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Sphingosomes: Advancements and Emerging Applications in Advanced Drug Delivery Systems

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Keywords

Sphingosomes, Drug delivery, Sphingomyelin, Vesicular system, Preparation, Applications

Abstract

In a variety of different scientific fields, vesicular systems have proven to be very effective carrier systems. Sphingosomes are bilayered vesicles having a fully enclosed aqueous membrane lipid bilayer made primarily of sphingolipid, natural or synthetic. The instability, in vivo circulation duration, and cancer loading efficacy in cancer therapy are important limitations of the vesicle system (liposomes, niosomes) that are addressed by sphingosomes. The information was acquired by searching for Sphingosomes in the Scopus and Google Scholar databases. In clinical contexts, Chemotherapy, biological macromolecules, and diagnostics are delivered via sphingosomes. Due to their size and content, sphingosomes can take several forms. The report suggests that sphingosomes are a potential vesicular drug delivery system that may transport pharmaceutical substances for a variety of purposes.

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1. Introduction

Innovative medicine delivery methods (NDDS) have garnered interest recently. An innovative drug delivery system is a new formulation and channel for medicine. NDDS should meet two criteria. The medicine should be given at the body's pace during treatment. The action location must receive the active object. Extended-release formulations are standard [1]. New medicine delivery methods have failed despite repeated efforts modern drug delivery systems provide users with temporal, geographical, or both control over drug release in the body. Innovative drug delivery strives to reduce adverse effects while maintaining a steady pharmacological activity or effective medicine level in the body. It can also localize medication activity by inserting controlled-release devices near or inside the affected tissue or organ, or target an individual cell type via carriers or pharmacologic derivatization [2].

Pharmaceutical carriers vary in size. Cellular, macromolecular, polymeric, and particulate carriers exist. Colloidal carrier systems include lipid particles (LDL and HDL), microspheres, nanoparticles, polymeric micelles, liposomes, sphingosomes, niosomes, pharmacosomes, and virosomes. Amphiphilic construction creates vesicular systems, highly organized lipid bilayer assemblies materials that meet water. Amphiphilic elements compose vesicles. Bingham discovered the biological genesis of these vesicles in 1965, naming them Bingham bodies. Liposome vesicles are surrounded by lipid membranes [3]. Most liposomes contain one lipid membrane, although the structure may have more. Unilamellar liposomes are single-layered, while multilamellar ones are multilayered. Preferred liposomes are lipids that form stable vesicles. Several lipids can be used to stabilize a liposome. Neutral or negatively charged phospholipids, sphingolipids, and sterols like cholesterol are desired. Liposome size and circulatory

stability determine the lipid [4].

Liposomal drug delivery systems offer tailored drug dispersion, active moiety release preservation and control, and endocytosis-mediated cellular absorption. Liposomes also suffer from disintegration, hydrolysis, and oxidation. Liposome stability difficulties are far more serious, making liposomal stability improvement a priority. These alterations may cause liposome phospholipids to oxidize, hydrolyze, agglomerate, fuse, or leak. Ester linkage hydrolysis delays at neutral pH. Avoid hydrolysis by using sphingolipid or phospholipid derivatives with carbomoyloxy activity instead of ester connections. Sphingolipids are being used to make stable liposomes termed sphingosomes [5]. Despite advancements in liposomal drug delivery, issues like instability and short circulation time limit their clinical utility. Sphingosomes, composed primarily of sphingolipids, offer a promising alternative due to their superior stability, extended plasma circulation, and enhanced drug retention. This review aims to critically evaluate the recent advancements in sphingosome technology, highlighting their preparation methods, classification, advantages over traditional systems, and future potential. Unlike previous reviews, this article emphasizes clinical translation and formulation challenges, providing a bridge between fundamental understanding and therapeutic application [6].

1.1. Sphingosome

A concentrated bilayer sphingosome includes an aqueous volume contained by a membrane lipid bilayer mostly made of manufactured or natural sphingolipid. Sphingosomes overcome the primary drawbacks of the vesicle system (liposomes, niosomes): less stability, shorter in vivo circulation time, and limited tumor loading efficacy in cancer therapy structure shown in figure 1 [7]. Chemotherapeutics, macromolecules in biology, and diagnostics are delivered by sphingosomes. Different sphingosomes have been created and developed due to their size and composition flexibility. Sphingosomes resist acid hydrolysis and retain drugs better. Sphingosomes are administered intravenously, intramuscularly, subcutaneously, and intra-arterially. It will be given intravenously or sometimes inhaled. It's frequently injected into the superior or inferior vena cava to supply a highly concentrated solution to large-volume and flow arteries. Consume or apply sphingosomes [8].

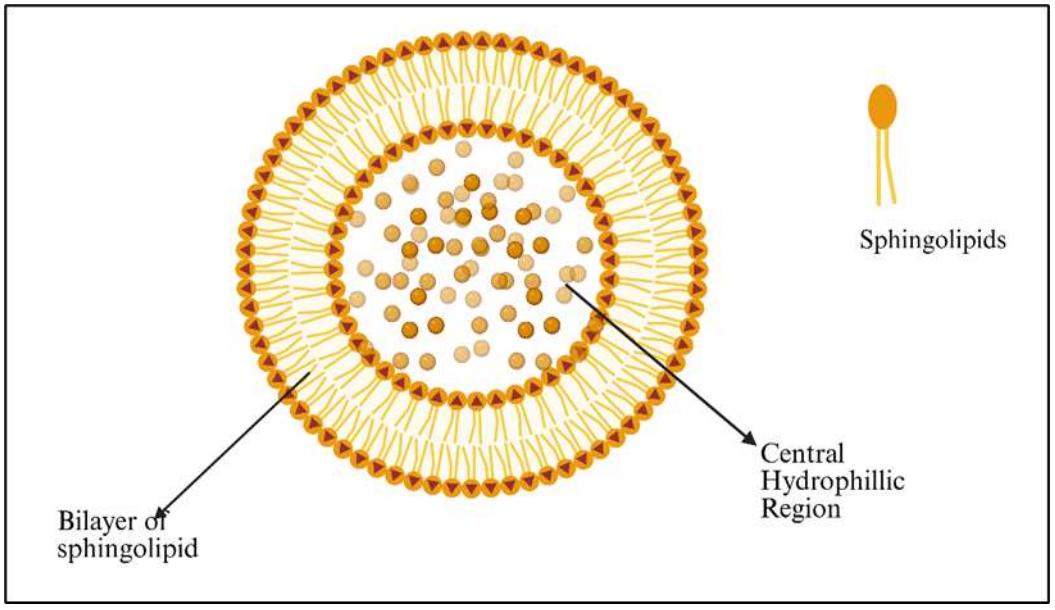

Figure 1. Structure of sphingosomes.

1.2. Advantages of Sphingosomes

To effectively target tumor tissue, passive targeting strategies can be employed to enhance drug accumulation at the site. Encapsulation of therapeutic agents not only improves their stability but also reduces toxicity, thereby enhancing their therapeutic index. Additionally, increasing the circulation time of the drug helps optimize pharmacokinetic properties. Active targeting can further improve specificity by using ligands that bind selectively to receptors at the desired site, ensuring more efficient and localized drug delivery [9].

1.3. Advantages Over Phospholiposomes

Sphingolipids, composed entirely of amide and ether linkages, are more hydrolytically stable than the ester-linked lecithin, making them less prone to degradation. Their lower double bond content also reduces the risk of rancidity and oil absorption compared to lecithin. Sphingosomal technology utilizes these properties to enhance liposomal drug delivery. The increased stiffness of the liposomal wall extends circulation time, allowing more drug to reach and remain at the tumor site. This prolonged presence ensures sustained drug release, increasing exposure during various phases of the tumor cell cycle. Moreover, the leaky vasculature of tumors during angiogenesis, with gaps up to 800 nm, enables sphingosomes to penetrate and deliver drugs effectively over time [10].

1.4. Disadvantages

Despite their advantages, sphingolipid-based vesicular systems have certain limitations. Their high cost makes formulation and large-scale production more challenging. Additionally, they may exhibit inefficient drug trapping, which can reduce the overall therapeutic efficacy and limit their practical application [11].

2. Sphingosomes Classification

Sphingosomes are classified based on their size and the number of lipid bilayers. They can be unilamellar (with a single bilayer) or multilamellar (with multiple bilayers), and their diameters typically range from 0.05 to 0.45 μm, with most falling between 0.05 and 0.2 μm. Small unilamellar vesicles (SUVs) are 10–100 nm in diameter and consist of a single bilayer. Large unilamellar vesicles (LUVs) are also single bilayered but range from 100 nm to 1 μm. Multilamellar vesicles (MLVs) contain several bilayers and range from 100 nm to 20 μm. Oligolamellar vesicles (OLVs) have more than one but fewer bilayers than MLVs, typically sized between 0.1 and 1 μm. Multivesicular vesicles (MVVs) are 100 nm to 20 μm in size and contain multiple internal vesicles. Giant vesicles (GVs) are larger than 1 μm and may serve specialized purposes in drug delivery research [12].

2.1 Omposition of Sphingosine

Sphingomyelin and cholesterol make up sphingosomes, which have an acidic intraliposomal pH ratio of 75–25 mol%/mol% (ideally 55/45). Sphingomyelin-cholesterol liposomal compositions have many benefits over others. Sphingosomes resist acid hydrolysis and retain drugs better. Sphingolipids, a significant type of phospholipid, are more than just membrane structural components; they also transmit signals and recognize cells.21-22 Cells contain sphingolipid (Figure 2) [13]. J.L.W. Thudichum named them in 1884 for their mysterious character. Sphingolipids have hydrophobic bodies and polar heads. Polar sphingolipid is related to human skin lipids, particularly in the epidermis. Mammalian milk, particularly bovine milk, brain, egg yolk, and animal blood erythrocytes, notably sheep's blood, contain sphingolipids. Semi-synthetic sphingolipids exist. Sphingosine and ceramide are the simplest sphingolipids. Whereas the most complex sphingolipids include sphingomyelin (SM) and glycosphingolipids. Table 1 lists the many kinds of sphingolipids that may be employed in sphingosomes [14].

Table 1. Sphingolipid Classification.

S. No.	Classification	Examples	References
1.	Sphingoid bases	Sphing-4-engines (sphingosines) Sphinganines 4-Hydroxysphinganines (phytosphingosine) Hexadecasphinganine (Sphingoid base homologs and variants) Sphingoid base 1-phosphates Lysosphingomyelins and lysoglycosphingolipids *N-methylated* sphingoid bases Sphingoid base analogs	[15]
2.	Ceramides	N-Acylsphingosines (ceramides) N-Acylsphinganines (dihydroceramide) N-Acyl-4-hydroxysphinganines (phytoceramides) Acylceramides Ceramide 1-phosphates	[16]
3.	Phosphosphingolipids	Ceramide phosphocholines (sphingomyelins) Ceramide phosphoethanolamines Ceramide phosphoinositols	[17]
4.	Neutral glycosphingolipids	GalNAcβ1-3Galα1-4Galβ1-4Glc- (globo series) GalNAcβ1-4Galβ1-4Glc- (ganglio series) Galβ1-3GlcNAcβ1-3Galβ1-4Glc- (lacto series) Galβ1-4GlcNAcβ1-3Galβ1-4Glc- (neolacto series) GalNAcβ1-3Galα1-3Galβ1-4Glc- (isoglobo series) GlcNAcβ1-2Manα1-3Manβ1-4Glc- (mollu series) GalNAcβ1-4GlcNAcβ1-3Manβ1-4Glc- (arthro series) Gal- (gala series) Other	[18]
5.	Acidic glycosphingolipids	Gangliosides Sulfoglycosphingolipids (sulfatides) Glucuronosphingolipids Phosphoglycosphingolipids Other	[19]

2.2. Cholesterol

Cholesterol prefers to interact with sphingolipid over phosphatidylcholine, which contains an acyl chain. Cholesterol desorption or exchange studies in monolayer membranes and bilayer systems have shown that cholesterol desorbs faster from sphingomyelin-rich membranes or traps more avidly. Additionally, liposomes may bind substances that bind to specific surface receptors on target cells [20].

3. Sphingosomes Theory

3.1. Ordered membranes

A normal lipid bilayer assembly links and interacts with lipid molecules' hydrophobic acyl chains, and the polar head groups face the assembly's outside. Sphingosomes form ordered membranes because sphingolipids break into domains. Sphingolipids have several head groups and acyl chain configurations. Sphingolipid membrane domains are organized by long-chain ceramide moieties and saturated N-acyl chains. The partitioning of these lipids depends on their polar head groups, which can range from a single hydroxyl in ceramide to the phosphocholine group in sphingomyelin to massive carbohydrates in complex glycosphingolipid [21].

3.2. Stability Against Hydrolysis

Liposome dispersions exhibit heat instability. Reducing the interfacial area always decreases the free energy of a distributed system. The appealing van der Waals interactions among negatively charged liposome surface groups induce this aggregation tendency. A substantial hydrophilic moiety safeguards the negative charge in sphingosomes, which is essential for preventing vesicle aggregation during preparation and storage, and perhaps quickly after injection. Phospholipids in liposomes may undergo oxidation and hydrolysis due to ester linkages. Sphingosomes are hydrolysis-resistant. Sphingolipids are physiologically inert macromolecules characterized by amide and ether bonds in their backbone, which provide resistance to hydrolysis [22]

3.3. Interaction Between Cholesterol and Sphingolipids

Cholesterol preferentially interacts with sphingolipids rather than acyl-chained phosphatidylcholine. It has long been established that cholesterol and sphingolipid levels in certain membrane fractions exhibit a positive correlation. In monolayer and bilayer membranes, sphingomyelin-rich membranes or acceptor vesicles retain cholesterol for an extended duration. Phosphatidylcholines with acyl chains, based on cholesterol desorption and exchange assays. These interactions may enhance the biological efficacy of sphingosomes [23].

3.4. Encapsulation

Transmembrane pH gradients enhance drug trapping in sphingosomes. This ensures drug encapsulation and reduces vesicle efflux.[14] In response to the transmembrane pH gradient, sphingosomes entrap drugs efficiently. This reduces drug efflux from vesicles and improves drug encapsulation [24].

3.5. Circulation Time

The fast removal of liposomes from the bloodstream by the reticuloendothelial system has prevented their use for systemic medication administration. Sphingosomal walls with increased stiffness extend drug release and sphingosine lifespan. Sphingosome surface negative charge is hidden by a bulky hydrophilic group, which slows reticuloendothelial clearance and improves biological half-life [25].

3.6. Drug Loading in the Tumor

Sphingosomes readily enter the tumor via leaky tumor arteries produced during angiogenesis. The resilient sphingosomes gradually release the encapsulated medicine after they are situated in the interstitial region. Prolonged drug release from extravasated sphingosomes increases tumor drug concentrations, prolongs drug exposure across several cell cycles, and markedly promotes tumor cell cytotoxicity [26].

4. Preparation of Sphingosomes

Sphingosome production requires vesicle drug loading. Streptokinase and urokinase load passively or actively. A transmembrane pH gradient can encapsulate 100% of medicinal compounds into sphingosomes. Maintaining a gradient retains lipophilic compounds in vesicles in this approach. Passive loading required drug buffer reconstitution. If the drug had not been lipid-soluble, it would have stayed in the vesicles. Passive loading produces most sphingosomes [27].

4.1. Mechanical Dispersion Method

Drug-loaded vesicles produce sphingosomes. Urokinase and streptokinase load passively. A transmembrane pH gradient encapsulates 100% of therapeutic substances in sphingosomes. Maintaining a gradient keeps lipophilic chemicals in vesicles. Passive loading needed drug buffer reconstitution. Without lipid solubility, the medication would have persisted in the vesicles. Passive loading creates most sphingosomes [28].

4.2. Lipid Film Method

A flash rotary evaporator under reduced pressure (or handshaking) casts a stack of film from this organic solution with adequate lipid proportions, which is subsequently dispersed in an aqueous medium. MLSVs form when lipids hydrate and peel away from the flask wall. Handshaking or nitrogen exposure for 15 minutes, followed by swelling in an aqueous solution, supplies the mechanical energy needed for lipid swelling in dispersion-casted lipid films. MLSVs shake, while huge unilamellar sphingosomal vesicles don't. Lipid hydration may alter MLSV size and other characteristics [29].

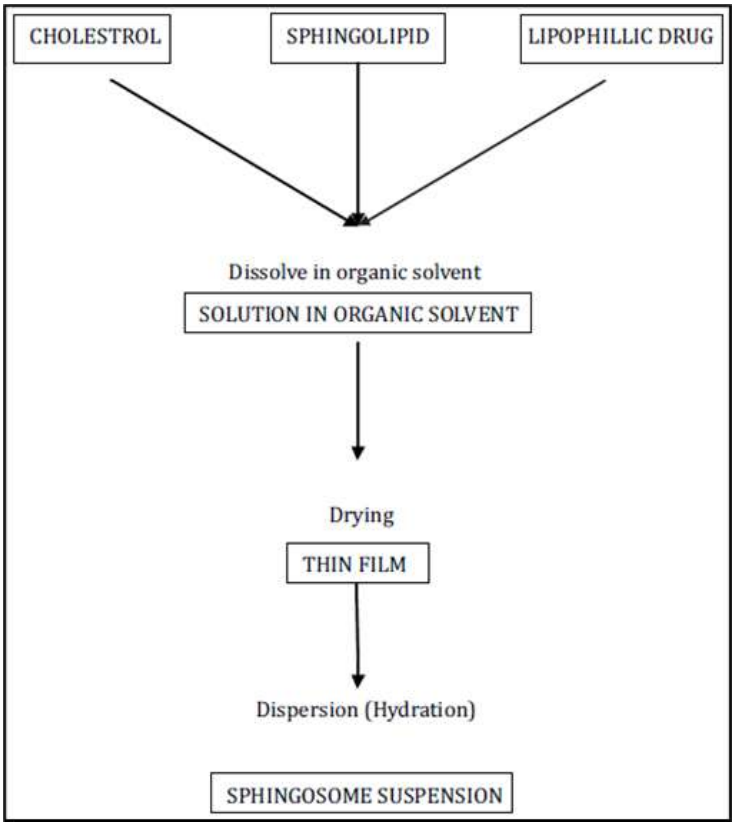

Figure 2. Steps in sphingosome preparation.

4.3. Extrusion Technique

In most instances, it is used to reduce sphingosine. A polycarbonate membrane/asymmetric ceramic membrane, a filter with a core of 0.6 µm (once) and 0.2 µm, and a 0.6 µm filter are used in this approach to extrude all of the dispersion (ten times). To improve sphingosome encapsulation, the dispersion underwent ten cycles of freezing and thawing. The non-entrapped medication was retrieved after 30 minutes of ultracentrifugation at 55,000 rpm and 4°C. The buffer disseminates the pellets [30].

4.4. Sonication

Sphingosomes shrink significantly at high energy levels. MLSVs were ultrasonically irradiated to create tiny vesicles, which is still the most prevalent approach. A probe or bath may sonicate. Ultrasonic disintegrator bath sonicators prepare tiny unilamellar vesicles [31].

4.5. Microfluidization

Small MLVS are made using this novel method. A 10,000-psi micro fluidizer forces fluid through a screen. Energy is efficiently transferred by forcing fluid through microchannels that cause two streams to meet at right angles. Fats may now be added to the fluidizer. The pump may recycle fluid until spherical vesicles develop. Therefore, completed items are more homogeneous, smaller, and repeatable [32].

4.6. French Pressure Cells

High-pressure French presses extrude premade sphingosomes. This method produces mostly unilamellar or oligolamellar sphingosomes. These sphingosomes are not as unstable as sonicated ones [33].

4.7. Microemulsification Technique

Create tiny multilamellar vesicles using a microfluidizer pump. The microfluidizer pumps fluid via 5 m orifices at 10,000 psi. After one pass, vesicles shrink to 0.1 and 0.2 µm in diameter [34].

4.8. Solvent Spherule Method

Sphingolipids dissolved in volatile hydrophilic solvents are disseminated as tiny spheres in aqueous solvent spherules. Multi-lamellar vesicles arise when a volatile hydrophilic organic solvent evaporates in a water bath under regulated circumstances [35].

4.9. Calcium-induced Fusion Method

Multilamellar vesicles arise when calcium and SUV sphingosomes interact. Sphingosomes may be made from multilamellar vesicles by adding EDTA to big unilamellar ones. This approach encapsulates macromolecules [36].

5. Characterization

Sphingosomes are vesicular structures that must be characterized for morphology, biophysics, drug loading, release, and stability. Gravimetric study of formulation lipids, lamellarity, particle size, and size distribution, phase transition temperature, vesicle charge, osmotic and pH characteristics, and light scattering index is indicated for biophysical parameters of the final medicinal product [37]. DLS, electron microscopy with cryofixation or negative staining, AFM, and ultracentrifugation can analyze particle size and distribution. NMR spectroscopy, small-angle x-ray scattering, and cryo-electron microscopy can identify liposome lamellarity [38].

Zeta potential tests can estimate liposomal vesicle electrophoretic mobility (microelectrophoresis) and surface charge density 31-32. These drug delivery systems' therapeutic efficacy and in vivo performance are measured by crucial parameters such as drug loading and liposomal vesicle release32-33. Drug loading and liposomal vesicle release from these drug delivery systems are utilized to evaluate their therapeutic efficacy and in vivo performance [39].

5.1. Transport Mechanism of Sphingosomes

SUSVs interact with cells in several ways. They include stable adsorption, endocytosis, fusion, and lipid transfer [28].

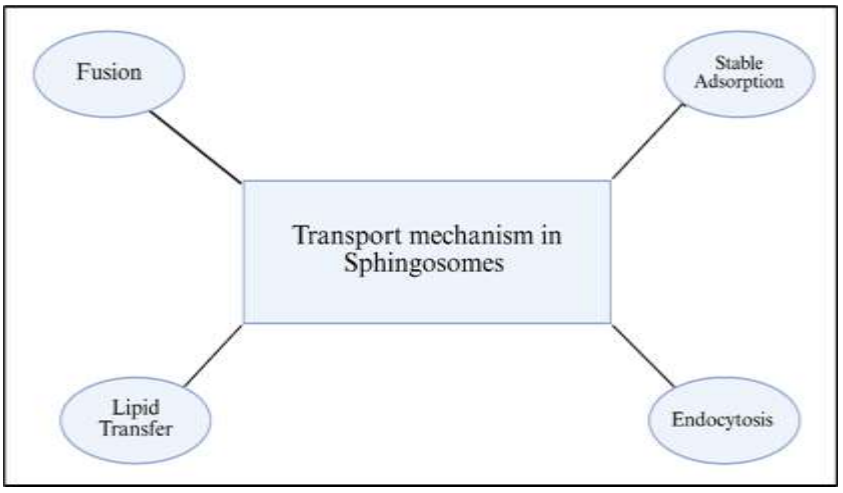

Figure 3. Transport Mechanism of Sphingosomes.

5.2. Stable Adsorption

The cell surface contacts intact vesicles for stable adsorption. A component on vesicles or cells using non-specific electrostatic, hydrophobic, or other forces [40].

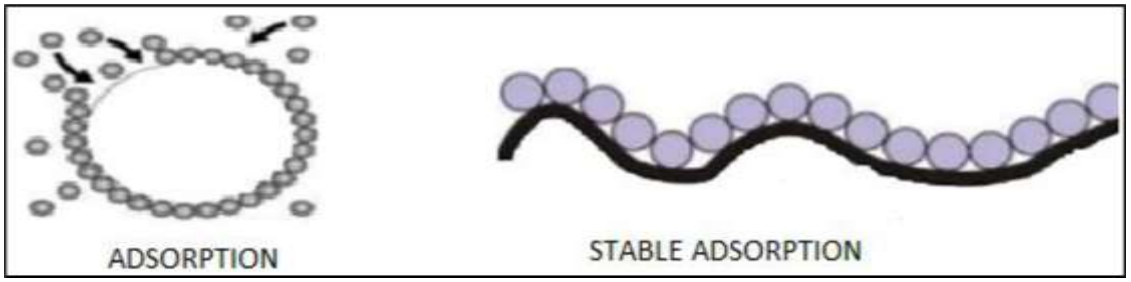

Figure 4. Adsorption Phenomena.

5.3. Endocytosis

Endocytosis is the process by which intact vesicles are scooped up by endocytotic vesicles and delivered to the lysosomes [41].

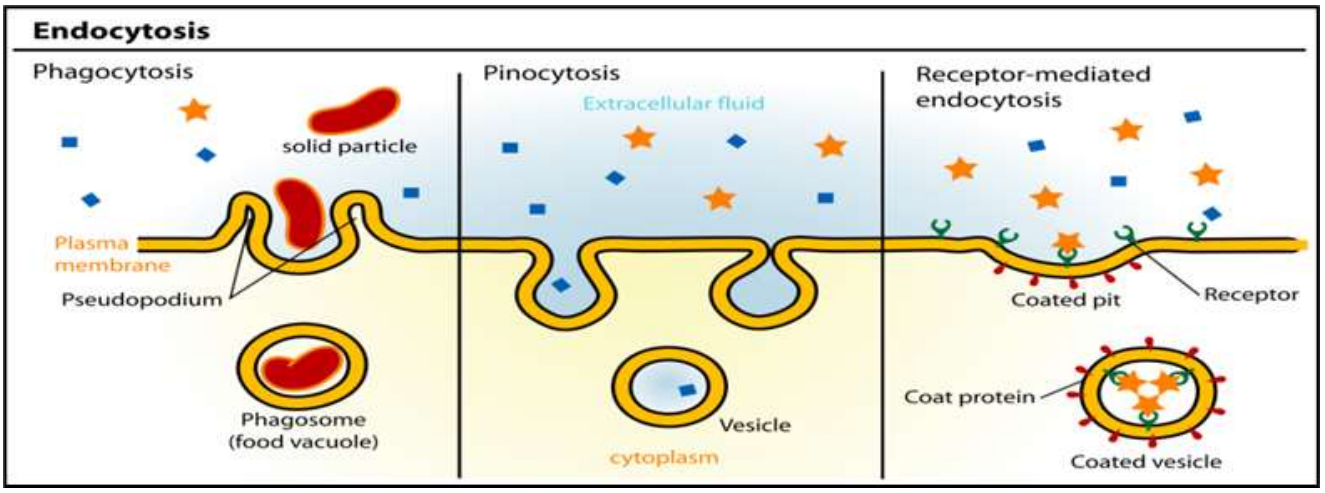

Figure 5. Endocytosis.

5.4. Fusion
Fusing is described as the straightforward amalgamation of vesicle and plasma membrane bilayers, resulting in the release of vesicle contents into the cytoplasm. Lipid molecules may be transferred between vesicles and the cell surface without aqueous vesicle content [42].

6. Applications of Sphingosomes
Sphingosomes deliver numerous medicines. Nucleic acids, proteins, peptides, anxiolytics, anti-infectives, anxiolytics, psychotropics, ionotropics, gelonin, and eukaryotic protein synthesis inhibitors are therapeutic. Lipophilic cations trap sphingosomes. Lipophilic drugs can partition into the sphingosomes' lipid bilayer phase and interact membrane-like. Sphingosomes may carry drugs due to their biodegradability, benign nature, and resemblance to biological membranes. Cosmetic industry Sphingosomes are utilized in cosmetics and medicine for the transdermal delivery of medications. Topically applied sphingolipids exhibit significant compatibility with the skin. Sphingosome membrane lipids possess characteristics that facilitate penetration, as they are part of the same chemical compound family as epidermal lipids [43].

6.1. Drug Delivery Vehicles
Sphingosomes are lipid structures characterized by aqueous interiors and can exist as either unilamellar or multilamellar, contingent upon the number of lipid membranes formed. Drugs can be sphingosome-linked, lipid bilayer-incorporated, or liposome-encased. Liposomal medicines work better. Liposomal vincristine was safer and more effective than free vincristine. Sphingosomes treat infectious, immunological, vascular, rheumatic, and inflammatory illnesses. Steroids include progesterone, testosterone, estradiol, beclometasone, vitamin E esters, dexamethasone, and others [44].

6.2. Enzyme Delivery
Streptokinase, urokinase, and esterase are enzymes contained within sphingosomes. Sphingosomes have been employed to catalyze various processes, including the synthesis of esters, peptides, and the conversion of sugar acetals [45].

6.3. Tumor Therapy
Angiogenesis creates leaky tumour arteries that allow sphingosines to enter and concentrate in the tumour. The durable sphingosomes facilitate the gradual release of medication from the interstitial space. Prolonged drug release from extravasated sphingosomes enhances tumor drug concentrations, prolongs drug exposure across multiple cell cycles, and significantly increases tumor cell mortality. Sphingosomal products, such as MarqiboTM (sphingosomal vincristine), contain active, cell cycle-specific anti-cancer agents [46]. Enhanced targeting and extended drug exposure at the tumor site may provide therapeutic benefits. This encapsulation was chosen for vincristine, vinorelbine, and topotecan sphingosomal formulations. Vincristine (Oncovin®; Eli Lilly and Company) treats ALL and other hematologic malignancies by inhibiting microtubules. Microtubule inhibitor vinorelbine (Navelbine®; GlaxoSmithKline) can be used alone or with cisplatin to treat advanced non-small cell lung cancer that is incurable. Relapsed small-cell lung and ovarian cancers are treated with topotecan (Hycamtin®; GlaxoSmithKline) [47].

7. Specific Research Works
Sphingosomes have gained a lot of interest in recent years owing to their prospective uses. The functional characteristics of sphingolipids are used in several applications. Numerous investigations on the manufacture and delivery of medicinal sphingosomes have been documented. Table 2 presents a list of sphingosome formulations that have been generated [48].

Table 2. Therapeutic uses of sphingosomes.

S. No.	Class	Formulations	Applications	References
1.	Anti-fungal therapy	Sphingosine and sphinganine, stratum corneum-free sphingolipids	Treating infections	[49]
2.	Cancer therapy	5-Fluorouracil in combination with sphingomyelin	Colonic tumor	[50]
		Alocrest (vinorelbine tartrate liposome injection)	Breast cancer, NSCLC	
		Swasinosine in combination with interferon	Colon cancer and melanoma	
		Topotecan (Hyacamtin®)	Relapsed small-cell lung and ovarian cancer	
		Vincristine (sulfate liposome injection)	Non-Hodgkins lymphoma	
		Vincristine with Rituximab (Oncovin®)	Large B-cell lymphoma	
		Vinorelbine (Navelbine®) single or in combination with cisplatin	Non-small cell lung cancer, metastatic breast cancer	

3.	Cosmetics	Beclomethasone	Skin / Dermal therapy	[51]
		Sphingosomes™ MOIST	Skin cleansing and makeup removal efficiency	
4.	Drug vehicles	Prostaglandins, amphotericin B, methotrexate, cisplatin, vincristine, vinblastine, doxorubicin, camphothecin, ciprofloxacin, progesterone	Immune, infectious, vascular, rheumatoid, and proliferative diseases	[52]

8. Future Aspects

The use of sphingosomes as a therapeutic agent or bioactive carrier remains unrefined. Researchers from all across the globe are working to enhance the vesicular system by stabilizing it to prevent content leaching, oxidation, and absorption by natural defense mechanisms. The genetic engineering aspect may be used with the current cellular drug carrier notion to enhance its functionality [53]. The immobilization of enzymes, the concealment of drug taste, gastrointestinal absorption, transdermal medication delivery, prolonged release, and treatment of medication overdose are all possible therapeutic applications. These systems might serve as prospective carriers for pharmaceutical and cosmetic agents, contingent upon the development of novel manufacturing, stability, and characterization methods [54].

9. Discussion

Sphingosomes constitute a great improvement on the conventional liposomal formulations, especially in terms of chemical stability and strength to keep drugs stable in a physiological environment. Liposomes are affected by the phospholipid degradation through ester contact, whereas sphingosomes use amide and ether bonds, which are more difficult to hydrolyze. Moreover, they have a long blood circulation time; thus, they provide prolonged delivery of drugs, especially in cancer treatment [55].

Nonetheless, the high price of sphingolipids and the challenge of formulation methods are two feasible obstructions to the clinical use. Sphingosomes, unlike the conventional phospholipid vesicles, cannot be handled and prepared using simple equipment and procedures. Despite positive results in oncology results of the study there is little information on their effectiveness in chronic and non-cancerous conditions [56].

Multiple experiments are extensively based on in vitro or small animals. The big hole is that there is a lack of large-scale, controlled clinical trials confirming sphingosome in a broader application of therapeutics. Future viewpoint should be the scalable methods of production cost-efficiency as well as the head-to-head comparison with other developed vesicular systems, which include the ethosomes, transfersomes, and the niosomes [57].

Conclusion

Sphingosomes offer a robust platform for targeted drug delivery with demonstrated advantages in stability, biocompatibility, and therapeutic efficacy. Their potential in oncology, enzyme delivery, and ophthalmology illustrates their versatility. However, high production costs and limited clinical data pose challenges for mainstream adoption. This review not only summarizes the structural and functional aspects of sphingosomes but also critically analyzes their limitations and highlights avenues for future research. By addressing these gaps, sphingosomes could transition from experimental formulations to frontline drug delivery tools in modern therapeutics.

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Author Contributions

P.D. Conceptualized the study, **D.K.** Supervised the review, **V.G.** Prepared the manuscript draft, **S.G.** Contributed to data analysis**, R.T.** Reviewed the manuscript critically for intellectual content, **K.B.** Visualization.

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Conflicts of Interest

No conflicts of interest are disclosed by the authors.

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