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A Review on Potency of Vesicular Systems in Targeting Drug Delivery

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ABSTRACT

The focus of this review is to development of a novel drug delivery system. Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and channel the active entity to the site of action. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, vesicular systems such as liposomes, niosomes, ethosomes and elastic, deformable vesicles provide an alternative for improved skin drug delivery. The function of vesicles as topical delivery systems is controversial with variable effects being reported in relation to the type of vesicles and their composition. In fact, vesicles can act as drug carriers controlling active release; they can provide a localized depot in the skin for dermally active compounds and enhance transdermal drug delivery. A wide variety of lipids and surfactants can be used to prepare vesicles, which are commonly composed of phospholipids (liposomes) or non-ionic surfactants (niosomes). Vesicle composition and preparation method influence their physicochemical properties (size, charge, lamellarity, thermodynamic state, deformability) and therefore their efficacy as drug delivery systems. The focus of this review is to bring out the application, advantages, and drawbacks of vesicular systems.

Keywords: Vesicles, lipid based drug delivery systems, liposomes, niosomes, ethosomes, Pharmacosomes.

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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]. There are different types of pharmaceutical carriers are present such as 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, niosomes pharmacosomes, virosomes, etc[2-5]. The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, 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. Biologic origin of these vesicles was first reported in 1965 by Bingham,[6] and was given the name Bingham bodies. Much water has flown since then.
In this article, an attempt has been made to touch upon different aspects related to the vesicular system, including method of preparation, stabilization, drawbacks, and applications. Various types of vesicular systems such as liposomes, niosomes, transfersomes, and pharmacosomes, have been discussed in detail, while other emerging systems have been discussed briefly.

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 can be overcome by use of vesicular drug delivery systems. The phagocytic uptake of the systemic delivery of the drug-loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects.

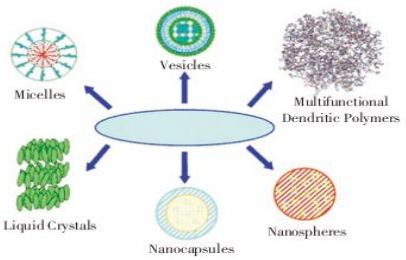

Fig 1. Shows some of pharmaceutical carriers

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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. There are a number of components present in liposomes with phospholipid and cholesterol being the main ingredients.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 shown in figure.2 are typically in the lower size range with various targeting ligands attached to their surface allowing for their surface-attachment and accumulation in pathological are as for treatment of diseases. All methods of preparation of liposomes involve dissolution of cholesterol, lecithin, and charge in organic solvent, followed by drying it to a thin film, and then dispersion of film in an aqueous medium to obtain liposome suspension at a critical hydrating temperature. The hydrating temperature used to prepare liposomes should be above the phase transition temperature of phospholipid used i.e. temperature at which there is transition from gel to liquid phase. It can be altered by using phospholipid mixtures, or by adding sterols e.g. cholesterol. Gel state vesicular delivery system can be improved by adding cholesterol to the lipid in case of liposomes, or to the surfactant in case of niosome. This temperature can give good clues to vesicular delivery, system stability, and permeability. The methods of preparation have been classified to the three basic modes of dispersions.

- Physical dispersion involving hand shaking and non-hand shaking method[7-8]
- Solvent dispersion involving ethanol injection, ether injection, double emulsion vesicle method, reverse phase evaporation vesicle method,and stable plurilamellar vesicle method [9-15]
- Detergent solubilization[16-17]

The liposomes are characterized for their physical attributes i.e. size, shape, and size distribution,[18-21] surface charge,[22] percent capture,[23-24] entrapped volume,[25] lamellarity through freeze fracture microscopy and P-NMR,[26] phase behavior,[27] drug release,[28-29] quantitative determination of phospholipids,[30] and cholesterol analysis,[31] 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 fusion during storage. Approaches to increase liposomes stability involve efficient formulation and lyophilization.

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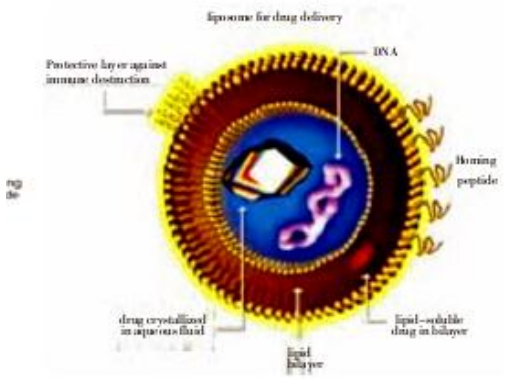

Fig 2. Unilaminar liposomes

NIOSOMES OR NON-IONIC SURFACTANT VESICLES

Niosomes or nonvesicular 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) non-ionic surfactant vesicles. 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, 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, provide charge to the vesicles, and thus shows increase entrapment efficiency. Other charge-inducers are stearylamine and diacylglycerol, that also help in electrostatic stabilization of the vesicles. Niosomes have unique advantages over liposomes. Niosomes are quite stable structures, even in the emulsified form[32-33]. They require no special conditions such as low temperature or inert atmosphere for protection or storage, and are chemically stable as like liposomes. 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,[34-39] Brij,[40-41] and a series of spans and tweens,[42-45] Niosomes can be formulated by lipid layer hydration method, or by reverse phase evaporation method, or by transmembrane pH gradient uptake process (remote loading), to form multilamellar vesicles. Other methods include hand shaking, ether injection, and sonication,[46-47] These methods are based on whether the drug is actively or passively entrapped in vesicles. In passive trapping, the technique drug and lipids are codispersed with a fraction of drug being entrapped, according to hydrophobicity and electrostatic charge. If the drug is hydrophilic, it will be entrapped in the internal aqueous phase, and the hydrophobic drug will primarily be entrapped in the lipid region. Active trapping can be achieved in response to ion gradients placed across niosomal membranes. This allows drug entrapment after the niosomal carrier has been formulated. Similar to liposomes, there are 3 major types of

niosomes -multilamellar vesicles (MLV, size >0.05 µm), small unilamellar vesicles (SUV, size -0.025-0.05 µm), large unilamellar vesicles (LUV, size >0.10 µm). MLVs vesicles exhibit increased-trapped volume and equilibrium solute distribution, and require hand-shaking method. They show variations in lipid compositions. SUVs are commonly produced by sonication, and French Press procedures. Ultrasonic electrocapillary emulsification or solvent dilution techniques can be used to prepare SUVs. The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV. But the better method of preparation of LUV is reverse phase evaporation,or by detergent solubilisation method [48-51].

Niosomes are characterized for different attributes such as vesicle diameter using light microscope, photon correlation microscopy, freeze capture microscopy, entrapment efficiency, and *in vitro* release rate. Other aspects studied are drug stability, drug leakage in saline and plasma on storage, pharmacokinetic aspect, toxicity, etc.

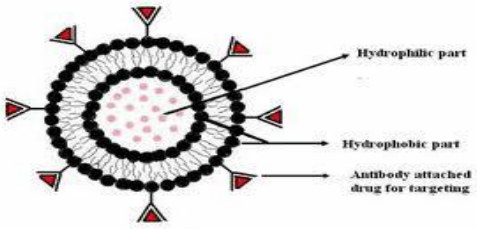

Fig 3. Diagrammatic representation of Niosome

TRANSFERSOME

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,[52-53] 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 [54]. 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, [55-56] Surfactants such as sodium cholate, sodium deoxycholate, span 80, and Tween 80, have been used as edge activators, [57-59] Transfersomes are prepared in two steps. First, a thin film, comprising phospholipid and surfactant is prepared, hydrated with buffer (pH 6.5) by rotation, and then brought to the desired size by sonication. The concentration of surfactant is very crucial in the formulation of transfersomes, because at sublytic concentration, these agents provide flexibility to vesicles membrane, and at higher concentration, cause a destruction of vesicles. In the second step, sonicated vesicles are homogenized by extrusion through a polycarbonate membrane [60].

`Transfersomes are characterized for different physical properties such as vesicle diameter using photon correlation spectroscopy or dynamic light scattering method,[61]

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entrapment efficiency,[62] vesicle diameter,[63-64] degree of deformability or permeability, *in vitro* drug release, Confocal Scanning Laser Microscopy (CSLM) study for investigating the mechanism of penetration of transfersomes across the skin, 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, [65] pharmacokinetic aspects, [66-68] toxicity studies, etc.

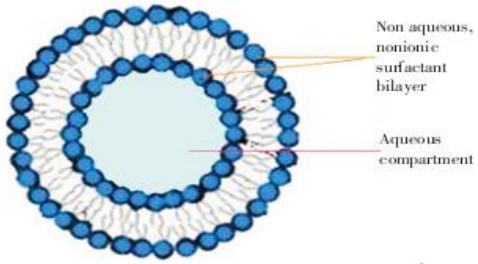

Fig 4. Structure of Transfersome

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, -NH2, 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.

Table 1 Shows summary of commercially available delivery system

S.No	Name	Supplier	Application
1	Natipide ii liposome	Rhone-poulenc	Reinforces skin's own moisture retention capabilities
2	Ultrasome	Applied	Genetics sun-care product
3	Photosome	Applied	Genetics sun-care product
4	Catezomes	Collaborative labs	Versatile active delivery

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RECENT ADVANCES IN VESICULAR SYSTEMS

Photosomes

Liposomes are the most widely used cosmetic delivery systems.[69] These are artificial spherical submicroscopic vesicles with diameter between 25 and 5000 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.

Following are the promising vesicle delivery systems in cosmetics:

a)Liposomes; b)Silicone vesicles and matrices; c) Multi-walled delivery systems.
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. 6 wavelength between about 300 nm to about 400 nm, providing release of fluid from lipid membrane in response to effective amount of irradiation at predetermined wavelength. 2) Light sensitive lipid is a glycerol derivative defining 1 position carbon and a 2 position carbon; one retino 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 pha a biologically active component; 5) Contain fluid includes pharmaceutical and a membrane in the releasing position permits substantially all fluid to leak.

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.

Particulate systems

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

Delivery devices

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,[70-73] tumor,[74] involving three key components: a photosensitizer, light, and tissue oxygen[75]. It is also being investigated for treatment of psoriasis, lung sparing treatment,[76] 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[77].

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

- 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.
- High singlet oxygen quantum yield
- Low photobleaching
- Natural fluorescence

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

- High chemical stability
- Low dark toxicity

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

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,[78] intramuscular, and oral. The efficacy of the archaeosomes and also of conventional liposomes can be further improved in these applications, by incorporation of coenzyme Q10 and/ or polyethyleneglycol-lipid conjugate into liposomes made from these archaeosomes.

A liposome composition comprising,[79]

- The total polar lipids extract of an archaeobacterium;
- A pharmaceutical agents;
- Coenzyme Q10;
- A polyethyleneglycol lipid conjugate.

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

Characteristics

- 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 Q10, and a polyethyleneglycol lipid conjugate, as a carrier for said pharmaceutical agent
- 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,[80] and as a carrier for said pharmaceutical or biological agent[81].
- The liposome is administered to an animal orally,[82] intraperitoneally, intramuscularly, subcutaneously, or intravenously.
- It is used as beneficial carriers of antigens, immunogenic compounds, DNA, drugs, therapeutic compounds, oral delivery of peptides,[83] pharmaceutical compounds, natural antioxidant,[84] imaging agents or tracers, and to deliver these to specific cells such as the macrophage or to specific tissues, in life-forms such as the human.

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.

Archaeosome immunostimulatory vaccine delivery systes

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.

Stealth liposomes

Incorporation of polymers, such as polyethylene glycol (PEG-lipid derivatives, or glycolipids, such as monosialoganglioside GM1; 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,[85] dose-independent pharmacokinetics, and increased uptake in vivo by solid tumours,[86-87] breast cancer[88--89]. 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 following[90].

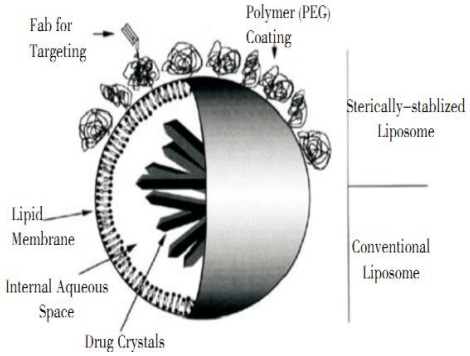

Fig 5. Stealth liposome

Discomes

Non-ionic surface active agents based discoidal vesicles discomes containing timolol maleate were prepared. The prepared system characterized for size, shape and *in vitro* drug release profile. 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.Non-ionic surface active agents based discoidal vesicles (discomes) bearing timolol maleate was prepared. Niosomes were incorporated with Solulan C24 in order to affect vesicle to discome transition. The discomes were relatively large in size, 12-60 micron.

Genosomes

They are the artificial functional complexes for functional gene or DNA delivery to cell [91]. Cationic lipids are more suitable because they posses high biodegradability and stability in the blood stream.

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[92].

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[93-94].

CONCLUSION

Vesicular system over the year has been investigated as the major drug deliveries due to their flexibilities to be tailored for varied desirable purposes. Vesicular systems have been realized as extremely useful carrier systems in various scientific domains. In spite of certain drawbacks, the vesicular delivery systems still play an important role in the selective targeting, and the controlled delivery of various drugs. 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.

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