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Vesicular Drug Delivery System - An Over View

Ravi Buchiraju*, Sreekanth Nama, Bhargavi Sakala, Babu Rao Chandu, Arun Kommu, Jaya Kishore Babu Chebrolu, Narasimhamurthy Yedulapurapu

Don Bosco P.G. College of Pharmacy, 5th Mile, Pulladigunta, Kornepadu (V),Vatticherukuru (M), Guntur-522017, Andhra Pradesh.

ABSTRACT

The application of vesicular system in drug delivery has changed the definitions of diagnosis and treatment in different aspects of biomedical field. The vesicular system as liposome's, niosomes, sphinosomes, transferosomes, pharmacosomes and ufasomes are used to improve the new drug molecules by encapsulating an active medicament inside vesicular structure in one such system. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity. Such different systems are widely used in gene delivery, tumor targeting to brain, oral formulations, in stability and permeability problems of drugs. In this review we really focused on different aspects of vesicular system in terms of its advantages, limitation, applications and different marketed product of vesicular system as novel drug delivery.

Keywords: Vesicular System, Drug Delivery, Encapsulation.

Corresponding author

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INTRODUCTION

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayer formed, when certain amphiphillic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphillic building blocks. Biologic origin of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies. Drug carrier can be engineered to slowly degrade, react to stimuli and be site-specific. The ultimate aim is to control degradation of drug and loss, prevention of harmful side effects and increase the availability of the drug at the disease site. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved .Lipid vesicles are one type of many experimental models of biomembranes which evolved successfully, as vehicles for controlled delivery. For the treatment of intracellular infections, conventional chemotherapy is not effective, due to limited permeation of drugs into cells. This can overcome by the use of vesicular drug delivery systems. [1, 2, 3]

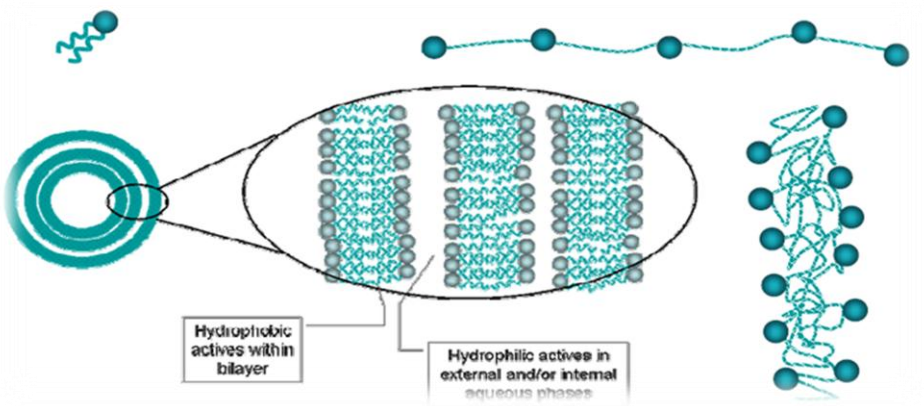

Fig: 1 Structure of Vesicular system

Objectives of Vesicular Drug Delivery Systems:

[1] Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
[2] Improves the bioavailability especially in the case of poorly soluble drugs.
[3] Both hydrophilic and lipophilic drugs can be incorporated.
[4] Delays elimination of rapidly metabolizable drugs and thus function as sustained release Systems.

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TYPES

Vesicular system	Description	Application
Aquasomes	Three layered self-assembly compositions with ceramics carbon nanocrystalline particulate core coated with glassy cellobiose	Specific Targeting, molecular shielding.
Cryptosmes	Lipid vesicles with a surface coat composed of pc and of suitable polyoxoyethylene derivative of phosphotidyl ethanolamine	Ligand mediated drug Targeting
Discomes	Niosomes solublized with non-ionic surfactant solutions (polyoxyethylenecetyl ether class)	Ligand mediated drug Targeting
Emulsomes	Nanosize Lipid particles (bioadhesives nano emulsion) consisted of microscopic lipid assembly with a polar core.	Parenteral delivery of poorly water soluble drugs
Enzymosomes	Liposomal constructs engineered to provide a mini bioenvironmental in which enzymes are covalently immobilized or coupled to the surface of liposomes.	Targeted delivery to tumor Cell
Ethosomes	Ethosomes are lipid "Soft malleablevesicles" embodying a permeation enhancer and composed of phospholipid, ethanol and water	Targeted delivery to deep skin layer
Genosomes	Artificial macromolecular complexes for functional gene transfer .Cationic lipids are most suitable because they posess high biodegradability and stability in blood serum	Cell specific gene transfer
Photosomes	Photolysis encapsulated in liposomes ,which release the content photo-triggered charges in membrane permeability characteristics	Photodynamic Therapy
Virosomes	Liposomes spiked with virus glycoprotein, incorporated into the liposomal bilayers based on retro viruses derived lipids.	Immunological adjuvants
Vesosomes	Nested bilayer compartment in vitro via the interdigested bilayer phase formed by adding ethanol to a variety of saturated phospholipids.	Multiple compartment of the vesosomes give better protection to the interior
Proteosomes	High molecular weight multi-submit enzyme Complexes with catalytic activity, which is specifically due to the assembly pattern of enzymes.	Better catalytic activity turnover than non associated enzymes.

LIPOSOMES [4, 5, 6, 7, 8, 9]

The liposome's have emerged as most practically useful carriers for in-vivo drug delivery as majority of reports has concentrated on the use of phospholipid vesicles or liposome's as potential drug carrier systems. Liposomes or lipid based vesicles are microscopic (unilamellar or multilamellar) vesicles that are formed as a result of self-assembly of phospholipids in an aqueous media resulting in closed bilayered structure. The assembly into closed bilayered

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structures is a spontaneous process and usually needs some input of energy in the form of physical agitation, sonication, heat etc. Since lipid bilayered membrane encloses an aqueous core, both water and lipid soluble drugs can be successfully entrapped into the liposome's. The lipid soluble or lipophilic drugs get entrapped within the bilayered membrane whereas water soluble or hydrophilic drugs get entrapped in the central aqueous core of the vesicles Liposomes are potential carrier for controlled drug release of tumors therapeutic agents and antibiotic, for gene and antisense therapy through nucleic acid sequence delivery, immunization through antigen delivery and for anti-Parkinson's. In last one decade, pharmaceutical researchers use the tools of biophysics in evaluating liposomal dosage forms. Liposomes have covered predominantly medical, albeit some non-medical areas like bioreactors, catalysts, cosmetics and ecology.

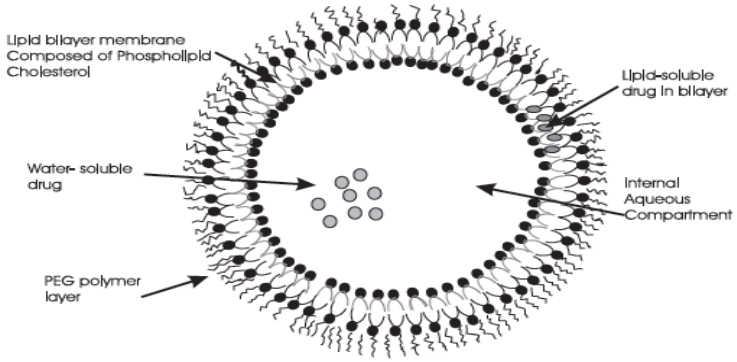

Fig:2 Structure of liposomes

Advantages

[1] Liposomes supply both a lipophilic environment and aqueous "milieu interne" in one system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs and agents.
[2] Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon-g.
[3] Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation
[4] (eg. Amphotericin B, Taxol).
[5] Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
[6] Alter the pharmacokinetic and pharmacodynamic property of drugs (reduced elimination, increased circulation life time).

Limitation

[1] High production cost
[2] Leakage and fusion of encapsulated drug / molecules.
[3] Sometimes phospholipid undergoes oxidation and hydrolysis.
[4] Short half-life.
[5] Low solubility.
[6] Less stability.

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NIOSOMES [12, 13, 14, 15, 16, 17, 18, 19]

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposome's, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery. The figure below will give a better idea of what a niosome looks like and where the drug is located within the vesicles. In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, noisome have been used to solve the problem of insolubility, instability and rapid degradation of drugs.

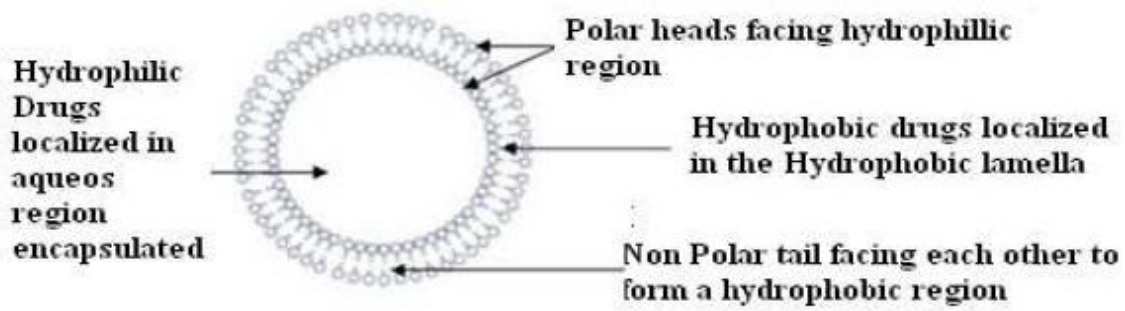

Fig: 3 Niosomes Structure

Advantages associated with Niosomes

[1] Niosomes are biodegradable, biocompatible and non immunogenic to the body.
[2] Niosomes can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic as well as amphiphilic drugs.
[3] Niosomes shows controlled and sustained release of drugs due to depot formation.
[4] Niosomes show a greater bioavailability than conventional dosage forms.
[5] Shape, size, composition, fluidity of niosomes drug can be controlled as and when required.
[6] Niosomes had been effectively used in targeting drugs to various organs.

Limitation

Physical instability in niosomal dispersion during storage occurs due To vesicles aggregations, fusion and leaking. This may leads to hydrolysis of encapsulated drugs which affect the shelf life of the dispersion

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SPHINOSOMES [20, 21, 23]

Liposome stability problems are of course much more severe so it is very important task to improve the liposomal stability. Liposomal phospholipid can undergo chemical degradation such as oxidation and hydrolysis either as a result of these changes or otherwise liposome maintained in aqueous suspension may aggregate, fuse, or leak their content. Hydrolysis of ester linkage will slow at pH value close to neutral. The hydrolysis may be avoided altogether by use of lipid which contains ether or amide linkage instead of ester linkage (such are found in sphingolipid) or phospholipid derivatives with the 2- ester linkage replaced by carbomoyloxy function .Thus sphingolipid are been nowadays used for the preparation of stable liposome's known as sphingosomes. Sphingosome may be defined as "concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid. Sphingosomes are administered in many ways these include parentral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Generally it will be administered intravenous or some cases by inhalation. Often it will be administered into a large central vein, such as the superior vena cava and inferior vena cava to allow highly concentrated solution to be administered into large volume and flow vessels. Sphingosomes may be administered orally or transdermally. In simple way we can say sphingosome is liposome which is composed of sphingolipid.

Advantages

[1] Provide selective passive targeting to tumor tissue.
[2] Increase efficacy and therapeutic index.
[3] Increase stability via encapsulation.
[4] Reduction in toxicity of the encapsulated agent.
[5] Improve pharmacokinetic effect (increase circulation time).
[6] Flexibility to couple with site specific ligands to achieve active targeting.

Limitations

[1] Higher cost of sphingolipid hinders the preparation and use of these vesicular systems.
[2] Low entrapment efficacy.

PHARMACOSOMES [24, 25]

Pharmacosomes bearing unique advantages over liposome and niosome vesicles have come up as potential alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, miscellar, or hexagonal aggregates. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as pharmacosomes. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug. Any drug

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possessing an active hydrogen atom (- COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilc characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior.

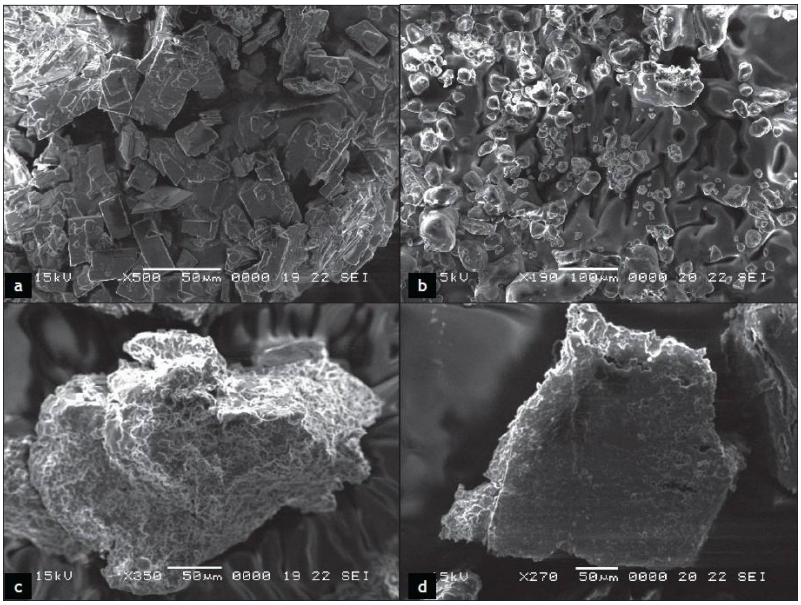

Fig: 6 Pharmacosomes structure

Advantage

[1] As drug is covalently bound, membrane fluidity has no effect on release rate, but in turn depends upon the phase-transition temperature of the drug-lipid complex.
[2] No leakage of drug take place as the drug is covalently linked to the carrier.
[3] Drug can be delivered directly to the site of infection.
[4] Drug release from pharmacosomes is by hydrolysis (including enzymatic).
[5] Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of the lipids, and the spacer.
[6] Reduced cost of therapy.

Limitation

[1] Synthesis of a compound depends upon its ampiphilic nature.
[2] Required surface and bulk interaction of lipids with drugs.
[3] Required covalent bonding to protect the leakage of drugs.

[4] Pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis

TRANSFEROSOMES [26]

Transferosomes was introduced for the effective transdermal delivery of number of low and high molecular weight drugs. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties It consist of both hydrophilic and hydrophobic properties, high deformability gives better penetration of intact vesicles .These vesicular transfersomes are several orders of magnitudes more elastic than the standard leptosomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transfersomes membrane is achieved by mixing suitable surface-active components in the proper ratios. Transferosome based formulations of localanesthetics-lidocaine and tetracaine showed permeation equivalent to subcutaneous injections. Anticancer drugs like methotrexate were tried for transdermal delivery using transferosome technology. This provided a new approach for treatment especially of skin cancer.

Advantage

[1] Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
[2] Transferosomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
[3] Posess high entrapment efficiency, in case of lipophilic drug near to 90%.
[4] Used for both systemic as well as topical delivery of drug.

Limitation

Transferosomes are chemically unstable because of their predisposition to oxidative degradation.

Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.

Transferosomes formulations are expensive.

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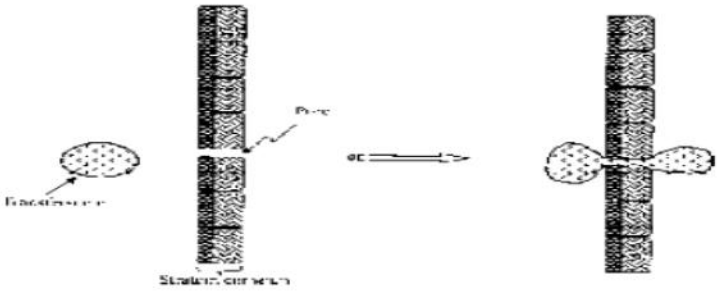

Fig:4 Transfersomes Structure

UFASOMES [27, 28]

Fatty acid vesicles are colloidal suspensions of closed lipid bilayers that are composed of fatty acids and their ionized species (soap). They are observed in a small region within the fatty acid-soap-water ternary phase diagram above the chain melting temperature (Tm) of the corresponding fatty acid-soap mixture. Fatty acid vesicles always contain two types of amphiphiles, the nonionized neutral form and the ionized form (the negatively charged soap). The ratio of nonionized neutral form and the ionized form is critical for the vesicle stability. Fatty acid vesicles are actually mixed "fatty acid/soap vesicles," but for the sake of simplicity, we just call them fatty acid vesicles. The formation of fatty acid vesicles was first reported by Gebicki and Hicks in 1973 and the vesicles formed were initially named "ufasomes," "unsaturated fatty acid liposome's." Later investigations have shown that fatty acid vesicles form not only from unsaturated fatty acids such as oleic acid, linoleic acid, but also from saturated fatty acid such as octanoic acid and decanoic acid. In liposome formulation, phospholipids are generally used. However, even natural phospholipids are chemically heterogeneous, and pure synthetic phospholipids are not yet available in reasonable quantities. The advantage of ufasomes over liposome's is the ready availability of fatty acids

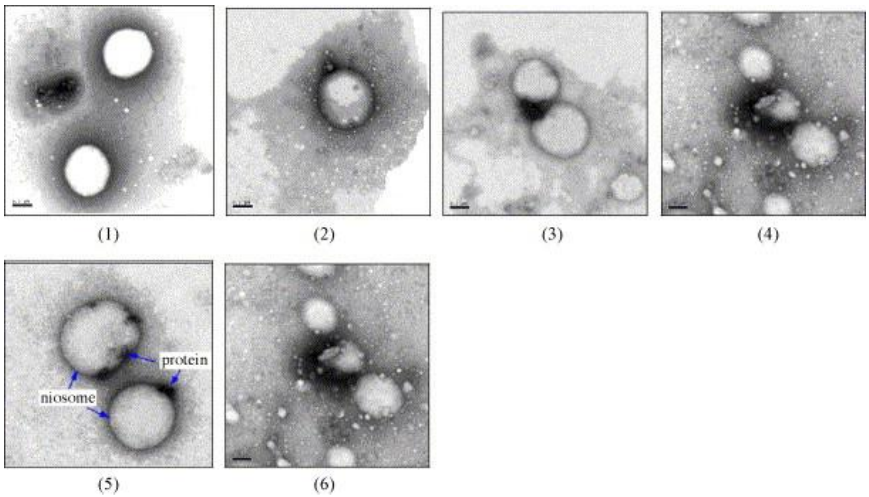

Fig: 5 Ufasomes structure

Recent Innovation in Conventional Ufasomes

Applications of fatty acid vesicles in the fields of food additives and drug delivery are largely unexplored, which is at least partially due to concerns regarding the colloidal stability of fatty acid vesicles (pH- and divalent cation-sensitivity). However, there are some recent studies, using either new types of fatty acids or mixed systems with other surfactants, which may changes the situation in future.

Comparison of Ufasomes and Liposomes [29, 30]

It seems profitable to discuss ufasomes by comparing them with the thoroughly studied liposome's.

Method of Preparation

Virtually identical techniques can be used for either type of vesicle. The one interesting difference is that intensive sonication of fatty acid dispersions does not lead to uniformly-sized particles. Instead, there is some evidence to suggest that oleic and linoleic acids can be forced into the solution to produce a clear supersaturated system that becomes turbid after standing for a few minutes. Ufasomes prepared by sonication retain less solute per unit weight of fatty acid. This is probably due to the much smaller size of spheres prepared by the more drastic treatment.

PH sensitivity [27]

Compared to liposome's, ufasomes are much more sensitive to pH and ionic strength of medium. While the phospholipid vesicles tolerate the range of conditions, fatty acid membranes fail to form, except at slightly alkaline pH and at low ionic strengths.

Light scattering property

Comparison of the light scattering properties of ufasomes and liposome's shows that the phospholipid vesicles are stronger scatterers per mole of material. It is not easy to make an exact comparison; roughly, a 10^{-3} molar liposome suspension has absorbance of 0.7, while a similar preparation of ufasomes reads about 0.2. Part of this difference may lie in the relatively large cross section area of phospholipids

Cross-sectional area

Reasonable cross-sectional areas at 10-20 dyne cm^{-1} are 0.8 nm^2 for lecithin and 0.4 for oleic and linoleic acids. It appears likely, therefore, a mole of lecithin forms a membrane twice as large as that formed from a mole of either of these acids.

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Osmotic response [29, 31, 32]

Measurements of the effects of osmotic pressure changes on the amount of light scattered by ufasomes and liposome's are made with an Aminco-Morrow stopped-flow apparatus operated in conjunction with an Aminco DW-2 spectrophotometer. For osmotic shrinking measurements, a 2 ml suspension of vesicles is diluted to 20 ml with 0.1 M tris pH 8. This is placed in one storage reservoir of the stopped-flow machine. The other reservoir is filled with a similarly buffered sucrose solution. Because of the geometry of the apparatus, the ufasomes are exposed on mixing to sucrose concentration equal to a half of that in the storage reservoir. For swelling experiments, the ufasomes are prepared in buffered sucrose and diluted 1 : 1 with buffer in the mixing chamber during flow. From the results of Bangham and Hicks, it is clear that unlike liposome's, the ufasomes are permeable to sucrose. The swelling curve shows that although over 90% of the volume change occurs in the first 2 min following mixing, the process continues at a decreasing rate. Banghamet al. showed that addition of KCL to suspensions undergoing swelling resulted in contraction of both spheres. The opposite effect, reswelling of liposome's shrunk by sucrose, was reported by Rendi. Hicks et al., found that swelling of ufasomes cannot be reversed by addition of, sucrose Solute, entrapment, and capacity. Ufasomes and liposome's have a similar capacity to entrap glucose. Liposomes made up from lecithin with added cholesterol and dicetyl phosphate held about 1200 nM glucose per µM lipid. When lecithin is replaced by sphingomyelin, this amount was nearly doubled. Compared to this, ufasomes entrap about 450 nM of glucose per µM of fatty acid. This may again be due to a smaller number of spheres forming per mole of fatty acid.

Internal arrangement

A liposome is a microvesicle composed of a bilayer of phospholipid molecules enclosing an aqueous compartment. In ufasomes, the membrane fatty acids are oriented in a bilayer form with their hydrocarbon tails toward the membrane interior and the carboxyl groups in contact with, water.

Cost [33,34,35,36,37]

Conventional fatty acids are inexpensive, certainly cheaper than purified diacylglycero-phospholipids. Ufasomes are relatively less costly than liposome's. Intestinal absorption. In rats, orally delivered insulin, encapsulated into liposome's, proved to exert a considerably smaller hypoglycemic response than i.p. delivered free or encapsulated insulin as reported by Patel and Ryman. Entrapment into egg phosphatidylcholine-cholesterol liposome's strongly reduced carboxy fluorescein absorption from the rat everted jejunum and only marginally increased absorption of fluorescein isothiocyanate-conjugated dextran. It was reported that an irreproducible increase of plasma immunoreactive insulin on administration of liposomal insulin in the dog duodenum. As the subsequent fall in plasma glucose was negligible, it was concluded that a very small amount of insulin of not more than 1% was absorbed intact. Because of the unfavorable results of the majority of studies, it was concluded that liposome's do not appear to have any absorption promoting properties of practical importance. It was reported that

carboxyfluorescein absorption proved to be enhanced by entrapment into ufasomes. Results indicate that the fusogenic lipid, liberated on intestinal degradation of the ufasomes, promotes drug absorption. Future research will be necessary to decide on the applicability of this type of lipid vesicle as an intestinal absorption enhance

CONCLUSION

The forgoing review shows different aspects related with the vesicular system approaching a vital role to deliver a drug. Inspite of certain drawbacks, the vesicular delivery systems still play an important role in the selective targeting and controlled delivery of various drugs. Researcher are implementing their efforts in improving the design of vesicular system by making them steady in nature, in order to prevent leaching of contents, oxidation and their uptake by natural defense mechanism. As their flexibility in design possess a wide range of potential, its application must be explored throughout the world by encouraging the participation of researcher in the field of vesicular drug delivery system

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