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Sphingosomes: Highlights of the Progressive Journey and their Application Perspectives in Modern Drug Delivery

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ABSTRACT

Vesicular systems have shown to be highly successful carrier systems in a range of scientific domains. Sphingosomes are bi-layered vesicles with an aqueous volume entirely enclosed by a membrane lipid bilayer mostly composed of natural or synthetic sphingolipid. Sphingosomes solve some of the vesicle system's major shortcomings (liposomes, niosomes), such as instability, in vivo circulation time, and tumor loading efficacy in cancer therapy. The material was gathered using the term Sphingosomes in the Google Scholar and Scopus databases. Sphingosomes are used to deliver chemotherapeutic drugs, biological macromolecules, and diagnostics in clinical settings. As a consequence of their size and composition flexibility, many types of sphingosomes have been developed. According to the conclusions of this research, sphingosomes are a possible vesicular drug delivery system that might carry medicinal compounds for a range of applications.

Key Words: Sphingosomes, Drug delivery, Sphingomyelin, Vesicular system, Preparation, Applications

INTRODUCTION

In recent decades, the development of innovative medicine delivery methods has gotten a lot of attention (NDDS). This method is referred to as an innovative drug delivery system, and it happens when a new or existing medicine is given a new formulation and supplied via a novel channel. The NDDS should ideally meet two conditions. To begin, the drug should be given at a rate set by the body's needs during the duration of treatment. The active object must then be sent to the action location. Conventional dose forms, including extended-release dosage forms, cannot meet any of these requirements. Although serious attempts have been made to achieve these through various innovative medication delivery technologies, no current drug delivery system today functions perfectly. [1]

A revolutionary drug delivery system's purpose is to provide the user some control over medication release in the body, whether it's temporal, spatial, or both. The purpose of innovative drug delivery is to keep drug activity at a defined rate or to maintain a somewhat constant, effective medication level in the body while avoiding undesired side effects. It might also focus drug action by using carriers or chemical derivatization to deliver medicine to a particular target cell type, or it could localise drug action by spatially putting controlled release devices near to or within the diseased tissue or organ. [2]

Pharmaceutical carriers are available in a wide range of sizes and forms. The four categories of carriers are particulate, polymeric, macromolecular, and cellular. Particulate type carriers, also known as colloidal carrier systems, include lipid particles (low-density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles, and vesicular such as liposomes, sphingosomes, niosomes, pharmacosomes, and virosomes. Vesicular systems are highly ordered assemblages of one or more concentric lipid bilayers that form when certain amphiphillic building pieces come into contact with water. Vesicles are constructed from a number of amphiphilic components. Bingham bodies are named after Bingham, the scientist who first discovered the biological origin of these vesicles in 1965. Liposome vesicles are lipid-containing membranes that surround an aqueous interior. The structure may have one or more lipid membranes unless otherwise specified, but most liposomes will only have one. Unilamellar liposomes are single-layered

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liposomes, while multilamellar liposomes are multilayered liposomes. The preferred liposome is made up of lipids that when combined form vesicles that are relatively stable. There are a variety of lipids that may be used to create a more stable liposome. Phospholipids and sphingolipids that are neutral or negatively charged, as well as sterols like cholesterol, should be preferred lipids. The lipid is selected based on the size of the liposome and its circulatory stability. [3-5]

The preservation and control of active moiety release, as well as targeted drug delivery and cellular absorption by endocytosis, are all benefits of a liposomal drug delivery system. Liposomes have problems with disintegration, hydrolysis, and oxidation, as well as sedimentation, drug leakage, and aggregation or fusion during storage. Liposome stability difficulties, on the other hand, are much more problematic, making enhancing liposomal stability a key task. These changes may cause chemical degradation of liposome phospholipids, such as oxidation and hydrolysis, or liposomes held in aqueous suspension may agglomerate, fuse, or spill their contents. Ester linkage hydrolysis will be slow at a pH close to neutral. It is possible to totally avoid hydrolysis by using lipids with ether or amide linkages instead of ester linkages (such as sphingolipid) or phospholipid derivatives with the 2-ester linkage replaced by carbomoyloxy activity. As a consequence, sphingolipids are now often used to generate sphingosomes, which are stable liposomes. [6,7]

SPHINGOSOME

A sphingosome is defined as a "concentric, bilayered vesicle (Figure 1) in which an aqueous volume is entirely enclosed by a membranous lipid bilayer made up primarily of natural or manufactured sphingolipid." "In a word, a sphingosome is a sphingolipid-containing liposome." The process for encapsulating sphingosomes was developed by Inex Pharmaceutical Corp. after it was discovered at the University of British Columbia. In May 2006, Hana Biosciences licenced three medicinal candidates from Index based on this technique. A liposomal formulation based on sphingomyelin-based cholesterol has a number of advantages over other formulations. Sphingosomes are more acid hydrolysis resistant and have better drug retention qualities. Sphingosomes are delivered by parenteral methods such as intravenous, intramuscular, subcutaneous, and intra-arterial. It will be administered intravenously or, in rare situations, by inhalation. It's usually injected into a major central vein like the superior or inferior vena cava to provide a highly concentrated solution to large volume and flow arteries. Sphingosomes may be consumed or used topically. [8]

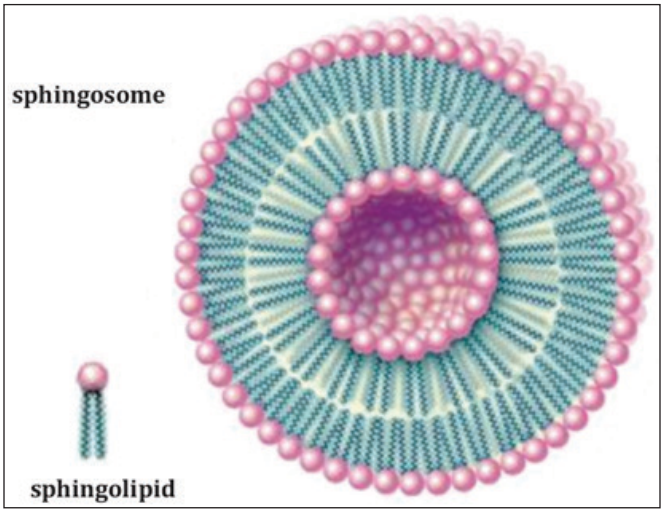

Figure 1: Structure of Sphingosomes.

ADVANTAGES OF SPHINGOSOMES

1. Use passive targeting to selectively target tumor tissue.
2. Increase therapeutic index and efficacy.
3. Improve the stability of your code by encapsulating it.
4. The toxicity of the encapsulated drug is lowered.
5. Increase the pharmacokinetics' influence (increase circulation time).
6. The capacity to target particular sites using site-specific ligands.[9]

ADVANTAGES OVER THE PHOSPHOLIPID LIPOSOMES

It is more stable than the phospholipid liposome due to:

1. Sphingolipids are totally made up of amide and ether links. They withstand hydrolysis better than lecithin's ester linkage.
2. They contain fewer double bonds than lecithin, reducing the risk of rancidity.
3. They also absorb less oil than lecithin.
4. A longer plasma circulation time permits more therapeutic medication to reach the target region and stay there for longer. To maintain the active drug in the aqueous interior while lipid bilayer barriers are stabilized. The rigidity of the liposomal wall is increased by this new sphingosomal technology, which extends the vesicle's circulation life and drug release time.

5. Slow drug release from extravasated sphingosomes increases tumor drug levels, extends drug exposure across several cell cycles, and promotes tumor cell killing. Sphingosomes readily pass through these perforations and gather within the tumor, slowly releasing the encapsulated drugs. During angiogenesis, the tumor's juvenile neovasculature is created, and it has numerous flaws, holes, and discontinuities up to 800 nm in size. [10]

DISADVANTAGES

1. The greater expense of sphingolipid makes these vesicular systems more difficult to prepare and utilize.
2. Ineffective trapping.[11]

CLASSIFICATION OF SPHINGOSOMES

Sphingosomes are classified based on structural features like the number of bilayers created and the diameter of the vesicles produced. With a typical diameter of 0.05 µm to 0.45 µm, sphingosomes are either unilamellar or multilamellar. The diameter range of 0.05 µm to 0.2 µm is the most common.

1. Small unilamellar vesicles (SUV): These vesicles are made up of a single lipid bilayer with a diameter of 10 nm to 100 nm.
2. Large unilamellar vesicles (LUV): LUVs have a larger diameter than SUVs and are made up of a single lipid bilayer. It has a size range of 100 nanometers to one metre.
3. Multilamellar vesicles (MLV): These vesicles are made up of many lipid bilayers and vary in size from 100 nm to 20 µm.
4. Oligolamellar vesicles (OLV): OLVs have more than one bilayer but fewer than MLVs. With a size range of 0.1 µm to 1 µm
5. Multivesicular vesicles (MVV): MMVs are small vesicles with a diameter of 100 nm to 20 µm.
6. Giant vesicles (GV): GVs are vesicles that are longer than 1 µm. [12]

COMPOSITION OF SPHINGOSOMES

Sphingosomes are composed of sphingolipids (sphingomyelin) and cholesterol, with an acidic intraaliposomal pH ratio of sphingomyelin to cholesterol ranging between 75 and 25 mol%/mol% (more preferably 55/45 mol%/mol%). A liposomal formulation based on sphingomyelin and cholesterol has a number of advantages over other formulations. Sphingosomes are more acid hydrolysis resistant and have better drug retention qualities. [13]

Sphingolipid

Sphingolipid is a kind of lipid present in cells (Figure 2). They were given their name by J.L.W. Thudichum in 1884 because of their cryptic nature. In sphingolipids, a polar head is connected to a hydrophobic body. Sphingolipid is a polar lipid with a link to the composition and structure of human skin lipids, notably in the epidermis layer. Natural sources of sphingolipids include mammalian milk, especially bovine milk, brain, egg yolk, and erythrocytes from animal blood, mainly sheep's blood. Sphingolipids may be synthetic or semi-synthetic. The simplest sphingolipids are sphingosine and ceramide, whereas the most complex sphingolipids include sphingomyelin (SM) and glycosphingolipid. Table 1 lists the many kinds of sphingolipids that may be employed in sphingosomes.

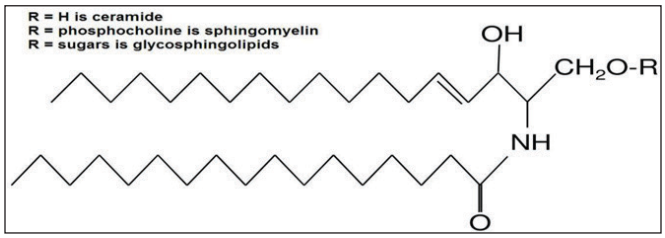

Figure 2: Structure of sphingolipid.

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 inclusion in the sphingosome bilayer might alter the membrane's preparation significantly. Cholesterol cannot form a bilayer structure on its own, but it can be incorporated into sphingolipid membranes at exceptionally high concentrations, with a cholesterol-to-sphingolipid molar ratio of 1:1 or even 2:1. Cholesterol incorporation lengthens the distance between the choline head group and removes electrostatic and hydrogen-bonding interactions. Sphingosome stability may be improved by adding stearylamine (SA), a positive charge producing chemical. Other components may be added to sphingosomes to concentrate them on certain cell types. Sphingosomes, for example, may be linked to monoclonal antibodies or monoclonal antibody binding fragments that bind to epitopes present only on particular cell types, such as cancer-related antigens, enabling the sphingosomes to be targeted after systemic distribution. Alternatively, ligands that bind to the surface receptors of the target cell types might be bound to the liposomes. [13]

THEORETICAL ASPECTS OF SPHINGOSOMES

Formation of ordered membranes

In a conventional lipid-bilayer assembly, the hydrophobic acyl chains of a lipid molecule link and interact with those of nearby molecules, and the polar head groups orient themselves to the assembly's exterior. Because sphingolipids split into ordered domains in general, sphingosomes generate ordered membranes. Sphingolipids come in a variety of head group configurations and acyl chain compositions in nature. Ceramide moieties with a long chain base and long saturated N-acyl chains divide sphingolipids into organized membrane domains. The polar head group of these lipids, which may vary from a single hydroxyl in ceramide to the phosphocholine group in sphingomyelin to huge assemblies of carbohydrates in the complex glycosphingolipid, will undoubtedly affect their partitioning. [14]

Stability against hydrolysis

Liposome dispersions are thermodynamically unstable. The total free energy of a distributed system may always be lowered by lowering the interfacial area. This aggregation tendency is caused by the attractive van der Waals interactions between the negatively charged groups on the liposome surface. A large hydrophilic group protects the negative charge in sphingosomes, which is crucial for avoiding vesicle aggregation during preparation and storage, as well as perhaps shortly after injection. Phospholipids in liposomes may be subjected to chemical degradation such as oxidation and hydrolysis as a result of ester linkages. The structure of sphingosomes renders them resistant to hydrolysis. Sphingolipids are physiologically inert macromolecules containing amide and ether linkages in the backbone that resist hydrolysis. [14]

Interaction between cholesterol and sphingolipids

Cholesterol favors sphingolipids over acyl-chained phosphatidylcholine for interaction. It has long been known that cholesterol and sphingolipid concentrations in distinct membrane fractions have a positive relationship. In monolayer and bilayer membranes, cholesterol desorbs more slowly from sphingomyelin-rich membranes or is held more easily in sphingomyelin-containing acceptor vesicles than acyl-chain phosphatidylcholines, according to cholesterol desorption and exchange tests. These interactions may benefit sphingosomes by boosting their biological efficiency. [14]

Encapsulation

Sphingosomes exhibit high drug entrapment efficiency in response to a transmembrane pH gradient. This guarantees efficient drug encapsulation while also lowering drug efflux from the vesicles. [14]

Circulation time

The reticuloendothelial system's rapid clearance of liposomes from the circulation has been a major barrier to using liposomes for systemic pharmaceutical delivery. The circulation life of sphingosomes and the time it takes for drugs to be released are both significantly increased when the sphingosomal wall stiffness is increased. Furthermore, a bulky hydrophilic group covers the negative charge on the surface of sphingosomes, slowing their clearance by the reticuloendothelial system and lengthening their biological half-life. [14]

Drug loading in tumor

Sphingosomes readily extravasate via the pores of leaky tumor arteries generated during angiogenesis and accumulate inside the tumor. These tough sphingosomes slowly release the encapsulated drug after they've been lodged in the interstitial space. Slow drug release from extravasated sphingosomes enhances tumor drug levels, extends drug exposure across many cell cycles, and significantly improves tumor cell killing. [14]

PREPARATION OF SPHINGOSOMES

Drug loading into vesicles is required for sphingosome synthesis. Loading might be passive (streptokinase, urokinase) or active (streptokinase, urokinase) (streptokinase, urokinase). A wide spectrum of therapeutic substances may be loaded into sphingosomes using a transmembrane pH gradient, with encapsulation efficacy reaching 100%. This method involves producing a gradient that draws lipophilic compounds to the interior of vesicles, where they may remain as long as the gradient is maintained. In most situations, passive loading required adding medication to the buffer during the reconstitution phase. This allowed the drug to be entrapped within the vesicles' interior, where it would have ordinarily remained if it had not been lipid-soluble. The most common method for preparing sphingosomes is passive loading. The following are some of the passive loading techniques that have been used:

Mechanical dispersion method

When utilizing the mechanical dispersion approach, start with a lipid solution in an organic solvent and conclude with lipid dispersion in water. The multiple components are normally combined by co-dissolving the lipid in an organic solvent and then vacuum film deposition is used to remove it. After all of the solvents have been removed, the solid lipid mixture is hydrated with an aqueous buffer. When lipids expand and hydrate spontaneously, sphingosome vesicles form. At this point, procedures change their properties by including essential processing factors (such as sonication, freeze-thawing, and high-pressure extrusion) in various ways. [15]

Lipid Film method

In 1965, Bangham et al. described the film method. A mixture of adequate proportions of lipid is cast as a stack of film from this organic solution using a flash rotary evaporator under reduced pressure (or by handshaking), and then the casted film is dispersed in an aqueous medium. When lipids are hydrated, they expand and peel away from the flask wall, resulting in multilamellar sphingosomal vesicles (MLSVs). The mechanical energy required for lipid swelling in dispersion casted lipid films is provided by manual agitation (handshaking technique) or by exposing the film to a stream of nitrogen for 15 minutes followed by swelling in an aqueous medium without shaking (non-shaking methods). Non-shaking vesicles are large unilamellar sphingosomal vesicles, while handshaking vesicles are MLSVs. The size and other features of MLSVs created by lipid hydration might be modified even further. 15 Figure 3 depicts the stages involved in preparing sphingosomes.

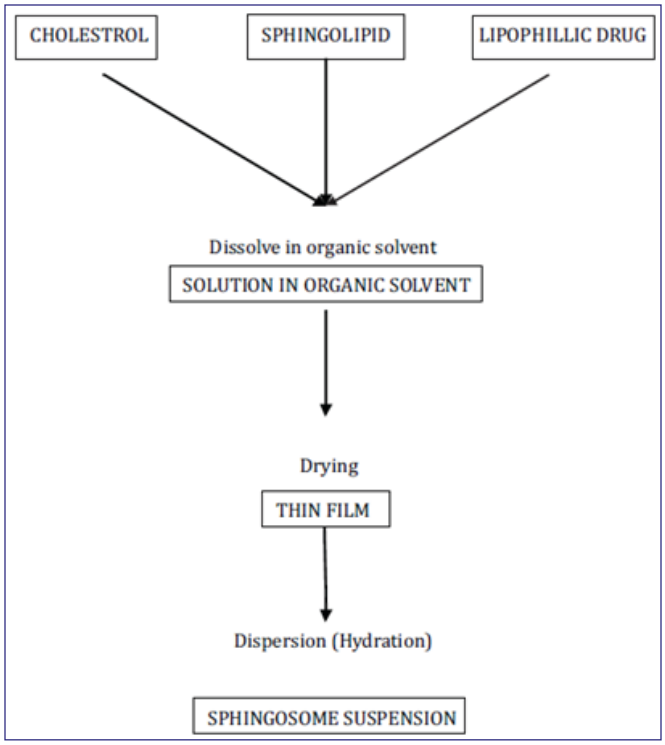

Figure 3: Steps in sphingosome preparation.

Extrusion technique

In most situations, it is utilized to shrink sphingosomes. A polycarbonate membrane/an asymmetric ceramic membrane,

a filter with a core of 0.6 µm (once) and 0.2 µm, and a filter with a core of 0.6 µm (once) are used in this approach to extrude all of the dispersion (ten times). To enhance sphingosome encapsulation, the dispersion was frozen and thawed 10 times. The non-entrapped medicine was extracted after 30 minutes of ultracentrifugation at 55,000 rpm and 4°C. The pellets disperse in the buffer after that. [15]

Sonication

At high energy levels, the average size of sphingosomes decreases even further. This was first done by subjecting MLSVs to ultrasonic irradiation, and it is still the most common method for producing small vesicles today. Sonication may be accomplished in one of two ways: with a probe or in a bath. Ultrasonic disintegrator bath sonicators are often used to prepare small unilamellar vesicles. [15]

Microfluidization

This is a brand-new technique for making small MLVS. The fluid is pushed through a screen at high pressure using a Micro fluidizer (10,000 psi). The fluid is then forced through microchannels that induce two streams of fluid to collide at right angles, resulting in a highly efficient energy transfer. Now you may add the lipids to the fluidizer. The fluid collected may be recirculated via the pump until spherical vesicles form. As a result, the finished products are more uniform, smaller, and reproducible. [15]

French pressure cells

This is a really realistic strategy. In a French press, prefabricated sphingosomes are extruded under high pressure. This approach yields predominantly unilamellar or oligolamellar sphingosomes. These sphingosomes are more stable than those made from sonicated vesicles. 15

Microemulsification technique

A microfluidizer pump is used to create microscopic multilamellar vesicles. The microfluidizer pumps the fluid via 5 m orifices at a very high pressure of 10,000 psi. After a single pass, vesicles are shrunk to 0.1 µm and 0.2 µm in diameter. [15]

Solvent Spherule Method

Sphingolipids are dispersed as small spheres in aqueous solutions in solvent spherules after being dissolved in a volatile hydrophilic solvent. When a volatile hydrophilic organic solvent is evaporated in a water bath under controlled conditions, multi lamellar vesicles form. [15]

Calcium-induced Fusion Method

Multilamellar vesicles are formed when calcium sphingosomes combine with SUV sphingosomes. By adding EDTA to large unilamellar vesicles, sphingosomes may be generated from multilamellar sphingosome vesicles. This method is used to encapsulate macromolecules. [15]

CHARACTERIZATION

Sphingosomes are vesicular systems with morphological, biophysical, drug loading, drug release, and stability features that must be investigated. For determining the biophysical parameters of the finished medicinal product, 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. Particle sizing and size distribution may be studied using dynamic light scattering (DLS), electron microscopy with cryofixation techniques or negative staining, atomic force microscopy (AFM), and ultracentrifugation. Liposome lamellarity may be detected via NMR spectroscopy, small-angle X-ray scattering, and cryo-electron microscopy. Using zeta potential measurements, the electrophoretic mobility (microelectrophoresis) of liposomal vesicles may be evaluated, and therefore the surface charge density of the vesicles can be estimated. The therapeutic efficiency and in vivo performance of these drug delivery systems are evaluated using some of the most essential properties, such as drug loading and in vitro release from liposomal vesicles. [16]

TRANSPORT MECHANISM OF SPHINGOSOMES

Small unilamellar sphingosomal vesicles (SUSVs) have a range of interactions with cells. Stable adsorption, endocytosis, fusion, and lipid transfer are among them (Figure 4).

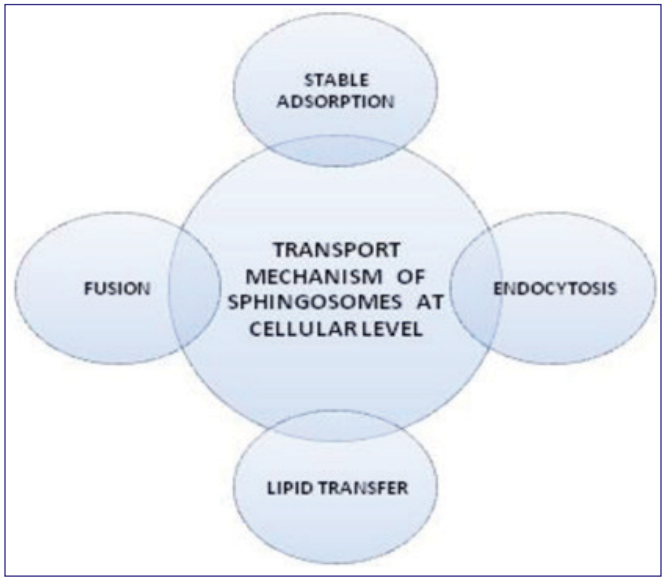

Figure 4: Transport Mechanism of Sphingosomes.

Stable adsorption

Stable adsorption is the contact of intact vesicles with the cell surface. This mechanism or a component found on the surface of vesicles or cells involves non-specific electrostatic, hydrophobic, or other forces 17 (Figure 5).

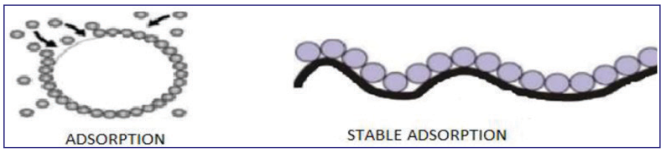

Figure 5: Adsorption Phenomena.

Endocytosis

Endocytosis is the process by which intact vesicles are picked up by endocytotic vesicles and transported to the lysosomes 17 (Figure 6).

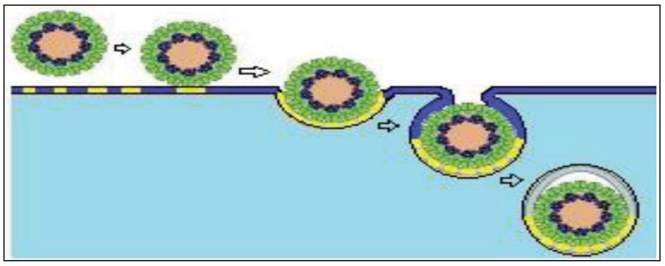

Figure 6: Endocytosis.

Fusion

Fusing is defined as the simple fusion of vesicle and plasma membrane bilayers, with components releasing vesicle content into the cytoplasmic space 17 (Figure 7).

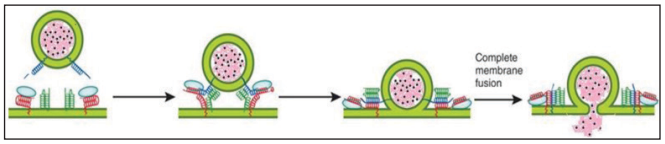

Figure 7: Fusion.

Lipid exchange

Individual lipid molecules may be transported between vesicles and the cell surface without aqueous vesicle content being connected with the cell. [17]

APPLICATIONS OF SPHINGOSOMES

A wide spectrum of therapeutic substances may be delivered through the sphingosome. Therapeutic substances include nucleic acids, proteins, peptides, oncolytics, anti-infectives, anxiolytics, psychotropics, ionotrops, toxins like gelonin, and inhibitors of eukaryotic protein synthesis. One of the most popular therapeutic compounds for trapping in sphingosomes is "lipophilic cations." Among them are therapeutic drugs from the family of lipophilic substances that may partition into the lipid bilayer phase of sphingosomes and so interact with them in a membrane form. Sphingosomes may show to be a useful carrier for transporting medications to the site of action due to their biodegradability, benign nature, and resemblance to biological membranes. [18]

Cosmetic industry

Sphingosomes are also used in the cosmetic industry and in the administration of transdermal medications. Topically applied sphingolipids have a high degree of skin compatibility. Sphingosome membrane lipids have features that allow them to penetrate since they belong to the same chemical compound family as epidermal lipids. [18]

Drug delivery vehicles

Sphingosomes are lipid structures with an aqueous interior that may be unilamellar or multilamellar, depending on how many lipid membranes are formed. Medicines may be put inside liposomes, which are encased in the vesicle's core, or pharmaceuticals can be linked to the sphingosome or incorporated into the lipid bilayer. In comparison to free medications, such pharmaceuticals, such as liposomal formulations, have been shown to be more efficacious. For example, researchers discovered that a liposomal formulation containing the vinca alkaloid vincristine was more efficacious and had lower overall toxicity than free vincristine. Sphingosomes may be used to treat proliferative sickness, immunological disease, infectious disease, vascular disease, rheumatic disease, and inflammatory disease. Examples of representative medications include prostaglandins, amphoterecin B, methotrexate, cisplatin, vincristine, vinblastine, doxorubicin, camphothecin, ciprofloxacin, progesterone, testosterone, estradiol, beclometasone and esters vitamin-E, dexamethasone, and other steroids. [18]

Enzyme delivery

Streptokinase, urokinase, and esterase are among the enzymes enclosed in sphingosomes. Sphingosomes have been used to catalyze a variety of processes, including the generation of esters, peptides, and the transformation of sugar acetals. [18]

Ophthalmic drug delivery

In ocular therapeutics, delivering an optimal medicine concentration at the site of action is a major challenge. Ocular drug bioavailability may be influenced by the physical and chemical qualities of the medicine, as well as the physical characteristics of the vehicle in which the drug is administered. The selection of vehicles has been limited to semisolid kinds because to the anatomical design of the conjunctival sac and the sensitivity of the cornea to exterior objects. In ocular medicine administration, vesicles, among other vehicles and carriers, have sparked a lot of attention. In the treatment of acute and chronic herpetic keratitis, idoxuridine entrapped in sphingosomes is more effective

than a comparable therapeutic regimen of unentrapped medicine. [18]

Tumor therapy

The bulk of pharmaceutical applications that have advanced to the preclinical and clinical stages are in cancer; for example, the sphingosomal chemical Vinorelbine (semi-synthetic vinca alkaloid) is now in phase-I clinical trials. Increased clinical activity in sphingosomes is associated to higher drug concentration at the tumor site. Cell cycle-specific drugs such as vincristine, vinorelbine, and topotecan, which kill tumor cells by interfering with mitosis at a specific phase in the cancer cell cycle, have a high link between exposure and anti-tumor efficacy. As a consequence, our patented sphingosomal drug delivery technique encases approved anti-cancer drugs in the aqueous core of microscopic liposomes, potentially boosting its therapeutic index. Sphingosomal products like MarqiboTM (sphingosomal vincristine) are rich in active, cell cycle-specific anti-cancer medications that might benefit from better targeting and longer drug exposure at the tumour site. Vincristine, vinorelbine, and topotecan sphingosomal formulations were selected for their potential to benefit from this novel encapsulation. Vincristine (Oncovin®; Eli Lilly and Company) is a microtubule inhibitor that has been approved for the treatment of acute lymphoblastic leukaemia (ALL) and is widely used for the treatment of hematologic malignancies such as lymphomas and leukemias as a single agent and in combination regimens. Vinorelbine (Navelbine®; GlaxoSmithKline), a microtubule inhibitor, has been approved for use as a single agent or in combination with cisplatin in the first-line treatment of unresectable, advanced non-small cell lung cancer. Topoisomerase-I inhibitor topotecan (Hycamtin®; GlaxoSmithKline) has been approved for the treatment of relapsed small-cell lung cancer and ovarian cancer. [18]

Other therapeutic application of sphingosomes

Antimicrobial, antifungal, and antiviral (anti-HIV) treatment using sphingosomes.

Sphingosomes might be employed to transport genes.

Sphingosomes may be employed to immobilize enzymes.

Immunology may benefit from sphingosomes.

SPECIFIC RESEARCH WORKS

Sphingosomes have attracted a lot of attention in recent years due to their potential applications. Sphingolipids' functional properties are employed in a variety of applications. Sphingosomes are gaining popularity due to their application in stabilizing and prolonging the circulation length of

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 Alocrest (vinorelbine tartrate liposome injection)	Colonic tumor
	Swasinosine in combination with interferon Topotecan (Hyacamtin®)	Non-small cell lung cancer, breast cancer
	Vincristine (vincristine sulphate liposome injection)	Colon cancer and melanoma
	Vincristine in combination with Rituximab (Oncovin®)	Relapsed small-cell lung cancer, relapsed ovarian cancer
	Vinorelbine (Navelbine®) single or in combination with cisplatin	Non-Hodgkins lymphoma
		Large B-cell lymphoma
		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, vincristine, vinblastine, doxorubicin, camphothecin, ciprofloxacin, progesterone	Proliferative disease, immune 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

liposomes for the design of customized drug delivery systems. Several research on the manufacture and use of sphingosomes in drug administration have been reported. Table 2 shows a list of sphingosome formulations that have been created.

Modrak et al. filed a patent for a sphingomyelin-containing preparation for the treatment of rheumatoid arthritis, in which they investigated the use of sphingomyelin in the manufacturing of rheumatoid arthritis medicine.

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, in which sphingomyelin is given in combination with an anthracyclin.

Vincristine, vinorelbine, and vinblastine encapsulated in liposomes were studied for drug loading and retention by Igor et al. They observed that different vinca alkaloids had different retention properties, with the more hydrophobic drugs releasing faster. They observed that using the ionophore technique for loading may improve the retention qualities of vinca medications with a low drug-to-fat ratio.

Modrak et al. filed a patent for Sphingomyelin augmentation of tumor therapy, claiming that co-administration of 5-fluorouracil and sphingomyelin slowed the progression of colonic tumors to a greater degree and for a longer duration.

Webb et al. filed a patent for sphingosome formulations, claiming that the formulation enhanced drug dispersion of ciprofloxacin, swainsonine, vincristine, and vinblastine.

Hope et al. filed a patent for a more stable, cost-effective, and easy-to-manufacture method of loading a therapeutic medication into manufactured liposomes with a methylamine concentration gradient across the liposomes' lipid bilayer.

FUTURE ASPECTS

The use of sphingosomes as a medication or bioactive carrier has yet to be perfected. Researchers from all around the world are attempting to strengthen the vesicular system by making it more stable in nature, in order to prevent content leaching, oxidation, and absorption by natural defense systems. The genetic engineering component might be integrated with the existing cellular drug carrier concept to give it a new dimension. The immobilization of enzymes, the concealment of drug taste, improved gastrointestinal absorption, functioning as a carrier for sustained release and transdermal drug delivery, and the treatment of medication overdose are all potential therapeutic uses. These systems might be employed as potential carriers for drug cosmetics and medicines if new procedures for manufacture, stability, and characterisation are developed.

CONCLUSION

Vesicular systems have been investigated as a key drug delivery mechanism throughout the years due to their adaptability in being modified for a number of desired aims. Sphingosomes are bilayered vesicles with an aqueous volume entirely enclosed by a membrane lipid bilayer mostly composed of natural or synthetic sphingolipid. Lipophilic cations are the best candidates for encapsulation. Clinically, sphingosomes are used to provide chemotherapy drugs, for diagnostic reasons, and in the beauty industry. Sphingosomes contain lipids that are similar to those found in the skin, making them more appropriate and safe for the host cell. Sphingosomes are universally acknowledged as safe and have no restrictions in the EU or the US Food and Drug Administration.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1. Kamboj S, Saini V, Magon N, Bala S, Jhawat V. Vesicular drug delivery systems: a novel approach for drug targeting. Int J Drug Deliv. 2013;5(2):121-30.
2. Kamboj S, Saini V, Maggon N, Bala S, Jhawat VC. Novel vesicular drug carriers for bioavailability enhancement. Int J Pharm Sci Rev Res. 2013;22:92-7.
3. Ashara KC, Paun JS, Soniwala MM, Chavda JR, Nathawani SV, Mori NM, Mendapara VP. Vesicular drug delivery system: a novel approach. Mintage J Pharm Med Sci. 2014;3(3):1-4.
4. Shinde NG, Aloorkar NH, Kulkarni AS. Recent advances in vesicular drug delivery system. Res J Pharm Dosage Form Technol. 2014;6(2):110-20.
5. Biju SS, Talegaonkar S, Mishra PR, Khar RK. Vesicular systems: an overview. Indian J Pharm Sci. 2006;68(2):141-53.
6. Myneni GS, Radha GV, Soujanya GV. Novel Vesicular Drug Delivery Systems: A Review. J Pharm Res. 2021;11(4):1650-64.
7. Demetzos C, Pippa N. Advanced drug delivery nanosystems (aDDnSs): a mini-review. Drug Deliv. 2014;21(4):250-7.
8. Saraf S, Gupta D, Kaur CD, Saraf S. Sphingosomes a novel approach to vesicular drug delivery. Int J Cur Sci Res. 2011;1(2):63-8.
9. Chaudhari SP, Gaikwad SU. Sphingosomes: A Novel Lipoidal Vesicular Drug Delivery System. 2020;5(4):261-7.
10. Webb MS, Bally MB, Mayer LD. Sphingosomes for enhanced drug delivery. Biotechnol Adv. 1997;2(15):527.
11. Adams CA, Novellie L. Sphingosome. In: Tabrizi MM, Hosseini SA, Khiyavi AA. Liposome & Nanotechnology; 2016.

12. Lankalapalli S, Damuluri M. Sphingosomes: applications in targeted drug delivery. Int J Pharm Chem Biol Sci. 2012;2(4):507-16.
13. Ashok K, Kumar AR, Nama S, Brahmaiah B, Desu PK, Rao CB. Sphingosomes: A Novel Vesicular Drug Delivery System. 2013;2(2):305-12.
14. Ashok K, Kumar AR, Nama S, Brahmaiah B, Desu PK, Rao CB. Sphingosomes: a novel vesicular drug delivery system. Int J Pharm Res Biosci. 2013;2(2):305-12.
15. Brunke R. Sphingosomes in skincare. Manufact Chem. 1990;61:36-7.
16. Fathima KM, Nitheesh A, Paul A, Nair SC. Sphingosome vescicular system. Int J Pharm Sci Rev Res. 2016;41(1):208-13.
17. Erdogan S, Ozer AY. A New Approach for Liposomes in Dermatological Preparations: Sphingosomes. Hacettepe Univ J Facul Pharm. 1999;19(2):81-94.
18. Lankalapalli S, Damuluri M. Sphingosomes: applications in targeted drug delivery. Int J Pharm Chem Biol Sci. 2012;2(4):507-16.