JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Liponiosomal Drug Delivery System – A Review

Ashish Tripathi*, Dr. R.P.S Rathore, Dr.C.S Chauhan, Dharmendra sisodiya

Department of Pharmaceutics, Bhupal Nobles' College Of Pharmacy, Udaipur.

ABSTRACT:

Liponiosomes represent a promising drug delivery module. They present a structure similar to liposome and noisome. Hence they can represent alternative vesicular systems with respect to liposomes, and niosomes due to the liponiosome ability to encapsulate different type of drugs within their multi environmental structure. Liponiosomes are thoughts to be better candidate's drug delivery as compared to liposomes and niosomes due to various factors like cost, stability and wide range of drug delivery etc. Various types of drug deliveries can be possible using liponiosomes like targeting, ophthalmic, topical, parentral, etc.

Keyword: Liponiosomes, Liposome, noisome, Targeting, Ophthalmic, Topical, Parentral.

Article history:
Received 30 May, 2013
Accepted 27 June 2013
Available online 13 July 2013

For Correspondence:

Mr. Ashish Tripathi

Department Of Pharmaceutics , Bhupal Nobles' College Of Pharmacy, Udaipur, Rajasthan, India

Email: ashishtripathi.bn@gmail.com

(www.jpsbr.org)

INTRODUCTION:

At present no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes liponiosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue. Liponiosomes or non-ionic surfactant vesicles having lipid base are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol and phospholipid with subsequent hydration in aqueous media. In liponiosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of phospholipids and small quantity of cholesterol and some amount of anionic surfactant such as dicetyl phosphate. Schematic representation of a drug targeting through its linkage to liponiosome via antibody.[1, 2]

Advantages of Liponiosomes

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages: -

·The vesicle suspension is water–based vehicle [3, 4]

• This offers high patient compliance in comparison with oily dosage forms. ·They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility's.

• The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics. ·

• The vesicles may act as a depot, releasing the drug in a controlled manner. Other advantages of liponiosomes include:

• They are osmotically active and stable, as well as they increase the stability of entrapped drug.

• Handling and storage of surfactants requires no special conditions.

• They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

• They can be made to reach the site of action by oral, parenteral as well as topical routes.

METHODS

Ether injection method

This method provides a means of making liponiosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into phospholipid solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm**.** [(5)]

Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and phospholipid are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar liponiosomes film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication. [(5)]

Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/lipid mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield liponiosomes**.** [(5)]

Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of liponiosomes formation. The result is a greater uniformity, smaller size and better reproducibility of liponiosomes formed**.** [(5)]

Multiple membrane extrusion method

Mixture of surfactant, lipid and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling liponiosome size. [(5)]

Reverse Phase Evaporation Technique (REV)

Lipid and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous liponiosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield liponiosomes. Raja Naresh et al have reported the preparation of Diclofenac Sodium liponiosomes using Tween 85 by this method. [(6)]

Physical properties of Liponiosomes

Particle size

The particle size of liponiosomes was measured by dynamic light scattering (DLS) apparatus (NICOMP 380 ZLS, Particle Sizing Systems, Santa Barbara, CA). The dispersions were diluted to about 100 times with Dulbecco's PBS. The time-dependent correlation function on the scattered light intensity was measured at a scattering angle of 90 o and wavelength at 535 nm. [(7)]

Morphology

The dispersion of liponiosomes was rapidly frozen in liquid propane using cryopreparation apparatus (Leica EM CPC, Leica Co., Vienna, Austria). The frozen sample was fractured in freeze-replica-making apparatus (FR-7000A, Hitashi Science Co., Tokyo, Japan) at – 150 oC. The fracture surface was replicated by evaporating platinum at an angle of 45 oC and followed by carbon to strengthen the replica. It was placed on a 150 mesh copper grid after washing with acetone and water. The vesicles were observed under a transmission electron microscope (JEM-1200EX, JEOL Co.) [(7)].

Evaluation

Entrapment efficiency

After preparing liponiosomal dispersion, unentrapped drug is separated by dialysis centrifugation and gel filtration. The drug remain entrapped in liponiosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation.[(8,9)]

Particle size analysis

Particle size analysis was done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs were placed briefly in a drier and then coated with gold in an ion sputter. Pictures of liponiosomes were taken by random scanning of the stub and count. The diameter is about 30 liponiosomes was measured from the photomicrographs of each batch. Finally, average mean diameters were taken into consideration.[(8,10)]

In-vitro release study

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm2 area. Trimmed away the excessfat and sliced to 500 □ m thickness using a Daw's derma tone. These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C., filled with 100 ml of PBS) and add 10 mg liponiosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37°C □ 0.50°C and stirred magnetically at 50 r.p.m., aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by U. V. Spectrophotometer method at 294 nm. [(11, 12)]

Stability study

All liponiosomal formulations were subjected to stability studies by storering at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations were checked by method discussed previously in entrapped efficiency parameter. *In-vitro* release studies of selected formulations were also carried out. [(13)]

Applications

Therapeutic application

There are very less marketed liponiosomal formulations found in market. But some experimentally evaluated application of liponiosomal formulation identified in literature listed below.[(14-18)]

Anti-cancer drug

Daunorubicin HCl

Liponiosomal daunorubicin hydrochloride exhibited an enhanced anti-tumor efficacy when compared to free drug. The liponiosomal formulation was able to destroy the Dalton's ascitic lymphoma cells in the peritoneum within the third day of treatment, while free drug took around six days and the process was incomplete. The hematological studies also prove that the liponiosomal formulation was superior to free drug treatment. An enhanced mean survival time was achieved by the liponiosomal formulation that finally substantiates the overall efficacy of the liponiosomal formulation.

Doxorubicin

Rogerson et al., studied distribution of liponiosomal doxorubicin prepared from C16 monoalkyl glycerol ether with or without cholesterol. Liponiosomal formulation exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen. Doxorubicinloaded cholesterol-free liponiosomes decreased the rate of proliferation of tumor and increased life span of tumorbearing mice. The cardio toxicity effect of doxorubicin was reduced by liponiosomal formulation. Liponiosomal formulation changes the general metabolic pathway of doxorubicin.

Methotrexate

Azmin et al., quoted in their research article that liponiosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution, administered either intravenously or orally. Tumoricidal activity of liponiosomally-formulatedmethotreaxate is higher as compared to plain drug solution.

Bleomycin

Liponiosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the lever, spleen and

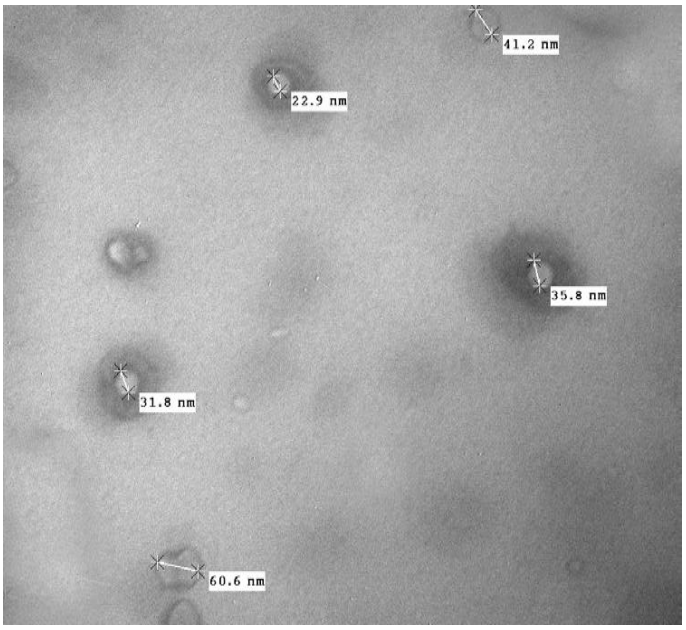

Figure 1: Transmission Electron Micrograph (TEM) of the liponiosomes

tumour as compared to plan drug solution in tumorbearing mice . There is no significant difference in drug concentration with liponiosomal formulation in lung as compared to plan drug solution. 10 Also, there is less accumulation of drug in gut and kidney in case of liponiosomal formulation.

Vincristine

Liponiosomal formulation of vincristine exhibits higher tumoricidal efficacy as compared to plain drug formulation (Parthasarathi G et al., 1994). Also, liponiosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plan drug solution and also less bone marrow toxic effect.

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leshmaniasis is a protozoan infection ofreticuloendothelial system. Liponiosomal or liposomal formulation of sodium stibogluconate exhibits higher levels of antimony as compared to free drug solution in liver . Antimony level is same in both formation i.e. liponiosome and liposome. Liponiosomal formulation of rifampicin exhibits better antitubercular activity as compared to plain drug.

Anti-inflammatory agents

Liponiosomal formulation of diclofenac sodium with 70% cholesterol exhibits greater anti-inflammation activity as compared to free drug. Liponiosomal formulation of nimesulide and flurbiprofen also exhibits greater anti-inflammation activity as compared to free drug.

CONCLUSION

The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They presents a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidate's drug delivery as compared to liposomes due to various factors like cost, stability etc. but liponiosome have more lipid solubility then niosomes. And more uses then liposome and noisome. Various type of drug deliveries can be possible using liponiosomes like targeting, ophthalmic, topical, parentral, etc.

REFERENCE

1. Theresa M.A., Drugs published by Adis international Ltd., 1998; 56(5):747-756.

2. Breimer D.D. and Speiser R. Topics in pharmaceutical Sciences. 5 Elsevier Science Publishers, New York, USA. 1985; p.291.

3. Malhotra M. and Jain N.K. Niosomes as Drug Carriers. Indian Drugs (1994), 31 (3): 81-86.

4. Buckton G., Harwood, Interfacial phenomena in Drug Delivery and Targeting Academic Publishers, Switzerland. 1995; p.154-155.

5. Rogerson A., Cummings J., Willmott N. and Florence A.T. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988; 40(5): 337–342.

6. Baillie A.J., Coombs G.H. and Dolan T.F. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stribogluconate J.Pharm.Pharmacol. 1986; 38: 502-505.

7. Chauhan S. and Luorence M.J. The preparation of polyoxyethylene containing non-ionic surfactant. vesicles. J. Pharm. Pharmacol. 1989; 41: 6p.

8. Chauhan S, Luorence MJ, The preparation of poly-oxyethylene containing non-ionic surfactant vesicles, J. Pharm. Pharmacol, 41, 1989, 6.

9. Yoshioka T, Stermberg B, Florence AT, Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85), International J. Pharm, 105, 1994, 1-6.

10. Gayatri Devi S, Venkatesh P, Udupa N, Niosomal sumatriptan succinate for nasal administration, International J. Pharm. Sci, 62(6), 2000, 479-481.

11. Szoka FJR, Papahadyopoulos D, Comparative properties and methods of preparation of lipid vesicles (liposomes), Ann. Rev. Biophys. Bioeng, 9, 1980, 467-508.

12. Sattuwar PM, Khandare JN, Nande VS, Niosomal delivery of ketoconozole, Indian Drugs, 38(12), 2001, 620-623.

13. Balasubramanium A, Dasaratha DM, Vangala AK, Formulation and *In-vitro* evaluation of niosomes encapsulated Daunorubicin hydrochloride ,Indian Drugs, 39(1), 2002, 27-31

14. Malhotra M. and Jain N.K. Niosomes as Drug Carriers. Indian Drugs (1994), 31 (3): 81-86.

15. Gregoriadis G. Targeting of drugs: implications in medicine. Lancet. 1981; 2(8240): 241-246.

16. Weissman G., Bloomgarden D., Kaplan R., Cohen C., Hoffstein S., Collins T., Gotlieb A. and Nagle D. A general method for the introduction of enzymes, by means of immunoglobulin-coated liposomes, into lysosomes of deficient cells. Proc. Natl. Acad. Sci.1975; 72(1): 88-92.

17. Cummings J., Staurt J.F. and Calman K.C. Determination of adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high-performance liquid chromatography. J. Chromatogr. 1984; 311: 125-133.

18. Suzuki K. and Sokan K. The Application of Liposomes to Cosmetics. Cosmetic and Toiletries. 1990; 105: 65-78.