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REVIEW ARTICLE

A novel lipoidal vesicular drug delivery system: Sphingosomes

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ABSTRACT

Sphingosomes are vesicular drug delivery systems in which sphingolipid bilayer membranes fully enclose an aqueous volume. Sphingosomes can be utilized for therapeutic, cosmetic and diagnostic purpose for the delivery of active to the target site or organ. Oral, parenteral, inhalation, transdermal, and other routes of administration are available. Sphingolipids found in sphingosomes provide a range of benefits to these vesicular systems, including passive and active targeting mechanisms. Bioeffector molecules such as sphingolipids are being produced to control cell growth, proliferation, and anticancer therapeutics. Because of their usefulness in improving the *in vivo* delivery of various chemotherapeutic agents, biological macromolecules, and diagnostics, sphingosomes have become a hot subject. The focus of this analysis is on the use of sphingosomes in drug delivery technology.

INTRODUCTION

Sphingosomes are bilayered vesicles with an aqueous volume enclosed by a membranous lipid bilayer mainly made up of natural or synthetic sphingolipids [1]. Sphingosomes are made up of sphingolipids and cholesterol, with an interior aqueous atmosphere with a lower pH than the outside.

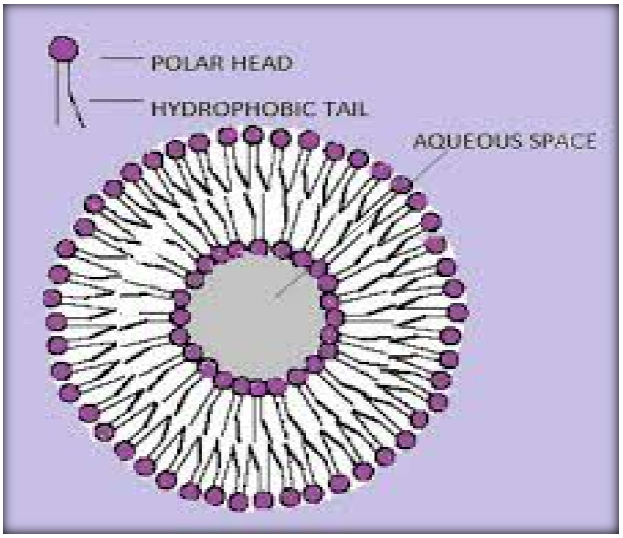

Figure 1: Sphingosomes

The drug is encapsulated within the lipid bilayer and distributed to the host at a preset rate, increasing effectiveness, increasing circulation time, and lowering toxicity [2]. Sphingosomes may be used to deliver active to a target site or organ for medicinal, cosmetic, or diagnostic purposes. Oral, parenteral, inhalation, transdermal, and other routes of administration are available. Sphingolipids found in sphingosomes provide a range of benefits to these vesicular systems, including passive and active targeting mechanisms. Drugs may be engineered to attack particular organs, systems, cells, or even intracellular organelles or molecules. Physical, biochemical, or molecular systems that result in high concentrations of pharmaceutically active agents at the targeted site, lowering their concentrations in the rest of the body, can be used to target drugs. Targeted drug delivery results in a lower dosage and improved treatment effectiveness, as well as a substantial reduction in drug toxicity. Drug targeting can be achieved using a range of methods that monitor the release and delivery of the therapeutic molecule. Vesicular drug delivery systems have shown functional applicability in the absorption and transfer of active agents to tissues and

organs via biological membranes. Bingham bodies were named after Bingham, who first recorded the biological origin of these vesicles in 1965 [3]. Drugs encapsulated in vesicular structures are required to achieve specific uptake, tissue-specific delivery, decreased contact with blood components, and toxicity reduction. When such amphiphillic building blocks come into contact with water, they form vesicular structures, which are highly organised assemblies of one or more concentric lipid bilayers. Both hydrophilic and lipophilic drugs can be used in vesicular drug delivery systems. They increase the bioavailability of poorly soluble drugs, prolong the removal of easily metabolised drugs, and retain drugs in the systemic circulation longer. Liposomes, sphingosomes, pharmacosomes, niosomes, virosomes, transferosomes, and other vesicular drug delivery systems have all been developed.

Liposomes, which are phospholipid bilayered vesicles, have received a lot of popularity as possible drug delivery systems. Rapid clearance from blood, minimal control of encapsulated molecule release, low or non-reproducible drug loading, physical and chemical instability, and large-scale sterile preparation are the major disadvantages of using traditional liposomes as drug delivery vehicles. Many of these topics have been discussed in studies over the last two decades. Sphingolipid-based liposome formulations outperform phospholipid liposomes in terms of potency, circulation time, encapsulation performance, resistance to oxidation, hydrolysis, improved acid stability, and versatility in coupling with site-specific ligands to achieve active targeting. These sphingolipids are now widely used to build sphingosomes, which are stable liposomes [4].

Composition of Sphingosomes

Sphingosomes are liposomal preparations that vary primarily in terms of lipid composition. Sphingolipids and cholesterol are present in one or more of their membranes. The sphingolipid and cholesterol are usually present in a percentage molar ratio of 75:25 to 30:50, with 55:45 being the most favoured. Other lipids can also be present, as long as they do not impair the drug's stability. When other lipids are added, the sphingolipid/cholesterol ratio normally decreases [5].

General Advantages of Sphingosomes

1. Provide selective passive targeting to tumor tissue.
2. Increase efficacy and therapeutic index.
3. Increase stability via encapsulation.
4. Reduction in toxicity of the encapsulated agent.
5. Improve pharmacokinetic effect (increase circulation time).
6. Flexibility to couple with site specific ligands to achieve active targeting.

Advantages over the Phospholipid Liposomes

1. Sphingolipid is made up of only amide and ether linkages, it is more stable than phospholipid liposomes. They are more resistant to hydrolysis than lecithin's ester linkage.
2. They also contain less double bond then lecithin and thus less subject to rancidity.
3. They also absorb less oil then lecithin which in consequence change in geometry and diameter.
4. Extend the circulation time *in vivo*.
5. A longer plasma circulation duration allows more of the therapeutic agent to enter the target site for a longer period of time. To keep the active drug in the aqueous interior when stabilising the lipid bilayer walls. This new sphingosomal technology increases the rigidity of the liposomal wall, which extends the vesicle's circulating life and the length of drug release.
6. Have better tumor loading characteristics.
7. Slow drug release from extravagated sphingosomes increases drug levels in the tumour, extends drug exposure over several cell cycles, and enhances tumour cell killing. Sphingosomes readily extravasate through these pores and accumulate within the tumour, slowly releasing the encapsulated drugs. The immature neo vasculature within the tumour is formed during angiogenesis and has various imperfections, pores and discontinuities up to 800 nm in size.
8. Have significantly better drug retention characteristics.
9. Better acid stability [6].

Disadvantages

1. The planning and use of these vesicular systems was hindered by the high cost of sphingolipid.
2. Low entrapment efficacy [7].

Classification of Sphingosomes

Sphingosomes are categorised based on structural characteristics such as the number of bilayers formed and the diameter of the vesicles produced. Sphingosomes can be unilamellar or multilamellar, with a mean diameter varying from 0.05 to 0.45 mm. The diameter range of 0.05 to 0.2 is preferred.

a. Small Unilamellar Vesicles (SUV):

It consists of single lipid bilayer and having diameter in size range 10nm-100nm.

b. Large Unilamellar Vesicles (LUV):

It consists of single lipid bilayer having greater diameter than SUV. Having size range 100nm-1μm.

c. Multilamellar Vesicles (MLV):

It consists of several bilayers of lipid and having size range 100nm-20μm.

d. Oligolamellar Vesicles (OLV):

Bilayer is more than one but not as many as MLV's. Having size range 0.1-1μ.

e. Multivesicular Vesicles (MVV):

Size range 100nm-20μm. Vesicles above 1 μm are known as Giant vesicles (GV) [8].

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% (most preferably 55/45 mol% /mol%). When compared to other formulations, a liposomal formulation dependent on sphingomyelin and cholesterol has many advantages. Sphingosomes are more resistant to acid hydrolysis and have enhanced drug retention properties [9].

Sphingolipid

Sphingolipids are a type of lipid that is present in cells. J.L.W. Thudichum gave them their name in 1884 because of their mysterious existence. A polar head is connected to a hydrophobic body in sphingolipids. Since sphingolipid is a polar lipid, it has a relation to the composition and structure of human skin lipid, especially in the epidermis layer. Sphingolipids are extracted from natural sources such as mammalian milk, preferably 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, and complex sphingolipids like sphingomyelin (SM) and glycosphingolipid are the most complex [10].

Preparation of Sphingosomes

Sphingosome preparation necessitates drug loading into vesicles. Loading may be passive (streptokinase, urokinase) or active (streptokinase, urokinase). By using a transmembrane pH gradient, a wide range of therapeutic agents can be loaded into sphingosomes with encapsulation efficacy approaching 100%. This approach involves creating a gradient that attracts lipophilic compounds to the interior of vesicles, where they can remain for as long as the gradient is preserved. In most cases, adding drug to the buffer during the reconstitution step was needed for passive loading. This allowed the drug to be entrapped inside the interior of the vesicles, where it would otherwise remain 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:

- ***Classical Method or Mechanical Dispersion Method***

Begin with a lipid solution in an organic solvent and end with a lipid dispersion in water by using the mechanical dispersion method. The different components are normally mixed by co-dissolving the lipid in an organic solvent, which is then extracted by vacuum film deposition. The solid lipid mixture is hydrated with aqueous buffer after all of the solvent has been extracted. The lipid swells and hydrates spontaneously to form a vesicle of sphingosomes. At this stage, methods use a variety of processing parameters (such as sonication, freeze thawing, and high pressure extrusion) to alter their properties in different ways [11].

- ***Film Method***

Bangham et al. defined the film method in 1965. In this process, a lipid mixture is casted as a stack of film from an organic solution using a flash rotary evaporator under reduced pressure (or by hand shaking), and the casted film is then dispersed in an aqueous medium. When the lipids are hydrated, they swell and peel away from the flask's wall, forming multi lamellar sphingosomal vesicles (MLSVs). Manual agitation (hand shaking technique) 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 formed by hand shaking, but the vesicles produced by non-shaking are large unilamellar sphingosomal vesicles. MLSV's formed on hydration of lipid could be further modified for their size and other characteristics.

Sphingosomes are usually reduced in size using the extrusion technique. All of the dispersion is extruded through a polycarbonate membrane/an asymmetric ceramic membrane, filter with 0.6m (once) and 0.2m cores in this technique (ten times). The dispersion was then frozen and thawed ten times to boost sphingosome encapsulation quality. Ultracentrifugation at 55,000 rpm and 4°C for thirty minutes eliminated the non-entrapped drug. After that, the pellets scatter in buffer.

Other method for size reduction of sphingosomes:

i. Sonication:

The average size of sphingosomes shrinks even further at high energy levels. This was first accomplished by exposing MLSVs to ultrasonic irradiation, and it is still the most common method for generating small vesicles. Sonication can be achieved in two ways: using a probe or using a bath. Small unilamellar vesicles are most commonly prepared with ultrasonic disintegrator bath sonicators.

ii. French pressure cells:

This is a high-pressure extrusion of preformed sphingosomes in a French press. This method creates sphingosomes that are either uni or oligo lamellar. In contrast to sonicated vesicles, these sphingosomes are more stable.

iii. Micro emulsification technique:

To make small multilamellar vesicles, a micro fluidizer pump is used. The fluid is pumped into 5m orifices at a very high pressure of 10,000 psi by the micro fluidizer. Vesicles are reduced to 0.1 and 0.2 m in diameter after a single pass [12].

Transport Mechanism of Sphingosomes

Transport Mechanism at Cellular Level:

Small unilamellar sphingosomal vesicles (SUSVs) interact with cells in a number of ways. Stable adsorption, endocytosis, fusion, and lipid transfer are among them.

1. 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. Alternatively, a portion may be located on the vesicles or cell surface.

2. Endocytosis:

Endocytosis is the process of intact vesicles being taken up by endocytotic vesicles and being delivered to the lysosomal apparatus.

3. Fusion:

Fusion is the simple fusion of the bilayers of vesicles and plasma membranes, with components releasing vesicle material into the cytoplasmic vacuum.

4. Lipid exchange:

Individual lipid molecules are transferred between vesicles and the cell surface without the need for aqueous vesicle material to be correlated with the cell [13].

Applications of Sphingosomes:

The sphingosome can carry a wide range of therapeutic compounds. Nucleic acid, proteins, peptides, oncolytics, anti-infectives, psychotropics, ionotrops, contaminants such as gelonin, and inhibitors of eukaryotic protein synthesis are all examples of therapeutic compounds. "Lipophilic cations" are one of the most favoured therapeutic compounds for entrapment in sphingosomes. Therapeutic agents in the class of lipophilic molecules that can partition into the lipid bilayer process of sphingosomes and thus interact with the sphingosomes in a membrane shape are among them. Because of their biodegradability, innocuous nature, and similarity to biological membranes, sphingosomes can prove to be an effective carrier for delivering drugs to the site of action [14].

1. Sphingosomes in Tumor Therapy:

The majority of medical devices that have advanced through the pre-clinical and clinical phases are in the field of cancer. Sphingosomal product Vinorelbine (semi synthetic vinca alkaloid) has reached phase I clinical trials. Increased drug concentration at the tumour site is related to increased clinical activity in sphingosomes. Cell cycle-specific agents like vincristine, vinorelbine, and topotecan, which destroy tumour cells by interfering with mitosis

at a specific point during the cancer cell cycle, have a clear correlation between drug exposure and anti-tumor efficacy. As a result, this patented sphingosomal drug delivery mechanism encapsulates permitted anticancer agents inside the aqueous interior of small liposomes, potentially raising their therapeutic index [15].

i. Sphingosomal products like Marqibo(TM) (sphingosomal vincristine) are loaded with active, cell cycle-specific anticancer agents that may benefit from better targeting and longer drug exposure at the tumour site. Sphingosomal formulations of vincristine, vinorelbine, and topotecan have been chosen for their ability to benefit from this novel encapsulation.

ii. Vincristine (Oncovin(R); Eli Lilly and Company), a microtubule inhibitor, is approved for the treatment of acute lymphoblastic leukaemia (ALL) and is commonly used as a single agent and in combination regimens for hematologic malignancies such as lymphomas and leukemias. Vinorelbine (Navelbine(R) GlaxoSmithKline), a microtubule inhibitor, has been approved for the first-line treatment of unresectable, advanced non-small cell lung cancer as a single agent or in combination with cisplatin. iii. Topotecan (Hycamtin(R); GlaxoSmithKline), a topoisomerase I inhibitor, is approved for use in relapsed small-cell lung cancer and in relapsed ovarian cancer [16].

2. *Sphingosomes as Drug Delivery Vehicles*

Sphingosomes usually refer to single or multiamellar lipid structures which contain a watery interior, according to the number of lipid membranes. Liposomes can usually be loaded with drugs, i.e. the drug is encapsulated inside the vesicle and/or drugs can be attached to or incorporated into the sphingosome. Such liposome drugs have shown increased efficacy compared to free drugs [17].

For example, Liposomal formulations including vinca alkaloid vincristine have been shown to be more efficient compared to free vincristine and to demonstrate less overall toxicity.
Sphingosomes work as an instrument for proliferative, immune, infectious, vascular, rheumatoid and inflammatory diseases therapy. Prostaglandins, amphoterecin B, methotrexate, vincristine, vinblastine, doxorubicin, camhothecin, ciprofloxacin, progesterone, testosterone, estradiol, beclometase and vitamin E esters are the representative medicines.

3. *Sphingosomes in Cosmetic Industry*

In cosmetic industries, sphingosomes are also used and medicines are supplied via the transdermal route. The topically applied sphingolipid skin compatibility is extremely high. Due to the sphingosome membrane lipid belonging to the same class as an epidermal lipid, it has features that improve its penets [18].

4. Sphingosomes in Ophthalmic Drug Delivery

The delivery of an ideal drug concentration at the scene of action is a major problem in ocular therapy. The physical and chemical characteristics of a drug as well as the physical characteristics of the vehicle in which a drug is placed often alter the bioavailability of the ocular drug. Thus, selection of vehicles was limited and semi-solid, mainly because of their anatomical structure and their sensitivity to foreign objects. Vesicles have received considerable attention among various vehicles and carriers for the delivery of ocular drugs.
Example: Idoxuridine impregnated in sphingosomes is more effective in the treatment of acute and chronic herpes keratitis than a comparable therapeutic drug.

5. Sphingosomes used for Enzyme Delivery:

A great number of enzymes such as streptokinase, sphingosome urokinase esterase enzyme catalysis were used for a variety of reactions, including ester synthesis, peptides, and the transformation of sugar acetals.

6. Other Therapeutic Application of Sphingosomes:

a. Sphingosomes in antimicrobial, antifungal and antiviral (anti-HIV) therapy.
b. Ex. ciprofloxacin, oflaxacin, vancomycin, amoxicillin, amphotericin B, iodoxuridine.
c. Sphingosomes may be used in gene delivery.
d. Sphingosomes may be used in enzyme immobilization.
e. Sphingosomes may be used in immunology [19].

Future Aspects

There is no need to further optimise sphingosome concept as a drug or bioactive carrier. Researchers worldwide continue to

improve their vesicular system by ensuring that they remain stable in nature in order to prevent leaching of content, oxidation and the use of natural defences. The aspect of genetic engineering can be linked with an existing concept of the mobile pharmaceutical carrier. Their potential pharmaceutical application includes enzyme immobilisation, drug taste masking, increased absorption and as a carrier for sustainable release and transdermal medicine delivery, drug overdose treatment. They can serve as potential suppliers of cosmetic and pharmaceutical drugs through the development of several new techniques of preparation, stabilisation and characterisation of these systems [20-21].

CONCLUSION

The use of these sphingosomes for biotechnology, medicine and pharmaceutical technology has great potential, but these techniques are not effectively applied to drug supplies. They can be viewed by the improved loading, stability, discharging and aiming of specific tissues or organ as efficient vesicular drug delivery systems. The vesicular system of drug delivery has a number of advantages which enhance the therapeutic effectiveness and maintain and monitor the action of medicines. The newly developed vesicular medication delivery systems are the liposomes, sphingosomes, ethosomes, cubosomes, pharmacasomas, niosomes, and transferosomes. This review paper focuses on the delivery system for sphingosomal drugs.

Sphingosomes are systems for the supply of vesicular drugs where the sphingolipid bilayer membranes are enclosed in an aqueous volume. Due to their applicability for improving the *in vivo* delivery of different chemotherapy agents, biological macromolecules and diagnostics, sphingosomes has a greater interest. Sphingosome has important advantages over other vesicular drug systems, such as high stability, longer *in vivo* cycles, high tumour stress in cancer therapy compared to liposomes, niosomes etc. Sphingosome has important advantages. Sphingosomes for chemotherapeutics, biological macromolecule and diagnostics are clinically employed vesicular drug delivery systems. Therefore, the design of new vesicular targeted drug supply systems has a great potential.

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