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SPHINGOSOMES: A NOVEL VESICULAR DRUG DELIVERY SYSTEM

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Abstract

Sphingosomes is bilayered vesicles in which an aqueous volume is entirely enclosed by membrane lipid bilayer mainly composed of natural or synthetic sphingolipid. Sphingosomes solve the major drawback of vesicle system (liposomes, niosomes) like less stability, less in vivo circulation time, low tumor loading efficacy in case of cancer therapy. The outcome of this review is that sphingosomes represents a promising vesicular drug delivery system to delivers therapeutic compounds for a range of possible application.

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INTRODUCTION:

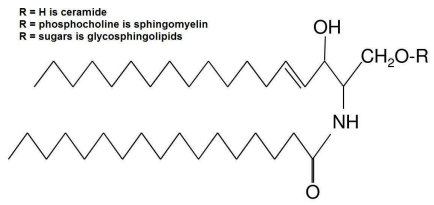
In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms, are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery [1]. Recently different carrier systems and technologies have been extensively studied with the aim of controlling the drug release and

Improving the efficacy and selectivity of formulation. Now a day's vesicles as a carrier system have become the vehicle of choice in drug deliver and lipid vesicles were found to be of value in immunology, membrane biology and diagnostic technique and most recently in genetic engineering [2]. Vesicular delivery system provides an efficient method for delivery to the site of infection, leading to reduce of drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both by hydrophilic and liophilic drugs [3]. Different novel approaches used for delivering the drug by vesicular system include liposomes, niosomes ,sphingosomes, transferosomes and pharmacosomes. Thus a main aim to design this review article is to introduce different vesicular drug delivery system with their marketed formulation and limitation for a student, guide or researcher or who might keen to know about vesicular drug delivery system [3].

DEFFINITION

Sphingosome may be defined as "concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid". Liposomal formulation based on sphingo myelin based cholesterol has several advantages when compared to other formulation [4]. The Sphingosomes are

much more stable to acid hydrolysis, have better drug retention characteristics. Sphingosomes are administered in many ways these include parental route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Generally it will be administered intravenous or some cases by inhalation. Sphingosomes may be administered orally or transdermally (Webb et al., 1996). Sphingosome are comprised of sphingolipid (sphingomyelin) and cholesterol and have an acidic intra liposomal pH ratio of sphingomylin and cholesterol varies in the range of 75/25 mol%/mol% (55/45 mol%/mol% most preferably).



General structure of sphingolipid

COMPOSITION

Sphingosomes are the liposomal preparations which mainly differ in the lipid composition. They are having one or more membranes which comprise sphingolipids and cholesterol. The sphingolipid and cholesterol are typically present at a percentage molar ratio from 75:25 to 30:50 and most preferable associate and interact with those of the neighboring molecules, and the polar head-groups orient themselves to the exterior of the assembly. Sphingosomes are forming ordered membranes as the sphingolipids in general show a preference for partitioning into ordered domains. The head group structures and acyl chain compositions of naturally occurring sphingolipids vary greatly. The ceramide moieties with the long- chain base and long saturated N-acyl chains promote the partitioning of sphingolipids into ordered membrane domains. The polar head group, which varies from the single hydroxyl of ceramide and the phosphocholine group of sphingomyelin, to large assemblies of carbohydrates for the complex glycol sphingolipid, will undoubtedly also affect the partitioning of these lipids [5,6].

General advantages of sphingosomes

Provide selective passive targeting to tumor tissue.

Increase efficacy and therapeutic index.

Increase stability via encapsulation.

Reduction in toxicity of the encapsulated agent.

Improve pharmacokinetic effect (increase circulation time).

Flexibility to couple with site specific ligands to achieve active targeting**:**

Vesicular drug delivery systems are emerging with the diverse application in Pharmaceutics,

Cosmetics and food industries. Their delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. It also reduces the cost of therapy by imparting better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs. Now a day's various non-steroidal anti inflammatory drugs, proteins, cardiovascular, anti neoplastic, anti glucoma, anti diabetic drugs that are incorporated with vesicular system are available in a commercial market that are playing a vital role to cure from a disease, hence improving the health of human kinds. Some of the emerging vesicular drug delivery system are listed below [7, 8].

METHOD OF PREPARATION OF SPINGOSOMES

Lipid film formation (Hand shaking method*)*

Surfactant/cholesterol mixture was dissolved in diethyl ether in a round bottom flask and ether was removed at room temperature under reduced pressure, in a rotary evaporator. The dried surfactant film was hydrated with aqueous phase at 50-60°C , Ether angham, in which a lipid solution in diethyl ether was slowly introduced into warm water typically the lipid mixture was injected into an aqueous solution of thematerial to be encapsulated (using syringe type infusion pump) at 55-65oC and under reduced pressure. Vaporization of ether leads to the formation of single layered vesicles (SLVs) depending upon the conditions used, the diameter of vesicles varies**.**with gentle agitation; this method produces multilamellar vesicles (MLVs) with large diameter [8,9]**.**

Micro fluidization

This is a recent technique to prepare small MLVS. A Micro fluidizer is used to pump the fluid at a very high pressure (10,000psi) through a screen. Thereafter; it is forced

along defined micro channels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipids can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This results in greater uniformity, small size and better reproducible niosomes [9, 10].

Reverse phase evaporation

The novel key in this method is the removal of solvent from an emulsion by evaporation. Water in oil emulsion is formed by bath sonication of a mixture of two phases, and then the emulsion is dried to a semi-solid gel in a rotary evaporator under reduced pressure. The next step is to bring about the collapse of certain portion of water droplets by vigorous mechanical shaking with a vortex mixture. In these circumstances, the lipid monolayer, which encloses the collapse vesicles, is contributed to adjacent intact vesicles to form the outer leaflet of the bilayer of large unilamellar niosomes. The vesicles formed are unilamellar and have a diameter of 0.5 µm [10,11].

Classification of sphingolipids [11,12]

1) Sphingoid bases

a. Sphing-4-enines (sphingosines)

b. Sphinganines

c.4-Hydroxysphinganines (phytosphingosines)

d. Hexadecasphinganine (Sphingoid base homologs and variants)

e. Sphingoid base 1-phosphates

f. Lysosphingomyelins and lysoglycosphingolipids

g. *N*-Methylated sphingoid bases

h. Sphingoid base analogs Ceramides

2) Ceramides

i. N-Acylsphingosines (ceramides)

j. N-Acylsphinganines (dihydroceramides)

k. N-Acyl-4-hydroxysphinganines (phytoceramides)

3) Neutral glycol sphingolipids

a. Simple Glc series (GlcCer, LacCer, etc.)

b. GalNAcβ1-3Galα1-4Galβ1-4Glc- (globo series)

c. GalNAcβ1-4Galβ1-4Glc- (ganglio series)

d. Galβ1-3GlcNAcβ1-3Galβ1-4Glc- (lacto series)

e. Galβ1-4GlcNAcβ1-3Galβ1-4Glc- (neolacto series)

f. GalNAcβ1-3Galα1-3Galβ1-4Glc- (isoglobo series)

g. GlcNAcβ1-2Manα1-3Manβ1-4Glc- (mollu series)

h. GalNAcβ1-4GlcNAcβ1-3Manβ1-4Glc- (arthro series)

4) Acidic glycosphingolipids

a. Gangliosides

b. Sulfoglycosphingolipids (sulfatides)

c. Glucuronosphingolipids

d. Phosphoglycosphingolipids

e. Other Amphoteric glycosphingolipids

Transport mechanism of sphingosomes

Transport mechanism at cellular level there are various ways by small unilamellar sphingosomal vesicles (SUSV's) interact with cell. These are as follows- stable adsorption, endocytosis, fusion, lipid transfer (Jain, 2001)- Stable adsorption: Stable adsorption represents the association of intact vesicles with the cell surface. Such process is mediated by non-specific electrostatic, hydrophobic or other forces or component present at the vesicles or cell surface. Endocytosis: Endocytosis is the uptake of intact vesicles in to endocytotic vesicles and result, presumably in their delivery to the lysosomal apparatus [13].

Other therapeutic application of sphingosomes [14, 15, 16]

1. Sphingosomes in antimicrobial, antifungal and antiviral (anti- HIV) therapy

Examples: Ciprofloxacin, Ofloxacin, Vancomycin, Amoxicillin Amphotericin B, Iodoxuridine.

2. Spingosomes in antifungal theraphy

3. Spingosomes in cosmetics

4. Spoingosomes in ocular drug delivery

5. Sphingosomes may be used in gene delivery

6. Sphingosomes may be used in gene theraphy

7. Sphingosomes may be used in enzyme immobilization

Future Aspects

Researchers all world continue to put in their in improving vesicular system by making them steady in nature to prevent leaching of content, oxidation and their uptake by natural defence mechanism [17]. Genetic engineering aspect can be coupled to give newer dimension to the existing cellular drug carrier concept. Their potential pharmaceutical application include immobilization of enzyme, masking the taste of drug, enhancement of gastrointestinal absorption and as carrier for sustained release and transdermal drug delivery, treatment of drug overdosing. With the evolution of various newer techniques of preparation, stabilization, characterization of these system, they can serve as potential carrier for drugs [18].

Conclusion

Sphingosomes is bilayered vesicles in which an aqueous volume is entirely enclosed by membrane lipid bilayer mainly composed of natural or synthetic sphingolipid. Lipophilic cations are the preferred category which is to be encapsulated. Application of sphingosomes clinically used for delivery of chemotherapeutic compound, diagnostic purpose and in cosmetic industry. Sphingosomes are generally accepted as safe delivery Systems.

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