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SPHINGOSOMES: HIGHLIGHTS OF THE PROGRESSIVE JOURNEY AND THEIR APPLICATION PERSPECTIVES IN MODERN DRUG DELIVERY

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ABSTRACT

Introduction: In a variety of scientific fields, vesicular systems have shown to be very effective carrier systems. Sphingosomes are bilayered vesicles with an aqueous volume completely contained by a membrane lipid bilayer mostly made up of natural or synthesized sphingolipid. Sphingosomes address some of the main flaws in the vesicle system (liposomes, niosomes), such as instability, *in vivo* circulation time, and tumor loading effectiveness in cancer treatment. **Method:** The literature was collected from Google Scholar and Scopus database with keyword of Sphingosomes. **Result:** Clinically, sphingosomes are utilized to transport chemotherapeutic agents, biological macromolecules, and diagnostics. Different kinds of sphingosomes have been created as a result of their size and composition flexibility. **Conclusion:** Sphingosomes are a potential vesicular drug delivery system that may transport medicinal chemicals for a variety of uses, according to the findings of this review.

KEYWORDS: Sphingosomes, Drug delivery, Sphingomyelin, Vesicular system, Preparation, Applications.

INTRODUCTION

The development of novel medication delivery systems has received a lot of attention in recent decades (NDDS). This technique is known as an innovative drug delivery system, and it occurs when a new medication or an old drug is given a modified formulation and delivered via a different route. Two requirements should preferably be met by the NDDS. To begin, it should administer the medication at a pace determined by the body's requirements throughout the course of therapy. Second, it must direct the active entity to the action location. None of these can be met by conventional-dose forms, including extended-release dosage forms. No existing drug delivery system now acts optimally, although genuine efforts have been made to accomplish them via different new drug delivery methods.[1]

The goal of a novel drug delivery system is to provide some control over drug release in the body, whether that control is temporal, spatial, or both. The goal of novel drug delivery is to either maintain drug activity at a preset pace or to maintain a reasonably constant, effective drug level in the body while minimizing unwanted side effects. It may also target drug action by utilizing carriers or chemical derivatization to deliver medication to a specific target cell type, or localize drug action by spatially placing controlled release devices next to, or in, the sick tissue or organ.[2]

Pharmaceutical carriers come in a variety of shapes and sizes. Particulate, polymeric, macromolecular, and cellular carriers are the four types. Lipid particles (low-density and high-density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles, and vesicular such as liposomes, sphingosomes, niosomes, pharmacosomes, and virosomes are all examples of a particulate type carrier, also known as a colloidal carrier system. When some amphiphillic building blocks come into contact with water, they create vesicular systems, which are highly organized assemblies of one or more concentric lipid bilayers. Vesicles are made up of a variety of amphiphilic building

components. Bingham bodies were named after Bingham, who initially revealed the biological origin of these vesicles in 1965. Liposome vesicles are defined as structures with a lipid-containing membrane surrounding an aqueous interior. Unless otherwise specified, the structure may contain one or more lipid membranes, but most liposomes will only have one. Single-layered liposomes are known as unilamellar, whereas multi-layered liposomes are known as multilamellar. The preferred liposome is made up of lipids that when combined create reasonably stable vesicles. There are several different lipids that may be utilized to make a more stable liposome. Neutral or negatively charged phospholipid or sphingolipid, as well as sterols such as cholesterol, should be preferred lipids. The lipid is chosen depending on the size of the liposome and its stability in the bloodstream.[3-5]

The advantages of a liposomal drug delivery method include the protection and control of active moiety release, as well as targeted drug delivery and cellular uptake through endocytosis. Aside from the benefits, liposomes have issues with disintegration, hydrolysis, and oxidation, sedimentation, drug leakage, and aggregation or fusion during storage. Liposome stability issues are, of course, considerably more serious, thus improving liposomal stability is a critical job. Chemical deterioration of liposome phospholipids, such as oxidation and hydrolysis, may occur as a consequence of these changes, or liposomes kept in aqueous suspension might agglomerate, fuse, or leak their contents. At a pH near to neutral, ester linkage hydrolysis will be sluggish. The usage of lipids with ether or amide linkages instead of ester linkages (such as sphingolipid) or phospholipid derivatives with the 2-ester linkage substituted by carbomoyloxy activity may completely prevent hydrolysis. As a result, sphingolipids are now often utilized to make stable liposomes known as sphingosomes.[6,7]

Sphingosome

A sphingosome is a "concentric, bilayered vesicle (**Figure 1**) in which an aqueous volume is completely contained by a membranous lipid bilayer mostly comprised of natural or synthesized sphingolipid." "In a nutshell, a sphingosome is a liposome that is made up of sphingolipid." The technique for encapsulating sphingosomes was discovered at the University of British Columbia and later developed by Inex Pharmaceutical Corp. Hana Biosciences licensed three therapeutic candidates based on this technology from Index in May 2006. When compared to alternative formulations, a liposomal formulation based on sphingomyelin-based cholesterol offers many benefits. Sphingosomes are more resistant to acid hydrolysis and have improved drug retention properties. Parenteral routes of administration, such as intravenous, intramuscular, subcutaneous, and intra-arterial, are used to deliver sphingosomes. In most instances, it will be given intravenously or, in rare cases, via inhalation. It is often injected into a big central vein, such as the superior vena cava or inferior vena cava, in order to provide a highly concentrated solution to large volume and flow arteries. Sphingosomes may be taken orally or used topically.[8]

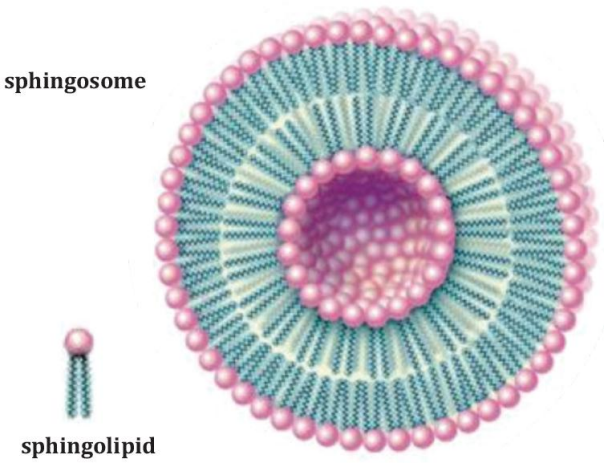

Figure 1: Structure of Sphingosomes.

Advantages of Sphingosomes

1. Provide tumor tissue with selective passive targeting.
2. Improve therapeutic index and effectiveness.
3. Use encapsulation to improve stability.
4. The encapsulated agent's toxicity is reduced.
5. Enhance the impact of pharmacokinetics (increase circulation time).
6. The ability to pair with site-specific ligands for active targeting.[9]

Advantages Over The Phospholipid Liposomes

It is more stable than the phospholipid liposome due to:

1. Sphingolipid is composed entirely of amide and ether linkages. They are more resistant to hydrolysis than lecithin's ester linkage.
2. They have fewer double bonds than lecithin, making them less susceptible to rancidity.
3. They absorb less oil than lecithin as well.
4. A prolonged plasma circulation time allows more of the therapeutic drug to reach the target location for a longer length of time. To keep the active medicine in the aqueous interior while stabilizing the lipid bilayer barriers. This novel sphingosomal technology increases the stiffness of the liposomal wall, which extends the vesicle's circulation life and the length of drug release.
5. Slow drug release from extravasated sphingosomes raises drug levels in the tumor, prolongs drug exposure across many cell cycles, and improves tumor cell death. Sphingosomes easily extravasate via these holes and collect inside the tumor, progressively releasing the encapsulated medicines. The juvenile neovasculature within the tumor is formed during angiogenesis and contains many defects, pores, and discontinuities up to 800 nm in size.[10]

Disadvantages

1. The higher cost of sphingolipid hinders the preparation and use of these vesicular systems.
2. Low entrapment efficacy.[11]

Classification of Sphingosomes

Sphingosomes are categorized based on structural characteristics such as the number of bilayers generated and the diameter of the vesicles produced. The sphingosomes are either unilamellar or multilamellar, with a mean diameter of 0.05 µm to 0.45 µm. The diameter range of 0.05 µm - 0.2 µm is preferred.

1. **Small unilamellar vesicles (SUV):** It consists of a single lipid bilayer and having a diameter in the size range of 10 nm - 100 nm.
2. **Large unilamellar vesicles (LUV):** It consists of a single lipid bilayer and having a greater diameter than SUV. It is having a size range of 100 nm - 1 µm.
3. **Multilamellar vesicles (MLV):** It consists of several bilayers of lipid and having a size range of 100 nm - 20 µm.
4. **Oligolamellar vesicles (OLV):** bilayer is more than one but not as many as MLV's. Having size range of 0.1 µm - 1 µm.
5. **Multivesicular vesicles (MVV):** size range 100 nm - 20 µm.
6. Vesicles above 1 µm are known as Giant vesicles (GV).[12]

Composition of Sphingosomes

Sphingosomes are made up of sphingolipids (sphingomyelin) and cholesterol, and their acidic intraliposomal pH ratio of sphingomyelin to cholesterol ranges between 75 and 25 mol% / mol% (more ideally 55/45 mol% / mol%). When compared to alternative formulations, a liposomal formulation based on sphingomyelin and cholesterol offers many benefits. Sphingosomes are more resistant to acid hydrolysis and have improved drug retention properties.[13]

Sphingolipid

Sphingolipid (**Figure 2**) is a kind of lipid that is found in cells. J.L.W. Thudichum gave them their name in 1884 because of their mysterious character. A polar head is linked to a hydrophobic body in sphingolipids. Because sphingolipid is a polar lipid, it has a connection to the composition and structure of human skin lipid, particularly in the epidermis layer. Sphingolipids are derived from natural sources such as mammalian milk, particularly bovine milk, brain, egg yolk, and erythrocytes from animal blood, preferably sheep's blood. Synthetic or semi-synthetic sphingolipids are available. Sphingosine and ceramide are the simplest sphingolipids, while complex sphingolipids like sphingomyelin (SM) and glycosphingolipid are the most complicated. Different types of sphingolipid can be used in sphingosomes and are described in **Table 1**.

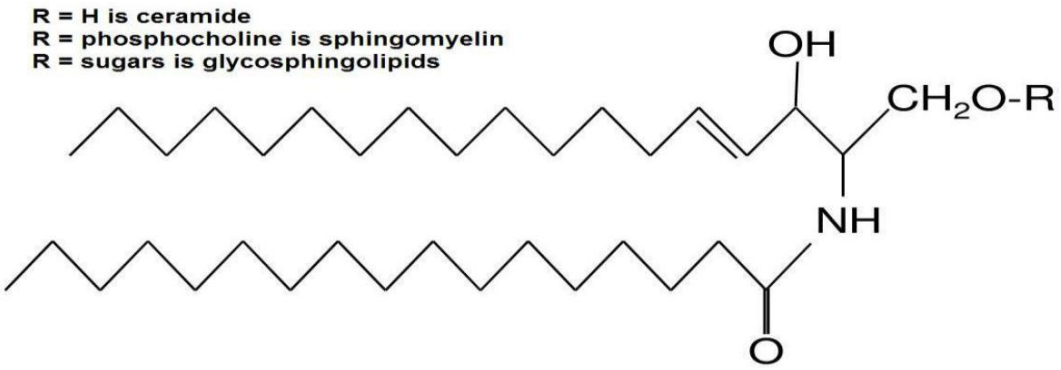

Figure 2: Structure of sphingolipid.

Table 1: Classification of sphingolipid.

CLASSIFICATION	EXAMPLES
Sphingoid bases	**1.** Sphing-4-enines (sphingosines) **2.** Sphinganines **3.** 4-Hydroxysphinganines (phytosphingosines) **4.** Hexadecasphinganine (Sphingoid base homologs and variants) **5.** Sphingoid base 1-phosphates **6.** Lysosphingomyelins and lysoglycosphingolipids **7.** *N*-Methylated sphingoid bases **8.** Sphingoid base analogs
Ceramides	**1.** N-Acylsphingosines (ceramides) **2.** N-Acylsphinganines (dihydroceramides) **3.** N-Acyl-4-hydroxysphinganines (phytoceramides) **4.** Acylceramides **5.** Ceramide 1-phosphates
Phosphosphingolipids	**1.** Ceramide phosphocholines (sphingomyelins)

	2. Ceramide phosphoethanolamines **3.** Ceramide phosphoinositols
Phosphonosphingolipids	
Neutral glycosphingolipids	**1.** GalNAcβ1-3Galα1-4Galβ1-4Glc- (globo series) **2.** GalNAcβ1-4Galβ1-4Glc- (ganglio series) **3.** Galβ1-3GlcNAcβ1-3Galβ1-4Glc- (lacto series) **4.** Galβ1-4GlcNAcβ1-3Galβ1-4Glc- (neolacto series) **5.** GalNAcβ1-3Galα1-3Galβ1-4Glc- (isoglobo series) **6.** GlcNAcβ1-2Manα1-3Manβ1-4Glc- (mollu series) **7.** GalNAcβ1-4GlcNAcβ1-3Manβ1-4Glc- (arthro series) **8.** Gal- (gala series) **9.** Other
Acidic glycosphingolipids	**1.** Gangliosides **2.** Sulfoglycosphingolipids (sulfatides) **3.** Glucuronosphingolipids **4.** Phosphoglycosphingolipids **5.** Other
Basic glycosphingolipids	
Amphoteric glycosphingolipids	
Arsenosphingolipids	

Cholesterol

Sterol incorporation in the sphingosome bilayer may result in significant modifications in the membrane's preparation. Cholesterol cannot form a bilayer structure by itself, but it may be integrated into sphingolipid membranes at extremely high concentrations, with a molar ratio of cholesterol to sphingolipid of 1:1 or even 2:1. Cholesterol inclusion increases the distance between the choline head group and eliminates the electrostatic and hydrogen-bonding interactions that normally occur. The inclusion of stearylamine (SA), a positive charge generating chemical, may improve the stability of sphingosomes. To focus sphingosomes on particular cell types, other components may be added. Sphingosomes, for example, may be coupled to monoclonal antibodies or binding fragments of monoclonal antibodies that bind to epitopes found exclusively on certain cell types, such as cancer-related antigens, allowing the sphingosomes to be targeted after systemic delivery. Alternatively, ligands that attach to the target cell types' surface receptors may be bound to the liposomes.[13]

Theoretical Aspects of Sphingosomes

Formation of ordered membranes

The hydrophobic acyl chains of a lipid molecule connect and interact with those of adjacent molecules in a traditional lipid-bilayer assembly, and the polar head groups orient themselves to the assembly's exterior. Sphingosomes produce ordered membranes because sphingolipids tend to divide into ordered domains in general. Naturally occurring sphingolipids have a wide range of head group configurations and acyl chain compositions. Sphingolipids are partitioned into ordered membrane domains by ceramide moieties with a long chain base and long saturated N-acyl chains. The polar head group of these lipids, which may range from a single hydroxyl in ceramide and the phosphocholine group in sphingomyelin to vast assemblies of carbohydrates in the complex glycosphingolipid, will certainly influence their partitioning.[14]

Stability against hydrolysis

Thermodynamically, liposome dispersions are unstable. A scattered system's total free energy may always be reduced by reducing the interfacial area. The attractive van der Waals interactions between the negatively charged groups on the liposome surface cause this aggregation propensity. The negative charge in sphingosomes is protected by a large hydrophilic group, which is responsible for preventing vesicle aggregation throughout preparation and storage, as well as perhaps soon after injection. Due to ester connections, phospholipids in liposomes may suffer chemical deterioration such as oxidation and hydrolysis. Sphingosomes have a structure that makes them resistant to hydrolysis. Sphingolipids are physiologically inert macromolecules with amide and ether connections that are resistant to hydrolysis in the backbone.[14]

Interaction between cholesterol and sphingolipids

Cholesterol prefers to interact with sphingolipids over acyl-chained phosphatidylcholine. The existence of a positive connection between cholesterol and sphingolipid concentrations in different membrane fractions has long been recognized. Cholesterol desorption and exchange experiments in monolayer and bilayer membranes have shown that cholesterol desorbs more slowly from sphingomyelin-rich membranes or is retained more readily in sphingomyelin-containing acceptor vesicles than acyl-chain phosphatidylcholines. Sphingosomes may benefit from these interactions by increasing their biological efficiency.[14]

Encapsulation

In response to a transmembrane pH gradient, sphingosomes have high drug entrapment efficiency.

This not only ensures effective drug encapsulation, but also reduces drug efflux from the vesicles.[14]

Circulation time

The fast removal of liposomes from the circulation by the reticuloendothelial system has been a significant obstacle to utilizing liposomes for systemic medication administration. Increased sphingosomal wall stiffness increases the circulation life of sphingosomes and the time of drug release considerably. Furthermore, the negative charge on the surface of sphingosomes is covered by a bulky hydrophilic group, which slows their clearance by the reticuloendothelial system and lengthens their biological half-life.[14]

Drug loading in tumor

Sphingosomes easily extravasate via the pores of leaky tumor arteries formed during angiogenesis, accumulating inside the tumor. Once stuck in the interstitial space, the encapsulated medication is slowly released by these tough sphingosomes. Slow drug release from extravasated sphingosomes raises drug levels in the tumor, prolongs drug exposure over many cell cycles, and improves tumor cell death substantially.[14]

Preparation of Sphingosomes

Sphingosome preparation requires drug loading into vesicles. Loading may be passive (streptokinase, urokinase) or active (streptokinase, urokinase). By employing a transmembrane pH gradient, a broad range of medicinal compounds may be loaded into sphingosomes with encapsulation effectiveness approaching 100%. This technique entails creating a gradient that attracts lipophilic substances to the inside of vesicles, where they may stay for as long as the gradient is maintained. In most cases, adding drug to the buffer during the reconstitution phase was needed for passive loading. This enabled the medication to be entrapped inside the interior of the vesicles, where it would otherwise stay if it was not lipid-soluble. In most cases, passive loading is used to prepare sphingosomes. Various methods for passive loading utilized are as followed:

Mechanical dispersion method

Begin with a lipid solution in an organic solvent and finish with lipid dispersion in water when using the mechanical dispersion technique. The different components are usually mixed by co-dissolving the lipid in an organic solvent, which is subsequently removed by vacuum film deposition. The solid lipid mixture is hydrated with an aqueous buffer once all of the solvents have been removed. Sphingosome vesicles arise when lipids expand and hydrate spontaneously. At this stage, techniques alter their characteristics by including certain key processing parameters (sonication, freeze-thawing, and high-pressure extrusion) in different ways.[15]

Lipid Film method

Bangham et al. described the film technique in 1965. Using a flash rotary evaporator under decreased pressure (or by handshaking), a combination of suitable amounts of lipid is cast as a stack of film from this organic solution, and then the casted film is disseminated in an aqueous medium. When the lipids are hydrated, they expand and peel away from the flask's wall, producing multilamellar sphingosomal vesicles (MLSV's). Manual agitation (handshaking approach) or exposing the film to a stream of nitrogen for 15 minutes followed by swelling in an aqueous medium without shaking provides the mechanical energy needed for lipid swelling in dispersion casted lipid films (non-shaking methods). MLSVs are generated by handshaking, whereas the vesicles produced by non-shaking are big unilamellar sphingosomal vesicles. The size and other properties of MLSVs produced via lipid hydration may be tweaked further.[15] The steps to sphingosome preparation could be understood in **Figure 3**.

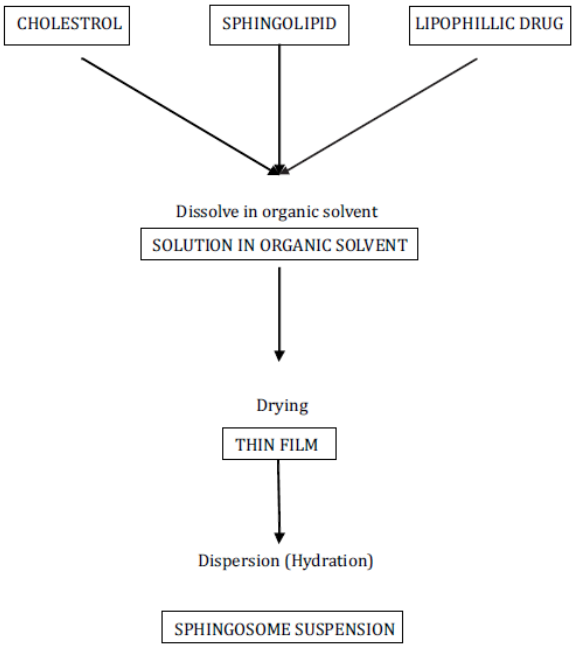

Figure 3: Steps in sphingosome preparation.

Extrusion technique

It is used to shrink sphingosomes in most cases. In this method, all of the dispersion is extruded via a polycarbonate membrane/an asymmetric ceramic membrane, a filter with a core of 0.6 µm (once) and 0.2 µm (ten times). The dispersion was then frozen and thawed 10 times to improve sphingosome encapsulation. Ultracentrifugation at 55,000 rpm and 4°C for 30 minutes removed the non-entrapped medication. Following that, the pellets scatter in the buffer.[15]

Sonication

The average size of sphingosomes shrinks much more at high energy levels. This was initially accomplished by exposing MLSVs to ultrasonic irradiation, and it is still the most used technique for generating tiny vesicles.

Sonication may be done in two ways: using a probe or using a bath. Small unilamellar vesicles are most often prepared using ultrasonic disintegrator bath sonicators.[15]

Microfluidization

This is a new method for preparing tiny MLVS. A Micro fluidizer is used to push the fluid through a screen at very high pressure (10,000 psi). Following that, it is pushed through specified microchannels that cause two streams of fluid to clash at right angles, resulting in a highly efficient energy transfer. The lipids may now be added to the fluidizer. The collected fluid may be recirculated via the pump until spherical vesicles are produced. As a consequence, the goods are more consistent, smaller, and more repeatable.[15]

French pressure cells

This is a highly practical approach. This is a high-pressure extrusion of premade sphingosomes in a French press. This method produces sphingosomes that are mostly unilamellar or oligolamellar. In comparison to sonicated vesicles, these sphingosomes are more stable.[15]

Microemulsification technique

To make tiny multilamellar vesicles, a microfluidizer pump is utilized. The fluid is pumped through 5 µm orifices at a very high pressure of 10,000 psi by the microfluidizer. Vesicles are reduced to 0.1 µm and 0.2 µm in diameter after a single pass.[15]

Solvent Spherule Method

Sphingolipids are dissolved in a volatile hydrophilic solvent and then distributed as tiny spheres in aqueous solutions in solvent spherules. Multi lamellar vesicles are produced when a volatile hydrophilic organic solvent is evaporated in a water bath under regulated circumstances.[15]

Calcium-induced Fusion Method

When calcium sphingosomes merge with SUV sphingosomes, multilamellar vesicles form. Sphingosomes may then be made from multilamellar sphingosome vesicles by adding EDTA to big unilamellar vesicles. Encapsulation of macromolecules is accomplished using this technique.[15]

Characterization

Sphingosomes are vesicular systems that must be studied for their morphological, biophysical, drug loading, drug release, and stability characteristics. Gravimetric examination of lipids in the formulation, lamellarity, particle size and size distribution, phase transition temperature, vesicle charge, osmotic and pH characteristics, and light scattering index are all suggested for determining the biophysical parameters of the finished medicinal product. Dynamic light scattering (DLS), electron microscopy with cryofixation methods or negative staining, atomic force microscopy (AFM), and ultracentrifugation may all be used to investigate particle sizing and size distribution. NMR spectroscopy, small-angle X-ray scattering, and cryo-electron microscopy may all be used to identify liposome lamellarity. The electrophoretic mobility (microelectrophoresis) of liposomal vesicles may be determined using zeta potential measurements, and therefore the surface charge density of the vesicles can be determined. Some of the most important characteristics, including drug loading and *in vitro* release from liposomal vesicles, are used to evaluate the therapeutic effectiveness and *in vivo* performance of these drug delivery systems.[16]

Transport Mechanism of Sphingosomes

Small unilamellar sphingosomal vesicles (SUSVs) interact with cells in a variety of ways. These are as follows stable adsorption, endocytosis, fusion, lipid transfer (**Figure 4**).

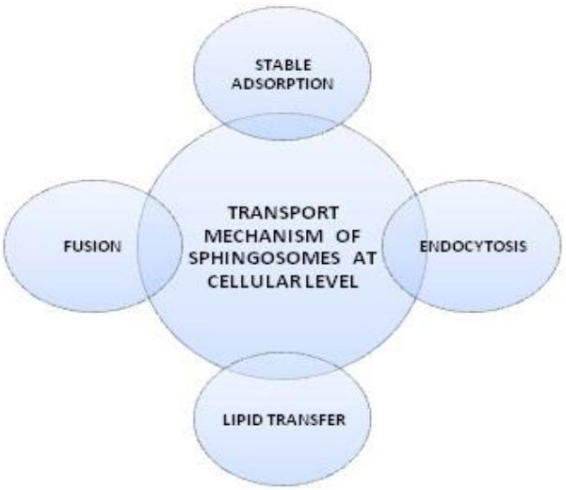

Figure 4: Transport Mechanism of Sphingosomes.

Stable adsorption

The interaction of intact vesicles with the cell surface is known as stable adsorption. Non-specific electrostatic, hydrophobic, or other forces are involved in this process or a component found on the surface of vesicles or cells.[17] (**Figure 5**).

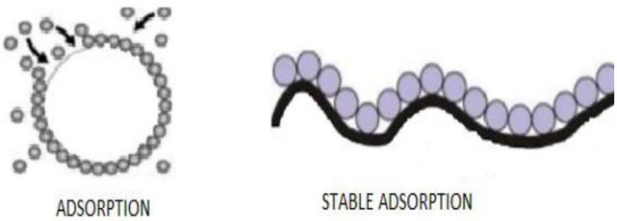

Figure 5: Adsorption Phenomena.

Endocytosis

Endocytosis is the process of intact vesicles being taken up by endocytotic vesicles and being sent to the lysosomal apparatus.[17] (**Figure 6**).

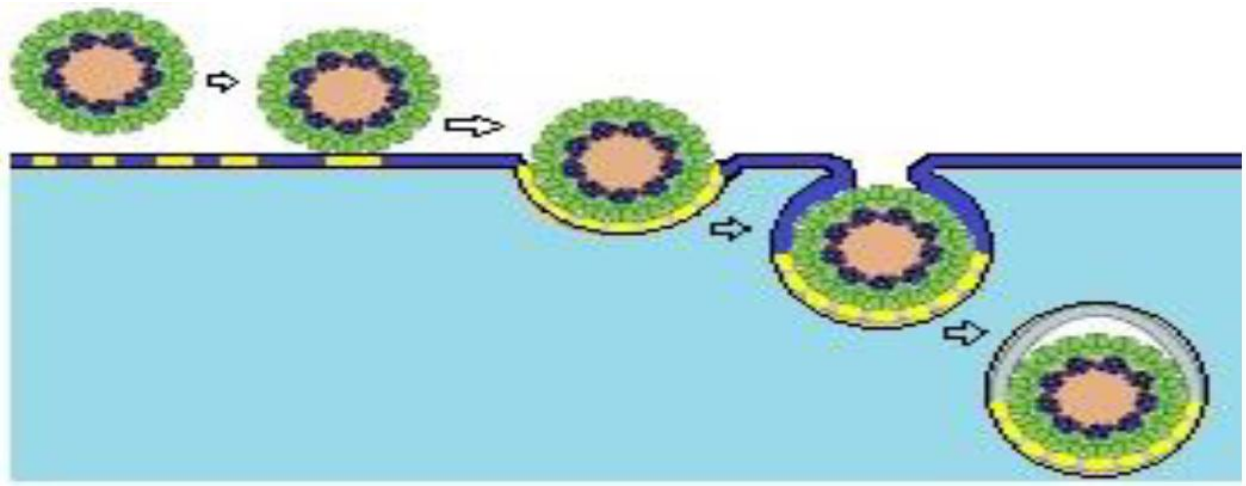

Figure 6: Endocytosis.

Fusion

Fusion is the simple fusion of the bilayers of vesicles and plasma membranes, with components releasing vesicle content into the cytoplasmic space.[17] (**Figure 7**).

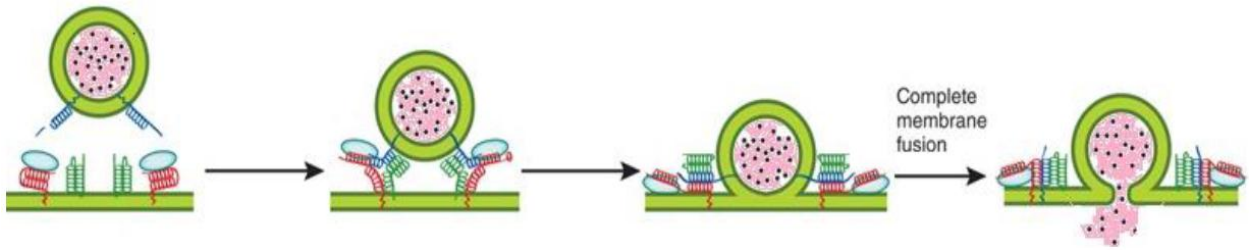

Figure 7: Fusion.

Lipid exchange

Individual lipid molecules are transferred between vesicles and the cell surface without the need for aqueous vesicle content to be associated with the cell.[17]

Applications of Sphingosomes

The sphingosome can deliver a broad range of medicinal compounds. Nucleic acid, proteins, peptides, oncolytics, anti-infectives, anxiolytics, psychotropics, ionotrops, toxins such as gelonin, and inhibitors of eukaryotic protein synthesis are examples of therapeutic compounds. "Lipophilic cations" are one of the most favored medicinal chemicals for entrapment in sphingosomes. Therapeutic medicines in the class of lipophilic compounds that may partition into the lipid bilayer phase of sphingosomes and therefore interact with the sphingosomes in a membrane form are among them. Because of their biodegradability, benign nature, and similarity to biological membranes, sphingosomes may prove to be an effective carrier for delivering drugs to the site of action.[18]

Cosmetic industry

Sphingosomes are also utilized in the beauty sector and in transdermal medication delivery. Sphingolipids administered topically have a high level of skin compatibility. Because sphingosome membrane lipids belong to the same chemical compound family as epidermal lipids, they have properties that let them penetrate.[18]

Drug delivery vehicles

Sphingosomes are lipid structures that enclose an aqueous interior and maybe unilamellar or multilamellar, depending on the number of lipid membranes produced. Medicines may be placed into liposomes, which are enclosed in the vesicle's core, and/or drugs can be connected to the sphingosome or integrated into the lipid bilayer. In contrast to free drugs, such drugs including liposomal formulations have been demonstrated to have enhanced effectiveness. For example, a liposomal formulation containing the vinca alkaloid vincristine has been found to have higher effectiveness and lower overall toxicity than free vincristine. Proliferative illness, immunological disease, infectious disease, vascular disease, rheumatoid disease, and inflammatory disease may all be treated using sphingosomes. Prostaglandins, amphoterecin B, methotrexate, cisplatin, vincristine, vinblastine, doxorubicin, camphothecin, ciprofloxacin, progesterone, testosterone, estradiol, beclometasone and esters vitamin-E, dexamethasone, and other steroids are examples of representative drugs.[18]

Enzyme delivery

Many enzymes are encased in sphingosomes, including streptokinase, urokinase, and esterase. Sphingosomes have been utilized to catalyze a number of reactions, including the production of esters, peptides, and sugar acetal transformation.[18]

Ophthalmic drug delivery

The delivery of an optimum medication concentration at the site of action is a significant issue in ocular therapies. The physical and chemical characteristics of medication, as well as the physical features of the vehicle in which the drug is put, may all affect ocular drug bioavailability. Because of the anatomical build of the conjunctival sac and the sensitivity of the cornea to external objects, the selection of vehicles has been restricted to semisolid types. Vesicles, among other vehicles and carriers, have gotten a lot of interest in ocular medication delivery. Idoxuridine entrapped in sphingosomes, for example, is more successful than a similar therapeutic regimen of unentrapped medication in the treatment of acute and chronic herpetic keratitis.[18]

Tumor therapy

The majority of medicinal applications that have progressed to the pre-clinical and clinical phases are in cancer; for example, the sphingosomal substance Vinorelbine (semisynthetic vinca alkaloid) is in phase I clinical trials. Greater medication concentration at the tumor site is linked to increased clinical activity in sphingosomes. Cell cycle-specific medicines like vincristine, vinorelbine, and topotecan, which kill tumor cells by interfering with mitosis at a particular point of the cancer cell cycle, have a strong connection between medication exposure and anti-tumor effectiveness. As a result, our unique sphingosomal drug delivery technology wraps authorized anti-cancer medicines inside the aqueous core of tiny liposomes, possibly increasing their therapeutic index. Sphingosomal products, such as Marqibo™ (sphingosomal vincristine), are high in active, cell cycle-specific anti-cancer medicines that may benefit from improved targeting and prolonged drug exposure at the tumor site. Sphingosomal formulations of vincristine, vinorelbine, and topotecan have been chosen for their potential to profit from this new encapsulation. Vincristine (Oncovin®; Eli Lilly and Company) is a microtubule inhibitor that has been authorized for the treatment of acute lymphoblastic leukemia (ALL) and is extensively used as a single agent and in combination regimens for the treatment of hematologic malignancies such as lymphomas and leukemias. Vinorelbine (Navelbine®; GlaxoSmithKline), a microtubule inhibitor, has been authorized for use in the first-line treatment of unresectable, advanced non-small cell lung cancer as a single agent or in combination with cisplatin. Topotecan (Hycamtin®; Glaxo Smith Kline) is a topoisomerase I inhibitor that has been authorized for the treatment of relapsed small-cell lung cancer and ovarian cancer.[18]

Other therapeutic application of sphingosomes

1. Sphingosomes in anti-microbial, anti-fungal, and anti-viral (anti-HIV) therapy.
2. Sphingosomes may be used in gene delivery.
3. Sphingosomes may be used in enzyme immobilization.
4. Sphingosomes may be used in immunology.

Specific Research Works

Because of their possible uses, sphingosomes have gotten a lot of interest in recent years. The functional characteristics of sphingolipids are used in many of their applications. Because of its use in stabilizing and extending the circulation duration of liposomes for the creation of tailored drug delivery systems, sphingosomes are gaining popularity. Several studies have been published on the production and use of sphingosomes in medication delivery. The list of developed sphingosomes formulations is depicted in **Table 2**.

Table 2: Therapeutic applications of sphingosomes.

CLASS	FORMULATIONS	APPLICATIONS
Anti-fungal therapy	Sphingosine and sphinganine, free sphingolipids of the stratum corneum	Treating infectious disease
Cancer therapy	5-Fluorouracil in combination with sphingomyelin	Colonic tumor
	Alocrest (vinorelbine tartrate liposome injection)	Non-small cell lung cancer, breast cancer
	Swasinosine in combination with interferon	Colon cancer and melanoma
	Topotecan (Hyacamtin®)	Relapsed small-cell lung cancer, relapsed ovarian cancer
	Vincristine (vincristine sulphate liposome injection)	Non-Hodgkins lymphoma
	Vincristine in combination with Rituximab (Oncovin®)	Large B-cell lymphoma
	Vinorelbine (Navelbine®) single or in combination with cisplatin	Non-small cell lung cancer, metastatic breast cancer
Cosmetics	Beclomethasone	Skin / Dermal therapy
	Sphingosomes™ MOIST	Skin cleansing and make-up removal efficiency
Drug vehicles	Prostaglandins, amphoterecin B, methotrexate, cisplatin,	Proliferative disease, immune

	vincristine, vinblastine, doxorubicin, camphothecin, ciprofloxacin, progesterone	disease, infectious disease, vascular disease, rheumatoid disease, and inflammatory disease
Enzyme delivery	Streptokinase, Urokinase	Treatment of malnutrition
Gene therapy	Sphingosine 1-phosphate analogs	Radiation-induced lung injury
Immunology	Ceramides, sphingosine 1-phosphate	Regulation of immune response
Ocular drug delivery	Idoxuridine	Acute and chronic herpetic keratitis

Modrak et al. have submitted a patent for a sphingomyelin-containing preparation for the treatment of rheumatoid arthritis, in which they examined the use of sphingomyelin in the production of rheumatoid arthritis medication.

Modrak et al. filed a patent for a sphingomyelin-containing preparation for tumor therapy enhancement, claiming that a therapeutically effective amount of sphingomyelin is used in the preparation of a medicament for enhancing cytotoxic tumor therapy, where sphingomyelin is administered in combination with an anthracyclin.

Igor et al. examined the drug loading and retention of vincristine, vinorelbine, and vinblastine encapsulated in liposomes. They discovered that various vinca alkaloids had varied retention characteristics, with the more hydrophobic medicines releasing more quickly. They discovered that when the ionophore method is employed for loading, the retention properties of vinca medicines with a low drug to fat ratio may be enhanced.

Modrak et al. submitted a patent for Sphingomyelin augmentation of tumor treatment, in which they discovered that co-administration of 5-fluorouracil and sphingomyelin decreased the pace of colonic tumor development to a larger extent and for a longer period of time.

Webb et al. submitted a patent for sphingosome formulations, demonstrating that the formulation increased ciprofloxacin, swainsonine, vincristine, and vinblastine drug distribution.

Hope et al. submitted a patent for a technique of loading a therapeutic drug into premade liposomes with a methylamine concentration gradient across the liposomes' lipid bilayer that is more stable, cost-effective, and simple to manufacture.

Future Aspects

Sphingosomes as drug or bioactive carrier ideas still need to be improved. Researchers across the globe are working to improve the vesicular system by making it more stable in nature to avoid content leaching, oxidation, and absorption by natural defense mechanisms. The genetic engineering element may be combined to give the current cellular drug carrier idea a new dimension. Immobilization of enzymes, concealing the taste of drugs, improving gastrointestinal absorption, serving as a carrier for sustained release and transdermal drug administration, and treating medication overdose are all possible medicinal applications. With the development of novel methods for production, stabilization, and characterization of these systems, they may be used as prospective carriers for drug cosmetics and pharmaceuticals.

CONCLUSION

Due to its versatility to be customized for a variety of desired objectives, vesicular systems have been explored as a significant drug delivery method throughout the years. Sphingosomes are bilayered vesicles with an aqueous volume completely contained by a membrane lipid bilayer mostly made up of natural or synthesized sphingolipid. The ideal category for encapsulation is lipophilic cations. Sphingosomes are clinically utilized for chemotherapeutic drug administration, diagnostic purposes, and in the beauty sector. Sphingosomes are made up of lipids that are comparable to skin lipids, making them more suitable and safe for the host cell. There are no limitations on their usage in the EU or the US Food and Drug Administration, and sphingosomes are widely recognized as safe.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Authors' Contribution

Madhukar Vitthalrao Shende: Wrote the manuscript
Prashant Dnyaneshwar Ghode: Literature survey
Tushar Kishor Sambre: Corrected grammar and removed typographical errors
Tanvi Tushar Sambre: Removed plagiarism
Atul Arjun Baravkar: Added Tables and Figures
Nilesh Ashokrao Nalawade: Set the references and did final proofreading.

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