World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Niosomes: A Versatile Drug Delivery System

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Received: 26-08-2018 / Revised Accepted: 23-09-2018 / Published: 30-09-2018

ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. It can be used as carriers of amphiphilic and lipophilic drug. In niosomes drug delivery system, the medication is encapsulated in a vesicle. Niosomes are biodegradable, biocompatible, and non-immunogenic and exhibit flexibility in their structural characterization. The main object of this review the application of niosomes technology is used to treat a number of diseases, niosomes have good opportunity in research and beneficial for researcher and pharma industries. Niosomes appears to be a well preferred drug delivery system over liposome as niosomes being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosomes can enhances by using novel drug delivery concepts like pro-niosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out or to make for commercially available niosomal preparation.

KEY WORDS: Niosomes, Pronoisome, Non-ionic surfactant, Cholesterol

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How to Cite this Article: Kothare Ashwini, Bhaskar Payal, Rane Pritishikha, Gavhane Mayuri, and Kad Dhanashree. Niosomes: A Versatile Drug Delivery System. World J Pharm Sci 2018; 6(10): 30-39.

INTRODUCTION

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 immunoglobulin's, serum proteins, synthetic polymers, liposome's, microspheres, erythrocytes, niosomes etc.[1] 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 non target tissue. In niosomes drug delivery system the medication is encapsulated in a vesicle.[2]The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. In niosomes, the vesicles forming amphiphilic is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate. [3]

STRUCTURE OF NIOSOME [4]

Fig.1 shows the Structure of Niosomes**.** A typical niosomes vesicle would consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle.

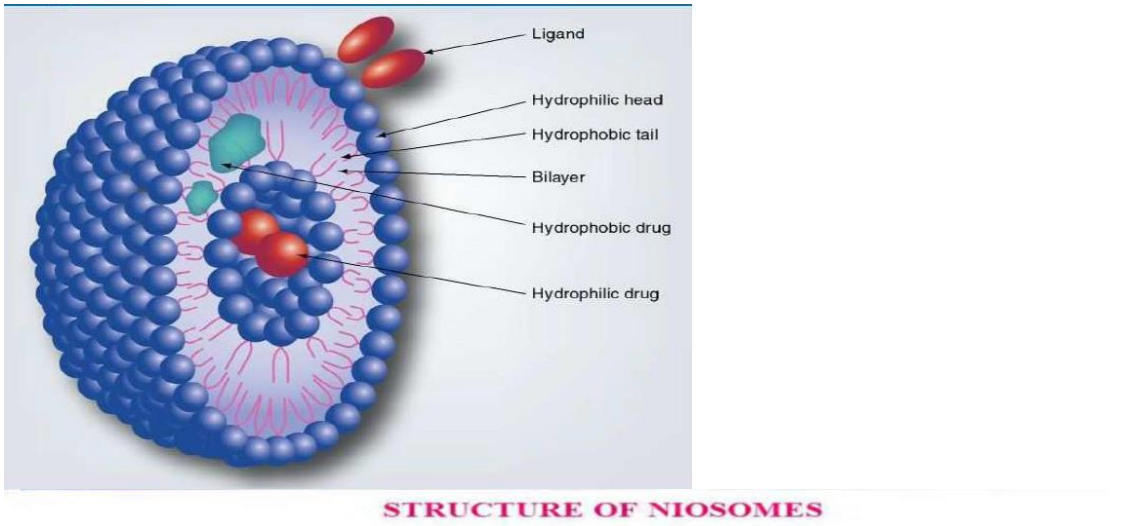

Fig.1: Structure of Niosomes

Compositions of niosomes: [4]
The two major components used for the preparation of niosomes are,
1. Cholesterol
2. Nonionic surfactants
3. Charged molecule

Cholesterol: Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to the niosomes preparations.

Nonionic surfactants
The following non-ionic surfactants are generally used for the preparation of niosomes.
e.g. Spans (span 60, 40, 20, 85, 80)
Tweens (tween 20, 40, 60, 80)

Brijs (brij 30, 35, 52, 58, 72, 76)
The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.

Charged molecule
Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are dicetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations

Types of niosomes [5]
The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation(e.g.REV,DRV). The various types of niosomes are described below
:i) Multi lamellar vesicles (MLV)(MLV, Size=>0.05 μm)
ii) Large unilamellar vesicles (LUV),(LUV, Size=>0.10 μm).
iii) Small unilamellar vesicles (SUV).(SUV, Size=0.025-0.05μm)

Multilamellar vesicles: It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. These vesicles are highly suited as drug carrier for lipophilic compounds.

Large unilamellar vesicles (luv): Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

Small unilamellar vesicles (suv): These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

Table 1: Advantages and Disadvantages of niosomes

Advantages of niosomes	Disadvantages of niosomes
1. The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.	1. Fusion
2. The vesicles can act as a depot to release the drug slowly and offer a controlled release.	2. Aggregation
3. Since the structure of the niosomes offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.	3. Leaking of entrapped drug
4. The vesicle suspension being water based offers greater patient compliance over oil based systems	4. Physical instability
5. They are osmotically active and stable.	5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.
6.They increase the stability of the entrapped drug	
7. Can enhance the skin penetration of drugs.	

Table 2: Route of administration with examples

Route of administration	Examples of drug
Intravenous route	Doxorubicin, comptothecin, insulin, zidovudine, cisplatin, rifampicin
Inhalation	All trans-retonic acids
Transdermal route	Piroxicam, estradiol, nimesulide
Ocular route	Timolol maleate,cyclopentol
Nasal route	Sumatriptan, influenzaviral vaccines

METHODS OF PREPARATION OF NIOSOMES

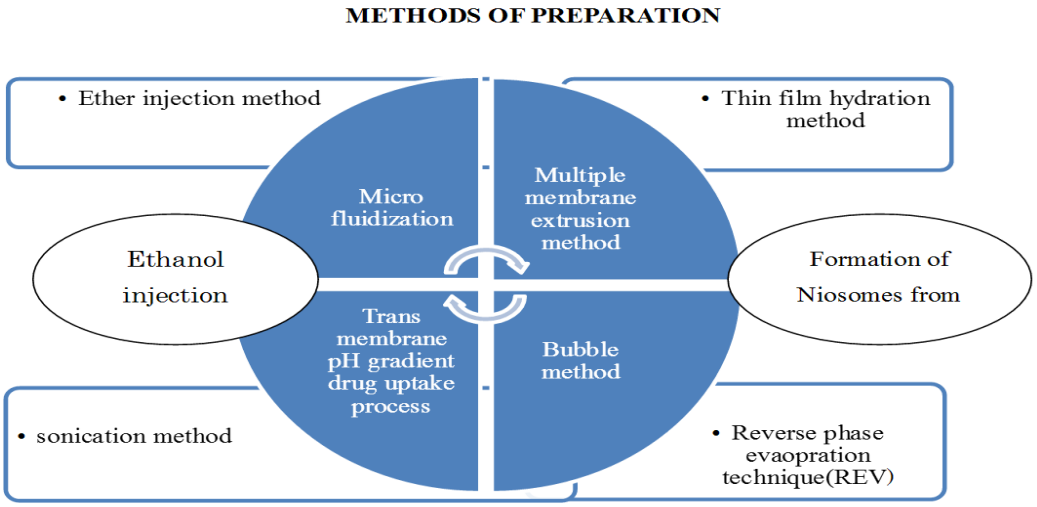

Fig.2: Methods of Preparation

Ether injection method: The injection of an organic solution of surfactants: lipids through a 14 gauze needle at a rate approximately 0.25 ml/m in to a preheated aqueous solution of the drug maintained at 60 [6,7,8].Subsequent removal of residual ether under vacuum leads to the formation of small unilamellar vesicles.

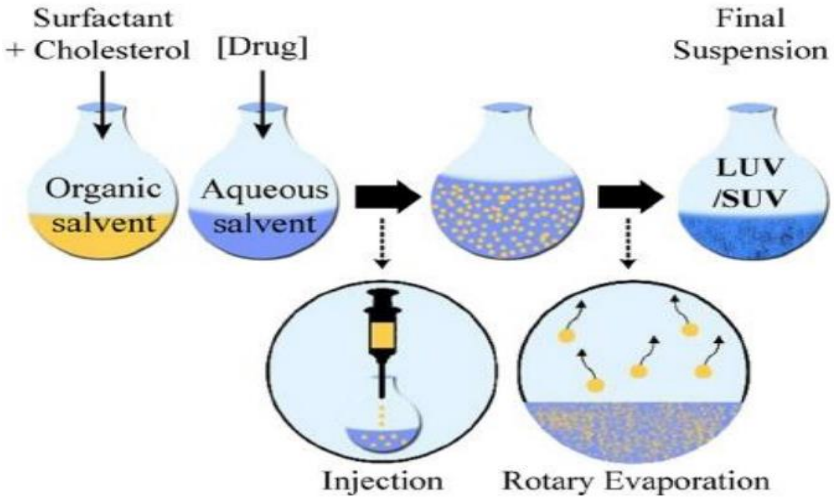

Fig.3: Ether injection method

Thin film hydration method (Hand shaking Method) [9]

Lipid and non - ionic surfactant are dissolved in an organic solvent in round bottom flask. The organic solvent is removed by means of rotary evaporator at reduced pressure, Multilamellar vesicles are formed spontaneously when an excess volume of aqueous buffer is added into dry lipid and shaken by hand or vortex mixer. The size and encapsulating efficiency of Multilamellar vesicles depends on the duration and intensity of shaking, the presence of change inducing agents in the bilayer, ionic strength of aqueous medium and lipid concentration.

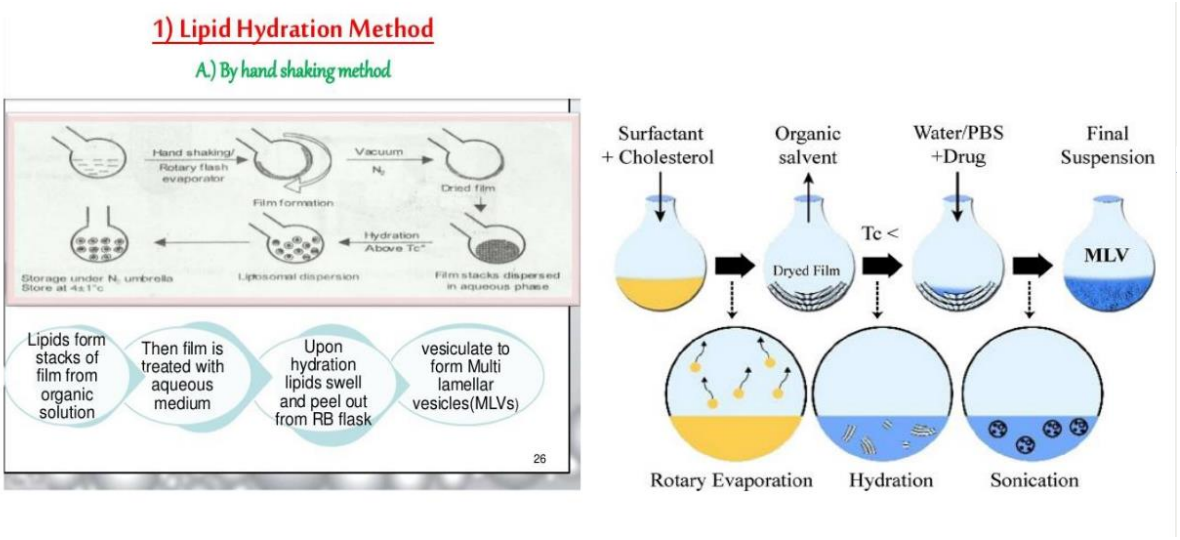

Fig.4: Thin film hydration method

Sonication method: The Multilamellar vesicles and large unilamellar vesicles are sonicated with a bath type or probe sonicator, under an inert atmosphere (usually nitrogen gas) to get the small unilamellar vesicles. During Sonication the Multilamellar vesicles structure is broken down to form small unilamellar Vesicles.[10-11]

Fig.5: Sonication method

Micro fluidization: This is recent technique to prepare small MLV's. A micro fluidizer is used to pump the fluid at a very high pressure (10,000 psi). The two phases are allowed to interact at ultra high speed in micro channels in an interaction chamber. The high speed impingement and the energy involved leads to formation of uniform and small Niosomes. This method has a high degree of reproducibility.[2]

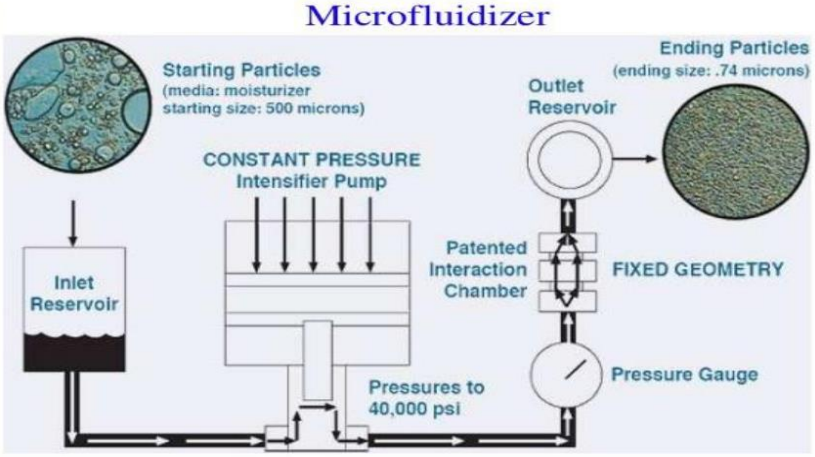

Fig.6: Micro fluidization method

Multiple membrane extrusion method: The basic principle involves extrusion that is forced passage of mixture/suspension/emulsion of the components through polycarbonate membranes repeatedly to obtain niosomes of desired size. The organic phase is dried in a rotary evaporator and is hydrated by aqueous phase; the resultant is extruded through the membrane.[12]

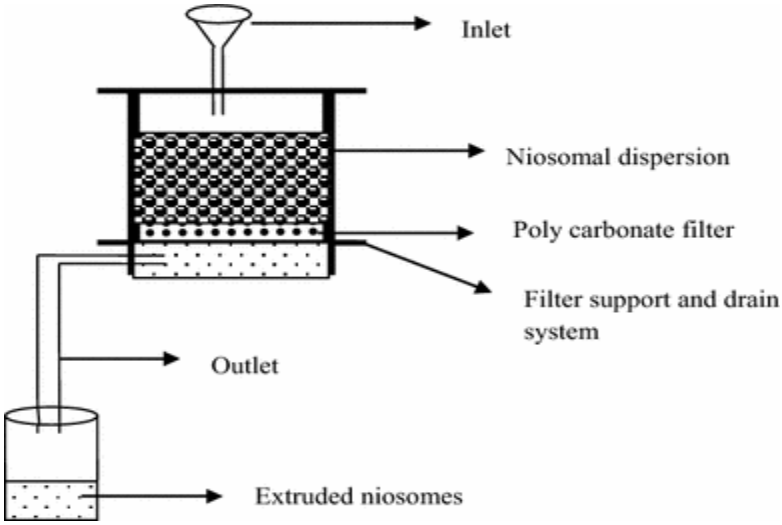

Fig.7: Multiple membrane extrusion method

Tran's membrane pH gradient drug uptake process: The organic phase with dissolved components is evaporated to form a thin layer and hydrated with citric acid, Multilamellar vesicles are formed which are freeze thawed 3 times and sonicated. To this Niosomal suspension aqueous solution with drug is added, vortexes and pH is raised up to 7.0-7.2 with 1M disodium phosphate. The mixture is later heated at 60 °C for 10 minutes to get drug loaded niosomes.[13, 14]

Bubble method[15]

It is novel technique for the one step preparation of liposome's and Niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flask with three necks positioned in water bath to control the temperature. Water cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through third neck .cholesterol and surfactant are dispersed together in this buffer(pH7.4) at 70oC, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70oC using nitrogen gas.

Reverse phase evaporation technique (REV): The surfactants are dissolved in a mixture of ether and chloroform to which an aqueous phase containing the drug is added. The resulting two-phase system is then homogenized and the Organic phase evaporated under reduced pressure to form Niosomes dispersed in the aqueous Phase.[16]

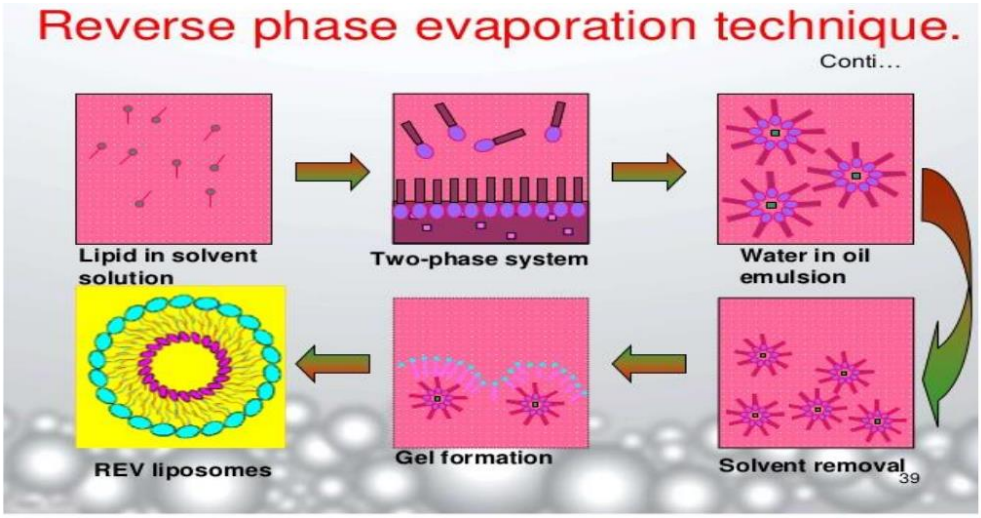

Fig.8: Reverse phase evaporation technique

FACTORS AFFECTING NIOSOMES FORMULATION

Drug: Entrapment of drug in niosomes influence charge and rigidity of the noisome bilayer. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

Nature and type of surfactant [17]
The mean size of niosomes increases proportionally with increase in the HLB surfactants like Span 85 (HLB 1.8) to Span 20 HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. A surfactant must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group.

Cholesterol content and charge [18]
Hydrodynamic diameter and entrapment efficiency of niosomes is increased by cholesterol. It induces membrane stabilizing activity and decreases the leakiness of membrane. An increase in cholesterol content of the bilayers resulted in a decrease in therelease rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in Multilamellar vesicle structure and leads to greater overall entrapped volume.

Resistance to osmotic stress
The diameter is reduced by addition of hypertonic salt solution to suspension of niosomes.

Temperature of Hydration
Hydration temperature influences the shape and size of niosomes.

CHARACTERIZATION OF NIOSOMES [19]

Measurement of Angle of repose
The angle of repose of dry niosomes powder was measured by a funnel method. The niosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Scanning electron microscopy [20]
Particle size of niosomes is very important characteristic. The surface morphology (roundness, smoothness, and formation aggregates) and the size distribution of niosomes were studied by Scanning Electron Microscopy (SEM). Niosomes were sprinkled on to the double- sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

Optical Microscopy
The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

Measurement of vesicle size [20]
The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Symantec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mw using a Fourier lens [R-5] to a point at the center of multielement detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes 7 in 1999 reported that the average particle size of niosomes derived niosomes is approximately 6μm while that of conventional niosomes is about 14μm.

Entrapment efficiency
Entrapment efficiency of the niosomal dispersion in can be done by separating the unentrapped drug by dialysis centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug. Where,

Osmotic shock
The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

Stability studies
To determine the stability of niosomes, the optimized batch was stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in niosomes and niosomes derived from pronoisome were selected

as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0,1,2,and 3months),observed for color change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical methods(UV spectroscopy, HPLC methods etc).

Zeta potential analysis [21]

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from pronoisome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of measurements were obtained directly from the measurement.

Table 3: Evaluation Parameters

Evaluation parameter	Generally used method in evaluation parameter
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

IN-VITRO METHODS FOR NIOSOMES [22]

Dialysis tubing

Muller et al, in 2002 studied in vitro drug release could be achieved by using dialysis tubing. The niosomes is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC etc). The maintenance of sink condition is essential.

Reverse dialysis

In this technique a number of small dialysis as containing 1ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method.

Franz diffusion cell

The in vitro diffusion studies can be performed by using Franz diffusion cell. Pronoisome is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The pronoisome is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (U.V spectroscopy, HPLC, etc). The maintenance of sink condition is essential.

APPLICATIONS OF NIOSOMES

- Niosomes have been used for studying the nature of the immune response provoked by antigens.
- It is used as Drug Targeting.
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- Niosomes as Carriers for Hemoglobin.
- It is used act as Delivery of Peptide Drugs.
- Niosomes can be used as a carrier for hemoglobin.
- It is used in Studying Immune Response.
- Transdermal Drug Delivery Systems Utilizing Niosomes.
- It is used in ophthalmic drug delivery.
- Niosomal system can be used as diagnostic agents.

Niosomes as a carrier for Hemoglobin [23]

Niosomal suspension shows a visible spectrum super imposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin

Transdermal delivery of drugs by niosomes [24]

An increase in the penetration rate has been achieved by Transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of Transdermal route of delivery for other dosage forms. The topical delivery of erythromycin from various formulations including niosomes has studied on hair less mouse and from the studies, and confocal microscopy, it was found that nonionic vesicles could be formulated to target pilosebaceous glands.

Ophthalmic drug delivery[25, 26]

From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide)

CONCLUSION

Niosomal drug delivery system is one of the best examples of great evolution in drug delivery technologies and nanotechnology. It is obvious that niosomes appears to be a well preferred drug delivery system over other dosage form as niosomes mostly stable in nature and economic.

There is lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs anti-viral drugs, etc. in niosomes and to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side effects of the drugs.

Thus these areas require further systemic consideration and research so as to bring out commercially and valuable available niosomal preparation. The concept of incorporating the drug into or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians.

Niosomes are very useful in bright future for pharma industries. So far only animal experimentation of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit niosomes as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS etc. Thus Niosomes present itself as a versatile tool in therapeutics.

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