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A REVIEW ON THE PREPARATION, MECHANISM OF ACTION AND CHARACTERIZATION OF NIOSOMES FOR THE NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Niosomes are a type of non-ionic surfactant vesicles that have gained significant attention in recent years as novel drug delivery systems due to their ability to encapsulate both hydrophilic and hydrophobic drugs. In this review, we present an overview of the preparation methods and characterization techniques used for niosomes, along with a discussion of their mechanism of action. We also highlight the advantages of niosomes over other conventional drug delivery systems, such as liposomes, and discuss their potential applications in various fields, including cancer therapy, gene delivery, and cosmetic formulations. Finally, we provide a critical analysis of the current challenges and future directions for the development of niosomes as effective drug delivery systems. Overall, this review aims to provide a comprehensive understanding of the potential of niosomes in the field of drug delivery and encourages further research in this area.

IndexTerms: **Niosomes, cancer therapy, novel drug delivery systems, non-ionic surfactant, gene delivery**

I.INTRODUCTION

As we know, designing and developing a new drug is expensive, difficult and time consuming. This process includes preclinical testing, Investigational New Drug application (IND), Clinical trials- Phase I, II, III & IV, New Drug Application (NDA) and FDA approval. Many attempts to improve the safety and efficacy of the already existing drugs was done using various methods like customizing drug therapy, dose titration and therapeutic drug monitoring among these the most important parameter is the delivery of drugs at controlled rates at the target sites.[1] Here, Drug delivery systems play a vital role. Drug delivery systems provide extended circulating half lives so that low amount of drug is used for the therapeutic effectiveness, relieving

the patient of side effects caused by non specific tissue uptake and provides protection against enzymatic degradation.[2]

This day, lipid and non-ionic surfactant based drug delivery systems have gained much attention from researchers as prospective carriers of various bioactive molecules that could be used for therapeutic demand. Many commercial liposome/niosome based drugs are already marketed with a huge success. Let's say, liposomes and niosomes are used to encapsulate colchicines[3],estradiol[4],tretinoin[5.6],dithranol, enoxacin for applications such as anticancer, anti-tubercular, antileishmanial, anti-inflammatory, hormonal drugs and oral vaccines.

According to the recent studies, it has been proved that niosomes have greater stability than liposomes.[7] Similar methods were used to synthesize the niosomes. The formulations used for niosomes involve various phospholipids like Span 60, Span 80, Span 40, which are inexpensive and are permitted as food additives. The potentiality of non -ionic surfactants to form bilayer vesicles instead of micelles is determined based on the Hydrophilic-Lipophilic balance values(HLB) of the surfactant, the chemical structure of the components and the critical packing parameter. For HLB values more than 6, cholesterol should be added to the surfactant in order for a bilayer vesicle to form. For lower HLB values, cholesterol is added to make vesicles highly stable. Apart from this, the addition of cholesterol permits more hydrophobic surfactants to form vesicles, suppresses the tendency of the surfactants to form aggregates and lends increased stability to the bilayer membranes by increasing the gel liquid transition temperature of the vesicle.

The reason why these nanoparticles are attractive for medical purposes depends on their important and unique features, like surface to mass ratio that is even more higher when compared to other particles, their quantum properties and their potentiality to absorb and carry other compounds. Nanoparticles have a relatively greater surface which is able to bind, absorb and carry other compounds such as drugs, probes and proteins.

The formulation of the engineered nanoparticles may vary. Source materials maybe of biological origin like phospholipids, lipids, lactic acid, dextran, chitosan or have carbon, silica and metals. The correspondence with the cells for some of the biological components like phospholipids will be quite divergent compared to the non biological components such as metals like iron or cadmium. One of the major challenges in drug delivery is to get the drug at the place it is actually required in the body, thereby avoiding potential side effects to non diseased organs. This is mostly challenging in cancer treatment, where the tumor maybe localised as distinct metastases in various organs. The unrestricted cytotoxicity of chemotherapeutics thus limits the full use of their therapeutic ability. Local drug delivery or drug targeting results in increased local drug concentrations and anticipates strategies for more specific therapy. Nanoparticles have certain particles as tolls to enable these procedures. These include benefits such as their small size which allows penetration of cell membranes, binding and stabilization of proteins and lysosomal escape after endocytosis.

II. NIOSOMES

Niosomes or non ionic surfactant vesicles are microscopic lamellar structures fored on an admixture of non ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with following hydration in aqueous media. Niosome is a novel vesicular drug delivery system by which we can attain the constant plasma drug concentration for the extended period fo time. Niosomes are alternative controlled drug delivery systems to liposomes in order to overcome the problems associated with sterilization, large scale production and stability. Surfactants play a vital role in the development of such combinations. A number of non ionic surfactants have been used to formulate vesicles like polyglycerol alkyl ethers, glucosyl dialkyl ethers, crown ethers, ester linked surfactants ,polyoxyethylene alkyl ether, brij and series of spans and tweens.

They contain biocompatible, non-toxic, non-immunogenic and non-carcinogenic agents. Niosome usually contains surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself. A 1:1 molar ratio of cholesterol to surfactant is commonly included in most formulations for the formation of physically stable niosomes. Niosomes can be prepared by various methods like Thin film hydration technique, Ether injection method, Reverse phase evaporation method, etc.[8]Niosomes are colloidal drug delivery systems that have definite advantages over conventional dosage forms. They possess a framework containing hydrophilic and hydrophobic together, so can encapsulate both lipophilic and hydrophilic drug moieties. They are biocompatible, biodegradable and non-immunogenic.

Drug delivery systems with vesicular structures like niosomes have definite advantages over the conventional dosage forms, as the vesicle can act as drug containing reservoirs. Niosomes are unilamellar and multilamellar vesicles containg aqueous phase that is encapsulated in highly ordered bilayer made up of non-ionic surfactant with or without other components like, cholesterol and dicetyl phosphate. Niosomes show a desired interaction with human skin when applied through topical preparation by improving , specifically the corny layer characteristics, which in turn,due to reduced transdermal water loss and increase in smoothness via replenishing skin lipids. Niosomes are preferred because of their low cost and higher stability of lipids which have been replaced by non -ionic surfactants. Niosomes loaded with drugs for dermal application shows interaction with the epidermal tissue without exerting immediate or strong systemic action.[9] Vesicular systems such as liposomes and niosomes are promising systems to enhance the drug delivery through the skin. They may act as vesicle or as permeation enhancers for drugs to enhance their penetration via stratum corneum. Moreover, they can be used as controlled percutaneous drug delivery vehicles. The applicability of these vesicular systems is, however limited because of their stability problems.

Many drugs, that are currently available in the market and those under development, have poor aqueous solubilities that result in variable bioavailabilities. This problem can be overcome by entrapping the drug into the niosome. Niosomes are non ionic surfactant vesicles that can entrap a solute in a manner analogues to liposomes.They are osmotically active and are stable on their own , while also increasing the stability of the entrapped drugs.[10,11] Handling and storage of surfactants require no special conditions. Niosomes possess and infrastructure containing hydrophilic and hydrophobic moieties together and as a result, can

accommodate drug molecules with a wide range of solubilities.[12]Despite the fact that, niosomes as drug carriers have shown advantages like being cheap and chemically stable, they are connected with problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage.

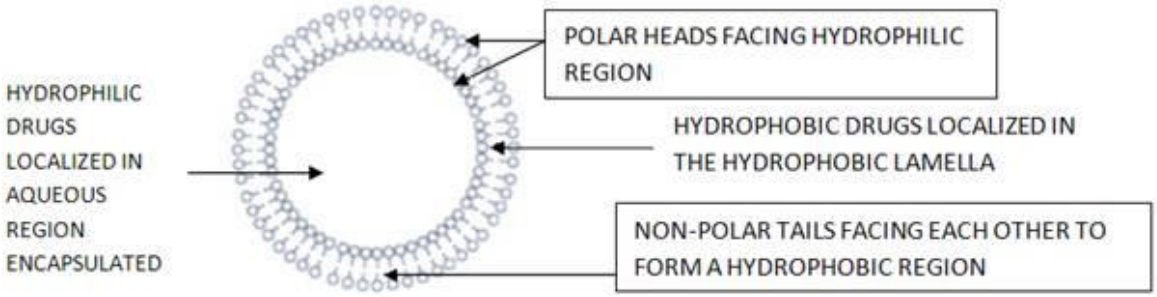

Fig1: *niosome structure*

2.2.MECHANISM OF ACTION

Niosomes diffuse from the stratum corneum layer of skin as a whole and they interact with stratum corneum with aggregation, fusion and adhesion to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface, which act as the driving force for the penetration of lipophilic drugs across the stratum corneum.

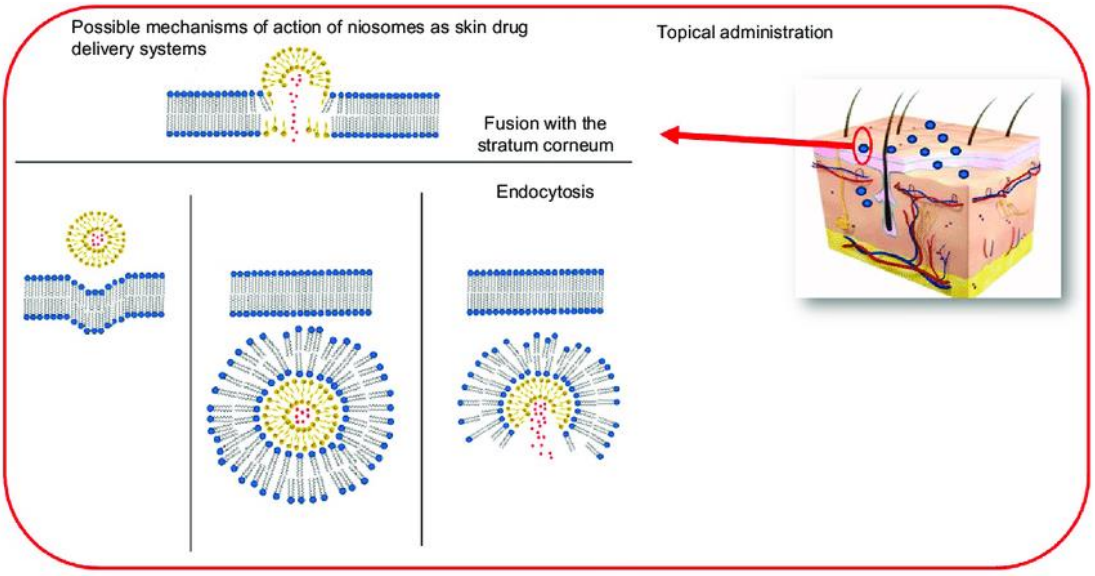

Fig 2 :*Mechanism of action of niosomes*

2.3. COMPOSITION OF NIOSOMES

Cholesterol and non ionic surfactants are two major components used for the preparation of niosomes. Cholesterol imparts rigidity and proper shape. The surfactants play a vital role in the formation of niosomes. Non ionic surfactants like Spans (Span40,60 and 80), Tweens(Tween 20,40,60,80) and Brij (Brij 30,35,52,72,76) are generally used for the preparation of niosomes.[13] Few other surfactants that are outlined to form niosomes are as follows:[14,15]

- Ether linked surfactant
- Di-alkyl chain surfactant
- Ester linked

- Sorbitan Esters
- Poly-Sorbates.

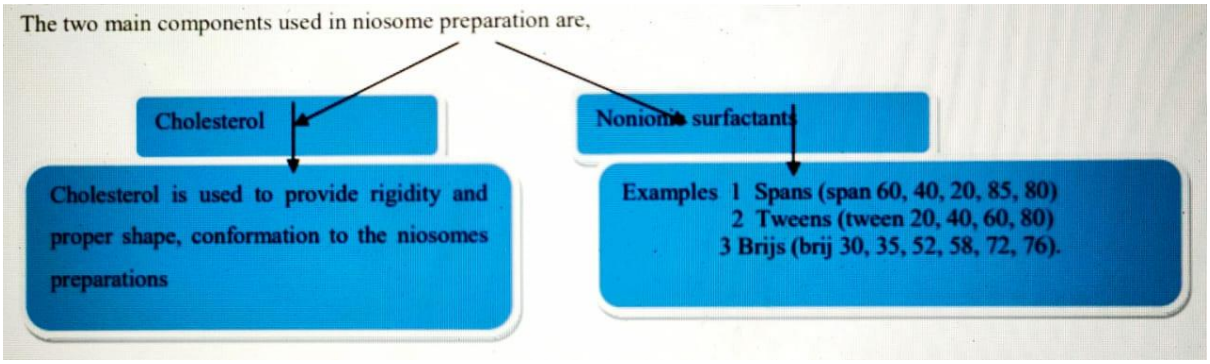

Fig 3: *depicts the components of niosome*

2.4. ADVANTAGES OF NOSOMES

- The application of vesicular systems in cosmetics and for therapeutic purpose may offer many advantages.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to the target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a non aqueous phase to regulated the delivery.
- 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 enhance oral bioavailability of poorly absorbed drugs and refine skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- They possess a framework containing hydrophilic, ampiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- The properties of the vesicle formulation are different and controllable. Altering vesicle composition, size, lamellarity , tapped volume, surface change and concentration can control the vesicle characteristics.
- The vesicles may act as dept, releasing the drug in a controlled manner.

2.5. DISADVANTAGES OF NIOSOMES:

The niosomes endure specific disadvantages, which include the following:[16]

- The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs and hydrolysis of encapsulated drugs.
- The methods of preparation of multilamellar vesicles such as extrusion, sonication are time consuming and may require specialized equipments for processing.

2.6. TYPES OF NIOSOMES

Niosomes can be divided into three groups on the basis of their vesicle size:

- **Small Unilamellar vesicles** (SUV, Size = 0.025-0.05μm):- They are regularly produced by *sonication* and *French press* methods. Ultrasonic electrocapillary emulsification or solvent dilution techniques can be used to prepare SUVs.[17]
- **Multilamellar Vesicles** (MLV, Size =>0.01 μm): These consist of a number of bilayers surrounding the aqueous fluid compartment separately and exhibit increased trapped volume and equilibrium solute distribution and require *hand-shaking method*. They show variations in lipid compositions.
- **Large Unilamellar Vesicles** (LUV, Size = >0.05μm): The injections of lipids solubilised in an organic solvent into an aqueous buffer can result in spontaneous formation of LUV. But the better technique of preparation of LUV is *Reverse Phase Evaporation method* or by *Detergent Solubilisation method*.[18]

2.7. METHODS OF PREPAPRATION OF NIOSOMES

Niosomes are prepared by different methods based on the desired sizes of the vesicles and their distribution, number of double layers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane.

Preparation of Small Unilamellar Vesicles

(a)Sonication: The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial.[19]The mixture is probe sonicated at 60^{o}C for 3 minutes to produce small and uniform in size niosomes.

(b) Mirco Fluidization: Micro Fluidizationis a recent technique to prepare unilamellar vesicles of defined size distribution. This method is based on the 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 niosomes formation. The result is greater uniformity,smaller size and better reproducibility of ofniosomes formed.[20]

Preparation of Multi-lamellar Vesicles

(a) **Hand Shaking method or Thin Film Hydration Method:**In this method, surfactant and cholesterol are dissolved in a volatile organic solvent (such as diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at a room temperature (20^{o}C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film is hydrated with aqueous phase containing drug at 50-60^{o}c with gentle agitation. This process forms typical multilamellar niosomes.[21]

Thin film hydration method

Preparation work flow

↓

Adjust the temperature of the water bath to the desired temperature

↓

Accurately weigh the appropriate amount of surfactant and cholesterol in a round bottom flask

↓

Add an appropriate organic solvent to dissolve the contents

↓

Attach the flask to the rotary evaporator and allow to run for 60 minutes

↓

Detach the flask and add the aqueous solution of the drug

↓

Re-attach the flask to the rotary evaporator and allow to run for 60 minutes

↓

Move the sample to a 25ml beaker and apply magnetic stirring on a gentle speed for 15minutes

↓

Probe sonicate the sample for 1-2 minutes

↓

Centrifuge at an appropriate rpm (13,500rpm) for 30 minutes

↓

A pellet of the drug-loaded niosomes will be formed

Fig 4.1: *Representing a flow chart of the step wise thin film hydration method*

Fig 4.2: *Depicting the Rotary Flash Evaporator.*

(b)Trans Membrane pH gradient (inside acidic)drug uptake process (remote landing): Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to attain a thin film on the wall pf the round bottom flask. The film is hydrated with 300mm citric acid (pH 4.0) by vortex mixing. To this niosomal suspension aqueous solution containing 10mg/mL of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60ºC for 10 minutes to produce the desire multilamellar vesicles.

8.3. Preparation of Large Unilamellar Vesicles:

(a)Reverse Phase Evaporation Technique(REV): Here, the cholesterol and surfactant are dissolved in a mixture of ether and chloroform.[22]An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5ºC. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline. The organic phase is removed at 40ºC under low pressure. The resulting viscous niosome suspension is diluted with phosphate buffered saline and heated in a water bath at 60ºC for 10 minutes to yield niosomes.

(b)Ether Injection Method: The ether injection technique is based on slow injection of niosomal ingredients in diethyl ether through a 14-guage needle at the rate of approximately 0.25mL/min into a preheated aqueous phase maintained at 60ºC.[21,23] The expected reason behind the formation of larger unilamellar vesicles is that the slow vapourization of solvemt results in an ether gradient extending towards the interface of aqueous-nonaqueous interface. The former maybe in charge for the formation of bilayer structure. The disadvantages of this method are that a small amount of ether is frequently present in the vesicle suspension and is difficult to remove.

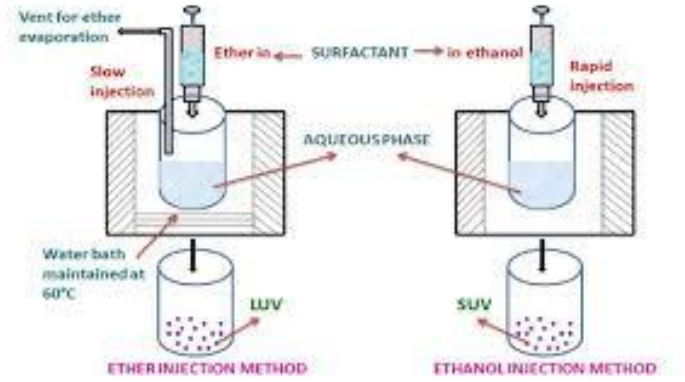

Fig 5:*A diagrammatic representation of Ether injection method*

Miscellaneous

(a)Multiple membrane extrusion method: A mixture of surfactant, cholesterol and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded via polycarbonate membranes, which are placed in a series for upto eight passages. This is a good technique for controlling the niosome size.[20]

(b)Emulsion method: The oil in water (o/w) emulsion is prepared from an organic solution of surfactant,cholesterol and an aqueous solution of the drug.[24,25] The organic solvent is then evaporated leaving niosomes dispersed in the aqueous phase.

(c)The "bubble" method: It is an inventive method 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 placed in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer(pH 7.4) at 70°C. The dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.[26]

(d)Formation of Niosomes from proniosomes: Another technique for the formation of niosomes is to coat a water- soluble carrier like sorbitol with surfactant. The result of the coating process is a dry formulation, in which each water soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T>Tm and brief agitation.[27] Where, T= Temperature and Tm= Mean Phase transition temperature.

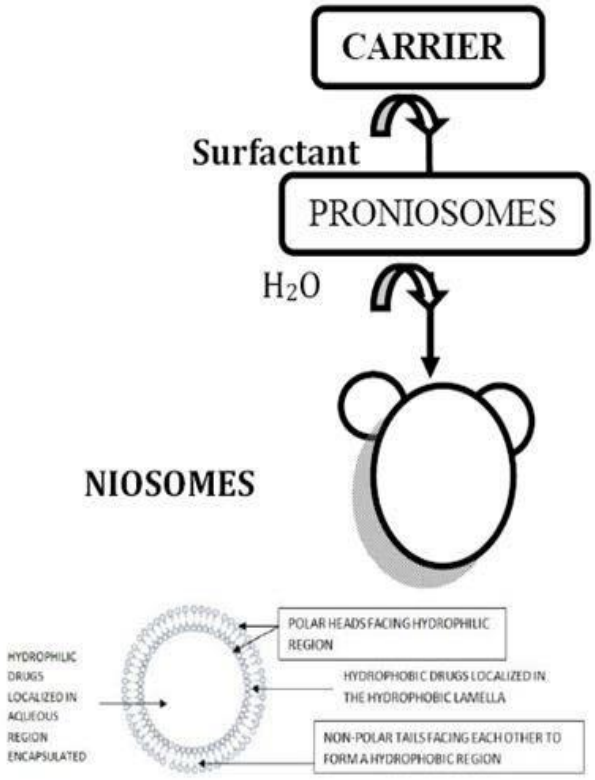

Fig 6:*Schematic diagram for the formation of niosomes from proniosomes.*

Method of Preparation	**Drug Incorporated**
Ether injection	Sodium stibogluconates13,22 Doxorubicin
Hand Shaking	Methotrexate23 Doxorubicin
Sonication	9-desglycinamide 8-arginine Vasopressin Oestradiol21

Table 1: *Drugs incorporated into niosomes by various methods*

Route of drug administration	Examples of drugs
Intravenous route	Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine,Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin,Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
Per-oral route	DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
Transdermal route	Flurbiprofen,Piroxicam,Estradiol,Levonorgestrol,Nimesulide,Dithranol, Ketoconazole, Enoxacin, Ketorolac
Ocular route	Timolol maleate, Cyclopentolate
Nasal route	S umatriptan, Influenza Viral Vaccine
Inhalation	All – trans retinoic acids

Table 2: *List of drugs formulated as niosomes*

2.8. SEPARATION OF UN-ENTRAPPED DRUG

The removal of unentrapped solute from the vesicle can be achieved through different methods, that include:

(i)Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.[26]

(ii)Gel Filtration: The unentrapped drug is removed by gel filtration of niosomal dispersion via a Sephadex-G- 50 column and elution with phosphate buffered saline or normal saline.

(iii)Centrifugation: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.[28.29]

2.9. CHARACTERIZATION OF NIOSOMES

(i) Size: Shape of niosomal vesicles is presumed to be spherical and their mean diameter can be adamant by using laser light scattering method. As well, diameter of these vesicles can be adamant by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy.[28] Freeze thawing (retaining vesicle suspension at -20^{o}C for 24 hrs and then heating to ambient temperature)ofniosomes increases the vesicle diameter, that might be imputed to fusion of vesicle during the cycle.

(ii) Bilayer Formation: Fabrication of non-ionic surfactants to form bilayer vesicle is characterized by an X-cross formation under light polarization microscopy.[30]

(iii)Number of Lamellae: This can be purposed by using Nuclear Magnetic Resonance(NMR) spectroscopy, small angle X-ray scattering and electron microscopy.

(iv)Entrapment Efficiency: After formulating niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration as reported 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 technique for the drug.[31]

Entrapment Efficiency= (Amount entrapped/total amount)X100

(v) *In Vitro* Release Study: A technique of *in vitro* release study has been reported with the help of Franz-Diffusion cell.The Franz diffusion cell consists of two compartments – the donor compartment and the receptor compartment.The test product is solicited to the membrane through the top chamber- the donor chamber. The bottom chamber- receptor compartment contains fluid from which samples are taken at regular intervals for analysis. The testing decides the amount of active drug that has permeated the membrane at each time point. The Transdermal diffusion cell apparatus is peculiarly simple to operate. The system is supplied with:[32]

- Six stage magnetic stirrer with digital RPM indicator.
- Water heater & Water circulation system with digital temperature controller and water level indicator
- Cell Holder
- Diffusion cells
- Teflon coated stirring bars.

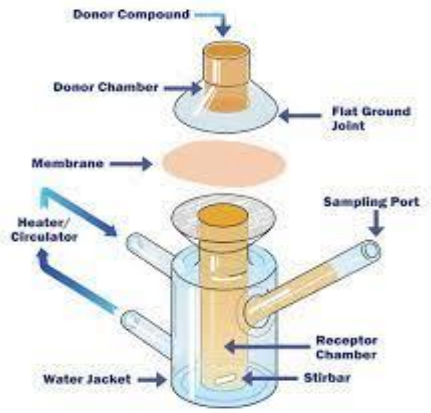

Fig 7:*Illustration of the Franz Diffusion cell*

2.10. FACTORS AFFECTING PHYSIO-CHEMICAL PROPERTIES OF NIOSOMES

Various factors that affect the Physio-Chemical characteristics of niosomes are further discussed:

(i) Nature of Surfactants:A surfactant used for the formulation of niosomes should 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.[25] The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than compatible dialkyl ether chain. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester- linked surfactant degraded by esterase's to triglycerides and fatty acid *in vivo*.[34] The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosomes.[35,36] Surfactants like span series having HLB values between 4 and 8 can form vesicles.[33]

Type of Non-ionic surfactant	Examples
Fatty alcohol	Cetyl alcohol, Steryl alcohol, Cetosteryl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Copolymers	Poloxamers

Table 3: *Different Types of Non-Ionic Surfactant*[34]

(ii) **Amount and type of surfactant :**The mean size of niosomes rises proportionally with rise in the HLB of the surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) as the surface free energy reduces with an increase in hydrophobicity of surfactant.[33] The bilayers of the vesicles are either in the so called liquid state or in gel state, based on the temperature , the type of lipid or surfactant and the presence of other components like cholesterol. In the gel state, alkyl chains are present in a well-ordered structure and in the liquid state , the structure of the bilayers is more disordered. The surfactants and lipids are determined by the gel liquid phase transition temperature(TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e., Span 60 having higher TC, provides better entrapment.

(iii) **Membrane Composition:**The stable niosomes can be prepared with addition of various additives with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by various additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C_{24} (Cholesteryl poly-35 oxyethylene ether), which prevents aggregation due to development of steric hinderance.[37] The mean size of niosomes is determined by membrane composition like the Polyhedral niosomes formed by C16G2: solulan C24 in ratio (91:9) having bigger size (8.0 ±0.03mm) than spherical /tubular niosomes formed by C16G2: cholesterol: solulan C24 in ration(49:49:2) (6.6± 0.2mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and decreases the leakage of drug from niosome.[38] Inclusion of cholesterol in niosome increases its hydrodynamic diameter and entrapment efficiency.[33] In general, the action of cholesterol is two folds; on one hand , cholesterol increases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid ordered phase.[29] An increase in content of the bilayers resulted in a decline in the release rate of encapsulated material and therefore a rise in the rigidity of the bilayers is obtained.[29] Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle and leads to greater overall entrapped volume.

(iv) **Nature of Encapsulated Drug:**The physio-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion among the surfactant bilayers and hence increase vesicle size.[39]The aggregation of vesicles is prevented due to the charge development on bilayer. In Polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size.[28] The hydrophilic lipophilic balance of the drug affects degree of entrapment.

(v) **Temperature of Hydration:**Hydration temperature determines the shape and size of niosome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation.[40,41] In an article by Arnothayanum, a polyhedral vesicle formed by C16G2:solulan C24 (91:9) at 25^{o}C which on heating transformed into spherical vesicle formed by C16G2:cholesterol:solulan C24 (49:49:2) shows no shape transformation on heating or cooling.[41,42] Along with the aforementioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

(vi) **Methods of Preparation:**Hand shaking method forms vesicles with greater diameter (0.35-13nm) compared to the ether injection method (50-1000nm). Small sized niosomes can be prepared by Reverse Phase Evaporation method. Micro fluidization method gives higher uniformity and small size vesicles.[22]Niosomes obtained by Trans membrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug.[45]

2.11. THERAPEUTIC APPLICATIONS OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against different diseases. Some of their therapeutic applications are mentioned below:

(i) Targeting of Bioactive Agents:

(a)To Reticulo-Endothelial System (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as “Opsonins”, which mark them for clearance. Such localized drug accumulation has, however been used in treatment of animal tumours known to metastasize to the liver and spleen and in parasitic infestation of liver.[46]

(b) To organs other than RES

It has been advised that carrier system can be directed to particular sites in the body by use of antibodies.[46] Immunoglobulins seem to bind quite readily to lipid surface, thus offering a easy means for targeting of drug carrier.[42] A number of cells exhibit the intrinsic ability to identify and bind specific carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

(ii) Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumour activity, shows a dose dependent irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumour increased their life span and decreased the rate of proliferation of sarcoma.[47]Niosomal entrapment increased the half-life of drug , prolonged its circulation and altered its metabolism. Intravenous administration of Methotrexate entrapped in niosomes to S-180 tumour bearing mice resulted inotal regression of tumour and also higher plasma level and reduced elimination.[46,47]

(iii) Leishmaniasis

Niosomes can be used for targeting of rug in treatment of diseases in which the infecting organism resides in the organ of Reticulo-Endothelial System. Leishmaniasis is such as disease in which parasite invades cells of liver and spleen. The commonly administered drugs are Antimonials, which are related to arsenic and at high concentration they damage the heart, liver, kidney. The study of antimony distribution in mice, performed by Hunter *et al* showed high liver level after intravenous administration of the carrier forms of the drug.[34]

(iv) Immunological Application of Niosomes

Niosomes have been used for studying the nature of the immune response produced by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity , low toxicity and stability.[49]

(v)Niosomes as carrier for Haemoglobin

Niosomes can be used as a carrier for haemoglobin.[50.51]

(vi)Transdermal Delivery of Drugs by Niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. A rise in the penetration rate has been obtained by transdermal delivery of drug incorporated in niosomes.

(vii)Other Application

- **(a) Sustained Release:**Sustained release action of niosomes can be applied to drugs with less therapeutic index and low water solubility since those could be maintained in the circulation through niosomal encapsulation.
- **(b) Localised Drug Action:**Drug delivery through niosomes is one of the approaches to attain localized drug action, since their size and low penetrability via epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time decreases its systemic toxic effects, for example, Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, rise in potency and hence reduced dose and toxicity.[34]

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