Journal of Science and Technology
ISSN: 2456-5660 Volume 5, Issue 4, July-August 2020

www.jst.org.in *DOI: https://doi.org/10.46243/jst.2020.v5.i4.pp261-267*

Sphingosomes: A Novel Lipoidal Vesicular Drug Delivery System

Shilpa P. Chaudhari[1], Sneha U. Gaikwad[2]

[1,2](DepartmentofPharmaceutics,Dr.D.Y.P.CollegeofPharmacy,Akurdi,Pune-411044, Maharashtra,India)

[2]Corresponding Author: snehagaikwad2797@gmail.com

To Cite this Article

Shilpa P. Chaudhari and Sneha U. Gaikwad, "Sphingosomes: A Novel Lipoidal Vesicular Drug Delivery System", Journal of Science and Technology, Vol. 05, Issue 04, July-August 2020, pp261-267

Article Info

Received: 05-04-2020 Revised: 10-07-2020 Accepted: 12-07-2020 Published: 14-07-2020

Abstract:*Vesicular drug delivery system has various advantages thereby improving therapeutic efficacy and by sustaining and controlling action of drugs. Liposomes, sphingosomes, ethosomes, cubosomes, pharmacasomes, niosomes, transferosomes are the newly developed vesicular drug delivery system. This review article mainly deals with the sphingosomal drug delivery system. Sphingosomes are vesicular drug delivery systems in which an aqueous volume is enclosed with sphingolipid bilayer membranes. Sphingosomes has an enhanced area of interest because of their applicability in improving the in vivo delivery of various chemotherapeutic agents, biological macromolecules and diagnostics. Sphingosome has major advantages over other vesicular drug delivery systems like high stability, more in vivo circulation time, high tumor loading efficacy in case of cancer therapy as compared to liposomes, niosomes etc. Sphingosomes are clinically used vesicular delivery system for chemotherapeutic agent, biological macromolecule and diagnostics. This review concluded that sphingosome represents a promising vesicular drug delivery system for a range of possible therapeutic applications.*

Keywords*: Targeted drug delivery, Vesicular drug delivery, Sphingosomes, Sphingolipids, Cholesterol.*

I. Introduction

Now day's novel drug delivery systems is the new system Recent advances in the understanding of pharmacokinetic & pharmacodynamics behavior of drug have offer a more rational approach to the development of optimal drug delivery system. The novel drug delivery systems (NDDS) are the carriers which maintain the drug concentration in therapeutic range for longer extended of time. An ideally designed drug delivery system delivers a specified amount of drug to focus on a particular site at an appropriate time and rate as dictated or desired by the etiological and physiological needs of the body. Conventional drug delivery systems are incapable of controlling the rate of drug delivery to target site. Due to which the distribution of drug to non-target tissue and body fluids required therapeutic doses that could far exceed the amount required in target cells, the higher dose of drugs can cause adverse effects during treatment thus, the novel drug delivery systems (NDDS) maintains the drug concentration in therapeutic range for longer period of time and also, in addition, may deliver the content to the site of action if so desired as per requirements [1].

The biological effects of a drug in the patients depend on the pharmacological properties of thedrug. These effects arise because of the interaction between the drug and receptors at the site of action of the drug. However, the efficacy of this drug-target interaction stands undermined unless the drug is delivered to its site of action at such amount and rate that causes the minimum side effects and maximum therapeutic effects [2]. Targeted drug delivery aims to achieve the same.

Targeted drug delivery is the smart drug delivery in which the method of treatment that involves the increase in quantity of medicament in one or few body parts in comparison to others. Therefore, it delivers the medication only to areas of interest within the body. This offers an improved efficacy of treatment and also reduces side effects [3]. The ideal goal of targeted drug delivery is to optimize therapeutic index of the drug by localizing its activity at the site or organ of action [4]. Drugs can be targeted to specific organs [5], systems, cells or even specific intracellular organelles [6] or molecules [7].

The vesicular systems are highly ordered assemblies of one or more concentric lipid bilayer formed, when amphiphillic building blocks are comes in contact with water. Vesicular drug delivery systems can carry both

hydrophilic and lipophilic drugs. They improve the bioavailability of poorly soluble drugs, delay elimination of rapidly metabolizable drugs and prolong the existence of drugs in the systemic circulation. A wide number of vesicular drug delivery systems such as liposomes, sphingosomes, pharmacosomes, niosomes, ethosomes, virosomes, transferosomes etc., were developed [8, 9].

Liposomes are the phospholipid bilayered vesicles have gained much importance as potential drug carrier systems in targeted drug delivery [10]. The major limitations of liposomes as drug delivery vehicles are rapid clearance from blood, restricted control of encapsulated molecule release, low drug loading, physical and chemical instability, and large-scale sterile preparation. Many of these problems have been addressed during the past two decades of research. Liposomal formulations containing sphingolipids are more propitious than the phospholipid liposomes as they have ability of improving the efficacy, circulation time, encapsulation efficiency, resistant to oxidation, hydrolysis, and increased stability towards acids and flexible to couple with site specific ligand to achieve active targeting [11]. Now a day's sphingolipids have been used for preparing stable liposomes, which are called as sphingosomes[12].

Vesicular drug delivery is classified on the basis of their composition [13].

They are of two types:
1. Lipoidalbiocarriers
2. Non lipoidalbiocarriers

Lipoidalbiocarriers	**Non lipoidalbiocarriers**
1. Liposomes 2. Emulsosomes 3. Ethosomes 4. Sphingosomes 5. Transferosomes 6. Pharmacosomes 7. Virosomes	1. Niosomes 2. Bilosomes 3. Aquasomes

Table1: Examples of Lipodialbiocarrier and Non-lipodialbiocarrier.

II. Sphingosomes

Liposomes are having certain issues related with their stability including oxidation, hydrolysis, degradation, leaching, sedimentation, drug aggregation, and so forth. Therefore, to improve their stability the researchers have led us to the development of Sphingosomes[14, 15]. They are a concentric, bilayered vesicle which consist of an aqueous core is enclosed within a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid. Sphingosomes consist of sphingolipid and cholesterol, an interior aqueous environment having pH less than that of exterior [16].Sphingosomes are the important targeted lipid vesicular drug delivery system. Sphingosomes contains membranous lipid bilayer that encloses an aqueous space inside where the drug can be enclosed (Figure 1).
Sphingosomes overcome the disadvantages of liposomes & niosomes because of its high stability to acid hydrolysis and have improved drug retention properties. There are several route through which sphingosomes can be administered into the body like parentral, inhalation oral, trasdermal route etc. Sphingosomes consist of sphingolipid which is mainly made of amide and ester linkage [17].

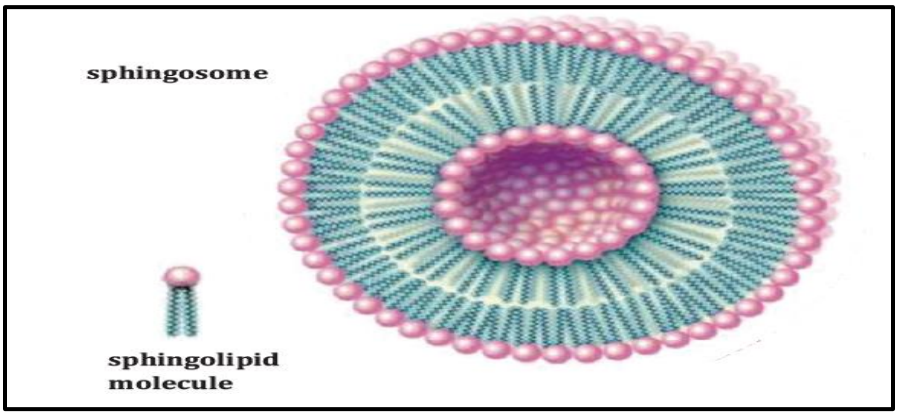

Figure 1: Cross section view of sphingosomes

Sphingosomes is more stable than the liposome because of the following reason:

1) Sphingolipid made up of only amide and ether linkage which are more resistant to hydrolysis than ester linkage of lecithin.
2) They also consist of smaller amount of double bonds than lecithin and thus less subjected to rancidity.
3) Sphingosomesalso absorb smaller amount oil than lecithin that in consequence change in geometry and diameter.

Advantages [18]:

1) Sphingosomes have better characteristic like drug retension.
2) They can be administered by subcutaneous, intravenous, intramuscular, oral and transdermal routes of drug administration and so forth.
3) They provide selective passive targeting to tumor tissue in cancer patients.
4) Sphingosomes increase efficacy and therapeutic index of the entrapped drug.
5) Sphingosomes are having increased stability.
6) Reduced toxicity of the encapsulated drug.
7) Sphingosomes improve pharmacokinetics of the entrapped drug simply by increasing the circulation time.
8) Structure of sphingosomes is so flexible to allow coupling with site specific ligands to achieve active targeting.

Disadvantages:

I. Sphingosomes are not economic, because sphingolipids are expensive
II. Sphingosomes have poor percentage entrapment.

Classification[19]:

Sphingosomes are classified on the basis of number of lipid bilayer formed and the size of vesicle. The typical mean diameter of sphingosomes was found to be 0.05-0.45µ. Most desirable diameter range was 0.05-0.2µ.

- Small unilamellar vesicles (SUV)
- Large unilamellar vesicles (LUV)
- Multilamellar vesicles (MLV)
- Oligolamellar vesicles (OLV)
- Multivesicular vesicles (MVV)
- Vesicles above 1µm are called as Giant vesicles (GV).

Composition Of Sphingosomes:

Sphingosomes consist of sphingolipid (sphingomyelin) and cholesterol at acidic intraliposomal pH ratio of sphingomyelin and cholesterol in the varying range of 75/25mol%/mol% (55/45 mol%/mol% most preferably) [16].

Sphingolipids:
Sphingolipid is a major constituent in the class of phospholipids. Sphingolipids are one of the cell components and has a hydrophobic body to which a polar head was joined (Figure 2). Sphingolipids synthesized from acyl-coA and serine and then it is converted in to ceramides, other lipids and other species [20].

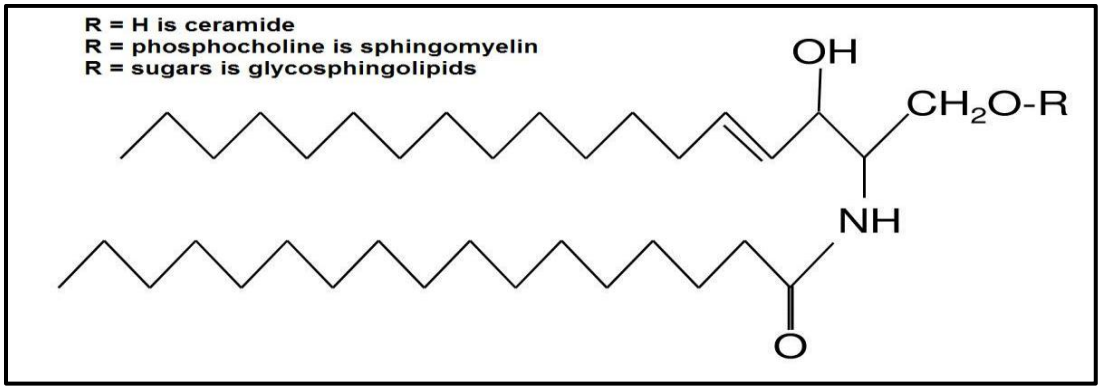

Figure 2: General structure of sphingolipid

Cholesterol:
Cholesterol is another component of sphingosomes which is used in the production of sphingosomes. By incorporation of sterol there was major change has been brought in the preparation of sphingosomal bilayer membrane. In sphingosomes the cholesterol:sphingolipid is incorporated in the ratio 1:1 / 2:1. Due to which the increased separation between choline groups and normal electrostatic and H_2 bond interactions are eliminated.

III. Methods of Preparations of Sphingosomes

1)Lipid Flim Formation (Hand Shaking Method):
Sphingolipids, Surfactant/cholesterol, lipophilic drug mixed together and dissolved in an organic solvent which has taken in round bottom flask. The organic solvent was removed by using a rotary flim evaporator under reduced pressure. Then the dried film is hydrated with aqueous phase at 50-60°C. As a result of hydration dried lipid layer swells & detaches from the inner side of round bottom flask and forms multi lamellar sphingosomal vesicles [21].

2) Solvent Spherule Method:
In solvent spherules method, the sphingolipids are dissolved in a volatile hydrophilic solvent which is then dispersed in to an aqueous solution. When the volatile hydrophilic organic solvent is evaporated in water bath under controlled conditions multi lamellar vesicles are formed [22].

3)Calcium Induced Fusion Method:
In calcium induced fusion, formation of multilamellar vesicles results, when calcium added get fused with SUV sphingosomes. Then on addition of EDTA large unilamellar vesicles sphingosomes can be formed from multilamellar sphingosome vesicles. This method is used for encapsulation macromolecules [23].

4) French Pressure Cell Method:
French pressure cell method is more useful method for producing more stable unilamellar or oligolamellarsphingosomes when compared to sonicated vesicles. This technique is carried out under very high pressure by using a French press [24].

IV. Transport Mechanism Of Sphingosomes [25]:

Following mechanism for the transportation of sphingosomes:

- *Stable adsorption:* Stable adsorption consists of the association of vesicles with the cell surface. These kind of process mediated by non-specific electrostatic, hydrophobic or other forces or component presents at the vesicles or cell surface.
- *Endocytosis:* Endocytosis involves the uptake of intact vesicles in to endocytotic vesicles and result, presumably in their delivery to the lysosomal apparatus.
- *Fusion:* Fusion is the simple merging of vesicles bilayer with the plasma membrane bilayer, with components release of vesicle content in to the cytoplasmic space.
- *Lipid exchange:* In lipid exchange, transfer of individual lipid molecular between vesicles and the cell surface without the cell association of aqueous of aqueous vesicle content.

V. Characterization Of Sphingosomes [26-30]:

1) Vesicular characterization: Used for measuring important vesicular characters like particle size, shape and zeta potential.
2) Transition Temperature: For evaluating transition temperature of bilayer vesicles differential scanning calorimetry is used.
3) Penetration Study: The mainly used method for penetration study is Confocal laser scanning microscopy (CLSM).
4) Vesicle Stability: The vesicular stability depends on the parameters like structure and shape. Changes in shape and structure can be viewed through transmission electron microscopy (TEM).
5) Entrapment Efficiency: Ultracentrifugation technique can be used for measuring entrapment efficiency.
*6) Sphingolipid Cholesterol Interaction***:** Differential scanning calorimetry and P31 NM can be used.
7) Permeation Study: Franz diffusion cell can be used for diffusion studies, by incorporating sphingosomes with gel permeation study can be done.
8) Surface Tension Activity Measurement: The ring method is for used determination of surface tension in a Du Nouy ring tensiometer can be used.
9) Drug Content: Ultra violet spectrophotometry and High performance liquid chromatography can be used for measuring the drug content.

VI. Therapeutic Applications of Sphingosomes [31-34]:

Table 2 summaries about the formulations and its applications.

Formulation	**Application**
Cancer therapy	
Vincristine (vincristine sulphate liposome injection)	Non-Hodgkins lymphoma
Vincristine in combination with Rituximab	Large B-cell lymphoma
VinorelbineNavelbine® single or in combination with cisplatin.	Non-small cell lung cancer, metastatic breast cancer
Alocrest (vinorelbine tartrate liposome injection)	Non-small cell lung cancer, breast cancer
TopotecanHyacamtin®	Relapsed small-cell lung cancer, relapsed ovarian cancer.
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.
Cosmetic	

Beclomethasone	Skin / Dermal therapy
SPHINGOSOMES™ MOIST	skin cleansing and make-up removal efficiency
Ocular drug delivery	
Idoxuridine	acute and chronic herpetic keratitis
Enzyme Delivery	
Streptokinase, Urokinase	Treatment of malnutrition
Antifugal therapy	
Sphingosine and sphinganine, free sphingolipids of the stratum corneum	Treating infectious disease
Gene therapy	
sphingosine 1-phosphate analogs	radiation-induced lung injury (RILI)
Immunology	
Ceramides, sphingosine 1-phosphate	Regulation of immune response

Table 2: Therapeutic applications of sphingosomes

VII. Conclusion

Sphingosomes because of its improved drug loading capacity, high stability, targeting to specific organs and tissues, its release and because of its most compatible nature and safe to the host cells is considered as most effective novel vesicular drug delivery system. There is a great potential in utilizing these sphingosomes in biotechnology, medicine and pharmaceutical technology, however these techniques are not effectively applied for the development of drug delivery systems. They may be considered as efficient vesicular drug delivery systems due to improved drug loading, stability, release and targeting to specific tissue or organ. Hence they have great potential in the design of novel vesicular targeted drug delivery systems.

References

1) Mohd. Gayoor Khan. Topic-The novel drug delivery system. World journal of pharmacy and pharmaceutical sciences, 2017; 6(7): 477-487.
2) Nidhi Mishra1*, Prerna Pant1, Ankit Porwal1, JuhiJaiswal. Targeted Drug Delivery: A Review. American Journal of PharmTech Research, 2016; 6(1): 1-24.
3) M. Gupta and V. Sharma, "Targeted drug delivery system: A review," Research Journal of Chemical Sciences, 2011; 1: 134-138.
4) Robinson JR, Lee VHL. Controlled drug delivery: Fundamentals and Applications. second edition., Informa healthcare; 20: 56-57.
5) Molema G, Meijer DKF. Drug Targeting Organ-Specific Strategies. Wiley-VCH Verlag GmbH, 2001: 157–170.
6) Shah Adarsh A et al. Organelle Specific Targeted Drug Delivery- A Review. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(3): 895-912.
7) Shailza Singh et al. Molecular drug targets and structure based drug design: A holistic approach. Bioinformation, 2006; 1(8): 314-320.
8) Stuti Gupta, Ravindra Pal Singh, PriyankaLokwani, SudhirYadav, Shivjee KG. Vesicular system as targeted drug delivery system: An overview. International journal of pharmacy and technology, 2011; 3: 987-1021.
9) MayankGangwar, Ragini Singh, Goel RK, Gopalnath. Recent Advances in various emerging vesicular system: An Overview. Asian Pacific Journal of Tropical Biomedicine, 2012:1-4.
10) Jain NK. Controlled and Novel Drug Delivery. First edition. CBS Publishers and Distributors, New Delhi, 2001.
11) Ravi Kumar, Shivjee Kumar, Shyam Shankar Jha, Amit Kumar Jha. Vesicular System- Carrier for Drug Delivery. Der Pharmacia Sinica, 2011; 2(4):192-202.
12) SwarnalathaSaraf, Paliwal S, ShailendraSaraf. Sphingosomes A novel approach to vesicular drug delivery. International Journal of current scientific research, 2011; 1(1):63-68.
13) Kumar D, Sharma D, Singh G, Singh M, Rathore M.S, Lipoidal soft hybrid biocarriers of supramolecular construction for drug delivery, International Scholar of research network pharm, 2012: 1-14.
14) S. Lankalapalli and M. Damuluri, "Sphingosomes: applications in targeted drug delivery," International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(4): 507–516.
15) K. Ashok, A. Rajendra Kumar, S. Nama, B. Brahmaiah, P. K. Desu, and C. B. Rao, "Sphingosomes: a novel vesicular drug delivery system," International Journal of Pharmaceutical Research and Bio-Science, 2013; 2(2): 305–312.
16) SrinivasLankalapalli and MadhupriyaDamuluri. Sphingosomes: applications in targeted drug delivery. International journal of pharmaceutical, chemical and biological sciences, 2012; 2(4): 507-516.
17) Shailza S. Molecular drug targets and structure based design: A holistic approach, bioinformation, 2006; 1(8): 314-320.
18) P. Divakar, D. Kumar, C. Praveen, C. Sowmya, and C. Suryaprakash Reddy, "Formulation and in vitro evaluation of liposomes containing metformin hydrochloride," International Journal of Research in Pharmaceutical and Biomedical Sciences, 2013; 4(2): 479–485.

19) Saraf S, Gupta D, Kaur C.D. Sphingosomes a novel approach to vesicular drug delivery, International journal of current scientific research, 2011; 1(2): 63-68.
20) Edward A.D. A comprehensive classification system for lipids, Journal of lipid research, 2005; 46: 851-854.
21) Tikshdeep C, Sonia A, Bharat P, Abhishek C. Liposome drug delivery: A review, International journal of pharmaceutical and chemical sciences, 1(3), 2012, 754-764.
22) Stuti G, Ravindra P.S, Priyanka L, Sudhir Y, Shivjee G.K. Vesicular system as targeted drug delivery system: An overview, International journal of pharmacy and technology, 3(2), 2011, 987-1000. 25.
23) Papahadjo P.D, Vail W.J, Ann N.Y, Acad Sci. 308, 1978, 259. 26.
24) Hamilton R. L, Guo L.S.S. Liposome Technology, CRC Press, Florida, 1, 1984, 37.
25) SwarnlataSaraf, S. Paliwal, ShailendraSaraf. Sphingosomes a novel appoach to vesicular drug delivery. International Journal of Current Scientific Research, 2011; 1(2): 63-68.
26) Vishakha, Ethosome: A novel vesicular drug delivery, World journal of pharmaceutical research, 2015; 4(4): 1199-1210.
27) Abhishek C, Ethosomes: A novel approach towards transdermal drug delivery, 2012; 1(2): 565.
28) Pooja V, Ethosomes: A novel drug carrier for transdermal drug delivery. IJPRSBS, 2012; 1(6): 1-9.
29) Dileep P. Formulation and evaluation of itraconazoleethosomal gel, 2015;5(2): 85-87.
30) Dave V, Dhirondra K. Ethosome for enhanced transdermal drug delivery of aceclofenac, International journal of drug delivery, 2015;2:81-83.
31) Rodriquez et al. Vincristine sulphate liposomes injection (Marqibo) in heavily pretreated patients with refractory aggressive non-hodgkin lymphoma: report of the pivotal phase 2 study. Cancer. 2009;115(15):3475-82.
32) Sphingosomes Moist LS 9871 – for optimal skin purifying with moisturizing and skin barrier strengthening benefits. SpecialChem.2009.
33) Mathew B et al. Role of sphingolipids in murine radiation-induced lung injury: protection by sphingosine 1-phosphate analogs. Faseb J. 2011;25(10):3388-400.
34) Baumruker T, Prieschl EE. Sphingolipids and the regulation of the immune response. Seminimmunol. 2002;14(1):57-63.