Chapter

Vesicular Carriers a Magic Targeted Delivery: A New Way of Drug Targeting via Liposomes and Niosomes

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Abstract

There has been a turn of heads among the researchers in the delivery of drugs through vesicles in the lately. Paul Ehrlich, 1909 introduced the concept of rocketing the drug directly to the affected site. There are number of vehicles that are reported to carry drugs to the target point. Although various carriers are documented, liposomes and niosomes prove an edge over the others in prolonging and providing controlled drug delivery at the targeted area. This advantage makes vesicular drug delivery as the most sought after method for delivering medicines to the specific tissue or organ affected. The below written chapter throws light on the benefits of vesicular drug targeting.

Keywords

Targeted Delivery; Controlled Fashion; Immunoglobulin; Serum Proteins; Synthetic Polymers; Liposomes; Niosomes

Introduction

Targeted drug delivery can be expressed as the ability to target the active pharmaceutical ingredient specifically to the desired site of action with zero side effects to the non target tissue [1]. The entanglement of the drug moiety within a lipid bilayer or surfactant vesicles is the base of any Vesicular drug delivery, providing an increased concentration of the drug at the targeted region. This leads the drug to be released in a sustained fashion ensuing greater bioavailability and boosting drug permeation. An added advantage is the easy administration of the drug and lessened the enzymatic metabolism of the medication. Reported ophthalmic vesicular drug delivery of biomolecules is an evidence for a propitious future for the vesicular mode of delivery of drugs [3].

Vesicular Drug Delivery System

Among vesicles of different makes, lipid carriers are known to have pronounced effects on targeting and transporting active agents

in immunology, membrane biology, diagnostic techniques and genetic engineering. To add a feather on the cap, these drug delivery systems can house both lipophilic and hydrophilic drugs [4].

The rate of drug penetration to the targeted sites is not a simple process and is highly influential by physicochemical properties of drugs like solubility, particle size. The entanglement of the active medicament inside lipid globules especially in niosomes and liposomes are highly favourable for the entry of drug through cell [5].

Liposomes

Liposomes are simple, few microns in size that are lipid bilayered vesicles consisting of hydrophilic space sandwiched between lipids. Also known as phospholipids vesicles described by Bingham et al (1965).

Liposomes are investigated by researches so much due to its superiorities than other drug delivery modules because they have the following ideal characteristics such as: [6]

- Ø Biodegradable and Biocompatible nanocarriers
- Ø Significant improvement in the penetration and absorption of poorly soluble drugs.
- Ø Residence time off the active medicament made possible corneal surface binding more suitable for anterior and posterior segments of eye disorders.
- Ø Housing of both hydrophilic and lipophilic drugs.
- Ø Improvement of pharmacokinetic and therapeutic profile of the drug.
- Ø Systemic toxicity is reduced.

Demerits of Liposomes [8]

Ø Difficulty in fabrication and storage of liposomes.

Ø Though toxicity is lessened, it is reported to cause long term ill effects.

ØIntraviteral route of administration has known to cause Vitreal condensation and retinal abnormalities.

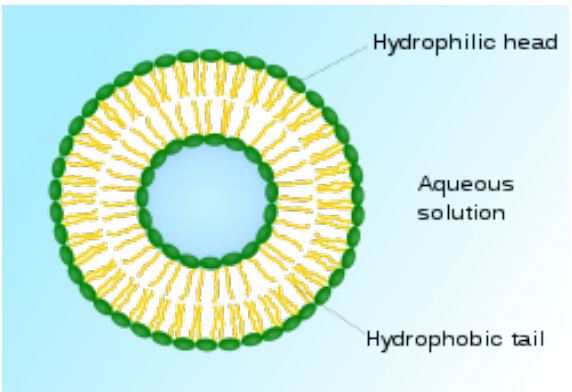
Size based classification of liposomes:

Ø Small Unilamellar Vesicles SUV- 10-100 nm

Ø Large Unilamellar Vesicles LUV- 100-3000 nm

Ø Multi Lamellar Vesicles MLV- > 3000 nm

Structure of Liposomes:



Method of Preparation [9]

The method of formulating a liposome involves the solvation of cholesterol, lecithin and charge inducers in non aqueous solvents accompanied drying it to a thin film. Hydration in the aqueous medium is done at the right critical hydrating temperature to obtain a liposomal suspension.

These are the methods by which the formulation of a liposome is carried out:

1. By Physical dispersion – hand shaking
2. By Solvent dispersion – Ethanol injection, Ether injection, reverse phase evaporation
3. Solubilization using detergent

Liposomes possess the following characteristic properties like size, shape and size distribution, surface charge, entrapment efficiency, drug content, lamellarity, phase behaviour, drug release etc.

Evidences for Liposomal Drug Delivery as the Most Sought after Novel Drug Discovery [10]

S.No	Drug	Therapeutic category	Conclusion	Reference	S.No
1	Idoxuridine	Anti-viral	Improved therapeutic efficacy, effective in the treatment of Herpetic Keratitis	Smolin et al. (1981	1
2	Ganciclovir	Anti-viral	Improved efficacy with no side effects	Cheng et al.(2000)	2
3	Acyclovir	Anti-viral	Enhanced penetration and better drug release	Law et al. (2000)	3
4	Levofloxacin	Antibacterial	Improved residence time	Danion et al. (2007)	4
5	Ciprofloxacin	Antibacterial	Higher drug concentration	Budai et al. (2007)	5
6	Acetazolamide	Anti-glaucoma	Improved efficacy in glaucoma treatment	Hathout et al. (2007)	6
7	Chloramphenicol	Antibacterial	Enhanced antibacterial activity	Mahmoud et al. (2008)	7
8	Fluconazole	Antifungal	Enhanced antifungal activity.	Habib et al. (2010)	8
9	Tacrolimus	Immuno suppressant	More effective and safer as compared to free drug	Zhang et al. (2010)	9
10	Ciprofloxacin	Antibacterial	Reduced toxicity of ciprofloxacin for safe delivery	Jain and Shastri (2011)	10
11	Latanoprost	Anti-glaucoma	Sustained delivery with enhanced intraocular pressure lowering effect.	Natarajan et al. (2012)	11

Niosomes

Niosomes are chemically stable and amphiphilic novel drug delivery systems [12] similar to liposomes containing a nonionic surfactant vesicle that is fabricated on the hydration of synthetic non ionic surfactant with the addition of cholesterol or other charge inducers. They are microscopic lamellar construction whose size range is between 10 to 100 nm. Cholesterol is mainly incorporated to obtain more fuller and rigid structures of niosomes to cease leakage. Entrapment efficiency is pronounced on the addition of diacetyl phosphate a charge inducer, which increases the vesicle size and builds up a charge on the niosome responsible for the effective drug entrapment. The vesicles are also electrostatically stabilized using charge inducers such as Stearyl amine and diacylglycerol [11].

Niosomes are chemically composed of biodegradable, nonimmunogenic and biocompatible surfactant.

Advantages of Niosomes

Ø The property of niosomes being amphiphilic utilizes the incorporation of active pharmaceutical ingredient with a vast range of solubility.

Ø Alteration of vesicle properties such as vesicle make, size, lamellarity, tapped volume, surface charge and this flexibility could be exploited to obtain Niosomes with unique characters.

Ø Vehicle based on water suspension provides better patient acceptance than oil based suspension systems.

Ø Aims to improve the performance of poorly absorbed drugs in vivo by improving bioavailability, delaying renal clearance and metabolism can be well achieved with liposomal drug delivery.

Ø Attributes of possessing good osmotic stability, these systems can be administered orally, parenterally and topically.

Lacunae

Ø Self degrading processes like fusion, hydrolysis, coagulation and oozing out of drugs from entrapped vesicle is a major pitfall to this system.

Formulation of Niosome

It is essential for the formulation of niosomes the presence of an amphiphile and an aqueous solvent, membrane additives such as cholesterol and non-ionic surfactants [6]. Initially, the monomers of the amphiphile fuse into vesicles. When these vesicles are hydrated, high interfacial tension between water and the hydrocarbon portion is produced promoting the association. On the other hand, the stearic hydrophilic forces and ionic repulsion between the head groups ensure that these groups are in contact with water. These two conflicting forces consequently develop as a supramolecular assembly. Thermodynamic stability, is achieved by an interesting phenomenon of pleating every bilayer folds over itself as continuous membrane i.e. The interface formed by the interaction of the HC and the water is no more prevalent.

However there are various methods that are described in detail in the figure given below [9-11].

Generally, the niosomes have been grouped according to the function of the number of the bilayer (eg: MLVs, SUVs) or as a size (eg:LUV's SUVs) or as a method of preparation (e.g: REV-Reverse phase evaporation, DRV – Dried Reconstituted vesicles)

Classification of Niosomes based on its Size

1. Multilamellar vesicles (MLVs) – 0.5µm to 10µm in diameter
2. Large Unilamellar vesicles (LUVs) – 0.1µm to 1µm in diameter
3. Small unilamellar vesicles (SUVs) – 25-500 nm in diameter

Composition of Niosomes

Some Common Non-ionic surfactants that play a major role in niosomal formation includes span (span 20,40,60,80), Tween (Tween 20,40,60,80) and brij (Brij 30,35,52,58,72,). Apart from common ones few other surfactants such as Ether linked surfactant, Di-alkyl chain surfactant, Ester linked, Sorbitan Esters, Poly-sorbates are known to be involved in the formulation.

The significance of Cholesterol

The presence of sterols in the cell membrane is considered influential in the bilayer fluidity and permeability of drugs. Such kind of

a naturally occurring sterol is cholesterol which finds a chief use in the formulation of niosomes. Besides providing permeability of membrane, rigid surface, efficiency in entrapment, it enhances the ease of rehydration of freeze dried niosomes and their ill effects. Stability in niosomes are achieved by cholesterol addition that inhibits vesicle agglomeration and imparts fullness to the system by stopping leakiness.

Charged Molecule

The overall stability of Niosomes is further enhanced by the addition of molecules of charged surface. Coagulation is troubleshooted by electrostatic repulsion of the charged species. Limiting the use of charged molecules to 2.5-5 mol percentage concentration is crucial as over concentrated charged molecules can cause termination of niosomal production.

Bioadhesive Polymer

To make the niosome release drugs in sustained profiles, adding in proven polymers like carbopol, chitosan can release the medicine up to 10 hours which was known to elicit better sustained effect on comparison with liposomes containing no bioadhesive polymers.

Isotonic Stabilizer

Topical construction of niosomes were difficult due to tortuous factors such as partition co efficient, solubility, permeability co efficient and poor stability at the pH. These problems are combated by the addition of isotonic stabilizers like Boric acid solution, Sodium chloride etc which preserves the correct pH and also upgrades the permeability and solubility of the drug species.

Factors are taken into Consideration while Engineering Niosomes

Structure of surfactants

The main factor that should be focused to obtain proper struc-

ture and geometry of the vesicles is the knowledge of critical packing parameter.

CPP (Critical Packing Parameters) = v/lc ×a0

Where v = hydrophobic group volume

lc = the critical hydrophobic group length

a0 = the area of hydrophilic head group

From the critical packing parameter value type of micellar structure formed can be ascertained as given below,

If CPP < ½ then the formation of spherical micelles

If ½ < CPP < 1 formation of bilayer micelles

If CPP > 1 formation of inverted micelles

Composition of Membrane

Morphologically, Niosomes can be intelligently membrane manipulated by different additives and surfactants considering its highest stability. Polyhedral , spherical and tubular Niosomes are some examples of morphologically altered niosomes.

Nature of Encapsulated Drug

Some of the basic physio chemical properties of encapsulated drug may have an effect on the charge and rigidity of the niosome. As mentioned earlier, inflation of the vesicle size is fulfilled by surfactant head group interaction that creates a mutual repulsion between surfactant bilayers and Charge development on the bilayer as a result of the addition of charge inducers is necessary for the vesicle to prevent it from agglomerating.

Temperature of Hydration

Shape and size are also governed by the temperature required for hydration. For an optimum size and shape of the globule, the temper-

ature should be above the transition temperature of the system.Temperature alterations may lead to vesicle shape transformation. Studies reported that, spheres are obtained on heating polyhedral vesicles and when cooled it produced a cluster of small spherical niosomes.

Methods of development of Small Unilamellar Vesicles

Sonication

A tri mixture of the drug, buffer and the surfactant are taken in a 10ml glass vial and a titanium probe sonicator or Sonicator containing bath if needed is operated at 60°C for 3 minutes to yield small and unilamellar vesicles.

Micro Fluidization

This technique has its application in the production of small vesicles with effective uniformity and reproducibility. The ideology of micro fluidization is submerged jet principle technique. Maintenance of ultra high velocities and the processes proceeded through the channels of micro tuned where the efficient transfer of energy is brought out by the interaction occurring at right angles. They are aligned in such a way where the impingement of thin liquid sheet occurs so that the energy supplied to the system remains within zone of niosomes formation.

Formulation of Multilamellar Vesicles

Hand Shaking Method (Thin Film Hydration Technique)

An evaporator round bottomed flask containing the ingredients of niosome formation such as cholesterol, surfactant and charge inducers are taken as specified. Surfactant, cholesterol and vesicle forming agents are uniformly mixed and this blend is dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol. After the evaporation of solvent it results to the deposition of thin film on the walls of flask. On rehydrationwith dried lipid film, on addition of

aqueous phase containing the dissolved drug at 60°C and mild occasional shaking ends up in the formation of multilamellar vesicles.

Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading)

Surfactant and cholesterol are quantised and taken in a round-bottom flask. Organic solvents such as chloroform are poured in to it and solvent evaporation is performed under reduced pressure it forms a thin film on the wall of the flask. On hydration of the film by vortex mixing with 300 mM citric acid (pH 4.0). After freeze thawing it three times followed by sonication process multilamellar vesicles are obtained. Vortexing is continued by dissolving 10 mg/ml of drug in aqueous solution and adding it into the sonicated mixture. pH of the sample is raised to 7.0-7.2 by the addition of 1M disodium phosphate and the mixture is then heated at 60°C for 10 minutes to yield the desired multilamellar vesicles.

Formulation of Large Unilamellar Vesicles

Reverse Phase Evaporation Technique (REV)

The method involves solvent evaporation technique in which ether and chloroform are added to the surfactant and cholesterol mixture (1:1). The drug is then dissolved in an aqueous medium and added to the above organic mixture. A two phased mixture is formed which is then sonicated at 4-5°C. A clear gel is observed to be formed. Phosphate buffer saline is added in optimal quantity and sonicated again. The organic phase is vapourised in low pressure at 40°C. Further dilution with phosphate buffer saline a viscous niosome suspension is obtained. This is heated on a water bath at 60°C for 10 min to yield the desired large unilamellar vesicles.

Ether Injection Method

This method is employed to produce single layered vesicles through vapourisation. The cholesterol and the optimum amount

of surfactant and mixed together separately and then slowly injected through a 14-gauge needle into warm water containing the drug maintained at 60°C. On solvent evaporation, vesicles of diameter ranges from 50 to 1000 nm are formed. This method suffers from the drawback of retention of small portions of ether in the formulation.

Miscellaneous

Multiple Membrane Extrusion Method

A mixture of surfactant, cholesterol and di acetyl phosphate are dissolved in chloroform and is subjected for solvent evaporation. As a result it produces thin film. On hydration of this film with aqueous solution it is then extruded through polycarbonate membranes positioned in such a way that the film passes through eight passages. Niosome size can be optimized by this method.

The "Bubble" Method

This method is a green technology using no solvents and is a one step technique. Bubbling unit encompasses three neck placed in the water bath to regulate temperature. Water cooled reflux, thermometer and nitrogen supply are connected in the first, second and third neck respectively. The bubbling is initiated by the dispersion of cholesterol and the surfactant at 70°C in the buffer (pH 7.4) which is then agitated for 15 seconds with a high shear homogenizer and using nitrogen gas when bubbling occurs immediately.

Determinants of Vesicle Size, Entrapment Efficiency and Release Characteristics [10]

Drug

The stability of hydrophilic and lipophilic moiety is noteworthy in the entrapment of the drug. Enlargement of the niosomes is brought out by the interaction of solute with surfactant head groups, consequently increasing the charge on the surface and the mutual repulsion between the surfactant bilayer.

Amount and Type of Surfactant

The concentration of liquid and entrapment efficiency are linearly correlated. The average size of niosomes shows a well ordered pattern of increase when the hydrophilic lipophilic balance is maintained throughout. Ascribing to the fact that when the lipophilicity of the surfactant is increased it decreases the surface free energy. Other factors such as Phase transition temperature (Tc) of surfactant determines the entrapment efficiency i.e., higher the phase transition temperature (span 60) higher the entrapment.

Cholesterol Content and Charge

Cholesterol works wonder in improving the hydrodynamic diameter , entrapment efficiency and membrane stabilization. It also diminishes permeability and betters the retention of the solute. Successive bilayer Interlamellar distance in multilamellar vesicle is amplified in the presence of charge thereby entrapped volume is greater. Sometimes there is an increase in the membrane curvature due to slight charge increase thus decreasing the size of the vesicle.

Method of Preparation

On comparison of various methods of preparation of niosomes, hand shaking method yields vesicles with a greater diameter (50-1000 nm), and vesicles of size range (0.35-13μm) are obtained by ether injectection technique. Size range varies on methods of hydration and vortexing with the lipid above phase transition temperature of surfactant. The smaller size of niosomes are directly proportional to the intensity of vortexing.

Unilamellar vesicles with noted reduced diameter are achieved on sonicating multi lamellar vesicles. The time of sonication plays a vital role in producing abated vesicles. Microfluidization method is more apt for preparing smaller vesicles with great uniformity. On comparing remote loading method, hand shaking method and reverse phase evaporation , the former showed best entrapment efficiency and optimum retention of the medicament.

Osmotic Effect

The size of vesicles can be cut down to several diameters on adding hypertonic salt solution that extravasates the contents of the vesicle and reducing its size eventually. Swelling of the vesicle may be an issue if the vesicle loosens up on osmosis.

Viability of Niosomes In Vivo [10]

The variation in the size of the vesicle is critical for the release of the drug and patterned niosomal dispersion from blood in the human body. The viability of niosomes and liposomes prove to be equi active. Residence and the functionality of the drug is dependent on the size of the vesicles. Lungs can accommodate the residence of larger vesicles in its alveoli, and smaller vesicles have trouble-free access to the spleen as they can easily route through fenestrations in the liver and the sinusoidal epithelium.

Niosomes that reaches the intact liver delivers the free drug to the systemic circulation to maintain the plasma concentration of the drug. Haemoglobin carrying niosomes are found to be compatible with the plasma proteins. Stability is preserved when Albumin and transferrin are absorbed on the surface of the vesicles. Niosomes that are cholesterol-free or cholesterol deficit also survive well in the systemic circulation owing to the fact that cholesterol from the erythrocytes are donated to these niosomes conserving their structural integrity and the less likely they are destabilised.

Niosomal Toxicity [10]

Niosomes are appropriate drug carrying vehicles that are proved biocompatible with no toxic or harmful effects through animal research. Fatalities so far are not reported on the administration of niosomes internally.

Stability of Niosomes [10,11]

In Vitro stability studies revealed that niosomes are superior to liposomes and observation of size deflation is seen on the addition of

hypertonic salt to the niosomal suspension. Swelling and mechanical loosening of the vesicle is a phenomenon of the result of the addition of a hypotonic salt solution due to inhibition of eluting fluid from vesicle under osmotic tension.

usefulness of Niosomes as Drug Carriers [9,6]

Some characteristics are to be possessed by productive drug carriers depending on their therapeutic activity such as:

1. Quantitative conservation of the drug
2. Exhibiting long plasma half-lives,
3. Possessing ideal entrapment efficiencies,
4. Safeguard the drug from enzymatic metabolism.
5. Site-directing is flawlessly achieved by allowing the attachment of the target ligands to the vesicle surface assisting in the movement of drugs across membranes.
6. They show no incompatibilities with hemoglobin and blood proteins and is non thrombogenic, non-immunogenic, and biodegradable.
7. Conventional methods as carriers of drugs are no match to these magic bullets, which has high stability

Several drugs have been tested using niosomes as carriers.

- Methotrexate - Intravascular delivery shows increased uptake of the drug by the liver and brain and produces prolonged action of drug
- Diclofenac sodium- Given as encapsulated niosomes significantly increase the plasma concentration, AUC and mean residence time than free diclofenac sodium.
- Antimony sodium stibogluconate – Intravenous administration enhances drug action in the liver.

- Doxorubicin - A constant release profile is noted after a sudden burst release of the drug.
- Insulin - Absorption rate is escalated.

Applications of Niosomes in Medicine

Pharmacologically Niosomes are highly potential in the treatment of various ailments.

Targeting of Bioactive Agents

(a) To reticulo – endothelial system.

The cells of reticulo endothelial system would preferentially take up vesicles from circulating serum factors known as opsonins which mark them for clearance. Also the localized drug accumulation has however been exploited in parasitic infestation of the liver and in the treatment of animal tumors.

To organs other than reticulo endothelial system:

The application of antibodies, immunoglobulin and carbohydrate determinants are the vehicular carrier system that are targeted to particular cells in the body.

Neoplasia

Doxorubicin an anthracycline, broad spectrum antitumour antibiotic produces irreversible cardiotoxicity depending on the dose. To tackle this adverse effect the drug is loaded in niosomes and administered. Studies reveal that the lifespan of the drug was increased and mitigation of the multiplying sarcoma cells was observed. Entrapped methotrexate niosomes to S-180 a tumour bearing mice intravenously resulted in total regression of tumor. The $t_{1/2}$ of the drug was improved by maintenance of C_{max} and slowing down the clearance of the drug.

Leishmaniasis

Parasites pervading the spleen and the liver amplify in the environment to cause Leishmaniasis. Metals such as arsenic at high concentrations are a foe to these parasites. Direct delivery of antimonials has the risk of causing cardiovascular toxicity, nephrotoxicity and liver damage.On encapsulation as niosomes these drugs are highly targeted and reduces the frequency of dosing in Leishmaniasis.

Peptide Type Delivery of Drugs

Yoshida et.al., investigated that the stability of the peptide desglycinamide ,8- arginine vasopressin given orally as niosomes elevated exceptionally in an in-vitro intestinal loop model

Application of Niosomes in Immunology

Antigen-Antibody immunological responses are explored by Niosomal drug delivery. Brewer and Alexander have disclosed that as adjuvants for protein antigens, niosomes show a promising result, further they have lesser toxicity and higher stability that makes it more commanding in the field of drug delivery.

Haemoglobin Housing

Visible spectra can be superimposed onto free haemoglobin by niosomal suspensions making it easy for oxygen to enter and modification of the hemoglobin dissociation curve can be done similar to that of non encapsulated haemoglobin.

Delivery of Drugs by Transdermal

The skin provides gazillions of barriers for penetration of drugs and the slow movement of drugs through and across the skin is extensively increased by seeding the drug inside a niosomal housing.

Other Applications

Sustained Release

Meticulous research on release profiles of niosomes shows that niosomes are capable of sustaining the release of drug constantly in the plasma, unlike other sustained released formulations. Technology has been developed to deliver niosomes as intravascular drug depots. Thus a solution to include drugs having low therapeutic index and low water solubility.

Localized Drug Action

Approaches to deliver the drug locally through niosomes is an area of research , since localization of the drug is possible due to their size and low penetrability through the epithelium and connective tissue , overall leading to enhanced potency, efficacy and turning down systemic toxicity.

Niosomes and Diagnostic Imaging [11]

New applications of niosomes as Radiopharmaceutical carrying niosomes, used in liver and spleen imaging, was proved by. Korkmaz et.al., 2000 who formulated DTPA carrying niosomes (hexadecyl triglyerol ether: cholesterol: DTPA: 10:1:4) and evaluated the in-vitro release, radio labeling in vivo distribution and also performed scintigraphic imaging studies.

Salient Features of Niosomes [10]

- The concept of carriers for drug delivery to the targets and modify drug disposition and entrapment of solute in liposomes and niosomes are quite similar.
- Niosomes have established the high stability of the entrapped drug within, and are osmotically dynamic drug delivery systems.

- There is ease of handling and storing the surfactants without any special conditions.
- Niosomes are versatile in holding drugs of a wide range of solubilities as its infrastructure accommodates both lipophilic and hydrophilic moieties.
- Poorly soluble drug's oral bioavailability is improved and is known to ameliorate permeability of drugs transdermally.
- Route of administration of niosomes orally, parenterally and topically is made easy with site targeting.
- Surface attachment of hydrophilic groups and incorporation of hydrophilic moieties in the lipid bilayer are pivotal on the behaviour of drug release from the shells in vivo.
- Niosomal dispersion in the aqueous phase can be emulsified in non aqueous phase to regulate delivery rate of drug and administer normal vesicles in external non aqueous phase.
- Surfactants used for the formulation of niosomes should be biodegradable, biocompatible, and nonimmunogenic.
- Niosomes have an effect on the reduction of clearance of the drug maintaining the plasma concentration of the drug relatively constant improving its therapeutic activity.
- Majorly the composition of the bilayer and the method of formulation decides the properties of the niosomes.
- Niosomes have a prosperous future in carrying chemotherapeutic agents to achieve better bioavailability nullifying the ill effects of the drugs.
- Tedious research on refinement of niosomes to provide controlled and sustained release kinetics of drugs as sterically stabilized niosomes, discomes, polymerized vesicles and emulsified niosomal dispersion, can be a breakthrough in the field of medicine .

Characterisation of Niosomes [12-14]

Size

The common shape of niosomes are spherical and various techniques such as scattering of light method, microscopical studies by electronic, optical,correlation, freeze thaw electron microscopy, molecular sieve chromatography, ultracentrifugation, can be used to determine the mean diameter of the niosome.

Bilayer Formation, Membrane Rigidity and Number of Lamellae

Assembly and association of nonionic surfactants form the bilayer vesicle and are assessed by X-cross formation under light polarization microscopy. Membrane fluidity can be measured by mobility of fluorescence probe as function of temperature.The number of lamellae are counted by NMR spectroscopy, small angle X-ray scattering and electron microscopy.

Entrapment Efficiency

Entrapment efficiency is calculated by separating the non entrapped drug from the entrapped ones in the niosomal dispersion by different methods like dialysis, centrifugation or gel filtration and/ or disrupting the full vesicle by adding 50% n-propanol or 0.1% Triton. Remaining drug entrapped in the niosome is estimated by X-100 and then appropriate assay methods are performed to analyse the resultant solution containing the active drug.

The formula to calculate, entrapment efficiency is,

Entrapment efficiency (EF) = (Amount entrapped/ total amount) x100.

In vitro Release Study

Dialysis

In vitro release profile is examined by dialysis tubing. The prepared niosomal suspension is pipetted out and is poured into a dialy-

sis bag previously washed and soaked in distilled water. The dialysis tube is knotted and sealed. 200 ml buffer solution was prepared and the bag being placed in it is agitated at 25°C or 37°C. The amount of drug released from the medium was analysed at regular intervals by apt assay procedures.

Reverse Dialysis

In this technique, a number of small dialysis tubes containing 1 ml of dissolution medium is taken and the niosomes are placed in them. Displacement of the niosomes by the dissolution medium are then analysed.

Franz Diffusion Cell

Franz diffusion cell, uses a cellophane membrane as the dialysis membrane. The niosomes are placed in this membrane against acceptable dissolution medium maintained at room temperature. The drug content is analysed by withdrawal of samples at various intervals.

Physical properties of Niosomes

Particle Size

To quantify the particle size of niosomes dynamic light scattering (DLS) apparatus is used. Phosphate Buffer Saline is used for the Dilution of the dispersions to about 100 times. The time-dependent correlation function on the scattered light intensity is measured at a scattering angle of 90 °and wavelength at 535 nm.

Scanning Electronic Microscopy (SEM)

It is another analytical tool that is used to determine the particle size of the niosomes. Briefly placing them in a drier and then are coated with gold in an ion sputter. Images of niosomes are taken by random scanning of the stab and count. About 30 niosomes are measured for their diameters from the microphotographs of every batch for more accuracy an average mean diameter of the niosomes are calculated.

Morphology

Rapid freezing of the niosomal dispersions in liquid propane using cryo preparation apparatus is carried out. Freeze-replica-making apparatus is then used to fracture the frozen sample at – 150º C. Replication of the fractured surface is done by evaporating platinum at an angle of 45° C tailed by strengthening the replica by carbon. A 150 mesh copper grid is washed thoroughly with acetone and water and the sample placed above it, are inferred for their morphology under a transmission electron microscope.

Stability Studies

Three temperatures (4°C, 25°C and 37°C) are chosen and every formulation encounters stability studies in a thermostatic oven for three months. The drug content is checked after a month by methods discussed in entrapment efficiency. Dissolution is a mandate study to check the consistency of release of the drug from the niosome.

Rheological Properties

Viscosity is the cardinal parameter that determines the release of drug from an ophthalmic preparation. There is a fallacy that greater the viscosity, higher the time taken for the drug to retain in the layers of the eye. Studies have proven that thick solutions may tend to occlude the vision causing lacrimation and blinking reflexes in the eye to regain its original viscosity of the tear fluid. Evacuation of the drug out of the solution may be a problem is the viscosity of the preparation is high.Thus ideal levels of viscosity is needed for trouble less drug release. Ostwald- U- tube Viscometer at 25º C is a helpful apparatus that is used to calculate the rheology of niosomal dispersions. Sample dilutions with water is made to achieve required concentrations and allow it still it to equilibrate for an hr. By comparing the efflux time realted to water viscosity value can be calculated relatively.

Drug delivery via Niosomes with their reported literature studies. [15]

S.No	Drug	Route of delivery	Preclinical and clinical study	Inference	Reference
1	Methotrexate	Oral	In vivo absorption study	Enhanced absorption	Azmin et al. (1985
2	Flurbiprofen and Piroxicam	Oral & transdermal	Bioavailability &in vivo anti- inflammatory activity	Enhanced bioavailability & effective anti- inflammatory activity	Reddy and Udupa (1993)
3	Erythromycin	Topical	In vivo CLSM	Enhanced penetration	Jayaraman et al. (1996)
4	Sumatriptan Succinate	Nasal	In vitro release &ex-vivo study	Enhanced nasal absorption & prolonged release.	Gayatri et al. (2000)
5	Enoxacin	Topical	In vitro permeation study	Enhanced permeation	Fang et al. (2001)
6	Insulin	Vaginal	In vivo Hypoglycaemic activity	Insulin became active and therapeutically effective for vaginal delivery,	Ning et al. (2005)
7	Propylthiouracil	Topical	In vitro drug release	Controlled drug delivery from Niosomes	Suwakul et al. (2008)
8	Minoxidil	Topical	xin vitro skin penetration and permeation study	Increased drug absorption and bioavailability as compared to commercial formulation	Balakrishnan et al. (2009
9	Rofecoxib	Topical	In vitro permeation study	Prolonged drug release with improved permeation.	Das and Palei (2011)
10	Clobetasol Propionate	Topical	In vivo pharmacodynamic study (anti-inflammatory activity).	Enhancement in the % reduction in paw oedema exhibited by niosomal gel.	Lingan et al. (2011)
11	Lornoxicam	Transdermal	In vitro permeation &in vivo inflammatory activity.	Enhanced permeation and better anti-inflammatory activity as compared to the solution of the drug.	Singla et al. (2012)
12	Silymarin	Hepatic	In vivo hepatoprotective activity & histopathological study.	Improved hepatoprotective efficiency & was found to be safe.	El-Ridy et al. (2012)

Conclusion

Ocular drug delivery systems consisting of lipid vesicles are an asset to pharmaceutical drug delivery systems that drag inquisitiveness to researchers at the present time. These systems are much in demand due to its merits of drugs being directly aimed to their target sites dodging the noxious systemic side effects thereby increasing the viability of therapeutics. As a result, elevating the pharmacokinetic and pharmacodynamic characteristics of the drug. There is axiomatic evidence of improving the bioavailability of the drug by embracing the drug within the vesicles [16]. Hence, liposomes and niosomes are a boon to targeting drugs ophthalmically in the near future. There is a striking inclination towards researching novel concepts of vesicular drug delivery to the eye all though 90% of dosage forms for the eye available are conventional. Having considered all the positives the scope of vesicular drug delivery may be revolutionary in the envisioned future of ocular care.

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