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Review Article

A Descriptive Review on vesicular drug delivery system: Sphingosomes

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ABSTRACT

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In sphingosomes, a membrane lipid bilayer made primarily of natural or synthetic sphingolipid completely encloses an aqueous volume. Sphingosomes address the main issues with the vesicle system (niosomes, liposomes), including their lack of stability, short in vivo circulation times, and poor tumour loading efficacy in cancer therapy. Sphingosomes are vesicular drug delivery systems that have an aqueous volume enclosed by a lipid bilayer membrane. Sphingosomes are a promising vesicular drug delivery system that can transport therapeutic compounds for a variety of potential applications, according to the review's findings.

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INTRODUCTION:

Vesicles have taken over as the preferred method of medicine delivery in recent years. In immunology, membrane biology, diagnostic procedures, and most recently, genetic engineering, lipid vesicles were discovered to be useful.[1-3] Vesicular drug delivery is one of the most modern and innovative medication delivery systems today. Bingham bodies are known as such because they were initially described as having biological origins by Bingham in the year 1965. [4] Vesicular drug transport is crucial for membrane modelling, active principle administration, and targeting. [5] Colloidal particles known as vesicles have an aqueous compartment that is surrounded by an amphiphilic concentric bilayer. [6-8]

Sphingosomes:

In sphingosomes, a membrane lipid bilayer made primarily of natural or synthetic sphingolipid completely encloses an aqueous volume. [9, 10] Improving liposomal stability is a very essential task since liposome stability issues are undoubtedly far more serious. Chemical breakdown of liposomal phospholipids, including oxidation and hydrolysis, is possible. When the pH is close to neutral, the hydrolysis of ester linkages slows. By using lipids with ether or amide linkages in place of ester linkages, or phospholipid derivatives with the 2-ester linkage substituted by carbomoyloxy function, the hydrolysis may be prevented altogether.[11] Sphingolipid (sphingomyelin) and cholesterol are combined to form sphingosomes, which have an acidic intracellular pH ratio of 75/25 mol%/mol% (more optimally, 55/45 mol%/mol%) between the two compounds. [12]

These offer substantially better features for drug retention and are much more resistant to acid degradation. Sphingosomes can be delivered intravenously, intramuscularly, subcutaneously, and intra-arterially, among other parenteral routes. Typically, it will be given intravenously, though in some circumstances, inhalation may be used. [13,

14] Sphingosomes are an effective medication delivery system since they are harmless, biodegradable, and equivalent to biological membranes. Sphingosomes flexible link with site-specific ligands to provide active targeting while providing selective passive targeting to tumour tissues.[15] Sphingolipids are now employed in the production of stable liposomes known as sphingosomes. The creation and application of these vesicular systems are hampered by the higher cost of sphingolipid. Despite having a lower entrapment efficacy than liposomes, they exhibit superior stability. [16] Sphingosomes are liposomes made of ceramides with the goal of restoring normalcy to the damaged or dehydrated skin since ceramides or other comparable molecules can make up for the lack of water and restore the skin's barrier function. [17] Sphingosomes address the primary problems of the vesicle system, including its lack of stability, short in vivo circulation period, and poor tumour loading efficacy in cancer therapy. Biological macromolecules, diagnostics, and chemotherapeutic agents are all delivered via sphingosomes in clinical settings. [18] Sphingosomes are liposomes made of sphingolipid, which can be stated simply. [19, 20]

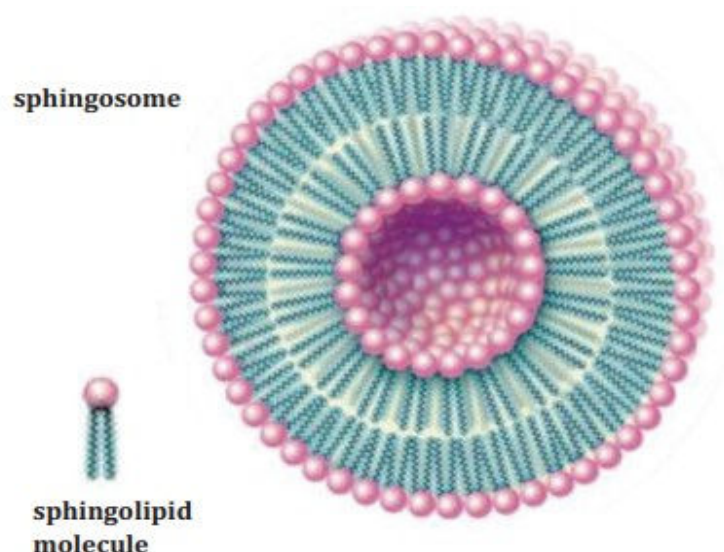


Fig: 1 Structure of sphingosome

ADVANTAGES OF SPHINGOSOMES [22, 23, 24]

1. Offer tumour tissue a selective passive target.
2. Increase the effectiveness of treatment.
3. Enhance stability by encapsulating.
4. Reduce the encapsulated agent's toxicity.
5. By lengthening circulation time, the pharmacokinetic effect is improved.
6. By giving the medicine superior biopharmaceutical qualities, which lead to improved bioavailability, especially in the case of poorly soluble pharmaceuticals, it lowers the cost of therapy.
7. Flexibility to combine with ligands that are tailored to a particular spot to achieve active targeting.

DISADVANTAGES OF SPHINGOSOMES [25]

1. The preparation and use of these vesicular systems are more challenging due to the higher cost of sphingolipid.
2. Unsuccessful trapping.

COMPOSITION OF SPHINGOSOMES

Sphingosomes are made up of sphingolipid (sphingomyelin) and cholesterol and have an acidic intracellular pH ratio of sphingomyelin and cholesterol that ranges between 75/25 mol%/mol% (most preferably 55/45 mol%/mol%). When compared to other formulations, liposomal formulations based on sphingomyelin and cholesterol have a number of benefits. The Sphingosomes have better drug retention properties and are significantly more resilient to acid hydrolysis.[26, 27]

Sphingolipids:

Sphingolipids are a component of cells and have a polar head connected to a hydrophobic body. Phospholipids play a role in cell identification and signal transmission. It is a member of a large class of substances with a sphingoid base backbone. Sphingosine, an aminoalcohol with 18 carbon atoms and an unsaturated C chain, is the source of sphingolipids. It is naturally produced from serine and acyl-coA, and it is subsequently transformed into ceramides, other lipids, and other species. [28, 29]

Cholesterol:

The preparation of this membrane can change significantly when sterol is added to the bilayer of sphingosomes. Cholesterol does not naturally form a bilayer structure, but it can be integrated into sphingolipid membranes at very high concentrations—up to 1:1 or even 2:1 molar ratios of cholesterol to sphingolipid. The typical electrostatic and hydrogen bonding interaction is eliminated and the spacing between the choline head group is increased by cholesterol inclusion. The inclusion of stearylamine (SA), a substance that induces a positive charge, can boost the stability of sphingosomes. The sphingosomes may incorporate extra components to direct them toward particular cell types. Following systemic injection, the sphingosomes can be targeted by, for instance, conjugating them to monoclonal antibodies or binding portions thereof that bind to epitopes present only on particular cell types, such as cancer-related antigens. Alternately, the liposomes may also contain ligands that bind to the target cell types' surface receptors. [26]

CLASSIFICATION OF SPHINGOSOMES:

The structural characteristics of sphingosomes, such as the quantity of formed bilayers and the size of the vesicles, are used to categorize them. Sphingosomes can be unilamellar or multilamellar, with a typical diameter of 0.05 to 0.45 μm . The most typical diameter range is between 0.05 and 0.2 μm .

1. Small unilamellar vesicles (SUV): These vesicles have a diameter of 10 nm to 100 nm and are composed of a single lipid bilayer.
2. Large unilamellar vesicles (LUV) are composed of a single lipid bilayer and have a bigger diameter than SUVs. It ranges from 100 nanometers to one metre in size.

3. Multilamellar vesicles (MLV): These vesicles range in size from 100 nm to 20 μm and are composed of several lipid bilayers.
4. Oligolamellar vesicles (OLVs): OLVs have fewer bilayers than MLVs but more than one, with a 0.1 to 1 μm size range
5. MMVs (multivesicular vesicles) are tiny vesicles with a diameter of between 100 nm and 20 μm .
6. Giant vesicles (GV): Vesicles longer than 1 μm are known as giant vesicles (GVs). [30]

TRANSPORT MECHANISM OF SPHINGOSOMES [31]

Transport mechanism at cellular level:

Small unilamellar sphingosomal vesicles (SUSVs) interact with cells in a variety of ways. These are as follows- stable adsorption, endocytosis, fusion, lipid transfer.

1. **Stable adsorption:** The interaction of whole vesicles with the cell surface is referred to as stable adsorption. Such a process is mediated at the vesicle or cell surface by non-specific electrostatic, hydrophobic, or other forces or components.
2. **Endocytosis:** Endocytosis is the process of vesicle ingestion into endocytotic vesicles, which is thought to result in the transfer of the vesicles to the lysosomal apparatus.
3. **Fusion:** Fusion is the straightforward joining of the vesicle bilayer and the plasma membrane bilayer, with the release of vesicle content into the cytoplasmic space.
4. **Lipid transfer:** Individual lipid molecules are transferred between vesicles and the cell surface without the help of the aqueous vesicle content and cell interaction.

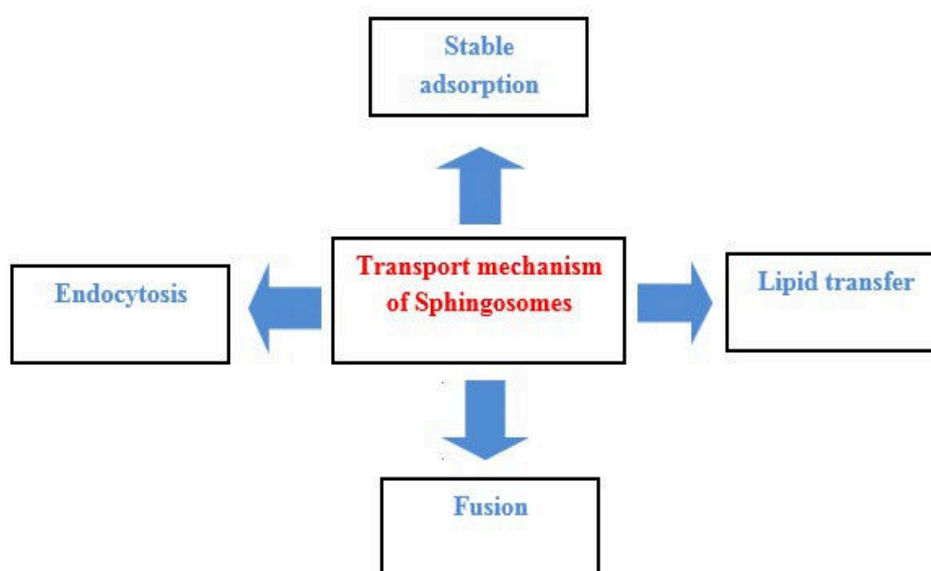


Fig: 2 Transport mechanisms of Sphingosomes.

METHOD OF PREPARATION OF SPHINGOSOMES

1.Lipid Film Formation (Hand Shaking Method) [32, 33]

In an R.B. flask, sphingolipids, surfactant/cholesterol, and a lipophilic medication were combined and dissolved in ether, an organic solvent. The organic solvent is eliminated under reduced pressure by employing a rotary film evaporator. The dried or lipid cast surfactant film is hydrated with aqueous phase at 50–60°C.

On hydration, the dried lipid layer expands and separates from the inner surface of the RB flask to generate multilamellar sphingosomal vesicles. Large unilamellar sphingosomal vesicles can also be obtained using a non-shaking technique in which the film is subjected to a stream of N₂ gas for 15 minutes before the lipid layer swells in an aqueous medium without shaking.

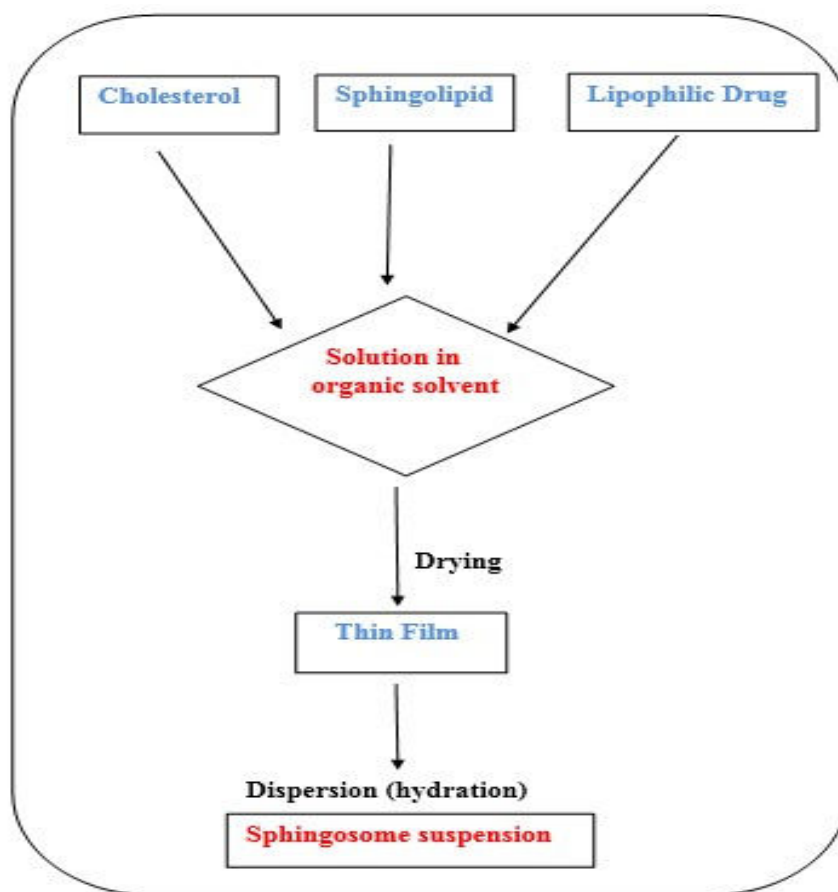


Fig: 3 Steps in Lipid Film Formation Method.

2. Sonication Method [34]

The most popular technique for creating tiny vesicles is sonication. Sphingosome size is further decreased when exposed to high energy levels. Small vesicles arise when the multilamellarsphingosomal vesicles are subjected to ultrasonic irradiation. Two different sonication techniques based on bath and probe. Ultrasonic disintegration bath sonicators are the most popular.

3. Solvent Spherule Method [35, 36]

Sphingolipids are dissolved in a volatile hydrophilic solvent and then dispersed as tiny spheres in an aqueous solution to form solvent spherules.

Multilamellar vesicles are created when the volatile hydrophilic organic solvent evaporates in a water bath under regulated circumstances.

4. Calcium Induced Fusion Method [37, 38]

When calcium is introduced and SUV sphingosomes are merged, multilamellar vesicles are formed. Then, from multilamellarsphingosome vesicles, huge unilamellarsphingosomes can be generated by adding EDTA. Macromolecules can be encapsulated using the calcium-induced fusion approach, but one drawback is that only acidic sphingolipids can be used to produce LUV sphingosomes.

5. French Pressure Cell Method [39]

When compared to sonicated vesicles, the French pressure cell approach is more useful for manufacturing more stable oligolamellarsphingosomes. Using a French press, this method is performed under intense pressure. Sphingosome extrusion is carried out here.

6. Solvent Injection Methods [40]

The sphingolipid is dispersed into an organic phase (ethanol or ether) using the solvent injection methods, and then the solution is injected into aqueous medium to create sphingosomes.

a. Ether Infusion Method: [40, 41, 42]

Since the ether is immiscible with the aqueous phase and is heated to remove the solvent from the sphingosomal product, the ether injection method varies from the ethanol injection method. The procedure entails injecting ether-sphingolipid mixtures into warmed aqueous phases above the ether's boiling point. When the ether comes into contact with the aqueous phase, it evaporates, and the distributed sphingolipid mostly takes the form of unilamellarsphingosome. The removal of the solvent from the product makes the ether injection method superior to the ethanol injection method because it enables the process to be run for longer periods of time, resulting in a concentrated sphingosomal product with high entrapment efficiencies.

b. Ethanol Injection Method: [40, 43]

The principal use of the ethanol injection method is the discovery that, without extrusion or sonication, a narrow distribution of tiny sphingosomes (less than 100 nm) may be produced by simply injecting an ethanolic sphingolipid solution into water in one step.

7. Detergent Removal Methods [44, 45, 46, 47]

Sphingolipids have been solubilized using detergents when their critical micelles concentrations were reached. The micelles' sphingolipid content increases as the detergent is removed, and they eventually gather together to form LUVs. Dialysis can be used to get rid of the detergents. The detergent dialysis approach has the benefits of good repeatability and the creation of populations of sphingosomes that are uniform in size. Detergents have also been removed using the following methods: (a) Gel chromatography with a column of Sephadex G-259 (b) Triton X-100 adsorption or binding to Bio-Beads SM-210 (c) Octylglucoside adsorption on Amberlite XAD-2 beads.

8. Freeze-Thaw Method [40, 48, 49, 50]

The manufacture of sterile, pyrogen-free, submicron-sized, narrow-sized sphingosomes using this novel technique was described. Its foundation is the creation of a uniform sphingolipid dispersion in water-soluble carrier materials. In the right proportions, sphingolipids that form sphingosomes and water-soluble carriers like sucrose were dissolved in tert-butyl alcohol/water cosolvent systems to create a transparent, isotropic monophasesolution. The monophase solution was then filtered for sterility and put into vials for freeze-drying. A laboratory freeze dryer was employed in a recent study, and the freeze-drying method was as follows: freezing at 40 °C for 8 hours; primary drying at 40 °C for 48 hours; and secondary drying at 25 °C for 10 hours. 20

Pascal was the constant chamber pressure during the drying operation. The lyophilized product spontaneously transforms into a homogeneous sphingosome preparation upon the addition of water.

Characterisation of Sphingosomes [51-55]

1) Vesicular characterization: Important vesicular characteristics such particle size, shape, and zeta potential are measured using it.

- 2) Transition temperature:** Differential scanning calorimetry is used to determine the bilayer vesicle's transition temperature.
- 3) Entrapment efficiency:** Entrapment efficiency can be determined using the ultracentrifugation technique.
- 4) Sphingolipid cholesterol interaction:** P31 NMR and Differential scanning calorimetry is employable.
- 5) Penetration study:** Confocal laser scanning microscopy is the primary technique utilised for penetration studies (CLSM).
- 6) Vesicle stability:** The characteristics like structure and form affect the vesicular stability. Transmission electron microscopy can be used to observe alterations in shape and structure (TEM).
- 7) Surface tension activity measurement:** The Du Nouy ring tensiometer can be used for the ring method to measure surface tension.
- 8) Drug content:** The drug content can be determined using high performance liquid chromatography and ultraviolet spectrophotometry.
- 9) Permeation study:** A study on gel permeation can be conducted by combining sphingosomes. For diffusion research, a Franz diffusion cell can be employed.

Table: 1 Different formulation of Sphingosine and uses:

CLASS	FORMULATIONS	USES	REFERENCE
Anti-fungal	Sphingosine and sphinganine, free sphingolipids Of the stratum corneum	Use in Fungal infection	[56]
	5-Fluorouracil in combination with sphingomyelin	Use in Colonic tumor	[57]
Cancer therapy	Swasinosine in combination with interferon	Use in Colon cancer and melanoma	[58]
	Topotecan (Hyacam [®])	Use in Relapsed small-cell lung cancer, relapsed ovarian cancer	[59]
	Vincristine(vincristine sulphate liposome injection)	Use in Non-Hodgkins lymphoma	[60]
	Vinorelbine (Navelbine [®])singleorin combination with th cisplatin	Use in Non-small cell lung cancer, Metastatic breast cancer	[61]
Enzyme delivery	Streptokinase	Use in Treatment of malnutrition	[62]
Gene therapy	Sphingosine 1-phosphate analogs	Use in Radiation-induced lung injury	[63]
Immunology	Ceramides	Use in Regulation of immune response	[64]
Ocular drug delivery	Idoxuridine	Use in acute and chronic herpetic keratitis	[65]

Applications of sphingosomes:**1.Sphingosomes in tumor therapy:**

Cancer-related medicinal applications make up the majority of those that have passed the pre-clinical and clinical stages. For instance, phase I clinical studies for the sphingosomal substance vinorelbine, a semi-synthetic vinca alkaloid, have been completed. Clinical action is more prevalent when sphingosomes are present, which increases medication concentration at the tumour site. Authorized anti-cancer medications are wrapped in the aqueous core of microscopic liposomes using sphingosomal drug delivery technology, potentially improving their therapeutic index.[66, 30]

2. Sphingosomes as drug delivery vehicles:

Depending on how many lipid membranes are created, the term "sphingosome" commonly refers to uni- or multilamellar lipid structures enclosing an aqueous interior. Drugs can typically be loaded into liposomes, which encapsulates them inside the vesicle. Drugs can also be connected to sphingosomes or incorporated into the lipid bilayer. Proliferative diseases, immunological diseases, infectious diseases, vascular diseases, rheumatic diseases, and inflammatory diseases can all be treated using sphingosomes. [67]

3. Sphingosomes in ophthalmic drug delivery:

Delivery of the ideal medication concentration to the site of action is a significant issue in ocular therapies. Physical and chemical characteristics of a drug, as well as those of the vehicle in which it is administered, frequently alter the bioavailability of drugs for use in the eyes. Due in large part to the anatomical design of the conjunctival sac and the cornea's sensitivity to foreign objects, the selection of vehicles has been constrained to semisolid kinds. Vesicles have drawn a lot of attention among different types of carriers and vehicles for delivering medications to the eyes. [31]

4. Sphingosomes used for enzyme delivery:

Sphingosomes contain many enzymes, such as streptokinase and urokinase esterase.

Sphingosomes have been employed for a variety of reactions involving enzyme catalysis, including the creation of esters, peptides, and the conversion of sugar to acetal.[68, 62].

Future Aspects:

Sphingosome designs for drug or bioactive carrier still require optimization. Researchers from all around the world are still working to improve vesicular systems by making them stable in nature to stop content from leaching, oxidising, and being absorbed by natural defence mechanisms. The genetic engineering component can be combined to offer the current cellular drug carrier notion a novel dimension. Their potential uses in medicine range from the immobilisation of enzymes to the treatment of medication overdose as well as improving gastrointestinal absorption and acting as a carrier for transdermal and prolonged release drug delivery. With the development of numerous newer preparation, stabilisation, and characterisation procedures, these systems can potentially serve as a vehicle for medicinal and cosmetic compounds.

CONCLUSION:

Because they may be tailored to serve a variety of desired purposes, vesicular systems have been studied as a crucial drug delivery method over the years. Sphingosomes are bilayered vesicles having a fully enclosed aqueous membrane lipid bilayer made primarily of sphingolipid, either natural or synthetic. The finest candidates for encapsulation are lipophilic cations. Clinically, sphingosomes are employed in the production of chemotherapeutic medications, in diagnostic procedures, and in the cosmetics business.

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