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Vesicular Drug Delivery System

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Abstract:

Vesicular drug delivery systems are nanoscale structures designed to deliver drug molecules or macromolecules, such as proteins and DNA, to target cells or tissues. These systems are composed of lipid or polymer vesicles that are formed from amphiphilic molecules. They can be engineered to improve the pharmacodynamic and pharmacokinetic properties of drugs, while reducing their toxicity. Vesicular drug delivery systems offer advantages such as increased stability, improved efficacy, and enhanced permeability. In addition, they can be used to target specific tissues or cell types, allowing for more targeted delivery of drugs

Keyword: Vesicle, Novel, Liposome, Niosome, Pharmacosomes, Transferosomes, Bioavailability.

Introduction:

Vesicular drug delivery system can be defined as highly ordered assemblies consisting of one or more concentric bilayers formed as a result of self-assembling of amphiphilic building blocks in presence of water. In previous years, noticable work had been done to develop Novel Drug Delivery System (ND1DS), fulfills desirable characteristics that it should deliver drug at a rate directed by need of body, over period of treatment & should channel active entity at site of action.Convetional dosage forms including prolonged released dosage forms unable to fulfilled none of these desired characteristics. At present, no available drug delivery systems behave ideally but attempts have been made to bridge gap between ideal & available.[1] 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.[2] Biologic origin of these vesicles was first reported in 1965 by Bingham and was given the name Bingham bodies. Drug carriers can be engineered to slowly degrade, react to stimuli and be site-specific. [3] Novel drug delivery system sustains drug action at a predetermined rate, relatively constant (zero order kinetics), efficient drug level in the body, and simultaneously minimizes the undesirable side effects.[4]

Vesicles have become the choice in drug delivery system called Vesicular Drug Delivery System." E. g: Liposomes, Niosome , Pharmacosomes etc. [5]

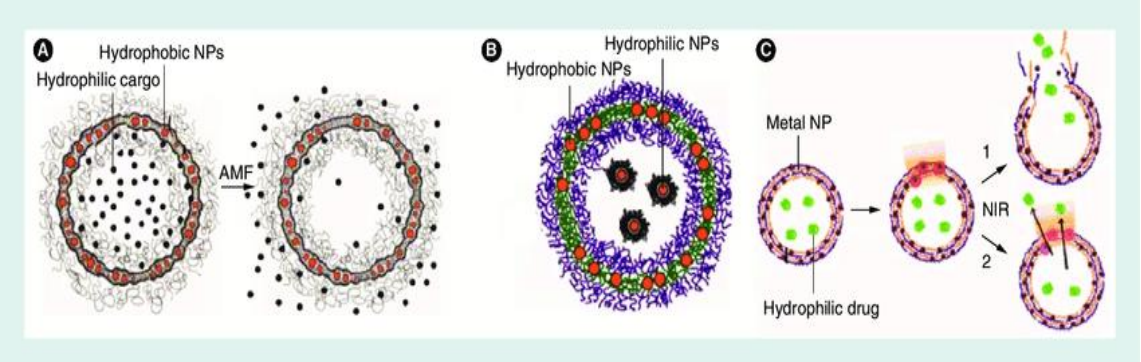

Fig.1 Structure of Vesicular System

Advantages of Vesicular Drug Delivery System: [6,7]

- Lifetime of drug in body can be prolonged.
- Bioavailability of drug is high.
- Targeted drug delivery can be achieved.
- Both type of drugs are incorporated (hydrophilic and lipophilic drugs)
- Delayed elimination period of the drugs which are rapidly metabolized.
- Sustained release of drug can be achieved.
- Overcomes the problems of drug insolubility, instability, and rapid degradations.
- Better therapy and improved comfort and standard of living
- The adverse effects and also toxic effects are minimized

Types of Vesicular System:

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 phosphatidyl 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
Enzymosome	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 possess 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 compartments 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.

LIPOSOME:

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 [8] Liposomes were first described by

British hematologist Dr Alec D Bangham in 1961.[9] 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.[10] Since lipid bilayered membrane encloses an aqueous core, both water and lipid soluble drugs can be successfully entrapped into the liposome's. [11] There are a number of components present in liposomes, with phospholipids and cholesterol being the main ingredient.[12] For drug delivery applications liposomes are usually unilamellar and range in diameter from about 50 – 150 nm. Larger liposomes are rapidly removed from the blood circulation. [13]

Classification of liposome: [14,15]

According to the size and number of bilayer membranes (lamellarity) forming vesicles, liposomes can be divided into the following categories:

- Small unilamellar vesicles (SUV): 20-100 nm.
- Large unilamellar vesicles (LUV): >100 nm.
- Giant unilamellar vesicles (GULV): >1000 nm.
- Oligolamellar vesicles (OLV): 100-1000 nm.
- Multilamellar large vesicles (MLV): >500 nm.
- Multivesicular vesicles: >1000 nm.

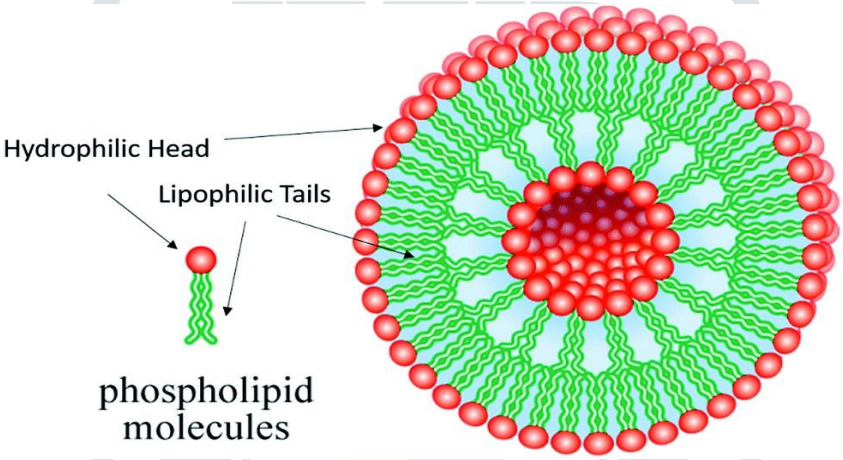

Fig. 2 Structure of Liposome

Advantages of liposomes [16,17]

- Liposomes offer several advantages in delivering genes to cells.
- Liposomes can complex both with negatively and positively charged molecules.
- Liposomes offer a degree of protection to the DNA from degradative processes.
- Liposomes can carry large pieces of DNA, possibly as big as a chromosome.
- Liposomes can be targeted to specific cells or tissues

Disadvantages of liposomes [18]

- Production cost is high.
- Leakage and fusion of encapsulated drug / molecules.
- Sometimes phospholipids undergo oxidation and hydrolysis-like reactions.
- Short half-life.
- Low solubility.
- Fewer stables.

Properties of liposomes [19]

- The system is composed of structures of bimolecular sheets intercalated by aqueous space.
- They are permeable to water.
- They are osmotically sensitive.

- Positively charged membranes are impermeable to cations and negatively charged ones are relatively permeable to anions.

NIOSOME :[20]

A niosome is a non-ionic surfactant-based vesicle. Niosomes are formed mostly by non-ionic surfactant and cholesterol incorporation as an excipient.

Compositions of Niosomes: (Gayatri et al., 2000) [21,22]

The two major components used for the preparation of niosomes are,

1. Cholesterol
2. Nonionic surfactants

- **Cholesterol**:

Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to the niosomes preparation.

- **Nonionic surfactants**

The following non-ionic surfactants are generally used for the preparation of the niosomes.

E.g. Spans (span 60, 40, 20, 85, 80.)

Tweens (tween 20, 40, 60, 80)

Brijs (brij 30, 35, 52, 58, 72, 76)

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.

Advantages of Niosome :[23]

- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non- aq media
- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- Niosomes possess an infrastructure consisting of hydrophilic, amphiphilic and
- lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities. The characteristics of the vesicle formulation are variable and controllable.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible and non-immunogenic hence can be used safely in preparation of Niosomes.

Disadvantages of Niosomes [24]

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limits the shelf life of the dispersion

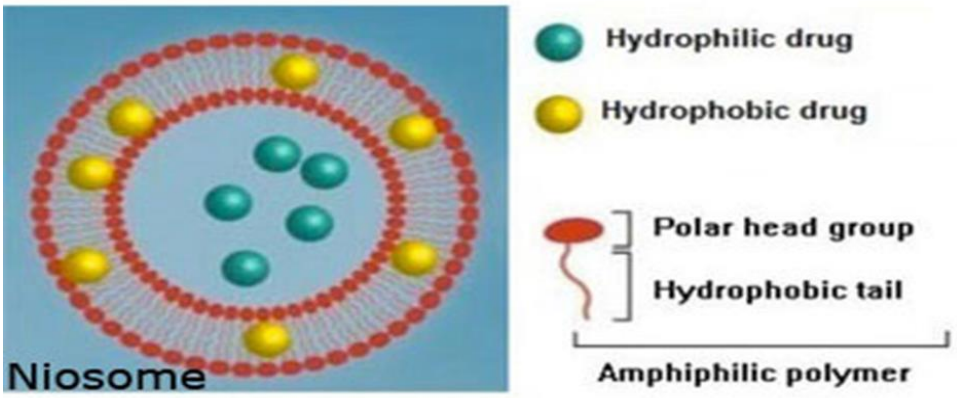

Fig.3 Structure of Niosome

Classification of Niosomes:[25]

The three factors of niosomes are classified as a function of the amount of bilayer or as a function of size or as a function of the tactic of preparation. The various types of niosomes are described below:

- Multi lamellar vesicles
- Large unilamellar vesicles
- Small unilamellar vesicles (SUV)

- **Multilamellar vesicles (MLV)**

It consists of a number of bilayers surrounding the aqueous lipid compartment separately. The approximate size of those vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the foremost widely used niosomes. This type of vesicles are highly suitable as drug carriers for lipophilic compounds.

- **Large unilamellar vesicles (LUV)**

Niosomes of this sort have a high aqueous/lipid compartment ratio, in order that larger volumes of bio-active materials are often entrapped with an economical use of membrane lipids.

- **Small unilamellar vesicles (SUV)**

The approximate size of this vesicle is 10-100 nm and this types of vesicles is prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization in that the inclusion of diacetyl phosphate in 5-carboxyfluorescein loaded Span based niosomes.

Method of preparation: [26,27]

Hand shaking method (Thin film hydration technique)

The hand shaking method is performed by the combination of vesicles forming ingredients like surfactant and cholesterol are dissolved during a volatile organic solvent in a round bottom flask. The ejection of organic solvent at normal temperature using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The drained surfactant film an often rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Ether injection method

This method provides a way of creating niosomes by slowly introducing an answer of surfactant dissolved in ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into a solution of fabric. Vaporization of ether results in formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000nm

Extrusion method

In this method, niosomes were prepared using C16G2, a chemically depend non-ionic surfactant by extrusion through a polycarbonate membrane. these studies not only demonstrate the effect of number of extrusions on vesicles size but also the effect of size on encapsulation of drug.

Reverse phase evaporation technique

In this method, surfactant is dissolved in chloroform and added into the 0.25 ml volume phosphate saline buffer solution is emulsified to get w/o emulsion. The mixture is then solicited and subsequently chloroform is evaporated under reduce pressure. The lipid or surfactant forms a gel first and subsequently hydrates to form vesicles.

Bubble method

It is modern technique for the one step preparation of niosomes without the use of organic solvents. It consists of round-bottomed flask with three necks placed in water bath to control the temperature. The water-cooling refluence and thermometer is capacity into the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are the dispersed together in this buffer (pH7.4) at 70c.

Sonication

The first time niosomes prepared by Baillie et al. 1986 with the help of sonication method. In this method, surfactant: cholesterol (150 micro.mol.) mixture was dispersed in 2ml aqueous introduce vial. Spread is subjected to probe sonication for the three minutes at six hundred centigrade. These systems confluent the formation of MLVs which are subjected to ultrasonic vibration. Sonicator is two type Probe and Bath sonicator. Probe sonicator is use when sample volume is small size and Bath sonicator is use when sample volume is large.

PHARMACOSOME:

Pharmacosome may be defined as a neutral molecule possessing both positive and negative charge, water-loving and fat-loving properties, and an optimum ratio of polyphenol with phospholipids in a complex form. The drugs are present in a dispersion form in these lipoidal drug delivery system conjugated by electron pair sharings and electrostatic forces or by forming a hydrogen bond with lipids [28]. Pharmacosome is derived from the word “Pharmakon” which means drug and “soma” meaning carrier. It means a vesicular system in which the drug is associated with the carrier

Advantages of Pharmacosome:

- Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drug. [29]
- In the vesicular & miceller state the phase transition temperature of pharmacosomes have significant effect on their interactions with members. [29]
- High and predetermined drug loading. [30]
- Deliver drug directly to the site of infection. [31]
- Reduction in adverse effects and toxicity. [32]
- Pharmacosomes can intact with biomembranes enabling a better transfer of active ingredient. [33]
- Amphiphilicity leads to improved bioavailability of poorly lipid and water soluble drugs. [34]
- Stable and efficiency due to covalent linkage. [35]
- Size, functional groups (drug molecule), chain length (lipids) and spacer decides the degradation velocity into active drug molecule. [36]
- Physiochemical properties of pharmacosomes depend on drug – lipid complex. [37]

- It can be given orally, topically, extra or intravascularly.[38]

Disadvantages of pharmacosomes:[39,40]

- Required surface and bulk interaction of lipids with drugs.
- Required covalent bonding to protect the leakage of drugs.
- On storage, undergo fusion and aggregation, as well as chemical hydrolysis

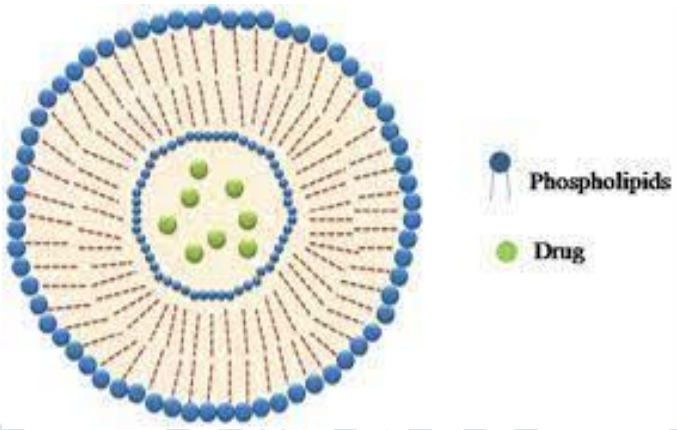

Fig.4 Structure Of Pharmacosome

TRANSFEROSOME:

Transferosomes are supramolecular entities composed of at least one type of amphipathic agent and, by the addition of at least one type of bilayer-softening agent (edge activator), result in greatly increased lipid bilayer flexibility and permeability [41]

Transfersomes are generally composed of

- firstly, the main ingredient, an amphipathic ingredient (e.g., soy phosphatidylcholine, egg phosphatidylcholine, etc.) that can be a mixture of lipids, which are the vesicle-forming components that create the lipid bilayer [42,43].
- secondly, 10–25% surfactants/edge activators; the most commonly used edge activators in transfersome preparations are surfactants as sodium cholates; sodium deoxycholate; Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65 and Span 80) and dipotassium glycyrrhizinate, which are biocompatible bilayer-softening compounds that increase the vesicles' bilayer flexibility and improve the permeability [44,45,46,47,48].
- about 3–10% alcohol (ethanol or methanol), as the solvent and, finally, hydrating medium consist with either water or a saline phosphate buffer (pH 6.5–7) [49,50].

Advantages of Transferosomes [51]

- Wide range of solubilities,
- Better penetration,
- Biocompatible and biodegradable

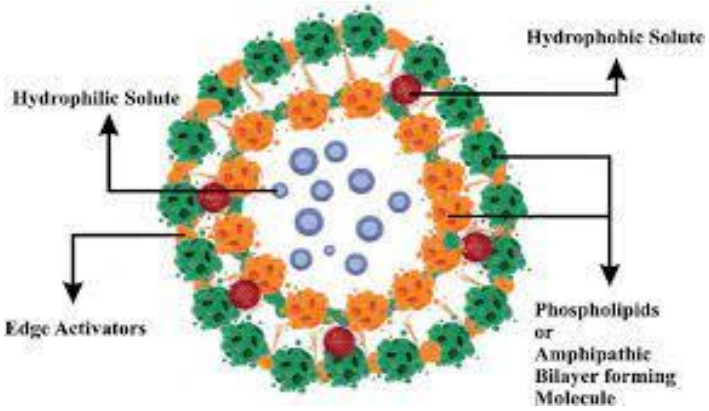

Fig.5 Strusture of Transferosomes

Result and Discussion:

The results of vesicular drug delivery systems are quite promising. In general, vesicular drug delivery systems have been found to be more effective than traditional drug delivery systems in terms of bioavailability and therapeutic efficacy. They are also capable of increasing drug solubility, improving drug absorption, and increasing the circulation time of the drug in the body. Additionally, they can also be used to target specific tissues or cells, and can be used to deliver multiple drugs simultaneously.

In terms of safety, vesicular drug delivery systems have been found to be safe and well-tolerated in preclinical studies. However, further research is needed to assess the long-term safety and efficacy of vesicular drug delivery systems in clinical trials.

Overall, vesicular drug delivery systems offer significant potential for the advancement of drug delivery technologies. They provide a more efficient and targeted way to deliver drugs, and could potentially revolutionize drug delivery in the near future.

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