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Advancements in Smart Vesicular Carriers: A Shift from Lipoidal to Non-Lipoidal Drug Delivery Systems

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Abstract

Vesicular drug delivery systems have revolutionized pharmaceutical technology by enhancing therapeutic efficacy, improving drug stability, and enabling targeted and controlled release. Among them, lipoidal and non-lipoidal vesicles represent two distinct yet complementary approaches in nanocarrier design. Lipoidal vesicles, such as liposomes, ethosomes, and transfersomes, are primarily composed of phospholipids and mimic biological membranes, offering excellent biocompatibility and encapsulation of lipophilic drugs. In contrast, non-lipoidal vesicular systems, including polymersomes, dendrimers, and other polymer-based carriers, utilize synthetic or natural polymers to achieve greater structural stability, tunable release profiles, and enhanced physicochemical versatility.

Key Words:

Vesicular drug delivery systems, Lipoidal vesicles, non-lipoidal vesicular systems, Ethosomes, Liposomes, Niosomes

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1.1 INTRODUCTION

A vesicular drug delivery system is a revolutionary drug delivery method that straddles the ideal and practical boundaries by encasing active molecules in a vesicular framework [1]. Novel vesicular drug delivery systems aim to release the medication at a rate that suits the body's requirements while delivering the active component to the site of action during the duration of treatment [2]. vesicular drug delivery, which paved the way for the creation of drug targeting strategies and the gradual or regulated release of traditional medications. Because of its

structure, the vesicular system's stability is still important [3]. When certain amphiphilic building blocks come into contact with water, they create highly organized assemblies of one or more concentric lipid bilayers. Vesicular systems are the name given to these assemblies [4]. Vesicular drug delivery, which led to the development of drug targeting techniques and the controlled or progressive release of conventional pharmaceuticals. Because of vesicle synthesis, the stability of the vesicular system remains an area of concern [5]. Bingham (1965) first described the physiological origin of these vesicles and named them "Bingham bodies [6]. Most research has been done on liposomes as a vesicular drug delivery method. Due to the agent's poor ability to lower viral burden, rapid emergence of resistance, and detrimental the negative effects have limited their long-term efficacy [7]. Vesicular drug delivery systems are a contemporary approach to drug delivery that target and regulate the release of medication by encasing active chemicals in a vesicular framework [8]. Vesicles dispersed in aqueous systems may face several challenges, including sedimentation, liposome fusion or aggregation, hydrolysis or oxidation-induced disintegration, and others during storage [9]. Novel vesicular drug delivery systems seek to transport the active ingredient to the site of action while distributing the medication at a rate determined by the body's needs during the therapeutic phase [10]. The composition and manufacturing process of vesicles affect their physicochemical properties (size, charge, lamellarity, thermodynamic state, and deformability), which in turn affects how efficient they are as drug delivery systems [11]. One such method involves encasing the drug in vesicular structures, which, if successful in promoting selective absorption, ought to decrease the toxicity of the drug and prolong its half-life in systemic circulation [12]. Extracellular vesicles pose a problem when loading foreign cargo, such as medications, because of their endogenous origin [13].

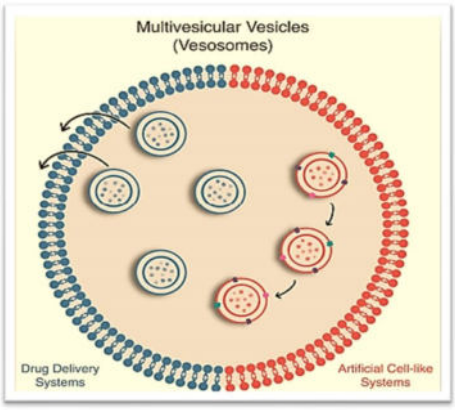


Fig. 1: The Structure of vesicular drug Delivery

1.2 ADVANTAGES [14], [15], [16]

- There are several benefits when vesicular drug delivery methods are contrasted with traditional dose forms and prolonged-release dosage forms.
- Increased bioavailability.
- Vesicular administration is a helpful method for reducing drug toxicity and getting medication to the intended place of action.

- The problems with the drug's degradation, solubility, and stability have been resolved
- The carriers of the vesicular drug delivery system are biocompatible and biodegradable as they are similar to biomolecular functions and structure.

The overall advantages of Lipoidal and Non-Lipoidal Vesicular Drug delivery systems are depicted in Table 1.

Table 1: Advantages of Lipoidal and Non-Lipoidal Vesicular Drug Delivery System

Feature	Lipoidal Systems	Non-Lipoidal Systems
Biocompatibility	High (due to natural lipids)	Variable (depends on polymer type)
Encapsulation Efficiency	High for lipophilic drugs	High for both hydrophilic & hydrophobic drugs
Drug Release Control	Moderate	More tunable with smart polymers
Ease of Surface Modification	Easy with PEGylation or ligands	Easy with functional groups
Toxicity	Generally low	May vary; some polymers cause toxicity

1.3 DISADVANTAGES [17], [18]

- This can result in medication loss and inadequate loading when prepared, given, and stored in living things.
- The requirement for intense sonication causes drug leaks while being stored.
- Medication/molecule encapsulation fusion and leaking

The overall advantages of Lipoidal and Non-Lipoidal Vesicular Drug delivery systems are depicted in Table 2.

Table 2: Disadvantages of Lipoidal and Non-Lipoidal Vesicular Drug Delivery System

Limitation	Lipoidal Systems	Non-Lipoidal Systems
Stability	Prone to oxidation, leakage	More stable
Scale-up	Challenging	Better scalability with polymers
Cost	Expensive lipids	May involve costly polymers
Storage	Requires cold conditions	Often better shelf life

2. CLASSIFICATION [2,4]

1) Lipoidal Vesicular Systems:

These are composed primarily of natural or synthetic lipids, particularly phospholipids, forming bilayered vesicles.

Examples:

- Liposomes
- Ethosomes
- Transfersomes
- Niosomes (though technically non-ionic surfactant-based, they are often grouped here due to bilayer structure)

2) Non-Lipoidal Vesicular Systems:
These are vesicles made using non-lipidic materials like synthetic polymers, biodegradable copolymers, or inorganic matrices.

Examples:

- Polymersomes
- Dendrimers
- Inorganic nanovesicles (e.g., silica vesicles, metal-organic frameworks)
- Exosomes (though naturally derived, they represent a biologically non-lipid dominant vesicle)

3. MECHANISM OF ACTION [5,6]

i. Drug Encapsulation:

- Drugs can be loaded in:
  - **Hydrophilic core** (for water-soluble drugs)
  - **Lipid bilayer or polymer matrix** (for lipophilic drugs)

ii. Drug Release & Targeting:

- **Passive targeting** via Enhanced Permeability and Retention (EPR) effect in tumors.
- **Active targeting** by surface modification with ligands, antibodies, or peptides.
- **Stimuli-responsive release** (pH, temperature, enzymes, etc.) in advanced systems.

4. TYPES OF VESICULAR DRUG DELIVERY SYSTEM

1) Lipoidal biocarriers
2) Non-lipoidal biocarriers

1) LIPOIDAL BIOCARRIERS

Lipid-based formulations can be used to affect how well active ingredients are absorbed through a variety of mechanisms [2]. These include altering how active ingredients release, increasing their bioavailability, altering the intestinal environment's composition and therefore its character, promoting the lymphatic transport of active ingredients, interacting with enterocyte-based transport processes, and minimising undesirable drug side effect [3]. Numerous Potential exist for combining medications with phospholipids to produce DDS [5]. Lipid-based innovations have advanced to unprecedented levels in recent years as a vital component of drug research [7]. A new technology platform called the microparticulate lipoidal

vesicular system can be utilised to deliver a variety of substances orally and systemically, such as genes, medicines, and vaccination antigens [8]. In order to create separated bilayer sheets, vesicles are usually formed from lamellar liquid crystalline dispersions of lipids, such as cholesterol, phosphatidylglycerols, and phosphatidylcholines, using a variety of mechanical and/or chemical techniques that work to disrupt the normal smectic stacking of the bilayers [9].

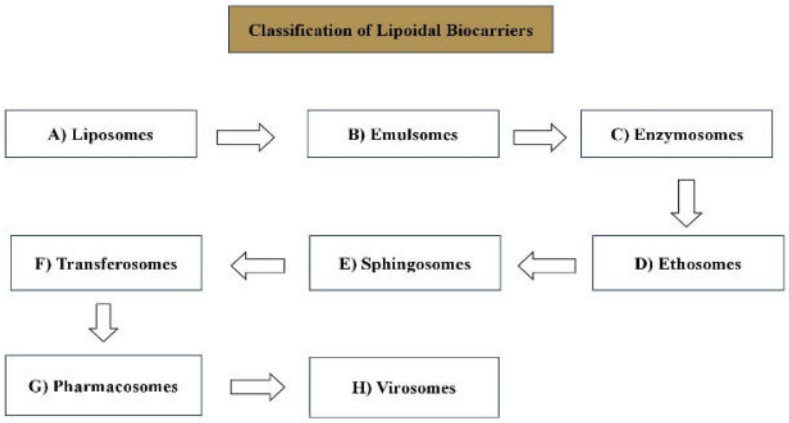


Fig. 2 Schematic representation that summarizes the lipoidal biocarriers

A) LIPOSOMES:

Liposomes are spherical, enclosed, bilayer-separated phospholipid compartments that separate an aqueous medium from another [19]. Liposomes are an essential feature from a therapeutic standpoint. Liposomes have the ability to alter the drug's tissue distribution and rate of excretion by causing it to take on the pharmacokinetic characteristics of the carrier [20]. Liposome uptake is fueled by the moisture gradient that exists between the stratum corneum, the epidermis, and the ambient environment [21]. Furthermore, multifunctional liposomes exhibiting a combination of these properties have been reported. Although liposomes were first reported on around half a century ago [22]. The soft spherical lipid bilayer vesicles, which are made of phospholipids and cholesterol, have these hydrophobic and hydrophilic zones. The primary forces responsible for their generation are hydrophobic interactions and other intermolecular forces [23]. Liposomes are practically ideal as a drug-carrier technology because of their biological membrane-like form and ability to carry a broad variety of chemicals [24]. A well-researched drug delivery technique, liposomes are present in many goods, including generic extensions. The characteristics of the liposome product are explained in order to facilitate a potential application of these findings [25]. Liposomes are an effective drug delivery system for a variety of applications. A few necessary elements must exist for liposomal activity to peak both *in vivo* and *in vitro* [26].

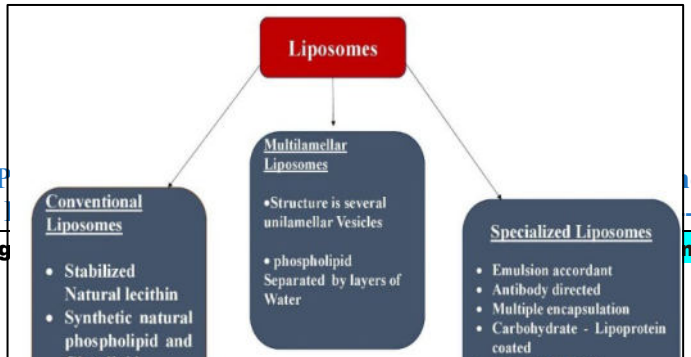


Fig. 3: The Classification of Liposomes

Advantage of Liposomes [28],[29],[30]

1) Ideal for administering medications that are hydrophilic, amphipathic, and hydrophobic.
2) outstanding biocompatibility and physical characteristics.
3) Liposomes improve the therapeutic index and biopharmaceutical properties of drugs and have a low toxicity profile.
4) Increasing efficacy and reducing side effects.
5) biocompatible, biodegradable, nontoxic and non-immunogenic nature.
6) Improve protein stabilization.

Disadvantage of Liposomes [27],[31],[32]

Production cost is high.
2) Leakage and fusion of encapsulated drug /molecules.
3) Sometimes phospholipids undergo oxidation and hydrolysis like reaction.
4) Short half-life, Low solubility and Less stability

Application of Liposomes

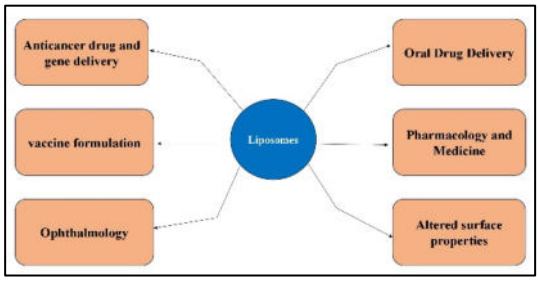


Fig. 4: The Application of Liposomes

B) EMULSOMES

Emulsomes are a unique kind of lipoidal vesicular system that have an internal core of solid fat and an outer layer of phospholipid bilayer; they are a cross between liposomes and emulsions [33]. Emulsomes are a lipid-based drug delivery technology that was developed specifically for parenteral administration of medications with low water solubility [34]. This feature allows for the encapsulation of larger concentrations of lipophilic substances and sets emulsomes apart from emulsions [35]. The outer layer of the particle is covered in several

phospholipid layers, stabilising the formulation and offering a passably smooth surface that is susceptible to further chemical changes [36]. Emulsome is regarded as a dependable drug delivery technique due to its efficient drug entrapment, biodegradability, biocompatibility, and controlled drug release [37]. Using emulsomes, drugs can be applied topically, intranasally, rectal, oral, parenterally, or ocularly [38]. Emulsomes, as opposed to liposomes, provide sustained release of the drug that is encapsulated; this release can last up to 24 hours [39]. The emulsome-based strategy for intracellular hepatic targeting, and it might be crucial for the effective treatment of severe viral infections such Epstein-Barr virus, HIV, and hepatitis [40].

Mechanism of Action

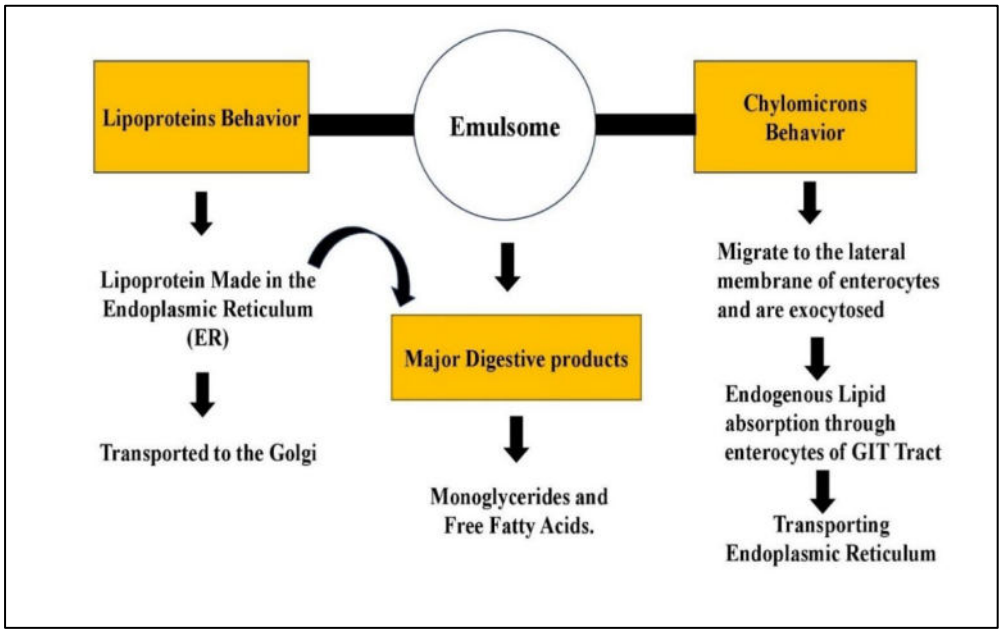


Fig. 5: The Mechanism of Emulsome

Advantages [33], [40], [41]

- Lower toxicity while maintaining greater pharmacological efficacy and higher drug concentrations in injured regions compared to conventional lipoidal formulations.
- Increase the solubility and bioavailability of drugs with limited water solubility.
- Low solubility in water indicates a drug's high load capacity.
- Modify the pharmacokinetics of the medicine.
- Emulsomes are a more affordable option for drug delivery than the lipid formulations seen in current commercial goods because they reduce the frequency of drug administration.

Disadvantage [33], [41],[42]

- The ability to load drugs is restricted.
- When administered parenterally, it has negative side effects.
- The high oil content of the mix compromises its stability

- The detergent characteristics of surfactants make them infrequently utilised in parenteral administration.

Application of Emulsome

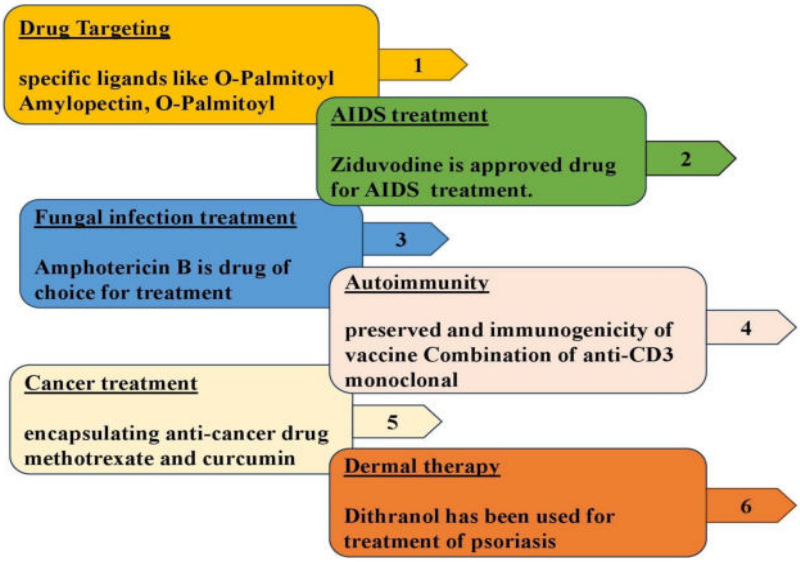


Fig. 6: The Application of Emulsome

C) ENZYMOSOMES

Currently under development is a revolutionary targeted vesicular drug delivery method called enzymosomes. The fundamental components of enzymosomes are enzymes with a particular catalytic role for a substrate that are incorporated into cell-like structures with a rich lipid backdrop [43]. These liposomal structures are intended to form a microbiome in which enzymes are covalently immobilised or attached to the surface [44]. Some definitions of enzymo include cell-like. Enzymes exhibit considerable potential as therapeutic agents due to their unique substrate selectivity and unparalleled reaction efficiency. The natural deficiencies of enzymes, including their short half-lives in circulation and extremely low levels of activity when exposed to physiological conditions [45]. Enzymosomes are liposomes designed to establish a microbiome in order to transport particular enzymes to cancerous cells. The enzymes are attached to the liposome surface or immobilised by covalent bonding [46]. Prior to liposome breakdown, enzymosomes can have a therapeutic impact because they are nanocarriers that combine the advantages of serving as an extended release of the enzyme and expressing enzyme activity in intact form [47]. The enzymes alkaline phosphatase, carboxy pepsidase, β-lactanase, and β-glucosidase are present in liposomal vesicles [48]. There are several methods for delivering therapeutic proteins, like enzymes, such as bilayered vesicles, lipid aqueous spaces, and polymeric carriers [49]. Enzymosomes are liposomal systems that form a tiny bio-environment for the enzymes by covalently attaching to the liposome surface [50]. Enzyme activity and the maintenance of vesicles' structural integrity are two advantageous properties of enzymosomes [51].

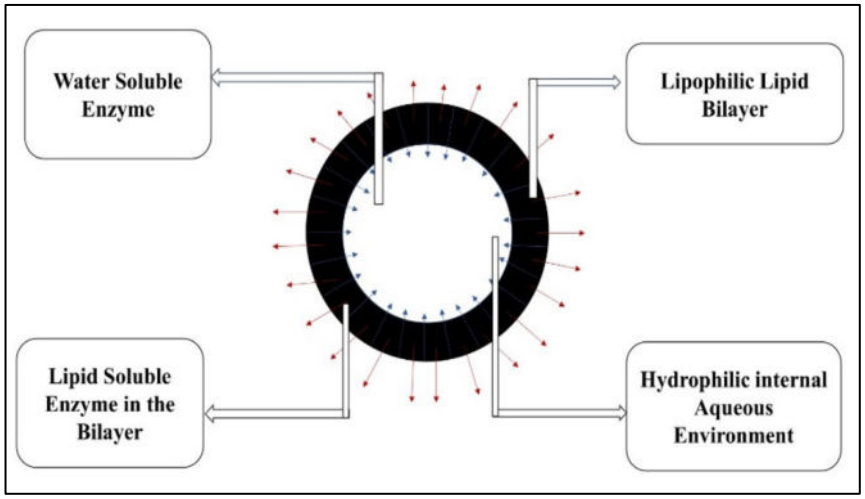


Fig. 7: Structure of Enzymosomes

Advantage [52], [53]

- Improves stability and encapsulation.
- Biodegradability of the substance
- Guards against harmful pharmaceutical exposure for sensitive issues.
- Improvements in pharmacokinetics (lengthen half-life, decrease elimination).
- It works in conjunction with site-specific ligands to provide effective medication targeting; both effectiveness and therapeutic index have been demonstrated.

Disadvantage [53], [54]

- Liposomes are often expensive to make since they fall under the category of nanotherapeutics.
- Lipid vesicular structures are composed of phospholipids, which are susceptible to hydrolysis and oxidation.
- Its short half-life and poor solubility reduce bioavailability.
- The drug molecule or molecules that have a fusion and leak cap.

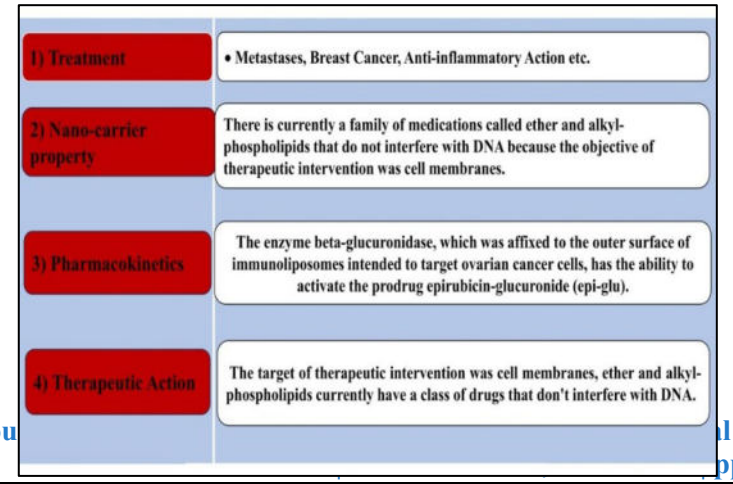


Fig. 8: Application of Enzymosomes

D) ETHOSOMES

Lipoidal vesicles with a high ethanol content are called etherosomes. Ethanolic liposomes are another term for Ethosomes [55]. Ethosomes are a novel kind of drug delivery that mostly permeates the biological membrane of the skin with a low penetration rate [56]. Lipid vesicles known as Ethosomes contain phospholipids, water, and comparatively large amounts of alcohol (ethanol and isopropyl alcohol). Larger concentrations of ethanol, water, and phospholipids make up the soft vesicles called Ethosomes [57]. The transdermal delivery of drugs is the main use of Ethosomes. Transdermal distribution is a crucial approach to drug administration [58]. The main obstacle restricting the utilisation of transdermal methods for drug delivery is the skin's ability to absorb medicines. Medication can preferentially pass through human skin [59]. Ethosome formulations, in which Ethosomes act as a reservoir mechanism for drug administration, allow drugs to be continually administered [60]. The imaging of Ethosomes using transmission electron microscopy showed that they could include one or more lamellae up to the core [61]. The size of Etherosome vesicles varies from tens of nano-meters to a few microns, depending on their composition, how they are applied, and how they are made, such as via sonication [62]. The Ethosomes are distinguished by their high concentration of ethanol, which is known to disturb the structure of the skin's lipid bilayer. This enables the vesicles to cross the stratum corneum by integrating the ethanol into their membranes [63]. Phagosomes transport a wide range of pharmaceutical compounds, such as insulin, bacitracin, testosterone, and acyclovir. Because of this, Ethosomal drug delivery systems are currently the focus of extensive research and development for novel therapies and could one day prove to be a useful drug delivery method [64]. Numerous molecules, including hydrophilic, lipophilic, and high molecular weight substances, can be entrapped by phagosomes. Both occlusive and nonocclusive skin disorders can be treated with Ethosomes to transfer the medication [65]. Ethosomes are pliable and flexible, with a size range of a few microns to thirty nm. It is possible to use Ethosomes to deliver medications via the skin in both occlusive and non-occlusive scenarios [66]. It is well recognised that Ethosomes are crucial in regulating a drug's release rate over a prolonged period of time and protecting it from the immune system or other clearance mechanisms [67]. In addition, these systems offer better patient compliance, fewer dose intervals, and regulated medication distribution [68].

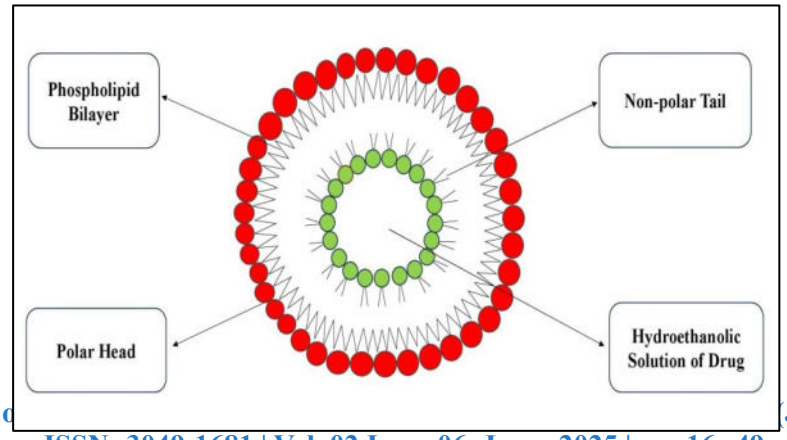


Fig. 9: The Structure of Ethosomes Vesicle

Table 3: Types of Ethosomes

S.NO.	Types	Introduction
1.	Classical Ethosomes	• Phospholipids, water, and a high ethanol content of up to 45% w/w make up classical ethosomes. They are a different kind of liposome. • In comparison to traditional liposomes, classical ethosomes demonstrated superior skin penetration and stability profiles
2.	Binary Ethosomes	• Binary ethosomes were produced by mixing one type of alcohol with the regular ethosomes. • In binary ethosomes (IPA), the most commonly used alcohols are propylene glycol (PG) and isopropyl alcohol
3.	Transethosomes	• This ethosomal system contains all the basic components of conventional ethosomes plus an additional component, such as a penetration enhancer or edge activator (surfactant). • These special vesicles aimed to develop transethosomes by combining the advantages of conventional ethosomes and deformable liposomes (transferosomes) in one formulation.

Advantages [57], [58], [59], [60]

1) Improved medication permeability through skin for transdermal administration.
2) It is feasible to deliver big molecules like proteins and peppers.
3) The formula incorporates non-toxic raw materials.
4) High patient compliance: The ethosomal medication is administered as a gel or cream, which is a semisolid, resulting in high patient compliance.
5) The ethosomal drug delivery system has broad applications in the domains of pharmacy, veterinary medicine, and cosmetics.

Disadvantages [60], [61]

1) Sufficient solubility of the medication in both lipophilic and aqueous environments to penetrate the dermal microcirculation and enter the bloodstream.
2) dermatitis, or skin irritation, caused by excipients and enhancers used in pharmaceutical delivery systems.
3) Limited practical yield.

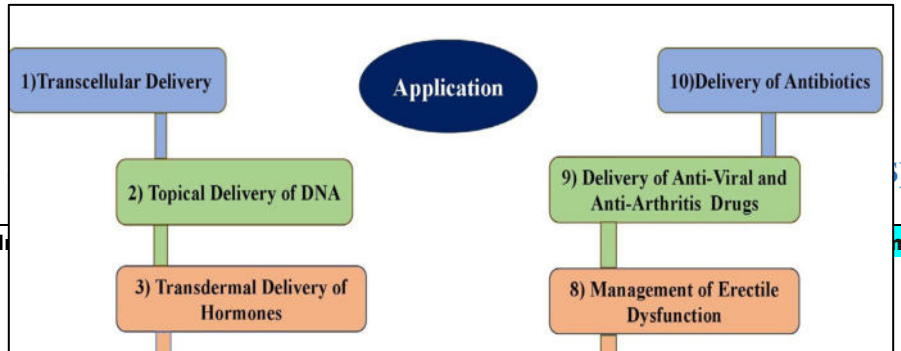


Fig. 10: The Application of Ethosomes

E) SPHINGOSOMES

One definition of sphingosomes is "concentric, bilayered vesicles in which an aqueous volume is contained." is entirely covered by a membranous lipid bilayer made primarily of synthetic or natural Sphingolipid [72]. They can be applied topically or orally. In an easy manner, we can Sphingosomes, as defined by are liposomes made of sphingolipid [73]. Phengosomes are vesicular carriers made of lipids that resemble liposomes physically and are distinguished by their Sphingolipids make up the majority of the makeup [74]. Sphingosomes are a fascinating choice for because to their innate biocompatibility and biodegradability, they are ideal for medication delivery and traditional methods for administering drugs [75]. Sphingosomes can be administered via a variety of parentral methods, such as intramuscular, intravenous, subcutaneous, and intra-arterial [76]. its inherent instability, short in vivo circulation lifetime, and insufficient tumour loading efficacy when combined with cancer therapy [77]. Chemotherapy drugs, diagnostic tools, and biological macromolecules are all delivered by sphingosomes [78]. These are bilayer vesicles with a circular, colloidal aquatic compartment fully contained in a bilayer membrane. They are mainly made of natural or synthetic sphingolipids [79]. Within the sphingoid base of sphingolipids is sphingosine, one of the aliphatic amino alcohols [80]. Sphingosomes have use in gene therapy, cancer treatment, and the delivery of enzymes [81]. Sphingosomes include a variety of active substances, such as vinblastine, doxorubicin, prostaglandins, methotrexate, amphoterecin B, cisplatin, progesterone, topotecan, ciprofloxacin, vinblastine, and campho-thecin [82].

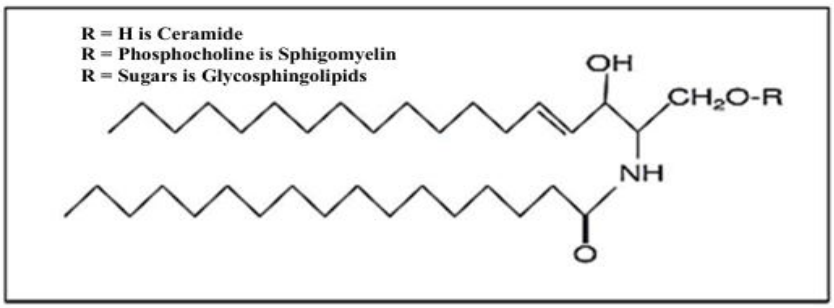


Fig. 11: The Structure of Sphingosomes Formula

Table 4: Various Classification of Sphignosomes [83], [84], [85]

S.NO	Classification	Introduction
1.	Small unilamellar vesicles (SUV)	It consists of single lipid bilayer and having diameter in dimension vary 10nm-100nm.
2.	Large unilamellar vesicles (LUV)	It consists of single lipid bilayer. Having increased diameter than SUV. Having measurement vary 100nm1µm.
3.	Multilamellar vesicles (MLV)	It consists of quite a few bilayers of lipid and having measurement vary 100nm-20µm.
4.	Oligolamellar vesicles (OLV)	Bilayer is extra than one but no longer as many as MLV's. Have measurement vary 0.1-1µ.
5.	Multivesicular vesicles (MVV)	Measurement vary 100nm-20µm.
6.	Giant Vesicles (GV)	Vesicles above 1 µm are recognized.

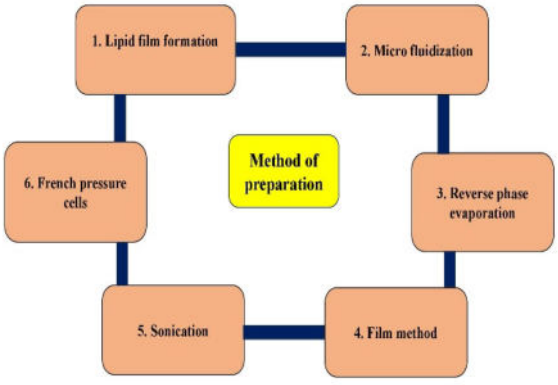


Fig. 12: Method of Preparation of Sphignosomes

Advantages [72], [74], [75]

1) Give specific passive therapy to the tumour.
2) Enhance therapeutic index and efficacy.
3) Specific site targeting and design flexibility.
4) Better medication retention.
5) Enhanced stability through encapsulation material
6) Enhance the pharmacokinetic effect (increase blood flow).
7) The ability to combine with ligands unique to a given spot and attain effective targeting.

Disadvantages [76], [81]

1) Highly Expensive
2) limited trapping efficiency
3) Higher sphingolipid costs make it more difficult to prepare and utilize vesicular system.

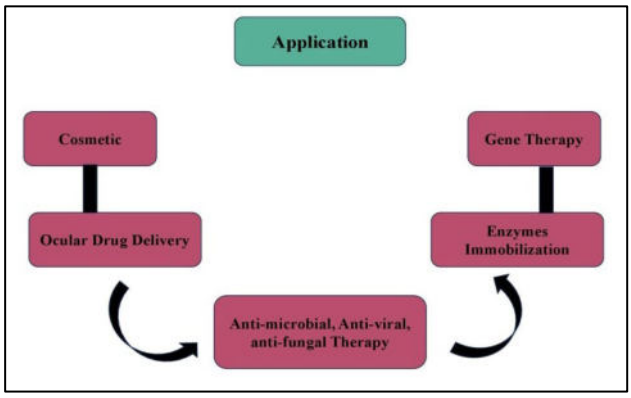


Fig. 13: The Application of Sphingosines

F) TRANSFEROSOMES

The word transferosomes is derived from the Greek word soma Which refer to a body, and the Latin word transferee which means to carry across one kind of liposomes is a transferosome [86]. These are colloidal vesicles with a water nucleus made up of surfactants and bi-layered structured lipids. Drug moieties that are hydrophilic, amphiphilic, or lipophilic can all be absorbed by transferosomes. These vesicles have the potential to form one or more condensed bilayers, which are perfect for controlling the distribution of specific drugs. Insulin and vaccines are examples of biogenic substances that can be distributed utilizing transferosomes without generating any breakdown. Transferosomes are a kind of elastic or flexible vesicle that was first characterized in the early 1990s. Transferosomes, or ultra-formable vesicles, can fit through pores several times smaller than their true size because of the skin's elasticity and flexibility. A special kind of

liposome called a transferosome is composed of phosphatidylcholine and an edge activator. They are an inventive and relatively new method of delivering medications. Phosphatidylcholine (C18) is the most common lipid in cell membranes, most transferosomes include this lipid, which is very skin-tolerable and lowers the risk of undesirable side effects. Transferosomes have been effectively used to encapsulate a wide range of drugs, including macromolecules like insulin, microscopic hydrophobic drugs, and phytocompounds. Clinical trials using a licensed topical ketoprofen transferosomal gel have demonstrated promising results in the treatment of symptoms associated with orthreothritis in nonsevere skin and subcutaneous tissue disorders [87-88].

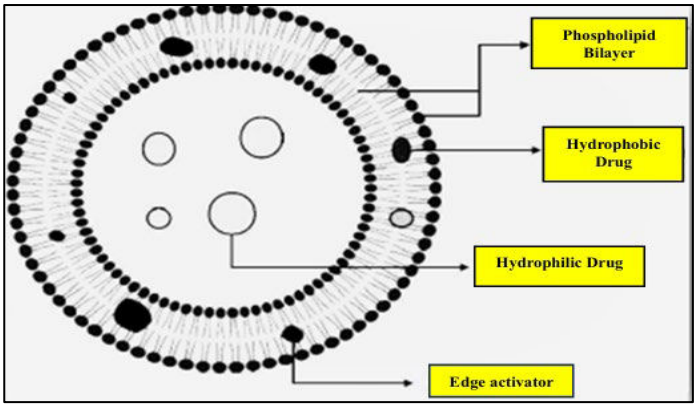


Fig. 14: The Structure of Transferosomes

Composition of Transferosome: [87-88]

Main components of transferosomes are:

- Amphipathic agents or phospholipids, such as phosphor-idyl choline, are the main components of transferosomes. These molecules self-assemble into a lipid bilayer in an aqueous medium before contracting to form a vesicle.
- Surfactants like Tween 80, Span 85, Span 80, sodium cholate, sodium deoxycholate, etc. are examples of bilayer softening agents that help to soften the lipid bilayer and give vesicles their unique flexible and pliable properties.
- The ratio of surfactant to edge activator utilized determines the permeability and flexibility of the membrane, making transferosome extremely flexible.
- Various Additives for Transferosome Emulation: Phospholipids, Alcohol, Dye, Edge activators, Surfactant, Buffering Agent.

Method of Preparation [88-89]

1) Thin film hydration technique:

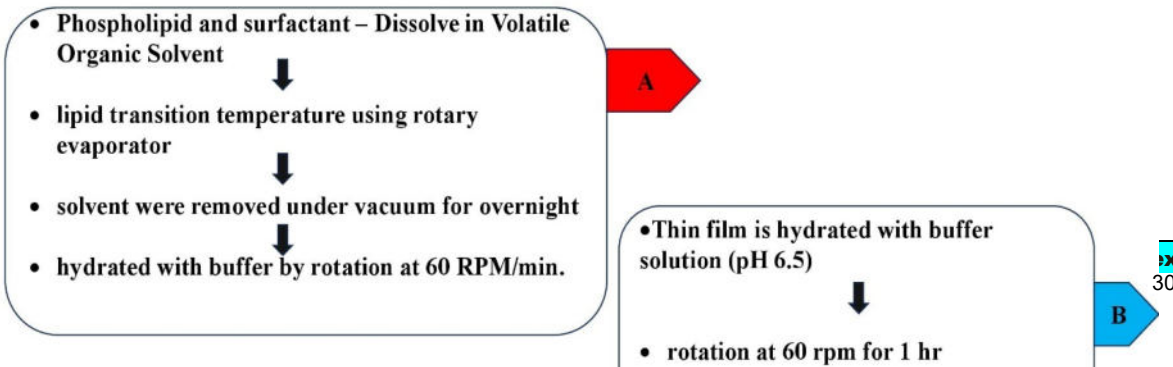


Fig. 15: The Method of Preparation Type – 1

2) Modified hand shaking (lipid film hydration technique):

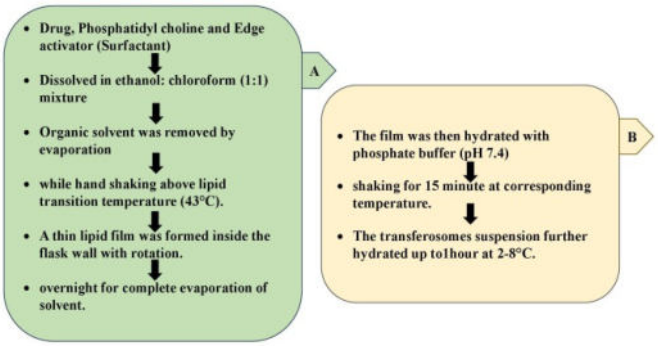


Fig. 16: The method of preparation Type-2

Advantages [89]

1) The characteristics of the very flexible and self-optimized membrane enable extremely effective medication distribution through or into the skin above me.

2) To have a comparable therapeutic impact, the daily dosage of the medication might be lowered.

3) The ability of transferosomes to follow the natural water gradient across the epidermis reduces the likelihood of vesicle rupture in the skin when they are used in non-occlusive settings.

4) The rate of drug release and the deposition to the target location can be regulated by changing the composition of the vesicles or the surface characteristics of the membrane.

5) A pharmacological dose that is less than necessary can still have an equivalent therapeutic effect.
6) Fits well with Skin penetration and allows entry through self- assembly in response to External mechanical Stress.
7) The rate of drug release and its deposit at the intended site can be modified through changes to the vesicular composition or surface characteristics of the transferosome membrane.
8) Give medications in a continuous or steady stream over an extended length of time, maintaining a sufficient concentration of powerful medicines in the plasma.
9) Because they offer a longer duration of action, this allows for a subsequent reduction in dosage frequency, which in turn increases patient compliance.
10) Transferosomes can lead to improved bioavailability and more convenience when administering medications.
11) Better therapy and fewer adverse effects due to plasma level maintenance till the conclusion of the dose interval.
12) Prevent intra- and inter-patient variations to increase therapeutic efficacy.

Disadvantages [89]

1) Unsuitable for high dosages of drugs.
2) There is a chance of skin pain and hypersensitivity reactions.
3) It is not feasible to provide medications that require elevated blood levels.
4) Extremely susceptible to transferosomes' unstable oxidative destruction.
5) One significant obstacle to the widespread adoption of these transferosomes is their high cost.
6) Many medications, especially those that are hydrophilic, permeate the skin too slowly to be thought of as therapeutically effective.
7) The function of the epidermal barrier varies with age, individual differences, and place; these factors impact the rate at which medicines are released.

Limitation [88-89]

1) Transferosomes are prone to oxidative destruction, which makes them chemically unstable.
2) The use of transferosomes as drug delivery vehicles is hampered by the natural phospholipids' lack of purity.
3) The formulations for transferosomes are costly.
4) Aqueous media that have been degassed and purged with inert gases like nitrogen and argon exhibit a considerable reduction in transferosome oxidation.

5) Hydrophobic medication loading is challenging.

Application [89]

1) The bioavailability of transferosomes is comparable to that of subcutaneous injection. It has been shown that transferosome-encapsulated human serum albumin can effectively elicit an immunological response when applied topically.

2) Transferosomes have the ability to stabilize labile pharmaceuticals and enable controlled release of administered medications since they contain phospholipids.
3) These methods are safe for treating cutaneous cancer by putting medications deep into the skin.
4) Medications with large molecular weights can cross mucosal membranes.
5) Ultra-deformable vesicles may be used to counteract medications such as NSAIDs that have been shown to have GI adverse effects.
6) Lipid vesicles are used to deliver drugs with physiological action and DNA.
7) The outcomes of transcutaneous hepatitis B immunizations were better. Proteins and peptides can be transferred very effectively using transferosomes.
8)Transferosomes make it simple for large molecules and heavy chemicals to move across the epidermis. For instance, the skin of mammals can transport interferons such as leukocyte derived interferon (INF) and insulin.

G) PHARMACOSOMES

Lipid-based drug delivery systems called Pharmacosomes have gained attention recently due to their ability to boost the bioavailability and efficacy of pharmaceuticals. Pharmacosomes are colloidal dispersions of drugs covalently linked to lipids; they can be ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical composition of the drug-lipid combination. The term "pharmacosome" was created by combining the terms "pharmakon" (drug) and "soma" (carrier). For this reason, they are called pharmacosomes. Pharmacosome—a unique type of vesicular drug delivery—lowers adverse effects by decreasing medication toxicity and raising the bioavailability of numerous treatments. It may be possible to increase permeability and solubility while lowering GI toxicity by creating phospholipid complexes called Pharmacosomes. The structural elements of Pharmacosomes' lipophilic capacities are responsible for their amphiphilic qualities which exhibit mesomorphic behaviour at larger contractions and lower interfacial tension. One of Pharmacosomes greatest qualities is its economical formulation creation process. Pharmacosomes are made using an intermediately polar solvent. Pharmacosomes have been developed for a range of cardiovascular drugs, proteins, nonsteroidal anti-inflammatory drugs, and anticancer drugs. This review covers the preparation method, applications, limitations, research update, and pharmacosome information. Pharmacosomes have the potential to penetrate the bio-membrane quickly and offer a number of advantages over other vesicle-based systems such as liposomes, niosomes, and transferosomes. When prodrugs, or pharmacosomes, come into contact with water, they create multilayers by assembling into pharmacosomes. There are several pharmacosomes available that contain protein, anti-tumor, non-steroidal anti-inflammatory, and vascular compositions. Pharmacosomes carry out a higher degree of medication transfer by moving with bio-membranes. Pharmacosomes are going to decrease difficulties connected to the defence of polar compounds such limited drug incorporation, solubility and withdrawal. Pharmacosomes are colloidal dispersions of drugs covalently bound to lipids, and may be found in micellar, hexagonal, or ultrafine vesicular aggregates, depending on the chemical drug-lipid complex structure [120]. Pharmacosomes were assessed according to several criteria. including dimensions, NMR, surface morphology, and rate of release *in vitro* [90].

Table 5. Materials of Pharmacosomes [90]

S.NO	Materials	Description
1.	Drug	• Any medication that has (-COOH-OH-NH2, etc.) is esterified to the lipid, either with or without a spacer chain, producing complexes that are both lipophilic and hydrophilic. • Since the molecule's production is influenced by elements that have a substantial impact on its hydrophilic and lipophilic qualities, it can aid in the transfer of membranes, particularly the plasma membrane, throughout the organism.
2.	Lipid	• Lecithin, or phenyl-choline, is the main molecular building block of cell membranes. • Phospholipid, a mixture of lipophilic and hydrophilic materials, is the drug that renders phospholipids hydrophilic and the drug soluble in lipids.
3.	Solvents	• The purity and volatile increasing nature of Pharmacosomes, solvents facilitate their production. Preferably, intermediately polar solvents are used to produce Pharmacosomes.

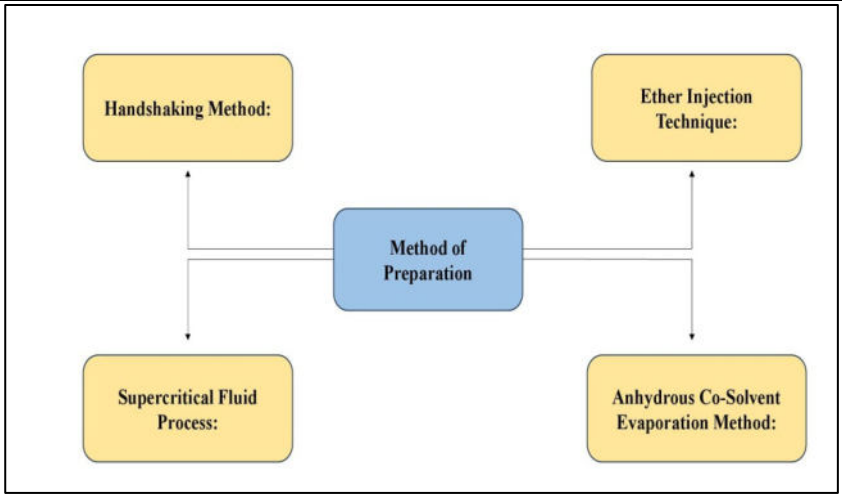


Fig. 17: Method of Preparation of Pharamacosomes

Advantages [90]

1) Hydrophilic and hydrophobic medications can both be found in pharmacosomes.
2) Entrapment efficiency is high.
3) Reduction of unfavourable effects.
4) There is no issue with medication incorporation

5) There's a decrease in side effects and toxicity as well as a decrease in therapy expenditures.
6) Pharmacosomes are an affordable way to deliver medication directly to the infection site.
7) Pharmacosomes release pharmaceuticals by chemical reactions most of the time.
8) Improvement in the bioavailability of water-soluble drugs
9) Pharmacosomes show better outcomes in several respects when contrasted with other classes of lipid-based delivery systems.
10) The medication forms vesicles when coupled with lipids, it is also predetermined. Furthermore, loss from drug leakage does not happen because the drug is covalently linked.

Disadvantages [90]

1) A molecule's propensity to be amphiphilic influences how it forms.
2) Medication and lipids must interact on both a bulk and surface level.
3) During storage, there is chemical hydrolysis, fusion, and agglomeration.
4) To stop drug leaks, covalent bonding is required.
5) Pharmacosomes are unable to encapsulate drugs that are insoluble in water; instead, they can only hold drugs in a small number of hydrobic zones inside the membrane bilayer.

Limitation [90]

1) A compound's amphiphilic character affects how it is synthesized.
2) It needs the interaction of medications with the bulk and surface of a lipid.
3) To stop medication leakage, covalent bonding is necessary.
4) When pharmacosomes are stored, they fuse, agglomerate, and go through chemical hydrolysis.
5) The drug's hydrophilic and lipophilic properties may affect this compound's production.
6) Both surface-level and bulk drug-lipid interaction are necessary.
7) The covalent bond type necessary to prevent medication leakage.
8) Their sensitivity, pharmacosomes fuse together, and drugs congregate or hydrolyze when stored.

Application [90]

1) Pharmacosomes have longer shelf lives and a wider stability profile.
2) Pharmacosomes increase the fluidity of the membrane, which increases the rate of penetration.
3) The temperature at which vesicles change into micelles may have a noticeable impact on vesicular
4) contact with the biomembrane, enhancing the drug's ability to cross the membrane.
5) Pharmacosomes are more selective regarding the cells they target during interactions with cells.
6) producing particles with the ability to transport physiologically active materials like nucleic acids.
7) enhanced transduction of the blood-brain barrier by the medication, both *in vivo* and *in vitro.*

H) VIROSOMES

A virosome is a revolutionary hybrid drug delivery system that combines the advantages of viral and non-viral vectors. virosomes may carry a range of physiologically active molecules such as nucleic acids, peptides, proteins, and small chemical compounds. Virosomes are spherical, unilamellar vesicles reconstituted of viral envelops phospholipids with removed nucleocapsid. Surface modifications in virosomes might be leveraged to allow for tailored drug administration using virosome-based devices. Virosomal technology provides a novel and demanding delivery technique. Molecules are inserted directly into cells to boost the efficacy of gene delivery. Virosomes are fusion genic viral cover proteins that incorporate antigen, medicine, and DNA, among other things. Improving virosome delivery ability in vivo is a major objective in virosome research. Virosomes are pure fusion activity vesicles that carry an incorporated substance, such as medicine, antigen, or genes, into the target cell. Virosomes protect pharmaceutically active substances from proteolytic degradation and low pH inside endosomes, allowing them to reach the cytoplasm intact. The virosome carrier system in excess of newly drug delivery vehicles like proteo liposomal and liposomal carrier systems. They are round, bilayer phospholipid vesicles with a scale of 120–200 nm in diameter. Virosomes bind through ligands to the selected cell, then taken up by endocytosis mediated by the receptor. This results in drug release into the cytosol of the cells. Virosomal delivery systems provide a strong safety design, have patent product protection, and have been licensed in humans [91].

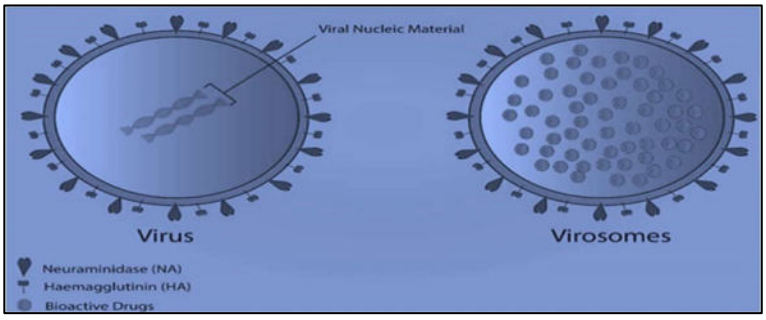


Fig. 18: The Structure of Virosomes

Advantages [91]

1) Virosomes decompose spontaneously.
2) Prevents corruption from training medication.
3) Non-lethal and biocompatible
4) Drugs are absorbed, distributed, and excreted by the body more quickly.
5) The selected cells cytoplasm contains no active material hazard enzyme.
6) Antibiotics, fungicides, proteins, enzymes, nucleic acids, and anticancer drugs are examples of common pharmaceuticals.

Disadvantages [91]

1) Problems with production.
2) The freight moves very slowly.
3) Issues with manufacturing.

4) Subpar foundational components
5) There is no proof the virosomes can be employed endlessly.

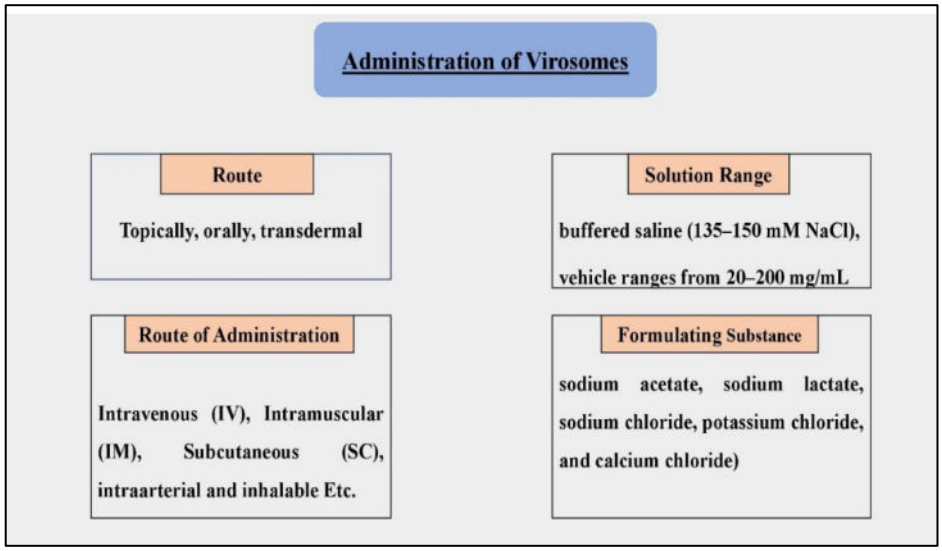
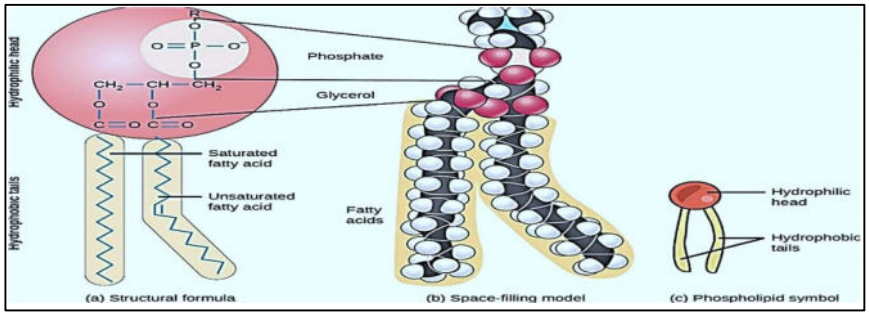


Fig. 19: Administration of Virosomes

Components and Formation of Virosomes

The main components of virosomes include phospholipids, cholesterol, and viral envelope proteins. Phospholipids and cholesterol contribute to the stability and integrity of the virosomal structure. Viral envelope proteins play a crucial role in facilitating membrane fusion with target cells [91].



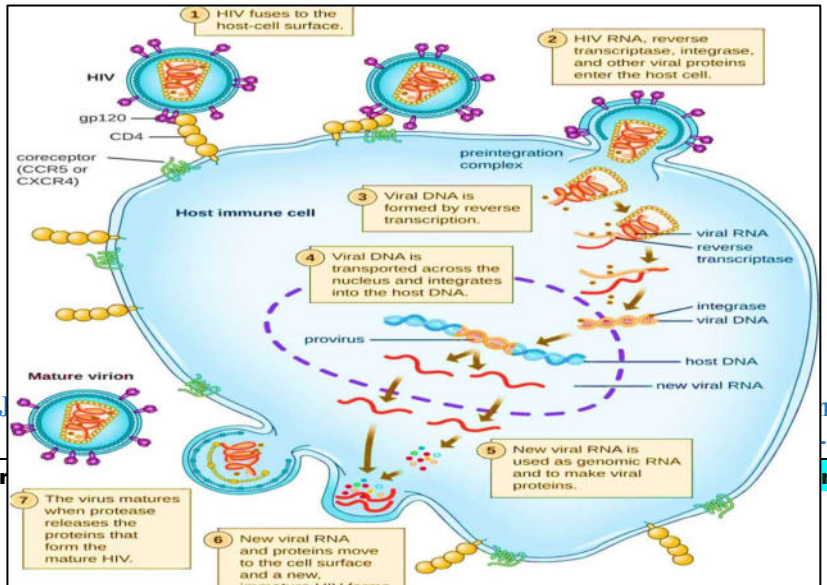


Fig. 21: The Formation of Virosomes

Mode of Action

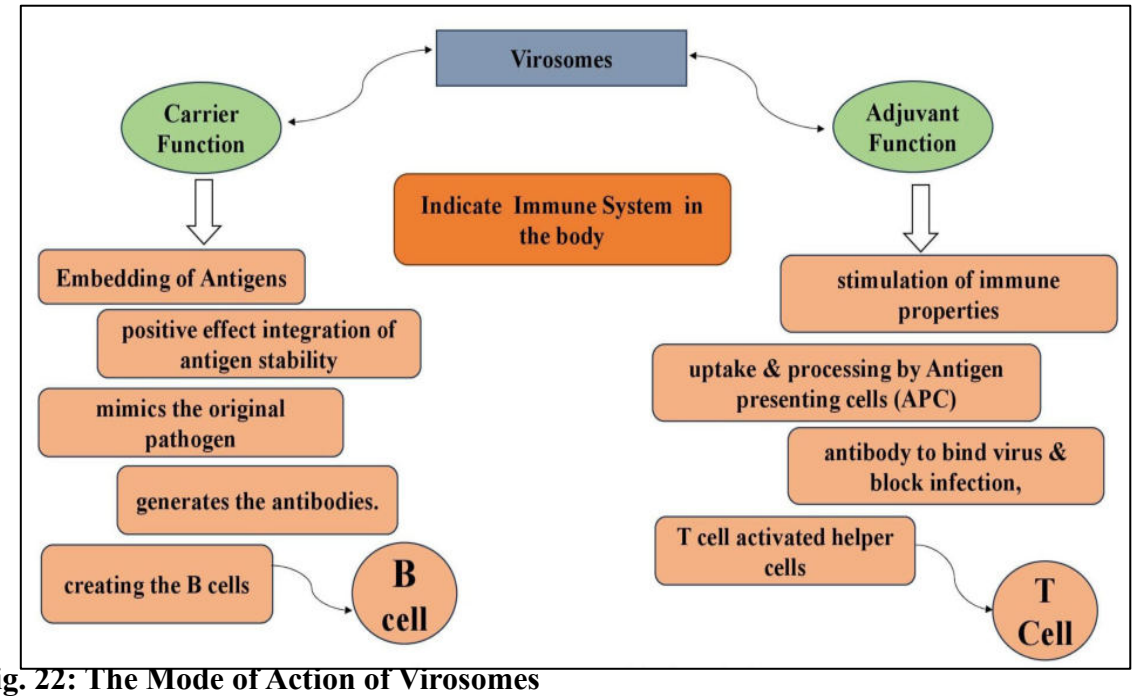


Fig. 22: The Mode of Action of Virosomes

Table 6. Evaluation of Virosomes

S.NO.	Areas	Evaluation Process
1.	Surface Shape and morphology	Techniques for electron microscopy: transmission and freeze break.
2.	Surface charge	Electrophoresis in free stream
3.	Lamellarity	13p-NMR, tiny edge x-beam dissipation, and freeze break electron microscopy.
4.	Phase conduct	Checking differential colorimetry and using freeze-crack electron microscopy.
5.	Drug discharge	Diffusion cells and dialysis.

6.	Pyrogenicity	The Limulus ambeocyte lysate (LAL) test or the rabbit fever reaction test
7.	Chemical examination	Auxiliary particle mass spectrometry of statics.

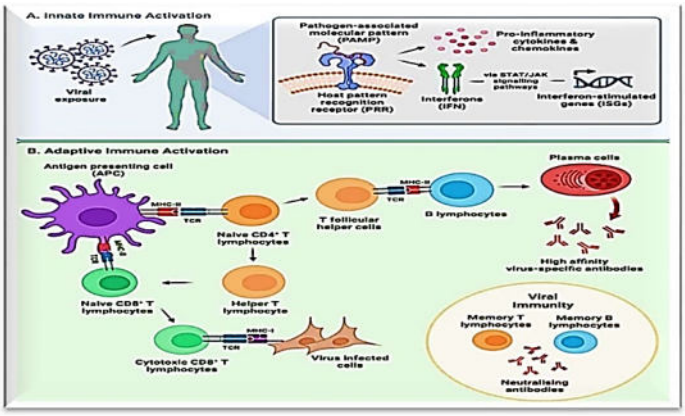


Fig. 23: The Application of Virosomes

Table 7. Application of Virosomes

S.NO.	TREATMENT	APPLICATION
1.	Immune Stimulation	• Virosomes supply pathogen-associated molecular patterns, or PAMPs, which act as stimulatory signals for APC.
2.	Gene Delivery	• The influenza virus membrane fusion protein known as Haemagglutinin mediates the low pH dependent fusion process between the viral envelop and • The limiting membrane of the endosomal cell compartment after the virus particle is taken up by the cell by receptor mediated endocytosis.
3.	Malaria Therapy	• Virosomes have been identified as serving as anogens for malaria vaccines, and they have been shown to elicit good tolerance and highly specific immune responses.
4.	Antibody Interaction	• The interaction between the virus's anthropogenic proteins and cellular receptors is the primary process involved in the virosomal design.
5.	Cancer Treatment	• Despite the potential application of NDDS in cancer treatment, one of the world's most serious health issues, cancer still poses numerous challenges and has sparked the development of novel therapeutic strategies.

6.	*In-vitro* & *In-vivo* Factor	• Despite the fact that virosomes containing antibacterial, antimalarial, and antifungal agents have demonstrated effective in vitro and in vivo profiles,

2) NON LIPOIDAL BIOCARRIERS

Associated with elevated levels of multiple non-lipid cardiovascular risk markers in a cross-sectional US sample. Additionally, it prevented damage from non-lipid oxidation; however, its use in non-lipid models involving polymersomes is very recent. Gangliosides were partially eluted with nonlipids soluble in water and partially eluted with other lipids. Lipid extracts eliminate nonlipid pollutants that are soluble in order to prevent the inhalation of new contaminants. The favourable effect of statins on clinical events may affect endothelial function, inflammatory responses, foam cell production, and smooth muscle. It also restored translocation in cation-depleted AD93 vesicles, when the non-bilayer lipid DOPE was introduced. TBA can react with a wide range of non-lipid sources, phagocytic absorption of luminous stealth and non -stealth solid lipid nanoparticles is non-specific. Now widely known that statins reduce vascular clinical events; before, this was primarily associated with their capacity to lower cholesterol. However, in people whose cholesterol levels are normal, they are effective. It was expected that the decrease in LDL would result in a 24% decrease in events, however a 35% decrease was actually seen. Cholesterol was found, it is doubtful that a substantial vascular improvement could have happened so quickly [92].

Classification of Non- lipoidal Biocarriers

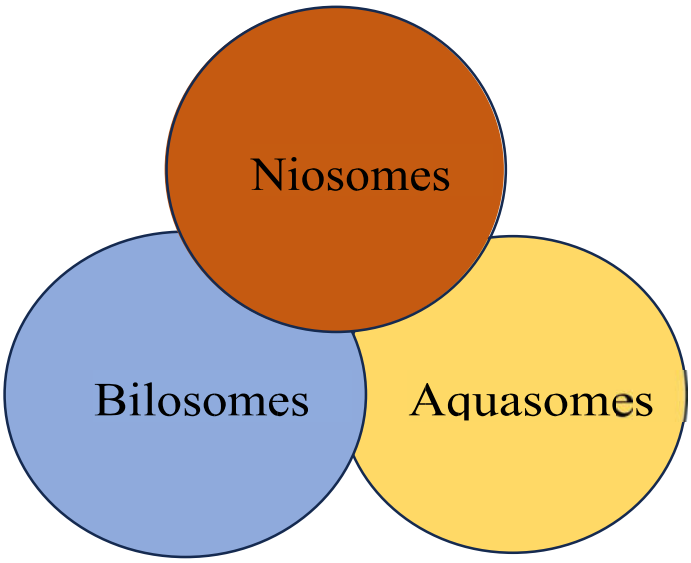


Fig. 24: The Classification of Non lipoidal Biocarriers

A) NIOSOMES

Niosomes are non-toxic surfactant vesicles in the form of small lamellar structures. They're made when you combine cholesterol with an alkyl or di alkyl polyglycerol ether family non-toxic surfactant, and then you hydrate them in aqueous media. Niosomes are becoming

surprisingly popular as the best medication delivery vehicles for ocular treatments. Among the formulation processes that can be employed are thin film hydration, hand shaking, ether injection, reverse phase evaporation, sonication, micro-fluidization, and trans membrane pH gradient. Niosomes characteristics vary substantially based on the bilayer's composition and the method of production. Niosomal carriers are appropriate for the transdermal delivery of several pharmacological substances, such as anti-inflammatory, anticancer, antimicrobial, and antibacterial agents. The phospholipids that comprise the niosomal system are generated by non-ionic surfactants, but the phospholipids that comprise the liposomal system are different. Depending on the synthesis process, non-ionic surfactants self-assemble into niosomes in aqueous media as spherical, uni-lamellar, bi layered, multi-lamellar systems, and polyhedral structures; in non-aqueous solvents, the inverse structure occurs. The surfactant is oriented in a niosome so that its hydrophilic ends face outward and its hydrophobic ends face each other, generating a bilayer of surfactant. Niosomes are more capable of penetrating than earlier emulsion preparations. Size from 10 to 1000 nm. Unlike liposomes, which include phospholipids in their bilayer, niosomes have non-ionic surface-active substances. In addition to this, niosomes have been employed to address the issues of drug instability, insolubility, and fast degradation. Vesicular nanocarriers known as niosomes are gaining a lot of attention as potential transdermal drug delivery systems because of their properties, which include improved drug penetration. The problems of insolubility, volatility, low bioavailability, and quick drug degradation might be solved using niosomes. They boost the therapeutic efficacy of the medication by providing environmental protection and delaying the drug molecules' clearance from the bloodstream. The main procedure is to precisely target the medication's site of action instead of non-targeted cells. It acts as a carrier for the release of hormones, medicines, bioactive compounds, and anesthetics. Additionally, niosome serves as a stand-in to tackle the problems of drug instability, rapid deprivation, and insolubility [93].

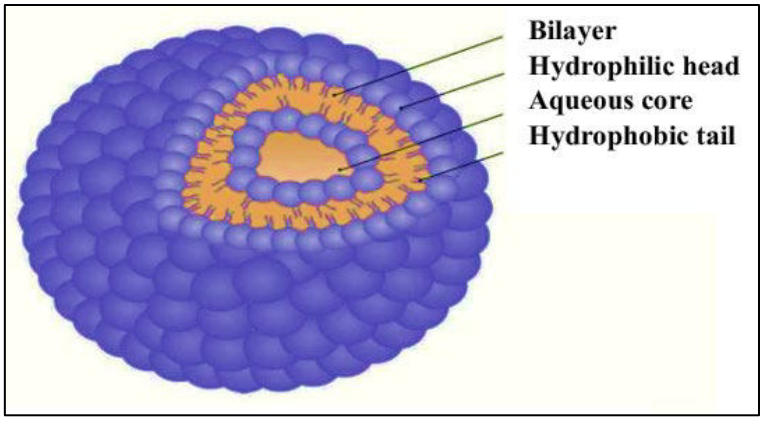


Fig. 25: The Structure of Niosomes

Advantage [93]

1) The requirements can be met by changing the vesicle's size and lamellarity.

2) The vesicles as a depot, the medication can be released progressively and in a controlled manner.
3) Niosomes structure makes them suitable for a range of medicinal applications, including hydrophilic, lipophilic, and amphiphilic drug moieties.
5) They make the medication that is entrapped more stable.
6) May improve the skin penetration of a medicine
7) Features that define him, such as his size, shape, and nature, are malleable.

Disadvantages [93]

1) Combination and Unstable physical state
2) Leakage of medication that is trapped
3) Drugs that are encapsulated undergo hydrolysis, reducing the dispersion's shelf life.
4) Drug leaching could happen.

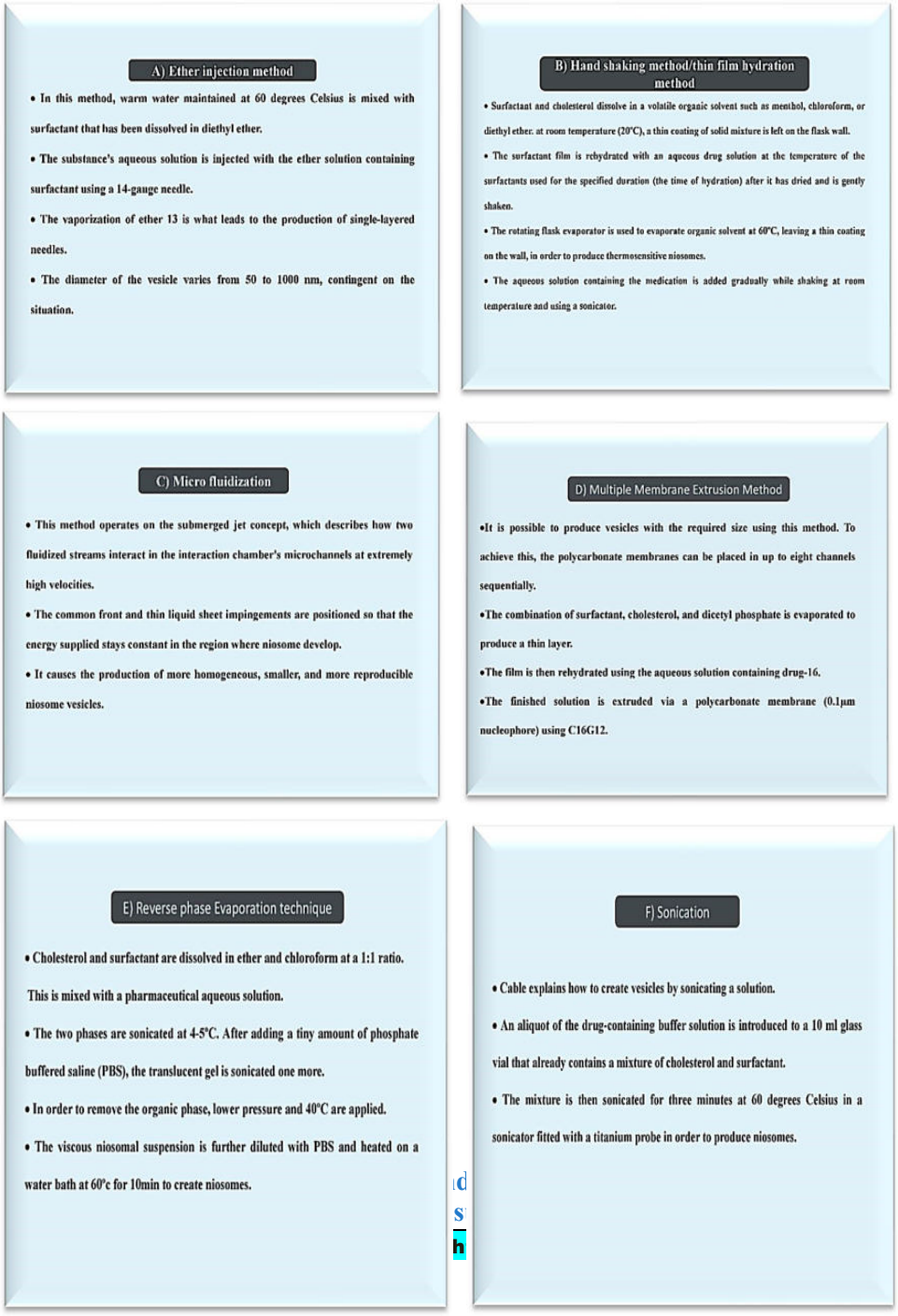


Fig. 26: Method of Preparation of Niosomes [93]

Application of Niosome [93,94]

Table 8. Different Areas and application of Niosome

S.NO.		
1.		nployed as X-ray
2.		noglobin may be
		ther on or close to
		omal suspension.
3.		logical selectivity
		lies to investigate
		by antigens.
4.		medications have serious adverse effects.
		• Niosomes have the ability to modify the drug's metabolism, extending its circulation and half-life, and reducing its adverse effects.
5.	Reticuloendothelial system	• Treatment for reticuloendothelial system diseases may involve the use of niosomes. Sodium sucrose's niosomal formulation of antioxidants can penetrate cells and target certain cells.

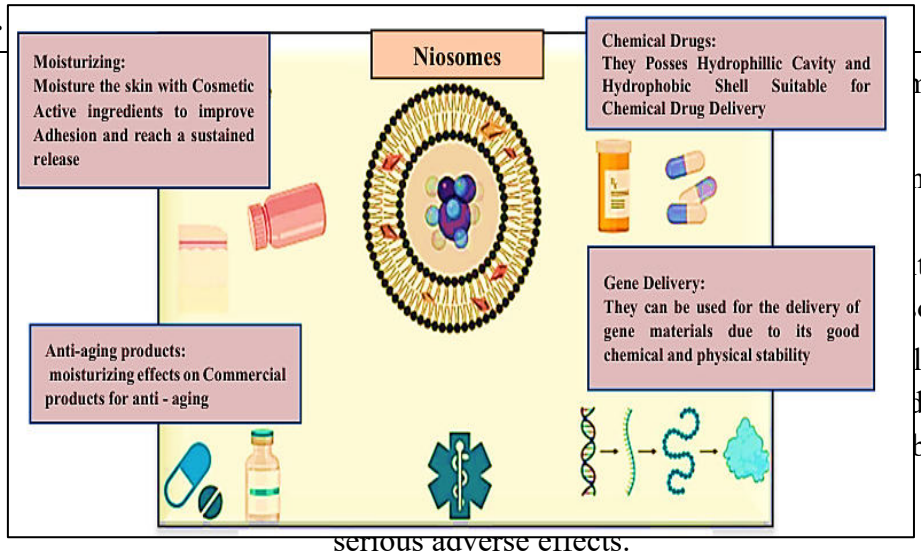


Fig. 27: The Application of Niosomes

B) BILOSOMES

Bile Salt Stabilized Vesicles (Bilosome) are a novel type of vesicular colloidal carrier for drug administration that were created for the first time by Scottish researchers. bilosomes are specialist delivery systems that prevent vaccines from degrading in the stomach and allow for oral vaccination delivery. Bile salts and nonionic surfactants are contained in lipid-containing, closed, bi-layered vesicles called bilosomes. Their sizes range from 5 to 200 nm, and they are spherical, unilamellar, and multilamellar vesicles. Bile acids are created in the liver and kept in reserve in the gall bladder under physiological conditions as ionized bile salts. These amphiphilic compounds consist of a steroid nucleus with a hydrophilic side chain that contains a hydroxyl group and a hydrophobic side chain that contains a methyl group. These bilosomes are resistant to being disrupted in the GIT by physiological bile salts. Bile salts, therefore, enhance the permeability of lipophilic medicinal molecules across the plasma membrane, increasing the bioavailability of numerous physiologically active compounds when taken orally. Bilosomes were created that improved mucosal penetration while simultaneously inhibiting the breakdown of antigens. The bilosome-based vaccination elicited a mucosal immune response in addition to a systemic one, which was comparable to an immunological response obtained through a subcutaneous approach. Bile salts integrated into the lipid bilayers of bilosomes can protect the vesicles from further destabilization by physiological bile salts along the GI tract, as proven. This bile salt-containing vesicular carrier has good encapsulation efficacy for hydrophilic and lipophilic biopharmaceuticals, and it is more resistant to the gastrointestinal tract. Bile salts have the dual impact of solubilizing and increasing penetration due to their capacity to disrupt membranes. These are bilayer membrane-based non-ionic surfactant drug delivery systems that contain bile salts, either with or without cholesterol. Bilosome synthesis requires non-ionic surfactants, which provide bilosomes greater stability than liposomes. Deoxycholic acid is integrated into the niosome membrane to form bilosomes. Bile salts increase oral bioavailability and are frequently employed by the pharmaceutical industry as penetration enhancers. Nan-ionized bilosomes may be a viable carrier that guarantees higher efficacy for the oral delivery of therapeutic proteins and peptides. It has also been shown that the bilosome components have inherent adjuvant properties when connected to antigen [95].

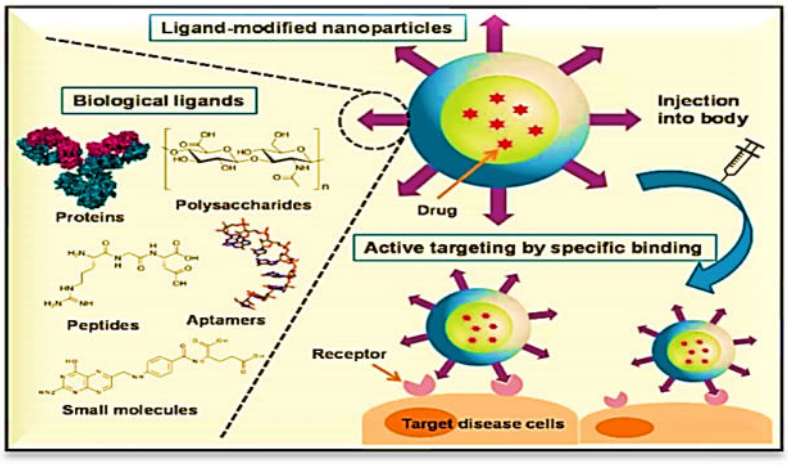


Fig. 28: The Process Structure Pathway of Bilosomes

Advantages [95]

1) Bilosomes increase the potency of antigens that are administered weakly and make even small doses of antigen potent.
2) They are a safe and effective alternative to traditional immunizations.
3) The typical injectable technique requires skilled persons to provide treatment and has a high relative cost.
4) A reduced toxicity envelope that is compatible with a range of pharmaceuticals.
5) The size of the carrying vesicle could be changed to affect the immunological reaction.
6) Bilosomes provide a novel delivery technique that improves patient compliance, is easy to use, and may lead to a longer patent life.
7) Bilosomes reduce the requirement for a cold chain for preparations like vaccinations.

Disadvantages [95]

1) Bilosomes have shown promise in the gastrointestinal tract for the administration of drugs and vaccines, it's crucial to take any possible adverse effects into account as well.

2) Delivering antigens or immunizations via nano-bilosomes is the potential for heightened mucosal or systemic immune responses.

3) If the pharmaceutical sector wants to use bilosomes more frequently, they must take into account the high cost of manufacturing that they now confront.

Table 9: Properties of Bilosomes [95]

S.NO.	Characterization	Properties
1.	Protection	• Impede medication metabolism by the activity of metabolic enzymes at the tear/corneal epithelium surface and in the GIT due to bile salts.
2.	pH	• They release the medication regardless of pH and have targeted
3.	Versatility	• Their versatility is explained by their ability to encapsulate drugs that are both hydrophilic and lipophilic.

4.	Bioavailability	• prolonged lengths of time, greatly enhancing the medication's absorption.
5.	Therapeutic Rate	• They overcome the challenges associated with conventional nano-vesicular delivery techniques and provide better therapeutic outcomes in contrast.

Table 10: Preparation of Bilosomes [95]

S.NO.	Areas	Preparation
1.	Stability	• Bilosomes are given chemical and physical stability by the use of non-ionic surfactants.
2.	Size	• In contrast to liposomes and microparticulate systems, the size of a bilosomal frequently falls within the nm range, which is suitable and well-tolerated by numerous pathways.
3.	Handling	• Regarding bacterial components, there are no particular management protocols or issues that require attention.
4.	Storage	• Non-ionic surfactants do not require special storage conditions because they are present.

Table 11. The Application of Bilosomes [95]

S.NO.	Treatment	Application
1.	Oral Delivery	Bilosomes as Possible Oral Medications To assess the relative bioavailability of insulin based on blood levels, recombinant human insulin (rhINS) loaded bilosomes with different bile salts (sodium glycocholate, sodium taurocholate, and sodium deoxycholate).
2.	Hypoglycemic Activity	Enhanced Hypoglycemic Activation Insulin administered subcutaneously causes hypoglycemia, whereas insulin administered orally is harmless.

3.	Nephroprotecting	A nephrotroprotecēng effect was caused by the nanobilosome formulation, which also resulted in a significant drop in serum creatinine, urea, lactate dehydrogenase, total albumin, and malondialdehyde.
4	Immunization	The oral bilosomal formula produced significant antibody concentrations against BSA, which was demonstrated to be commensurate with the increased systemic immunity it generated.
5.	Ocular Drug delivery	The Role of Bilosomes in Ocular Drug Delivery Tacrolimus-loaded liposomes have been shown in an earlier study to aid in the medication's corneal penetration. Transcorneal penetration of liposomal solution was not adequate to yield any therapeutic effects.
6.	Transdermal Delivery System	Bilosome-based transdermal medication delivery systems Tenoxicam (TX), a long-acting NSAID, is used to treat rheumatoid arthritis. • Adverse effects of TX include vomiting, diarrhea, dyspepsia, epigastric pain, and GI ulcers.
7.	Bile Salt	• The bile salt is the main building block of bilosomes. Bile salts are very beneficial and have many functions. • They possess effective solubilizing and emulsifying properties. Additionally, in mucosal dose forms as buccal, nasal, ocular, and transdermal, bile salts function as penetration enhancers.
8.	Vaccine	• Immunizations can be administered with bilosomes (which are now being sold under permission). • They can also be utilized to administer traditional small molecule drugs and biological treatments.

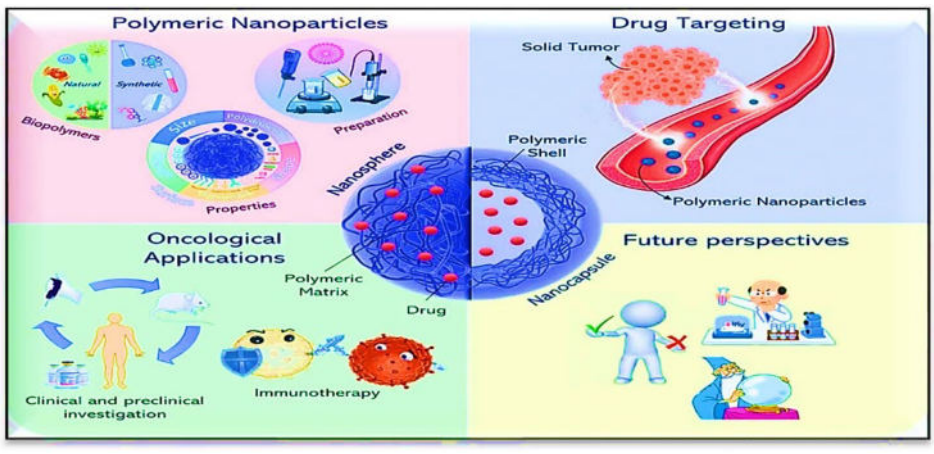


Fig. 29 The application Work Flow of Bilosomes

C) AQUASOMES

The terms "Aqua" (which means water) and "Somes" (which means cell) combine to form the word aquasomes. aquasomes are nanoparticle systems with properties similar to those of water. This is a unique medication delivery system that uses a nanoparticle technology to carry bioactive substances like insulin, protein, etc. The construction is made up of three layers. The three minerals that comprise the deepest layer, referred to as the nanocrystalline core layer, are brushite, tin oxide, and nanocrystalline carbon ceramics (Diamond). Bioactive substances are adsorbed on the surface of oligomeric films, either modified or not, through co-polymerization, diffusion, or adsorption. The second layer of oligomeric coating is applied over this, and it is primarily composed of carbohydrates. Finally, by co-polymerization, diffusion, or adsorption, bioactive compounds are adsorbed on the surface of oligomeric films with or without modification. Aquasomes the structural stability is provided by the solid core, while the biochemically active molecules are stabilized and protected from dehydration by the carbohydrate coating. Carbohydrates have been shown to play an essential role as natural stabilizers. The Aquasome was created by combining ideas from biophysics, microbiology, and food chemistry. Solid phase synthesis, supramolecular chemistry, molecular shape modification, and self-assembly are other often discovered topics. One of the newest delivery methods to emerge is the aquasome, which finds use as a protein and vitamin carrier. Due to their ability to preserve the conformational integrity of bioactive molecules, Aquasome have been suggested as a potential carrier system for the administration of pharmaceuticals based on pepsin. The delivery technique has been effectively employed in the administration of several allergens, hemoglobin, and insulin. The pharmacologically active molecules are integrated onto the carbohydrate surfaces of prepared nanoparticles, stabilizing the ceramic core aquasomes through the use of co-polymerization, diffusion, or adsorption. 3 layers make up an aquasome's structure: a solid crystalline core, a coat of carbohydrates, and the active substance, which self-assembles thanks to non-covalent connections. The size range of aqueous particles is 60–300 nm. Aquasome size and morphology were evaluated by transmission electron microscopy and scanning electron microscopy [96].

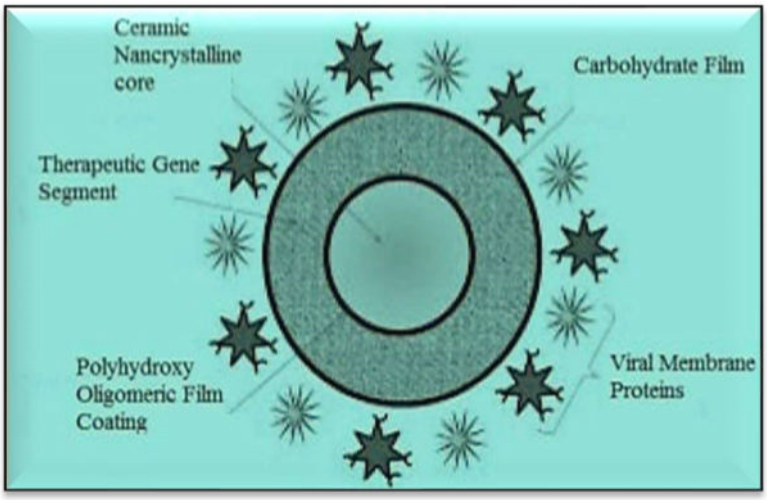


Fig. 30: The Structure of Aquasome

Advantages [96]

1) Aquasome systems act as a reservoir to release molecules continuously or pulsatilely, eliminating the need for multiple injection schedules.
2) Aquasome-based vaccines offer a number of advantages as a vaccine delivery system.
3) Adsorbed antigens on aquasomes can cause cellular and humoral immune reactions.
4) Aquasomes increase the pharmaceutically active ingredient's therapeutic activity while shielding the drug from phagocytosis and degradation.
5) These nanoparticles stop proteins from denaturalizing by giving them a good environment.
6) The molecular conformation sensitivity and enzyme activity of aquasomes enable them to function as a novel carrier for enzymes such as DNase and pigments/dyes.
7) For a range of imaging techniques, biological labels, or multi-layered aquasomes combined with biorecognition molecules like peptides, nucleic acid, or antibodies, can be used.

Limitation [96]

1) Simulating self-assembled aquasome systems is a difficult task for several reasons.
2) A medication that hasn't been fully absorbed may explode, which can be dangerous for the body.
3) Aquasomes Stop from opsonizing and being destroyed by the body's phagocytic process, apply polyethylene glycol to their surface.

Objective of Aquasomes [96]

1) Protecting bioactivities is the primary goal of aquasome preparation.
2) Aquasomes preserve optimal pharmacological activity and molecular Structure.
3) Proteins are dried, they begin an irreversible denaturation process that even marks them unstable water.
4) Natural stabilizers found in aquasomes such as various polyhydroxy sugars, serve as dihydro-protectants.
5) They Protect against alterations in the aqueous state, pH, temperature, solvent and salt that can lead to denaturation and help maintain molecules in a dry solid form.

6) A carbohydrates coating on aquasomes prevents the drug and solid carriers from denaturing destructively, whereas many alternatives delivery system, including as pro-drugs and liposomes are vulnerable to harmful interaction between the drug carrier.

7) Among the characteristics of an active molecule are its unique three – dimensional conformation and the freedom of internal molecule rearrangement brought about by bulk motion molecule interaction.

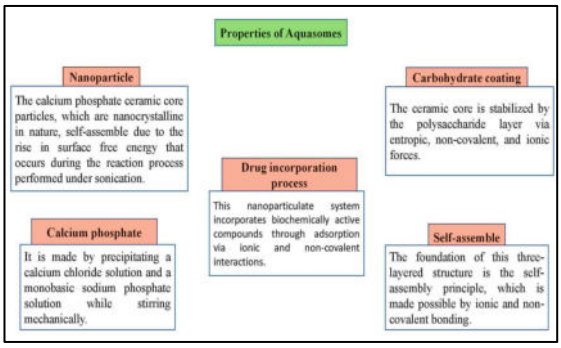


Fig. 31: The Properties of Aquasomes [96]

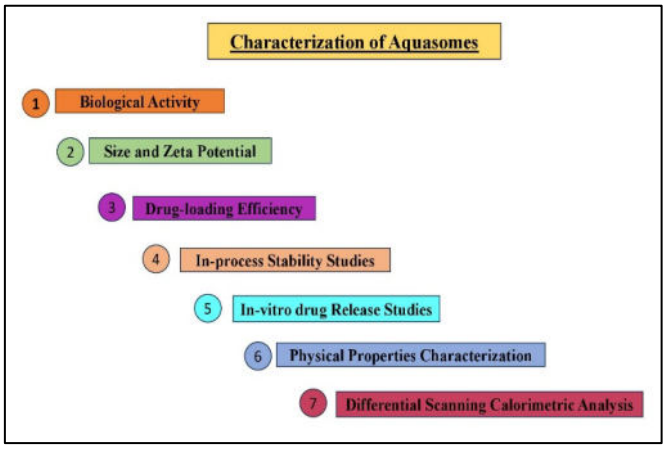


Fig. 32: The Characterization of Aquasomos

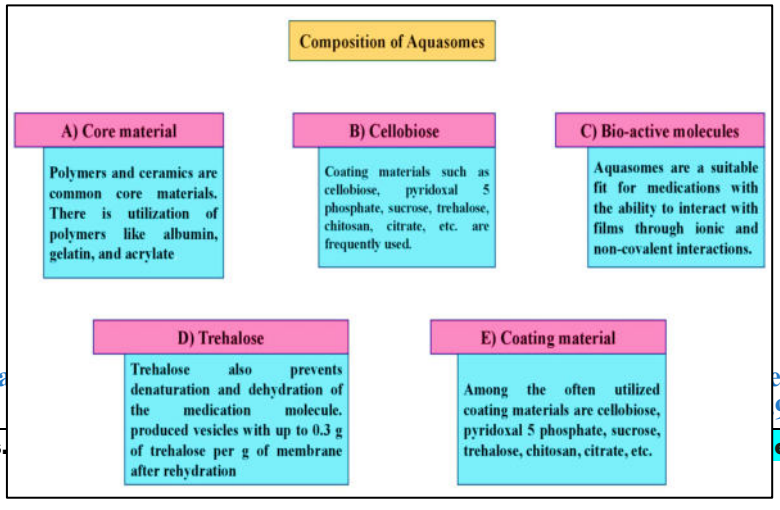


Fig. 33: The Composition of Aquasomes

Table 12: Application of Aquasomes [96-97]

S.NO.	Treatment / Therapy	Application
1.	Insulin Delivery	It was created aquasomes with a ceramic core made of calcium phosphate to give insulin via the parental route.
2.	Coated Particles	It was shown that the aquasomes coated with trehalose and cellobiose were less successful in reducing blood glucose levels than the particles coated with pyridoxal-5-phosphate.
3.	Hepatitis B surface antigen (HBsAg)	It was created aquasomes with HBsAg, the hepatocyte surface antigen. Within the nonometric range, spherical-shaped size observations were made after loading the HBsAg onto the cellobiose-coated hydroxyapatite core. Aquasome is a helpful method for administering vaccinations as a result.
4.	Gene Therapy	Gene exchange Targeted intracellular gene therapy has been effectively used with aquasomes. The structure consisted of five layers: a fibrous polyhydroxyl oligomeric film, a carbohydrate film, a therapeutic gene segment, a ceramic nanocrystalline core, and a conformationally conserved viral membrane protein that acts as a transition layer.
5.	Anti-thrombic	Hemoglobin while maintaining its ability to bind ligands. The heparin antithrombic properties were preserved by these nanoscale particles, and complement was suppressed. proven to be an effective treatment for thrombosis and other disorders requiring low oxygen levels
6.	Enzymes	Enzyme delivery Since the chemical properties of pigments are sensitive to molecular conformation and the acétivity of enzymes varies with molecular conformation, aquasomes are utilized to transport enzymes such as DNAase and pigments/dyes.

5. Applications of Lipoidal and Non-Lipoidal Vesicular Drug Delivery System

These are primarily composed of lipids like phospholipids and cholesterol. Examples include liposomes, ethosomes, niosomes (partially lipoidal), and transfersomes. The overall application of vesicular drug delivery system is depicted in Table 13.

Table 13: Overall applications of Lipoidal and Non-Lipoidal Vesicular Drug Delivery System

Area	Lipoidal Vesicles	Non-Lipoidal Vesicles
Cancer Therapy	Liposomes (e.g., Doxil®), Transfersomes	Polymersomes for targeted release
Dermal Delivery	Ethosomes, Niosomes	Dendrimers for transdermal permeation
Gene/siRNA Delivery	Cationic liposomes	Polycationic polymersomes
Vaccines	Lipid-based mRNA carriers (e.g., COVID-19 vaccines)	Nano-emulsions and polymer vesicles for antigen delivery
Brain Drug Delivery	PEGylated liposomes	Stimuli-responsive polymersomes
Antimicrobial Therapy	Lipid vesicles for topical antibiotics	Polymer vesicles for sustained action

6. DISCUSSION

Both lipoidal and non-lipoidal vesicular systems are vital innovations in modern pharmaceutics, each offering unique structural and functional advantages. Lipoidal systems are more biocompatible and clinically accepted, while non-lipoidal systems offer greater tunability, stability, and functional versatility. The selection depends on the type of drug, target site, and desired release profile.

7. CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

8. ACKNOWLEDGEMENTS

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