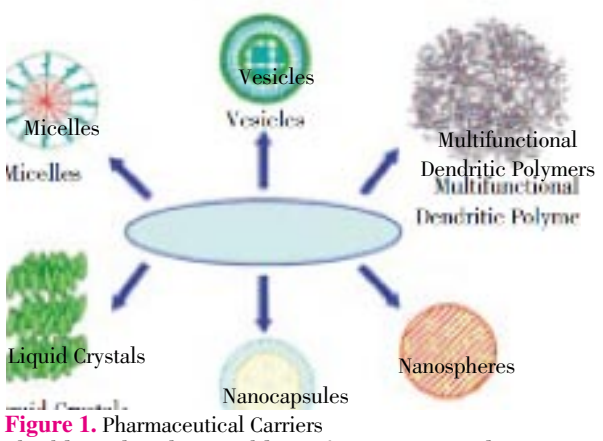

Figure 1. Pharmaceutical Carriers

are highly ordered assemblies of one or several concentric lipid bilayers, when certain amphiphilic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphilic building blocks. The terms such as synthetic bilayers allude to the non-biological origin of such vesiculogenes.

In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques,

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and most recently, genetic engineering. Vesicles can play a major role in modeling biological membranes, and in the transport and targeting of active agents.

2. Vesicular systems

Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation. Consequently, a number of vesicular delivery systems such as liposomes, niosomes, pharmacosomes *etc*, were developed.

2.1. Liposomes

Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule as shown in Figure 2. There are a number of components in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, and together with their hydrolysis products.

Liposomes are composite structures made of phospholipids and may contain small amounts of other molecules. Though liposomes can vary in size from low micrometer range to tens of micrometers, unilamellar liposomes, as pictured here, are typically in the lower size range with various targeting ligands attached to their surface allowing for their surface-attachment and accumulation in pathological areas for treatment of disease.

Application of liposomes in topical ocular drug delivery has also attracted considerable attention. Liposomes offer advantages over most ophthalmic preparations, which are completely biodegradable and non-toxic. Targeting has been done to ischemic penumbra part II using liposomes technology[8]. Idoxiuridine has been reported to entrapped in liposomes, which was more effective in treatment of acute and chronic herpetic keratitis in albino rats, than the unentrapped drug. Schaeffer *et al* reported that the transcorneal flux of liposome-entrapped penicillin G, indoxol, and carbachol, were approximately double than that of the unentrapped drug. Immunoliposomes bearing antibody against the cell surface viral glycoprotein, was suggested as targeting carriers in the treatment of ocular herpetic keratitis. Liposomes have the ability to intimately make contact with the corneal and conjunctival surfaces, and thereby increase the ocular drug absorption. Guo *et al* confirmed the importance of +ve charge in corneal retention of liposomes. Substantial reduction in retinal toxicity of cytarabin in liposomal form, was reported by Liu *et al* who suggested that this combination offers great promise in the treatment of ocular proliferative disorders (as an alternative to fluorouracil). The *in vitro* corneal penetration and *in-vivo* corneal absorption of acyclovir-containing liposome systems were investigated.

Liposomes as a potential delivery system for the oral administration of insulin, have been extensively studied[9-11]. It was observed by many scientists, that the liposomes had protective effects against proteolytic digestive enzymes like pepsin and pancreatin,, and they can increase the intestinal uptake of macromolecules and hence are capable of enhancing insulin uptake.

Liposomes with a specifically modified design, *i.e.* long-circulating and especially actively targeting liposomes, stand a better chance in becoming truly tumoritropic carriers of photosensitizers, and can hence be used successfully in photodynamic therapy.

Liposomal drug delivery system is advantageous in protection of the drug, controlling release of the active moiety along with the targeted delivery, and cellular uptake via endocytosis. Besides the merits, liposomes also pose certain problems associated with degradation by hydrolysis, oxidation, sedimentation, leaching of drug, and aggregation or fusionduring storage. Approaches to increase liposome

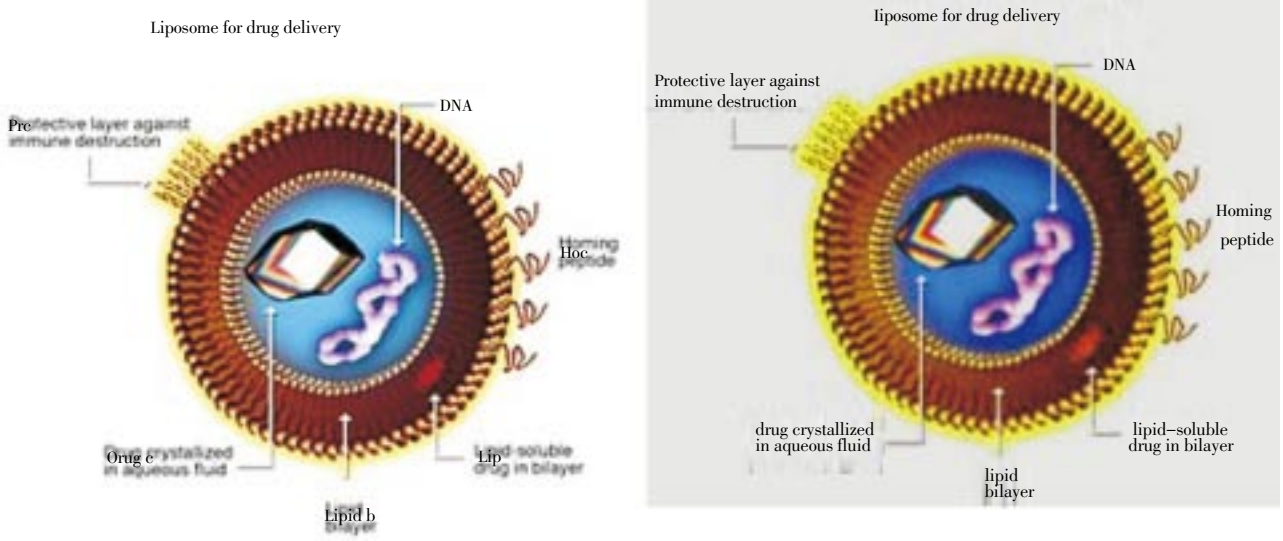

Figure 2. Unilaminar stealth liposome.

stability involve efficient formulation and lyophilization. Formulation involves the selection of the appropriate lipid composition and concentration of the bilayer, in addition to the aqueous phase ingredients, such as buffer, antioxidants, metal, chelators, and cryoprotectants. Charge-inducing lipids, such as phosphatidylglyceride are incorporated into the liposome bilayer to decrease fusion, while cholesterol and sphingomyelin can be incorporated in formulations, in order to decrease the permeability and leakage of encapsulated drugs. Buffers at neutral pH can decrease hydrolysis. Addition of antioxidants such as sodium ascorbate can decrease the oxidation. Freeze-dried liposome formulations should incorporate a lipoprotectant-like non-reducing disaccharide, such as trehalose and sucrose. Some problems associated with clinical applications of liposomes are difficulties in sterilization and large-scale production. Moreover, it is difficult to obtain large quantities of sterile products with defined and reproducible properties, which display adequate chemical and physical stability. The cost and purity of phospholipid is another limiting factor. They are suitable for parenteral administration but oral administration is not possible, because of inability of liposomes to survive in the action of bile salts and phospholipids.

2.2 Niosomes or non-ionic surfactant vesicles

Rigorous conditions required for handling liposomes under cryogenic atmosphere have prompted the use of non- ionic surfactant in vesicular drug delivery system, in lieu of phospholipids. Thus, the new vesicular delivery system consisting of unilamellar or multilamellar vesicles called niosomes was introduced. In general, vesicles made of natural or synthetic phospholipids are called liposomes whereas those made of nonionic surfactants (e.g. alkyl ethers and alkyl esters) and cholesterol constitute a nonionic surfactant vesicular system called niosomes (Figure 3).

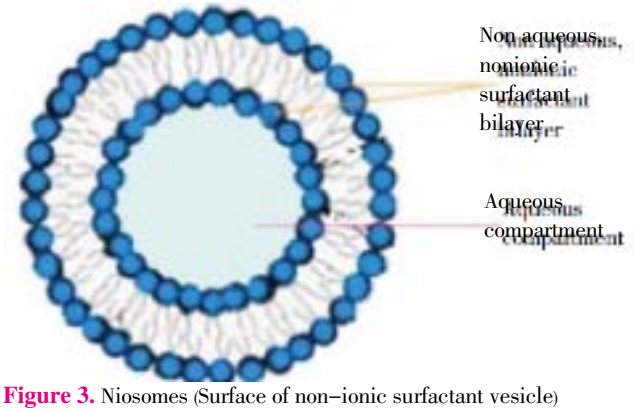

Figure 3. Niosomes (Surface of non-ionic surfactant vesicle)

In this case, an aqueous solution is enclosed in a highly ordered bilayer made up of non-ionic surfactant, with or without cholesterol and dicetyl phosphate, and exhibit a behaviour similar to liposomes *in vivo*. The bilayered vesicular structure is an assembly of hydrophobic tails of surfactant monomer, shielded away from the aqueous space located in the center and hydrophilic head group, and is in contact with the same. Addition of cholesterol results in an ordered liquid phase formation which gives the rigidity to the bilayer, and results in less leaky niosomes. Dicetyl phosphate is known to increase the size of vesicles, provides charge to the vesicles, and thus shows increase entrapment efficiency. Other charge-inducers are stearylamine and diacylglycerol that also help electrostatic stabilization of the vesicles. Niosomes have unique advantages over liposomes. Niosomes are quite stable structures, even in the emulsified form. They require no special conditions such as low temperature or inert atmosphere for protection or storage, and are chemically stable. Relatively low cost of materials makes it suitable for industrial manufacture. A number of non-ionic surfactants have been used to prepare vesicles *viz*. polyglycerol alkyl ether, glucosyl dialkyl ethers, crown ethers, ester linked surfactants, polyoxyethylene alkyl ether, brij, and a series of spans and tweens.

Niosomes entrap solute in a manner analogous to liposomes. They are osmotically active, and are stable on their own, as well as increase the stability of the entrapped drugs. Handling and storage of surfactants require no special conditions. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a wide range of solubilities. They exhibit flexibility in structural characteristics (composition, fluidity, size) and can be designed according to the desired situation. Niosomes improve the oral bioavailability of poorly absorbed drugs, and enhance skin penetration of drugs. They can reach the site of action by oral. Oral absorption of niosomes is better as compared to liposomes, because replacement of phospholipids by nonionic surfactants has made niosomes less susceptible to the action of bile salts, parenteral, as well as topical routes. They allow their surface for attachment of hydrophilic moieties in the bilayer, to bring about changes *in-vivo*, by incorporation of hydrophilic groups such as poly (ethylene glycol), concanavalin A, and polysaccharide to the non-ionic surfactant, thus acting as stealth or long circulating niosomes. Niosomal dispersion in the aqueous phase can be emulsified in non-aqueous phase to regulate delivery rate of drug, and administer to normal vesicles in extended non-aqueous phase.

Niosomal surfactants are biodegradable, biocompatible, and non-immunogenic. Niosomes improve the therapeutic performance of drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

2.3 Transfersomes

Liposomal as well as niosomal systems, are not suitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation, and fusion of vesicles[12]. To overcome these problems, a new type of carrier system called "transfersome", has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs. Transfersomes are specially optimized, ultradeformable (ultraflexible) lipid supramolecular aggregates, which are able to penetrate the

mammalian skin intact. Each transfersome consists of at least one inner aqueous compartment, which is surrounded by a lipid bilayer with specially tailored properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxycholate, span 80, and Tween 80, have been used as edge activators. It was suggested that transfersomes could respond to external stress by rapid shape transformations requiring low energy. These novel carriers are applied in the form of semi-dilute suspension, without occlusion. Due to their deformability, transfersomes are good candidates for the non-invasive delivery of small, medium, and large sized drugs. Multiliter quantities of sterile, well-defined transfersomes containing drug can be, and have been prepared relatively easily.

Transfersomes are characterized for different physical properties such as vesicle diameter using photon correlation spectroscopy or dynamic light scattering method, entrapment efficiency, vesicle diameter, degree of deformability or permeability, and *in vitro* drug release. The mechanism of penetration of transfersomes across the skin was investigated by confocal scanning laser microscopy[13]. They were also investigated for determining histological organization of the skin, shapes and architecture of the skin penetration pathways, and for comparison and differentiation of the mechanism of penetration of transfersomes with liposomes, niosomes, and micelles. Other parameters studied are *in vivo* fate, pharmacokinetic aspects, toxicity studies, *etc*.

Transfersomes have been proposed for a variety of applications in humans. They are used as a carrier for protein and peptides like insulin, bovine serum albumin, vaccines, *etc*. The delivery of these large biogenic molecules into the body is difficult. When given orally, they are completely degraded in the GI tract, and when used in a degradation preventing formulation, their uptake in the gut becomes problematic and extremely insufficient. These are the reasons why nearly all-therapeutic peptides still have to be introduced into the body through an injection needle, in spite of the inconvenience of this method. To overcome the above problems, numerous attempts have therefore been made for delivery of peptides and proteins across the skin. All recent approaches, either chemical (penetration enhancers, lipid vesicles), or physicals (iontophoresis, sonophoresis), have some limitations.

Proteins and other molecules, normally do not cross the intact mammalian skin. Despite this, it elicits antibodies against the subcutaneously applied proteins, such as fluorescein-isothiocyanate-labelled bovine serum albumin, if these macromolecules are associated with the specially optimized and ultradeformable agent carriers. A judicious combination of the integral membrane proteins and the ultradeformable membrane, also provides a solution to the problem of the noninvasive delivery of such molecules. Incorporation of gap junction protein into transfersomes for example, results in a maximum immune response to this type of macromolecules. Delivery of peptides by transfersomes provides a very successful means for the noninvasive therapeutic use of such large molecular weight drugs on the skin. Insulin-loaded transfersomes were prepared and evaluated, and it was found that transfersomes-associated insulin is carried across the skin with an efficacy of >50%, and often >80%, if properly optimized. After each transfersulin application on the intact skin, the first signs of systemic hypoglycemia are observed after 90 to 180 minutes, depending on the specific carrier composition. It was reported that the formulation of interleukin-2 and interferon-α containing-transfersomes, are able to deliver sufficient concentrations for immunotherapy. The same concept was used for transdermal immunization, using transfersomes loaded with soluble protein like integral membrane protein, gap junction protein, bovine serum albumin, *etc*. Corticosteroids are used topically for a large variety of dermatological conditions, but the dermally administered corticosteroids typically fail to deliver a sufficiently large drug amount into the body. Use of highly concentrated, or even supersaturated drug solution on skin, leads to the problem of drug precipitation, and higher chances of the adverse effects[14].

Transfersomes improve the site specificity, overall drug safety, and lower the doses several times than the currently available formulations for the treatment of skin diseases. Because of their good penetration power and flexibility, transfersomes formulations are used for effective delivery of non-steroidal anti-inflammatory agents like ibuprofen and diclofenac[15]. Transfersomes not only increase the penetration of diclofenac through intact skin, but also carry these agents directly into the depth of the soft tissues under the application site. Cevc, developed formulation of tamoxifen, the most common agent for the treatment of all stages of breast cancer, is based on ultradeformable vesicles, and applied on the shaved murine back. Most of the epidermally-applied transfersomes penetrated the skin, leaving less than 5% of the drug-derived radioactivity on the body surface. Such delivery of tamoxifen, lowers the incident of side effects like depression and thrombosis. Recently, the impact of the combined use of ultradeformable liposomes and iontophoresis on the penetration of tritiated estradiol, was compared with saturated aqueous solution. The tritium exchange study showed that extent of exchange correlated well with current density and time of application, with some shielding of estradiol by liposomal structure. Transfersomes enhanced passive estradiol penetration after occlusion. Estradiol flux was increased linearly with current density, although being delivered against electro-osmotic flow. Elastic vesicles with rigid vesicles, in terms of their interaction, was compared with human skin, and reported that unlike rigid vesicles, there is no ultra structural changes takes place in the human skin on application of elastic vesicles. It was reported, that *in vitro* transport of pergolide from L-595 #x2013; PEG-8-L, elastic vesicle showed highest skin permeation of pergolide, having a steady-state flux of 137.9 ng/h/cm^2. Transfersomes have been reported to improve transdermal delivery of drugs, when applied nonocclusively. Transfersomes have also been reported to improve the therapeutic efficacy of cyclosporine, and the site specificity and safety of corticosteroids.

2.4. Pharmacosomes

The limitations of transfersomes can be overcome by the "pharmacosome" approach. The prodrug conjoins hydrophilic and lipophilic properties, and therefore acquires amphiphilic characters. Similar to other vesicle forming components, it was found to reduce interfacial tension and at higher concentrations exhibits mesomorphic behavior. These are defined as colloidal dispersions of drugs covalently bound to lipids, and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of drug-lipid complex. Many constraints of various classical vesicular drug delivery systems, such as problems of drug incorporation, leakage from the carrier, or insufficient shelf life, can be avoided by the pharmacosome approach. The idea for the development of the vesicular pharmacosome, is based on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (-COOH, -OH, $-NH_2$, *etc*) can be esterified to the lipid, with or without spacer chain. Synthesis of such a compound may be guided in such a way that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. The salient features of pharmacosomes are as follows: a)Entrapment efficiency is not only high but predetermined, because drug itself is in conjugation with lipids forms vesicles; b) Unlike liposomes, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation; c)Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis; d)No problem of drug incorporation; e)Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in case of pharmacosome. These factors on the other hand have great influence on entrapment efficiency in case of liposomes; f)The lipid composition in liposomes decides its membrane fluidity, which in turn influences the rate of drug release, and physical stability of the system. However, in pharmacosomes, membrane fluidity depends upon the phase transition temperature of the drug lipid complex, but it does not affect release rate since the drug is covalently bound; g)The drug is released from pharmacosome by hydrolysis (including enzymatic). Phospholipid transfer/ exchange is reduced, and solubilization by HDL is low; h)The physicochemical stability of the pharmacosome depends upon the physicochemical properties of the drug-lipid complex; i)Due to their amphiphilic behavior, such systems allow, after medication, a multiple transfer through the lipophilic membrane system or tissue, through cellular walls piggyback endocytosis and exocytosis; j) Following absorption, their degradation velocity into active drug molecule depends to a great extent on the size and functional groups of drug molecule, the chain length of the lipids, and the spacer. These can be varied relatively precisely for optimized *in vivo* pharmacokinetics; k)They can be given orally, topically, extra-or intravascularly.

Pharmacosomes bearing unique advantages over liposome and niosome vesicles have come up as potential alternative to conventional vesicles. The system yet requires greater efforts towards investigating the non-bilayer phases, and exploring the mechanism of action. Furthermore, the effect of covalent linkages and addition of spacer group on rate of *in vivo* hydrolysis and subsequent pharmacokinetics is to be exhaustively studied, in order to exploit more advantages of this system. Like other vesicular drug delivery systems, pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis.

3. New advances in vesicular system

3.1. Photosomes

Liposomes are the most widely known cosmetic delivery systems[16]. These are artificial spherical submicroscopic vesicles with diameter between 25 and 5 000 nm. Vesicles are composed inevitably of amphiphilic molecules. Their centre consists of an aqueous cavity, which is encapsulated by one or more bimolecular phospholipid sheets, each separated from each other by aqueous layers. The polar head group forms the interface at both the external and internal surfaces of liposomal bilayers. The phosphatidyl moiety consists of two fatty acids, which are ester bridged to glycerol phosphate. The chain length of fatty acids (mainly C_{14}, C_{16} and C_{18}) and the degree of unsaturation (one or two bonds) may vary. The polar head group may be zwitterionic, negatively or positively charged.

Some important liposomal preparations having cosmetic potential are discussed. The skin care preparations with empty or moisture loaded liposome or niosome reduce the transdermal water loss and are suitable for the treatment of dry skin. They also enhance the supply of lipids and water to stratum corneum. Liposomal formulations would have an advantage that the active ingredient would be distributed optimally in the horny layer and also would acquire a certain water resistance.

Encapsulation techniques are most widely used in the development and production of improved delivery systems. Some of the important novel cosmetic vesicular delivery systems are discussed.

Following are the promising vesicle delivery systems in cosmetics: a)Liposomes; b)Silicone vesicles and matrices; c) Multi-walled delivery systems

Light sensitive liposomes are provided which release their contents on demand in response to irradiation with an appropriate wavelength of light. Substantially all the liposome contents can be released within about 60 seconds. Preferred embodiments of the light sensitive liposomes include lipids having at least one retinoyl group and being a structural component of the lipid membrane.

A light sensitive liposome comprising: 1)A lipid membrane, is a lipid membrane encapsulating a fluid, including a light sensitive lipid in an amount from about 50 wt.% to about 100 wt.% of the lipid membrane and having a polar head region and a nonpolar tail region, including one retinoyl group or two retinoyl groups covalently bonded in the nonpolar tail region, having an absorptive of light at a predetermined

wavelength between about 300 nm to about 400 nm, providing release of fluid from lipid membrane in response to an effective amount of irradiation at predetermined wavelength; 2)Light sensitive lipid is a glycerol derivative defining a 1 position carbon and a 2 position carbon; one retinoyl group esterified at said 1 position carbon or at 2 position carbon and two retinoyl groups esterified at both of 1 and 2 position carbons; 3)Retinoyl groups are derived in major part from transretinoic acid; 4)Includes a polar liquid phase, a biologically active component;5)Contain fluid includes a pharmaceutical and a membrane in the releasing position permits substantially all fluid to leak.

Liposomes which encapsulate fluids and which selectively release the fluids when irradiated with light. Release of the liposomes contents be finely tuned to an intensity and predetermined wavelength of light. Liposomes are capable of releasing substantially entire contents within about one minute after sufficient irradiation under light of a predetermined wavelength.

A light sensitive liposome comprises a liquid membrane surrounding a fluid to define an encapsulating position of the lipid membrane for the fluid. The lipid membrane includes a light sensitive lipid which absorbs light at a predetermined wavelength so as to form a modified light sensitive lipid in response to sufficient light at the predetermined wavelength. The modified light sensitive lipid adjusts the lipid membrane from the encapsulating position to a releasing position. In the releasing position the fluid communicates with the medium, or environment, outside the lipid membrane.

Light sensitive liposomes may be used, for example, to selectively deliver a fluid to cell cultures, tumor-specific chemotherapy[17], drug delivery[18]. Thus, the inventive light-sensitive liposomes may be introduced into one or more cell cultures, and irradiated when desired with sufficient light to release the fluid on demand. The fluid released may include various chemicals, biochemicals, genetic material or the like.

A representative light-sensitive lipid having two retinoyl groups esterified at the 1 and 2 position carbons of a glycerol derivative is illustrated by compound B (Figure 4), and a representative glycerol derivative having a single retinoyl group esterified at the 2 position carbon of a glycerol derivative is illustrated by compound A (Figure 4).

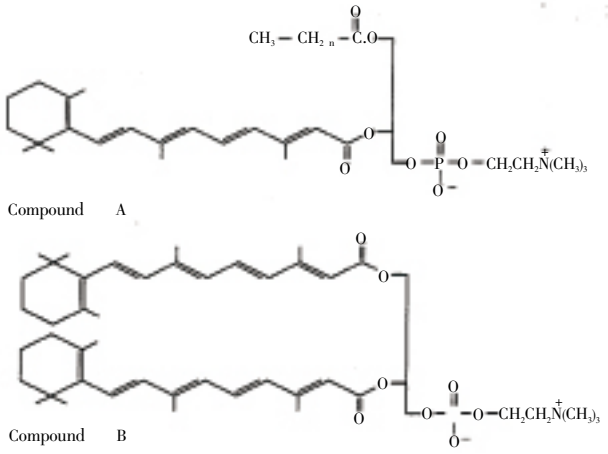

Figure 4. Compound A& B.

The compound A structure is di-retinoyl-sn-glycero-3-phosphocholine (sometimes hereinafter referred to as DRPC). Where n=14 the compound A structure is 1-palmitoyl, 2-retinoyl-sn-3-phosphocholine (which will sometimes hereinafter be referred to as PRPC). The fatty acid chain in the nonpolar tail region of the compound B, illustrative structure, can vary. For example, n of the-$(CH_2)_n$- compound A illustrative structure, can be various integers, most usually wherein n is from about 8 to about 18, or such a chain may include one or more double bonds, either conjugated or non-conjugated; and, as already discussed the moiety esterified to the phosphoric acid portion of the polar head regions can take a variety of forms.

There are various ways for the formation of liposomes: a) Light sensitive liposomes, with DRPC as the lipid membrane, were formed by the "mechanical dispersal" method. A quantity of DRPC was dried in a 100 mL round bottom flask, and then dispersed in 100 mM carboxyfluorescein at 38 ℏ . by gentle shaking. The dispersion was allowed to equilibrate to room temperature, and the light sensitive liposomes formed therefrom were applied to a column of suitable gel filtration medium, to separate the unencapsulated carboxyfluorescein from the light sensitive liposome vesicles. The light sensitive liposomes were collected from the column in a 50 mL volumetric flask, and brought to volume with phosphate buffered saline composed of 11.08 mM NaH_2PO_4, 23.43 mM Na_2HPO4 and 77.0 mM NaCl; b)Light sensitive liposomes, with DRPC as the lipid membrane, were formed by the "mixed phase, or ethanol injection" method. A quantity of DRPC was dissolved in a small volume of ethanol which was then injected directly into a rapidly stirring aqueous solution of 100 mM carboxyfluorescein. The light sensitive liposomes formed therefrom were separated from unencapsulated carboxyfluorescein by gel filtration (Figure 5, 6)

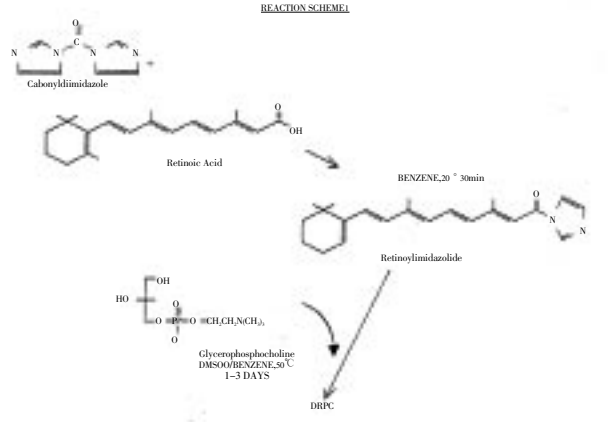

Figure 5. Reaction involved in photosomes.

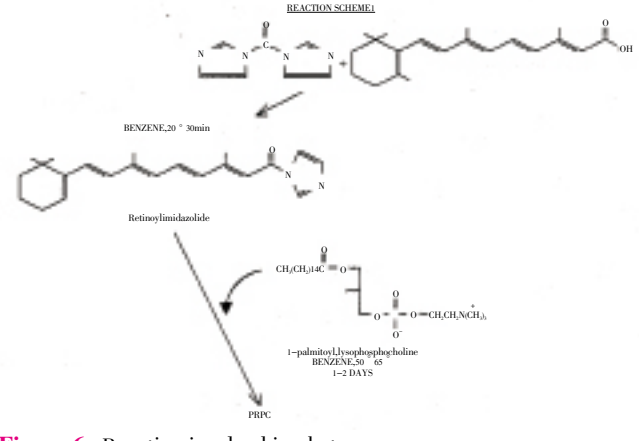

Figure 6. Reaction involved in photosomes.

Table 1.
Summary of commercially available delivery system.

Name	Supplier	Application
Natipide ii liposome	Rhone-poulenc	Reinforces skin's own moisture retention capabilities
Ultrasome	Applied	Genetics sun-care product
Photosome	Applied	Genetics sun care product
Catezomes	Collaborative labs	Versatile active delivery
Elespher	Laboratories serobiologiques,Natural	botanical vehicle; pleasing visual effect
Microsponge	Advanced polymer system	High payload; improves cosmetics elegance of liquid
Elesponge	Laboratories serobiologiques	Entaraps a wide range of actives whilst softening skin
Lipocd-SA	Lipo chemical	Able to deliver oils in powder form
Unispheres	Induchem	Less sensitive to pH and surfactants; pleasing visual effect
Orgasol	Elf atochem	Improves skin feel and adhesion

3.2. Particulate systems

The particulate delivery systems used in cosmetics include microparticulates, porous polymeric systems, nanoparticulates, cyclodextrin comple.

3.3. Delivery devices

Following different delivery devices[20] in the cosmetic delivery are discussed and the delivery systems which are commercially available summarized in Table 1.

Photodynamic therapy (PDT), matured as a feasible medical technology in the 1980s at several institutions throughout the world, is a third-leve treatment for cancer[21-24], tumor[25] involving three key components: a photosensitizer, light, and tissue oxygen[26]. It is also being investigated for treatment of psoriasis, lung sparing treatment[27] and is an approved treatment for wet macular degeneration.

PDT is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells[28].

Although these photosensitizers can be used for wildly different treatments, they all aim to achieve certain characteristics.

a) High absorption at long wavelengths

Tissue is much more transparent at higher wavelengths (~700-850 nm). Absorbing at longer wavelengths would allow the light to penetrate deeper, and allow the treatment of larger tumors.

b)High singlet oxygen quantum yield

c)Low photobleaching

d)Natural fluorescence

Many optical dosimetry techniques, such as fluorescence spectroscopy, depend on the drug being naturally fluorescent.

e)High chemical stability

f)Low dark toxicity

The photosensitizer should not be harmful to the target tissue until the treatment beam is applied.

3.4. Archaeosomes

Novel archaeosome compositions and their use in vaccine formulations as adjuvants and/or delivery systems, to enhance the immune response to immunogens in an animal such as a human, are described. Another aspect relates to the use of these archaeosomes to enhance the delivery of compounds such as pharmaceuticals to specific cell types and tissues in animals and other life forms, via various routes of administration such as subcutaneous[29], intramuscular, and oral. The efficacy of the archaeosomes and also of conventional liposomes can be further improved in these applications, by incorporation of coenzyme Q_{10} and/or polyethyleneglycol-lipid conjugate into liposomes made from these archaeosomes.

A liposome composition[30] comprising

a)The total polar lipids extract of an archaeobacterium;

b)A pharmaceutical agents;

c)Coenzyme Q_{10};

d)A polyethyleneglycol lipid conjugate.

Liposome size is in the range of not less than 50 nm, but less than 500 nm, in diameter.

3.4.1 Characteristics

a)A method for the delivery of a pharmaceutical agent to an animal, comprising administering to the animal a liposome prepared from a composition consisting essentially of the total polar lipids extract of an archaeobacterium, coenzyme Q_{10}, and a polyethyleneglycol lipid conjugate, as a carrier for said pharmaceutical agent;

b)A method for the selective delivery of a pharmaceutical or biological agent to specific tissues of an animal, comprising administering to the animal a liposome prepared from a composition consisting essentially of the total polar lipids extract of an archaeobacterium, archaeal lipid mucosal vaccine adjuvant and delivery system[31] and as a carrier for said pharmaceutical or biological agent[32];

c)The liposome is administered to an animal orally[33], intraperitoneally, intramuscularly, subcutaneously, or intravenously.

It is used as beneficial carriers of antigens[33], immunogenic compounds, DNA, drugs, therapeutic compounds, oral delivery of peptides[34], pharmaceutical compounds, natural antioxidant[35], imaging agents or tracers, and to deliver these to specific cells such as the macrophages or to specific tissues, in life-forms such as the human.

It is provided that archaeosomes that have enhanced adjuvant activity for the generation of an immune response to an immunogenic, and for vaccine applications in an

animal such as a human, wherein the antigen(s) can be encapsulated in, can be associated with, or not associated with the archaeosomes, at the time of administration via different routes. In some instances the immune response (the level of response and its duration) to an immunogen delivered via an archaeosome being comparable with better compatibility[36] to that obtained with Freund's adjuvant as the immunostimulator and M cell prefer it better[37].

1.Yet another object is to use archaeosomes prepared with lipids containing a high proportion of tetra ether bipolar lipid(s) that are found in, or mimic those found in, members of archaeobacteria, to enhance and prolong the immune response to an immunogen that is either codministered as part of the archaeosome or administered at the same time as the archaeosome, into an animal.

Incorporation of CoQ_{10} into archaeosomes and conventional liposomes, sometimes in combination with polyethylene glycol lipid conjugates, to increase the delivery of various associated compounds to specific organ tissues when the respective vesicles are administered to an animal via various routes such as *p.o.*, *i.m.*, *i.v.*, *s.c.*, and *i.p.* The combination of CoQ_{10} in archaeosomal or conventional liposomal vesicles, including vesicles that may have been sterically stabilized by association with polyethyleneglycol conjugates, would therefore further increase the utility of archaeosomes and of conventional liposomes, for delivery of compounds, including immunogens and CoQ_{10} itself, to phagocytic cells and to specific tissues.

Coenzyme Q_{10} was entrapped into archaeosomes prepared from the TPL of *Methanosarcina mazei*, which are known to be anionic, and into anionic conventional liposomes (DSPC:CHOL:DCP), with relatively high entrapment efficiencies . However, compared with anionic lipid mixtures, even higher entrapment efficiencies were obtained with vesicles prepared with neutral lipid mixtures DPPC:CHOL and DSPC:CHOL. The loading ratios shown are representative of those used in subsequent experiments.

The uptake by macrophages, of archaeosomes and of conventional liposomes lacking coenzyme Q_{10} is shown as a function of time using ^{3}H-chol as the tracer marker. At 37 ℏ, at the indicated times, it can be seen that *Methanosarcina mazei archaeosomes* are taken up substantially better than all formulations of conventional liposomes. The data serve as control values to assess the effect on vesicle uptake of incorporating coenzyme Q_{10} into the vesicles. These data show that the cellular accumulation of all vesicle types, by the macrophages, was markedly enhanced when the vesicles contained coenzyme Q_{10}. This enhancing effect of coenzyme Q_{10} was several times higher with the archaeosomes than with the conventional liposomes. Comparable profiles of accumulation and the enhancing effects of coenzyme Q_{10} entrapment on the uptake of archaeosomes and of conventional liposomes, was observed at all lipid concentrations tested.

These results clearly indicate the potential for inclusion of coenzyme Q_{10} into the vesicles for increased targeting of archaeosomes and of conventional liposomes to various cell types. An increased uptake of vesicles containing coenzyme Q_{10} by macrophages (antigen processing cells, and the sites for some infectious agents) dearly indicates application in delivery of antigens, and drugs (including antiviral and antimicrobial agents). Another application is to deliver the water-insoluble drug (coenzyme Q_{10}) to mammalian cells, via liposomes and archaeosomes in HIV infection.

3.4.2. Immune responses

The enhanced uptake of archaeosomes by phagocytic cells, compared to that of conventional liposomes, suggested that archaeosomes may be superior as adjuvants and/or carriers of antigens for raising an immune response to an immunogenic. This was found to be the case in animal model studies using mice.

Compared to control mice receiving the bare antigen, the antibody titer in sera from mice immunized with cholera toxin B subunit was found to be significantly higher when the antigen was entrapped in archaeosomes of *Methanobrevibacter smithii*, and this response was even comparable to that observed with Freund's adjuvant.

3.4.3. Archaeosome immunostimulatory vaccine delivery system

Archaeosomes are liposomes made from the polar ether lipids of Archaea. These lipids are unique and distinct in structure from the ester lipids found in Eukarya and Bacteria. The regularly branched and usually fully saturated isopranoid chains of archaeal polar lipids are attached via ether bonds to the sn-2, 3 carbons of the glycerol backbone(s). The polar head groups are usually the same as those encountered in the ester lipids from the other two domains, except that phosphatidylcholine is rarely present. These lipid structures provide formulary advantages, and contribute to the excellent physico-chemical stability of the archaeosomes and their efficacy as self-adjuvanting vaccine delivery vesicles. The uptake of archaeosomes by phagocytic cells is several folds greater than that of liposomes made from ester lipids. In addition, archaeosomes enhance the recruitment and activation of professional antigen presenting cells *in vivo*, and deliver the antigen to both MHC class I and II pathways for antigen presentation, without eliciting overt inflammatory responses. In murine models, systemic administration of archaeosomes containing encapsulated antigen(s) elicits strong and sustained antigen-specific antibody responses which are comparable, in some formulations, to those obtained with Freund's adjuvant. Additionally, archaeosomes promote robust antigen-specific cell-mediated immunity, including $CD8^+$ CTL responses. The immune responses induced by archaeosomes are sustained over long periods and exhibit strong memory responses. More importantly, immunization of mice with archaeosome-based vaccines induces robust protective immunity against intracellular pathogens, and prophylactic and therapeutic efficacies against the development of experimental cancers. Extensive murine model studies suggest that archaeosomes are safe[36].

3.4. Cryptosomes

Liposomes have been extensively used in the past decade as drug carriers. Desired properties of efficient carriers include the ability to evade the mononuclear phagocyte system to prolong the circulation half-life ($t_{1/2}$), and preferential release of the encapsulated drug at the targeted site. Use of sterically stabilized liposomes has increased the liposome circulation time considerably[38]. "Stealth" liposomes or "cryptosomes"[38] have been used to improve the efficiency of drug delivery by liposomes in

various cases of cancers[39] and tumors[40, 41]. Conventional liposomes are intercepted at an early stage of circulation by the mononuclear phagocyte system. Unlike conventional liposomes, "stealth" or sterically stabilized liposomes show reduced uptake by the MPS, thus prolonging their circulation half-life considerably.

Stealthing of conventional liposomes is done primarily by using polyethylene glycol (PEG) and poloxamers (polymer). The use of PEG conjugated lipids to form stealth liposomes is a well-accepted process. The predecessors of PEG-lipids, namely GM_1 ganglioside and phospatidylinositol , though effective in increasing $t_{1/2}$ of the conventional liposomes, did not match the superior shielding ability of PEG-lipids. Moreover, being a synthetic lipid.

Uncovering or de-stealthing of the PEG coated liposomes at the desired sites has proven to be difficult to achieve.

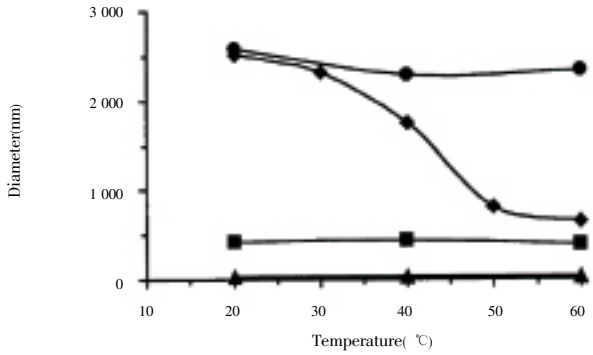

Figure 7. Effect of temperature on vesicle size.

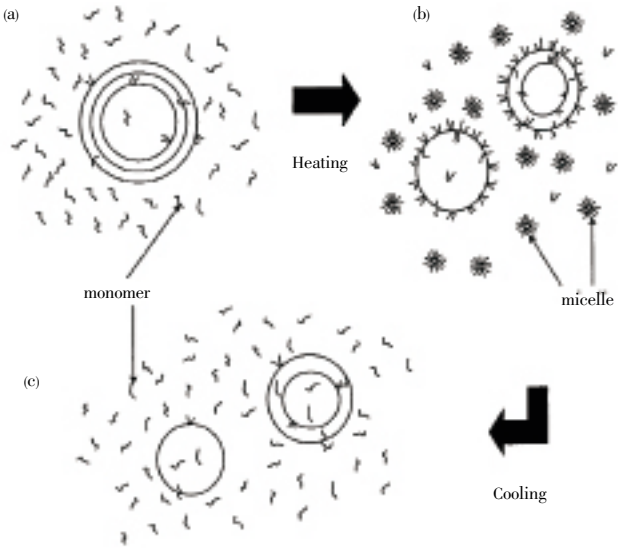

Figure 8. Schematic illustration of the proposed fate of EPC, along wih Pluronic F127 during thermal cycling.

It is a type of drug delivery system that more particularly provides a liposomal composition and method for preferential retention of liposomes at or near the target site. Cryptosomes is a liposomal composition for targeted delivery of drugs. The composition comprises poloxamer molecules and liposomes encapsulating one or more delivery agents. At above the critical micellar temperature of the poloxamer, a fraction of the poloxamer molecules form micelles and another fraction becomes incorporated into the liposome surface, thereby inhibiting their adhesion to cells. At a temperature below the critical micellar temperature, the poloxamer molecules dissociate into monomers allowing the liposomes to adhere to adjacent cells and effecting retention of the liposomes in the surrounding tissue. A method is provided for delivery of agents to target site comprising administering the composition to an individual and cooling the target site to cause retention of the liposomes at or near the target site.

The lipids useful for preparing liposomes include but are not limited to phospholipids such as phosphatidylcholine, phosphatidylserine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylinositol and their mixtures, and with added sphingolipids, glycolipids, fatty acids and cholesterol at various proportions if desired.

The polymer used is poloxamer (Pluronics). Poloxamers are polyethylene oxide (PEO)-polypropylene oxide (PPO)-polyethylene oxide tri-block co-polymers of different molecular weights. The hydrophobic PPO group in the middle links the two hydrophilic PEO groups. The hydrophilic PEO groups of a poloxamer, on either side of the central PPO unit, can provide steric protection to a bilayer surface. The amphiphilic nature of the poloxamers makes them extremely useful in various applications as emulsifiers and stabilizers. Although not intending to be bound by any particular theory, it is considered that the central PPO unit, being hydrophobic, would tend to push into the bilayer interior serving as an anchor. Dislodging the poloxamer molecule from the bilayer is achieved by reducing its hydrophobicity. Hydrophobicity is reduced by decreasing the temperature. In an aqueous medium, poloxamers stay as individual molecules at temperatures below their CMT, but at temperatures above the CMT, individual molecules are forced to form micelle to shield the lipophilic PPO units from the aqueous environment. In the presence of lipid bilayers, some poloxamer molecules would partition into the bilayers in addition to forming micelles with other poloxamer units. If the temperature again goes below the CMT, the poloxamer molecules dislodge themselves from the bilayers or micelles to become individual molecules again.

A large enough PEO (about 50 to 100 units) to cause complete stealthing. An optimum size PPO (about 20 to 60 units) which would provide enough anchoring to attach to the membrane; and most importantly. A CMT value around the physiological temperature (*i.e.* between about 33 ℃. to 43 ℃, preferably around 37 ℃) corresponding to a relatively small concentration (0.01 to 1% w/v) of the poloxamer to make it useful in the *in vivo* conditions.

Pluronic F127 (M.W.-12,600, PEO_{98}- PPO_{67}- PEO_{98}) is an example of a suitable poloxamer as shown in figure 8. Other poloxamers satisfying these criteria include but are Pluronic F87, F88, F98, F108, and P188. The liposomes are used as delivery vehicles and can be prepared by standard techniques. For example, lipid components (such as phopatidylcholine and cholesterol) in chloroform are mixed and dried to form a lipid film. The film is rehydrated in the presence of the drug to form MLVs. Small unilamellar vesicles (SUVs) can be prepared from the MLVs by standard techniques such as sonication and LUVs can be made by extrusion. Vesicles may also be made by other methods such as reversed phase evaporation, detergent dialysis and freeze-thawing. The LUVs and SUVs are separated from the free agent and poloxamer by standard techniques such as filtration or dialysis. The filtration method entails passing the sample through a filter device (such as Millipore® filter)

with the filter pore size smaller than the SUV or LUV, such that vesicles are retained behind the filter while free agents and poloxamers are filtered through. The dialysis method entails enclosing the sample within a dialysis bag or device, with the membrane pore size smaller than the SUV or LUV, such that free agents and poloxamer molecules may diffuse through to the dialysis medium, and vesicles are retained. In addition, veiscles may be separated from free agents and poloxamer molecules s by size exclusion column chromatography.

3.5. Stealth liposomes

Incorporation of polymers, such as polyethylene glycol (PEG-lipid derivatives, or glycolipids, such as monosialoganglioside GM_1; into liposomes results in sterically stabilized liposomes which have several advantages over liposome formulations traditionally used in the past, including reduced recognition and uptake by macrophages, extended circulation half-lives, targeted drug delivery[42], dose-independent pharmacokinetics, and increased uptake *in vivo* by solid tumours[43,44], breast cancer[45,46]. PEG-lipid derivatives such as PEG-distearoylphosphatidylethanola mine (PEG-DSPE) are particularily useful because of their ease of preparation and relative lack of expense. Optimum molecular weight of the PEG headgroup is approximately 2000 daltons and optimum concentration in the bilayer is 5 mol% to 7 mol% of phospholipids. Pegylated liposomes have the additional advantage of allowing[47].

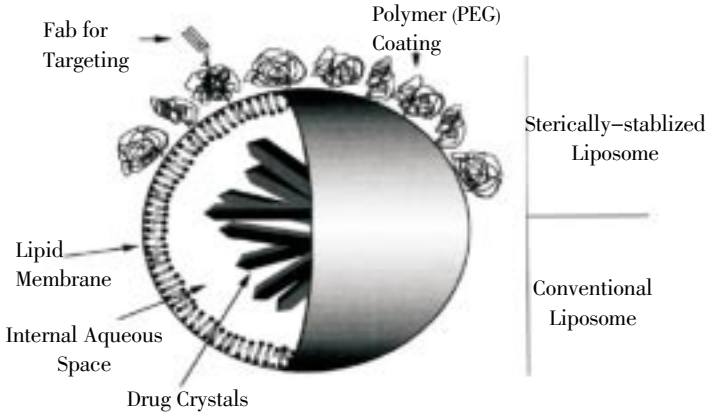

Figure 9. Stealth liposome (Optimization of liposomes for delivery of chemotherapeutic agents)

3.5.1. Stealth liposomes: an improved sustained release system for 1-beta-D-arabinofuranosylcytosine

Newly developed liposomes with prolonged circulation half-lives and dose-independent pharmacokinetics (Stealth liposomes) have been tested for their efficacy as a slow release system for the rapidly degraded, schedule-dependent, antineoplastic drug 1-beta-D-arabinofuranosylcytosine (ara-C) in the treatment of murine L1210/C_2 leukemia. Mice were given injections of either 10(5) cells or 10(6) cells by either the *i.v.* or the *i.p.* routes. Leukemia-bearing mice were treated with either *i.v.* or *i.p.* injections of free drug, *i.v.* or *i.p.* injections of liposome-entrapped drug, or 24-h *i.v.* infusions of free drug. Long-circulating liposomes contained, as the stealth component, either monosialoganglioside or polyethylene glycol-distearo ylphosphatidylethanolamine. Liposomes lacking the stealth components (non-stealth liposomes) were also injected for comparison. At lower dose ranges, stealth liposomes were superior to non-stealth liposomes in prolonging mean survival times of the mice, and all liposome preparations were superior to injections of the free drug. Drug entrapped in stealth liposomes, when administered at or near the maximum tolerated dose of 100 mg/kg ara-C were considerably superior to 24-h free drug infusions given at the same total drug dose. Therapeutic effect was related to the half-life of leakage of ara-C from the liposome formulations, as well as to circulation half-life, with maximum therapeutic effect achieved with long circulation half-lives and more rapid leakage rates. The therapeutic efficacy of non-stealth liposomes increased with increasing liposome (and drug) dose as a result of saturation of liposome uptake by the mononuclear phagocyte system, which resulted in longer circulation half-lives for these liposomes at higher doses (Michaelis-Menten pharmacokinetics). Liposome entrapment can protect rapidly degraded drugs from breakdown *in vivo*, with release of the drugs in a therapeutically active form over periods of up to several days. The dose-independent pharmacokinetics and reduced mononuclear phagocyte system uptake of stealth liposomes gives them distinct advantages over non-stealth liposome[48].

3.5.2. Polymer-grafted liposome: Physical basis for the "stealth" property

Polymer-bearing lipids have recently been incorporated into liposomes that are used in *in vivo* drug delivery. This strategy has improved the liposome's ability to avoid the reticuloendothelial system and has thereby increased its circulation time in the bloodstream. In order to understand the physical basis for this, so called, Stealth® effect, we have begun a series of studies that characterize the surface structure, interactive properties and *in vivo* performance of the polymer-bearing, Stealth lipids. For a 1 900 g/mol polyethylene glycol (PEG) moiety, we have used x-ray diffraction and micropipette manipulation methods to show that, (i) the polymer chains extend -50 out from the lipid bilayer surface; (ii) this surface polymer exerts a significant long range mutual repulsion between adjacent bilayers that prevents bilayer-bilayer adhesion. Furthermore, the measured polymer extension and repulsive pressure are well modelled by polymer scaling laws. These results imply that the interaction of macromolecules and cellular surfaces with the Stealth liposome is probably limited to a distance of -50 from the liposome surface. We conclude that the origin of the Stealth effect lies in a steric stabilization mechanism. By using fluorescence video microscopy to observe implanted tumor tissue, we have also shown that fluorescent Stealth liposomes extravasate through the leaky vessel walls of tumors. This method allows us to characterize, in real time, the accumulation of liposomes and release of drug at an implanted tumor site.

The agents that can be delivered by the liposomal composition include therapeutic drugs, pharmacologic active agents, nutritional molecules, diagnostic agents, image contrast agents and any other molecules that is desired to be delivered to a particular physiological site.

Therapeutic agents include antibiotics, anti-tumor agents[49], anti-inflammatory agents, anti-neoplastic agents[50], anti-microbial agents, anti-viral agents, immunosuppressive agents, antisense oligonucleotides,

plasmids, hydrolytic enzymes[51], hormones, nanoparticles and the like. When the delivery agents are small in size (such as nanoparticles), delivery vehicles including, but not limited to, micelles, hydrophobic beads or colloidal particles, can be used instead of liposomes. The stealthing and de-stealthing of the delivery vehicles is similar to the liposomes.

3.6. Discomes

Non-ionic surface active agents based discoidal vesicles (discomes) bearing timolol maleate were prepared. Niosomes were incorporated with Solulan C24 in order to affect vesicle to discome transition. The discomes were relatively large in size, 12-60 microm. They were found to entrap a relatively high quantity of timolol maleate. The prepared system characterized for size, shape and drug release profile *in vitro*. They were found to release the contents following biphasic profile particularly in the case where the drug was loaded using a pH gradient technique. The prepared system could produce or sustain a suitable activity profile upon administration into the ocular cavity; however, systemic absorption was minimized to a negliable level. The discomes were found to be promising and of potential for controlled ocular administration of water-soluble drugs.

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3.7. Genosomes

They are the artificial functional complexes for functional gene or DNA delivery to cell[53]. Cationic lipids are more suitable because they posses high biodegradability and stability in the blood stream.

3.7.1. Liposomal formulation technology: in the case of preparation of liposomes for gene delivery

When the cationic liposomes containing DNA were prepared by the conventional lipid-film method, significant degradation and conformational change of DNA was observed during homogenization and sizing procedures, though DNA itself was relatively stable against these procedures. On the other hand, when the freeze-dried empty liposomes (FDEL) method was used, no degradation, conformational change or loss of DNA was observed, and high transfection activity was obtained. These findings suggest that the FDEL method is very useful for preparation of liposomes containing DNA. If DNA/liposomes complex was formed using the commercialized cationic liposomes reagents, DNA was stable in the serum-containing medium but the structure of liposomes was disappeared. It was considered that this was the reason why serum-free medium had to be used for transfection. Among more than 300 formulations using the FDEL method, the novel cational liposomes were developed which had higher transfection activity even in the serum-containing medium[54].

3.7.2. Recent advances in liposome technologies and their applications for systemic gene delivery

The recent clinical successes experienced by liposomal drug delivery systems stem from the ability to produce well-defined liposomes that can be composed of a wide variety of lipids, have high drug-trapping efficiencies and have a narrow size distribution, averaging less than 100 nm in diameter. Agents that prolong the circulation lifetime of liposomes, enhance the delivery of liposomal drugs to specific target cells, or enhance the ability of liposomes to deliver drugs intracellularly can be incorporated to further increase the therapeutic activity. The physical and chemical requirements for optimum liposome drug delivery systems will likely apply to lipid-based gene delivery systems. As a result, the development of liposomal delivery systems for systemic gene delivery should follow similar strategies[55,56].

4. Conclusion

Vesicular system means the use of vesicles for various purposes, e.g. liposomes, niosomes, pharmacosomes *etc* as they have been realized as extremely usefull carrier systems, additives and tools in various scientific domains. This system over the year has been investigated as the major drug deliveries due to their flexibilities to be tailored for varied desirable purposes. It shall be now possible to design various vesicular system e.g. photosomes, archeaosomes, cryptosomes, discomes, genosomes, for ocular drug delivery, tumor therapy, gene delivery, immunization and bioreactor technology *etc*.

Finally, liposomes are showing particular promise as intracellular delivery systems for proteins/peptides, antisense molecules, ribozymes and DNA. The development of liposomes that can be administered systemically and exhibit targeted and fusogenic properties appears to be increasingly within our grasp.

Further in future by combining various other strategies, vesicular system will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *in vivo* delivery.

Conflict of interest statement

We declare that we have no conflict of interest.

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