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"Niosomes As Targeted Drugs Delivery System"– An Overview

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Abstract :

The self assembly of non-ionic surfactant into vesicles was first reported in the cosmetic industry. In recent years, it has been discovered that these vesicles can improve the bioavailability of encapsulated drug & provide therapeutic activity in a controlled manner for a prolonged period of time, niosome are vesicles composed of non-ionic surfactant which are biodegradable relatively non- toxic more stable & inexpensive, an alternatives to liposomes. This review describes all aspects of niosome including their structure, components, types, the various methods of preparation, loading methods, characterization, their use by various routes of administration, its application in chemical drugs, protein drugs & gene delivery and many more .

Keywords :

Niosomes, structure, composition, non-ionic surfactant, types, methods of preparation, loading methods, application.

Introduction :

The idea of Targeted drugs for specific organs, tissue or cells, was proposed a century ago by Paul Ehrlich. The selective & site directed delivery of a therapeutic agent to its site of action is called targeted drug delivery or drug targeting. [1] Different carriers have been used for targeting drugs, such as immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes & niosomes. Niosomes are one of the best among these carriers. Niosomes are nonionic surfactants based vesicles. [2] Niosomes were developed & panteted by L'OREAL in the 1970s & 80s. The first product 'Niosomes' was introduced in 1987 by Lancome.[3] Thus niosomes are unilamellar or multilamellar vesicles where in an aqueous solution is enclosed in highly ordered bilayer made up of Non-ionic surfactant with or without cholesterol and dicetyl phosphate [4] . Niosomes exhibit a behaviour similar to liposomes in vivo[2,4] .

Different methods have been used for preparation of niosomes technique the ether injection method . Niosomes can be administered through various routes such as oral , parenteral , occular etc [5] . The main aim of development of

niosomes is to control the release of drug in a sustained way , modification of distribution profile of drug and for targeting the drug to the specific body size [3] .

• Advantages of Niosomes :

1)Niosomes are osmotically active , chemically stable and have long storage time compared to liposomes [3,5,6,7] .

2) Their surface formation and modification are very easy because of the functional groups on their Hydrophilic heads [5,7] .

3)They have high compatibility with biological system and low toxicity because of their non- ionic nature [5] .

4) They are biodegradable and non-immunogenic [3,5,6,7] .

5) They can entrap lipophilic drugs into vesicular bilayer membranes and Hydrophilic drugs in aqueous compartments [5] .

6) They can improve the therapeutic performance of the drug molecules by protecting the drug from biological environment , resulting in better availability and controlled drug delivery by restricting the drug effects to target cells in targeted carriers and delaying clearance from the circulating in sustain drug delivery [5,6] .

7) They exhibit a high patient compliance because of the water based suspension of niosomes [5] .

8)In niosomes the handling and storage of surfactants require no any special conditions [3,5,6,7] .

9)They increase the oral bioavailability and skin penetration of drugs [3,5,6] .

10)They can regulate the drug delivery rate in the external non-aqueous phase by emulsifying an aqueous phase in a non-aqueous phase [5] .

11)The variable characteristics ; such as the type of the niosomes according to their size , entrapment efficiency and stability can be controlled by the type of preparation method , surfactants , cholesterol content , size surface charge and suspension concentration [5%] .

12) Niosomes can enhance absorption of some drugs across cell membrans , to elude the reticuloendothelial system [5] .

• Disdvantages of Niosomes :

1)The aqueous suspension of niosomes may have limited shelf life due to following reasons ; a) Fusion

b)Aggregations

c) Leaking of entrapped drug

d) Hydrolysis of encapsulated drug [7,8] .

2) The methods of preparation of multilamellar vesicles such as extrusion, sonication , are time consuming and may require specialized equipment for processing [7,8] .

•Comparision of Niosomes and Liposomes:[7,9]

Niosomes	Liposomes
1] Less expensive.	1]More expensive.
2] Non-ionic surfactant are neutral .	2]Phospholipids may be neutral charged.
3] Non-ionic surfactant are use for stability i.e chemically stable.	3]Phospholipids are prone to oxidation degradation i.e chemically unstable.
4] They do not require special storage & handling	4]They require special storage, handling & purity of natural phospholipid is variable
5] Niosomes are prepared from uncharged single chain surfactant & cholesterol.	5]Liposomes are prepared from double chain phospholipids.

•Structure and composition of Niosomes :

Niosomes are lamellar structures and microscopic in size [3,6,8] .The unique structure of niosomes are amphiphilic in nature , which encapsulating both Hydrophilic and Hydrophobic drug incorporated into noisomes [5,8] . The bilayer in niosomes is prepared for a Hydrophilic ends of the Non-ionic surfactant point outwards , while the hydrophobic ends face each other to form the bilayer because of high interfacial tension between Hydrophilic head and the Hydrophobic tail which forms as closed bilayer structure [6,7] . The structure of niosomes is given below in fig. No .1 [10] .

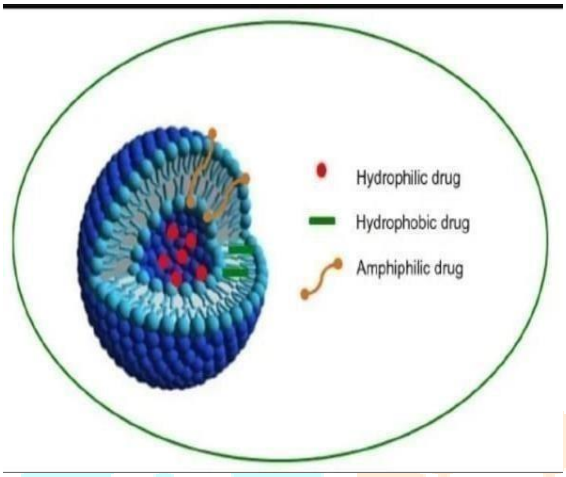

Fig. 1 structure of a non- ionic surfactant Vesicles (Niosomes) [10].

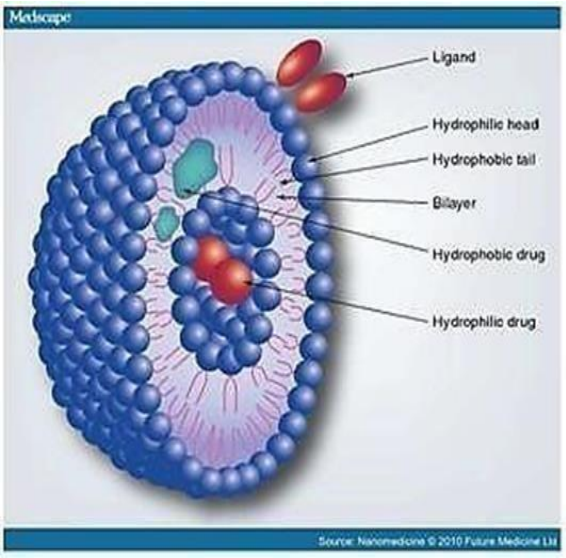

Fig .2Composition of Niosomes [11].

• Composition and components of Niosomes:

There are three major components used for the preparation of Niosomes are as follows [3] .

1) Non-ionic surfactant
2) Cholesterol
3) Other additives

1)Non-ionic surfactant : The Non-ionic surfactant play a important role in the formation of Niosomes . The following Non-ionic surfactants are generally used for the preparation of niosomes [3,5,7,8,11] .

Spans (Span 20 ,40 , 60 , 80 , 85)

Tweens (Tweens 20 , 40 ,60 , 80)

Brijs (Brijs 30 ,35 , 52, 58, 72, 76)

Non-ionic surfactants which having Hydrophilic head group and Hydrophobic tail group [3,7] . They are more stable and biocompatible and less toxic compared to their anionic , amphoteric or cationic counter parts [12] . Non-ionic surfactants are a class of surfactant which have no charged groups in their Hydrophilic heads . The Hydrophilic lipophilic balance (HLB) and critical packing parameter (CPP) values plays critical role in the selection of surfactant molecules for niosomes preparations [5] .

Hydrophilic Lipophilic Balance (HLB) : HLB is a dimensionless parameter which is the useful for the selection of surfactant molecule [5] . The HLB value describes the hydrophilic portion and Lipophilic Portion of Surfactant . The HLB range is from 0 to 20 for Non-ionic surfactant . The lower HLB refers to more lipophilic surfactant and higher HLB to more Hydrophilic surfactant [5] . Surfactants with a HLB between 4 to 8 can be used preparation of niosomes . Hydrophilic surfactants with a HLB value ranging from 14 to 17 are not suitable to form a bilayer membrane due to their high aqueous solubility [7,12] .

Critical Packing Parameter (CPP) : CPP is also dimensionless scale of surfactants [5] . During the niosomal preparation of the geometry of the Vesicles depend upon the critical packing Parameter depends on the symmetry of the Surfactants and can be defined using following equation [5,6,7,8,12] .

$$\mathbf{CPP = V/Ic \times ao}$$

Where ,

V = Hydrophobic group volume

Ic=Critical hydrophobic group length

Ao=Area of Hydrophilic head group

The type of micellar structure was predicted by the Critical Packaging Parameter value as , assumed

,

If CPP <1/2 formation of spherical micelles .

If 1/2 < CPP < 1 formation of bilayer micelles .

If CPP > 1 formation of inverted micelles

2) Cholesterol : Cholesterol provide rigidity and proper shape of niosomes [3,8,11] . In the bilayer structure of niosomes , cholesterol forms hydrogen bonds with Hydrophilic head of a surfactant . Cholesterol content of niosomes influence the structure of niosomes and physical properties such as entrapment efficiency , storage time , release of payload and stability [5,7] .

3)Other additives : Charged molecules increase surface charge density and there by prevent vesicle aggregation . Dicetyl phosphate and phosphatidic acid are mostly used negatively charged molecules for niosomes preparation . Similarly stearyl amine and stearyl pyridinium chloride are positively charged molecules used in niosomal preparations [3,5,7,13] .

• Types of Niosomes :

According to niosomes size they can divided into three categories are as follows [2,5,7,13] .

1)Small Unilamellar Vesicles (SUV) :

Vesicles size is 10 to 100 nm .

2) Large Unilamellar Vesicles (LUV) :

Vesicles size is 100 to 3000 nm .

3)Multilamellar Vesicles (MLVs) :

Vesicles size is greater than 5um

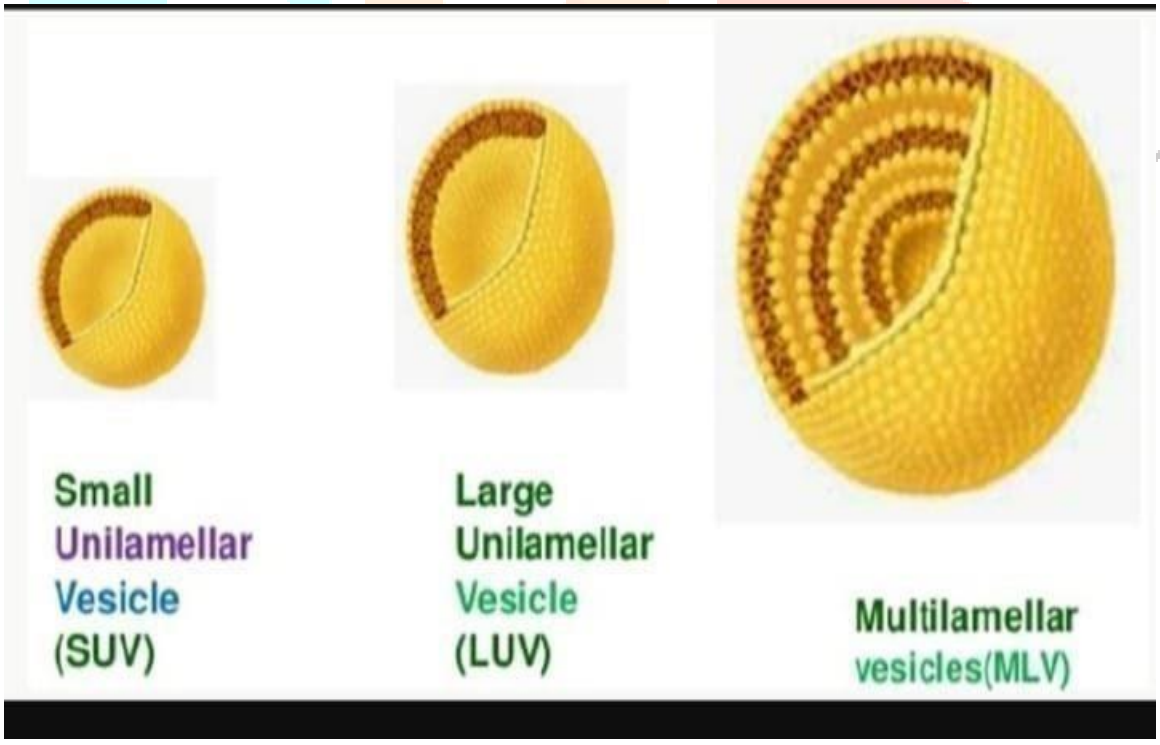

Fig. 3 Types of Niosomes [7] .

• Other types of Niosomes :

Niosomes made by bola surfactant : In these kinds of niosomes , bola surfactant compounds require two Hydrophilic heads which can link by one or two long lipophilic spacers . The surfactant use in bola surfactant containing niosomes is prepared of Omega hexadecylbis(1aza18crown -6) (bola surfactant) ; span 80 / cholesterol in 2:3:1 molar percentage [7] .

Proniosome : Proniosome also known as dry niosomes , so the reduces problems associated with the physical stability of niosomes such as aggregation , distribution , fussion and leaking also benefits in transportation , distribution storage and dosing . Proniosome are the niosomes formation that consist of water-soluble carriers and surfactants [7,12] .

Discomes : Discomes means disk- shaped structures , prepared niosomes from incubating in cholesteryl poly-24-oxyethelene ether (solulan 24) at 75°c for 1 hour to obtain Discomes . This has caused in the construction of large size approximately 11-60 um and multilayered vesicular structures . Discomes were shown to entrap water soluble solutes . Entrapment of 5(6)carboxyfluorescein (CF) release 50% solute after 24 hour at room temperature . The drug delivery potential of Discomes in field of ophthalmology [4,7,12] .

Aspasome (Ascorbyl palmitate vesicles) : Aspasome includes cholesterol , Ascorbyl palmitate and highly charged lipid such as dihexadecyl phosphate (DCP) . It hydrated by water solvent and sonicated to produce the final product . Aspasome can improve the transdermal drug delivery system and decrease the disorders which triggered using reactive oxygen species [5,7] .

Surfactant Ethosomes : Surfactant Ethosomes contain Non-ionic surfactants , a high concentration of ethanol or isopropyl alcohol and water. Surfactant Ethosomes permeate through the stratum corneum and posses significantly higher transdermal effect in comparison to liposomes . The exact mechanism by which they enhance permeation into deeper skin layers remains unclear
[7,12] .

Elastic Niosomes : These vesicles have Non-ionic surfactants , water and ethanol . They enhance penetration of a drug through intact skin by passing through pores in stratum corneum which are smaller than vesicles . Thus they can deliver drugs or compounds of both low and high molecular weight . The first detergent based elastic nanovesicles called or deformable niosomes consisting of surfactant L-595(sucrose laureate ester) and micelles forming surfactant PEG-8-L (octaoxyethylene laureate ester) [7,12] .

• Methods of preparation of Niosomes :

1)Thin film Hydration (Hand Shaking) method .

2)The Bubble Method .

3) Ether Injection Method.

4) Reverse Phase Evaporation Method.

5) Sonication Method.

6) Microfluidization Method .

7) Heating Method .

8)Freez and Thaw Method.

9) Dehydration Rehydration Method.

10)Formation of Niosomes from Proniosomes

11) Multiple membrane Extrusion Method

1)Thin film Hydration (hand shaking) method : Surfactant and the other vesicles forming ingredients like cholesterol are blended and mixture is dissolved in a volatile organic solvents like di-ethyl ether , chloroform or methanol in a round bottom flask using rotary evaporator organic solvent is removed at room temperature , by this a thin layer of solid mixture deposited on the wall of the flask . The dried surfactant film can be rehydrated with aqueous phase at 60°c with gentle agitation results in formation of multilamellar niosomes [5,8] .

2)The Bubble method : It is one step technique by which liposomes and niosomes are prepared without the use of organic solvents . Round bottom flask is used as bubbling unit with its three backs position in water bath to control the temperature is positioned in the first and second neck and Nitrogen supply through the third neck . At 70°c cholesterol and surfactants are dispersed together in the buffer [pH 7.4] and mixed with high shear homogenizer for 15 second and immediately afterwards “bubbled” at 70°cusing nitrogen gas [3,5, 8] .

3)Ether Injection Method : The method provide a mean of making niosomes by slowly introducing solution of surfactants dissolved in di-ethyl ether into warm water maintain at 60°c . The surfactant mixture in ether in injected through 14 gauge needle into an aqueous solution of material [3,5,6,8,11] . Small unilamellar vesicles produced by solvent injection technique , relatively have high entrapped aqueous volume . Depending upon the conditions , the diameter of the final vesicles ranges from 50 to 1000 nm . [5] .The disadvantage of this method is that a small amount of ether often present in the vesicles suspension and is difficult to remove very often [3,6,8]

4) Reverse Phase Evaporation : In this method , cholesterol and surfactants are dissolved in a mixture of ether and chloroform . An aqueous phase containing drug is added to this and the resulting viscous niosome suspension is diluted with phosphate buffered saline and heated in a water bath at 60°c for 10 minutes to yield large unilamellar vesicles niosomes [2,8] .

5] Sonication Method : It is a typical method of production of the vesicles in which a 10-ml glass vial solution in buffer is added to the Surfactant / cholesterol mixture . Then the mixture is probe sonicated at 60°c for 3 minutes using a sonicator with titanium probe to yield niosomes . The resulting vesicles are small and unilamellar [5,8] .

6) Microfluidization method : It is a recent technique based on submerged jet principal . In this two fluidized streams interact at ultra high velocities and more forward through precisely defined micro channel 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 which results in a greater uniformity , smaller size and better reproducibility of small unilamellar vesicles (niosomes) formed [5,8] .

7)Heating Method : Surfactants and some additives such as cholesterol were separately hydrated in phosphate buffer solution (pH 7.4) for one hour under nitrogen atmosphere at room temperature . Then , after about 15 to 20 minutes , the solution is heated (about 120°c) on a hot plate stirrer to dissolve cholesterol . The temperature is bought down to 60°c and the other components surfactants and other additives , are then added to the buffer in which cholesterol is dissolved while stirring continuous for another 15 minutes . Niosomes obtained at this stage are left at room temperature for 30° minutes and then kept at 4 to 5 °c under nitrogen atmosphere until use [5] .

8)Freez and Thaw Method (FAT) : This method can generate frozen and thawed multilamellar vesicles (FAT- MLVs) . Using THF method , were frozen in liquid nitrogen for 1 minute and thawed in a water bath at 60°c for another 1 minute [5] .

9)Dehydration Rehydration Method (DRM) : The dehydration Rehydration technique was first described by Kirby and Gregoriadis in 1984 . The dehydration Rehydration vesicles (DRVs) prepared by THF , are frozen in liquid nitrogen and then followed by Freeze drying overnight . Niosomes powders are hydrated with phosphate buffer solution (pH 7.4) at 60°c [5] .

10)Formation of Niosomes from Proniosomes : In this method of producing niosomes a water soluble carriers such as sorbitol is coated with surfactant resulting in the formulation in which each water soluble particle is covered with a thin-film of dry surfactant . This preparation is termed " Proniosome" . Then Proniosome powder is filled in a screw capped vial , and mixed with water or saline at 80°c by vortexing , followed by agitation for 2 minutes results in the formation of niosomal suspension [3,8] .

11) Multiple Membrane Extrusion Method : A blend of surfactant , cholesterol and dicetyl phosphate is dissolved in chloroform and the solvent is evaporated leading to formation of thin film using aqueous drug solution the film is hydrated and the resultant suspension extruded through polycarbonate membranes , which are placed in a series for upto eight passages [8] . In this method the size of niosome can be reduced by passing them through membrane filter . This method can be used for production of multilamellar vesicles [3] .

• **Loading methods :** The encapsulation process of drugs are called loading methods . Drugs can be entrapped based on their physical trapping , covalent and hydrogen bonds , adsorption, ionic interaction between drugs delivery systems , more than one of these parameters play role in loading process . Generally niosomes drug loading processes contain two types of methods [5] . 1) Direct Entrapment (passive loading)

2) Remote loading (Active loading)

a) Remote loading by using trans membrane pH gradient (inside acidic)

b) Remote loading by using trans membrane (ion gradient)

1)Direct Entrapment (passive loading) : Direct entrapment is the simplest loading method and is widely used where lipophilic drugs are dissolved in organic solvent and Hydrophilic drugs are dissolved in aqueous phase and a percent of drugs are loaded among the preparation process and unload drugs can be subtracted from suspension by dialysis, centrifugation, gel chromatography or filtration [5] .

2) Remote loading (Active loading) : This method enhance the efficiency drug loading by aid of pH and ion . Differential of these parameters is the real cause for some material transition across the niosome membrane [5] .

a) loading by using trans membrane pH gradient (in acidic range) : Basic drug in an unionised state passes the membrane barrier of the niosome , if the pH is higher in the outside of niosomes vesicles . The basic drug becomes ionized and precipitate , due to the lower pH inside the niosome . Thus , it becomes unable to leave the vesicles , after encapsulation . This method can experimentally be accomplished by hydration the thin film of surfactant and cholesterol with citric acid (pH 4) by vortex mixing . Therefore , the MLVs are frozen and thawed . Drugs are added into aqueous solution and suspension is vortexes . The pH is then raised to 7.0-7.2 and is later heated at 60°c for 10 minutes to give niosomes [5] .

b)Remote loading by using trans membrane ion gradient : An alternative remote loading method has also been developed for DOX using ammonium sulfate . In this trapping method , there is a trans membrane ion gradient where the concentration of ammonium sulfate [(NH4)2 So4] in Vesicle is more than this concentration in medium . However , these remote loading procedures have not been used to increase the niosome encapsulation of acid drugs [5] .

• Characterization of Niosomes :

Physicochemical characterization and analysis of niosomes contain vesicle size , morphology , size distribution , charge and zeta potential , entrapment efficiency , curve of drug release , lamellarity , rigidity , stability , viscosity , conductivity and homogeneity [5] .

1)Vesicle size and size distribution : shape of niosomal vesicles is assumed to be spherical , and their mean diameter can be determined by using laser light scattering method . Also, diameter of these Vesicles can be determined by using electron microscopy , molecular sieve chromatography , ultracentrifugation , photon correlation microscopy and optical microscopy and Freez fracture electron microscopy . Freez thawing of Niosomes increases the vesicle diameter , which might be attributed to a fusion of vesicles during the cycle [2,5,6,8,] . Also , niosomes size distribution and polydispersity index (PDI) can be measured by using dynamic light scattering particles size analyzer . Vesicles size can range from around 20 nm to around 50 micrometres [5] .

2)Charge of Vesicle and zeta potential : The zeta potential of vesicles can play an important role in the behaviour of niosomes . In general , charged niosomes are more stable against aggregation and fusion than uncharged vesicles . Also , negative zeta potential values ranging between -41.7 and -58.4 mV are sufficiently high for electrostatic stabilization and both Surfactant type or encapsulation efficiencies might affect the zeta potential values . Surface Zeta potential can be determined using zetasizer , mastersizer, microelectrophoresis, pH sensitive fluorophores , high performance capillary electrophoresis and DLS instrument [5] .

3)Stability study : The stability of the niosomes plays an important role in their formulation development . Stability of the nanocarriers , such as liposomes , polymerosomes and some other lipid or polymer based particulates remains a big concern for drug delivery . How to improve their stability during formulation / storage and to prevent premature disassembly before reaching the target sites still needs to be addressed . Compared with liposomes , niosomes posses better stability and have potential for clinical uses [13] . Stability of niosomes is influenced by the entrapped drugs it's concentration , type of surfactant and cholesterol content . Stability Studies are carried out to investigate the drug leaching from niosomes during storage and while in the general circulation . Using conditions that stimulate both situations , this leaching can be evaluated by determining mean vesicle size , size distribution and entrapment efficiency over several month , periods . The stabilization strategies must be optimized depending on the agent to be entrapped to provide chemical stability of both Surfactant and drug components [5] .

4)Bilayer formation : Assembly of Non-ionic surfactants to form a bilayer vesicles characterised by an x-cross formation under light polarisation microscopy [2] .

5)Number of Lamellae : This is determined by using nuclear magnetic resonance (NMR) spectroscopy , small angle x-ray scattering and electron microscopy [2] .

6)Membrane Rigidity : membrane Rigidity can be measured by means of mobility of fluorescence probe as a function of temperature [2,8] .

7)Entrapment efficiency : After preparing niosomal dispersion , unentrapped drug is separated by dialysis , centrifugation or gel filtration and /or complete vesicle disruption using 50% npropanol or 0.1 % Triton X-100 is done for estimation of the drug remained entrapped in niosome and then analyzing the resultant solution by the drug .where , Entrapment efficiency (EF) can be expressed as ,

Entrapment efficiency (EF) = (amount entrapped / total amount)×100

8)In-vitro Release : A method of in-vitro release rate study includes the use of dialysis tubing .
A dialysis sac is washed and soaked in distilled water . The vesicle suspension is pipetted into a bag made up of the tubing and sealed . The bag containing the Vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°c or 37°c . At various time intervals , the buffer is analysed for the drug content by an appropriate assay method [2,6,8] .

9) In-vivo Release : for in vivo study niosomal suspension was injected intravenously (through tail vein) to the albino rats using appropriate disposal syringe . These rats were subdivided into groups [2,8] .

• Factors governing niosome formation :

1)Composition of niosome : Theoretically for the niosome formation the presence of a particular class of amphiphile and aqueous solvent is needed but in certain cases cholesterol is required in the formulation to provide rigidity , proper shape and conformation to the niosomes . Cholesterol also stabilizes the system by prohibiting the formation of aggregates by repulsive steric or electrostatic effect . An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)carboxyfluorescein (CF) loaded Span 60 based niosomes [8].

2)Surfactant and lipid level : The level of surfactant / lipid used to make niosomal dispersion is generally 10-30 mM (1-2.5% w/w) . Altering the surfactant : water ratio during the hydration step may affect the system's microstructure and hence the system's properties . However increasing the surfactant / lipid level also increases the total amount of drug encapsulated , although highly viscous systems result , if the level of surfactant / lipid is too high [6,8] .

3) Nature of encapsulated drug : Physico-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 between the surfactant bilayers , and hence increases vesicle size . The aggregation

of Vesicles is prevented by using electrostatic stabilizers like dicetyl phosphate in 5(6)-carboxyfluorescein (CF) [2,6,8] . The effect of the nature of Drug on formation vesicles is given in Table 1.[2] .

Table .1 : Effect of the nature of drug on the formation of niosomes [2] .

Nature of the drug	**Leakage from the vesicle**	**Stability**	**Other properties**
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophilic drug	Increased	Decreased	-
Amphiphilic	Decreased	-	Increased encapsulation , altered electrophoretic mobility
Macromolecule	Decreased	Increased	-

4)Structure of surfactant : The geometry of Vesicle to be formed from Surfactants is affected by its structure , which is related to critical Packing Parameters . On the basis of critical Packing Parameters of surfactants can predicate geometry of Vesicle to be formed [6,8] .

5) Temperature hydration : Hydration temperature influences the shape and size of the niosome , temperature change niosomal system affects assembly of surfactants into vesicles by which induces vesicle shape transformation . Ideally the hydration temperature for niosome formation should be above the gel to liquid phase transition temperature of system [6,8] .

• Routes of administration :

Depending on the types of drugs, surfactants, disease, or locations of defects, various routes of administration exist for niosomal drug .

1)Oral Route : The oral route is the most preferred route for delivering a therapeutically active substance . But acids and digestive enzymes in the stomach and small intestine can degrade some active substances . However , niosomes have been reported as conceivable vesicles to deliver drug molecules to the desired mucous membrane or skin layers [5] . The oral delivery of recombinant human insulin using niosomal formulations was demonstrated by a study involving
polyoxyethylene alkyl ethers based niosomes . Significantly higher protection activity was seen in Brij 92/cholesterol (7:3 molar ratios) in which only 26.3±3.98% of entraped insulin released during

24 hour in simulated intestinal fluid (SIF) . Niosomes were prepared from Span40, span60 and cholesterol using reverse evaporation method . Niosomal formulation could be promising delivery system for gliclazide with improved bioavailability and prolonged drug release profile
[3].

2)Intravenous (IV) : Intravenous administration of drugs can directly put drugs into the circulation system and drug loaded niosomes compared to free drugs can enhance stability of the drugs and prolong the circulation time . Loaded drug can be released into the bloodstream or into target tissue under certain condition or into the targeted cells [5] .

3)Intramuscular (IM) : After IM injection of the drugs, a gentle drug penetration from tissues to capillaries has been observed [5] .

4) delivery : slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes [3] .

5)Subcutaneous (SC) : After SC injection , drug transit to capillaries and this route of administration is used for several drugs such as insulin, hydroxycamptothecin and so on [5] .

6)pulmonary : Pulmonary administration , through inhalation of drugs, is one of appropriate routes used for glucocorticoids such as beclomethasone dipropionate (BPD) for patients with asthma . Pulmonary delivery of BPD through polysorbate 20 niosomes offers the advantages of sustained delivery an, amplified therapeutic effect [5] .

7) Occular : The penetration of drug molecules into the eye depends on the Physico-chemical properties of both the drug and vehicle . Vesicular systems provide prolonged duration of action at y enzymes in the lachrymal fluid . Because of this , niosomes have gained popularity in occular drug delivery research and are a potential delivery system for the effective treatment of glaucoma and various other conditions [12] .

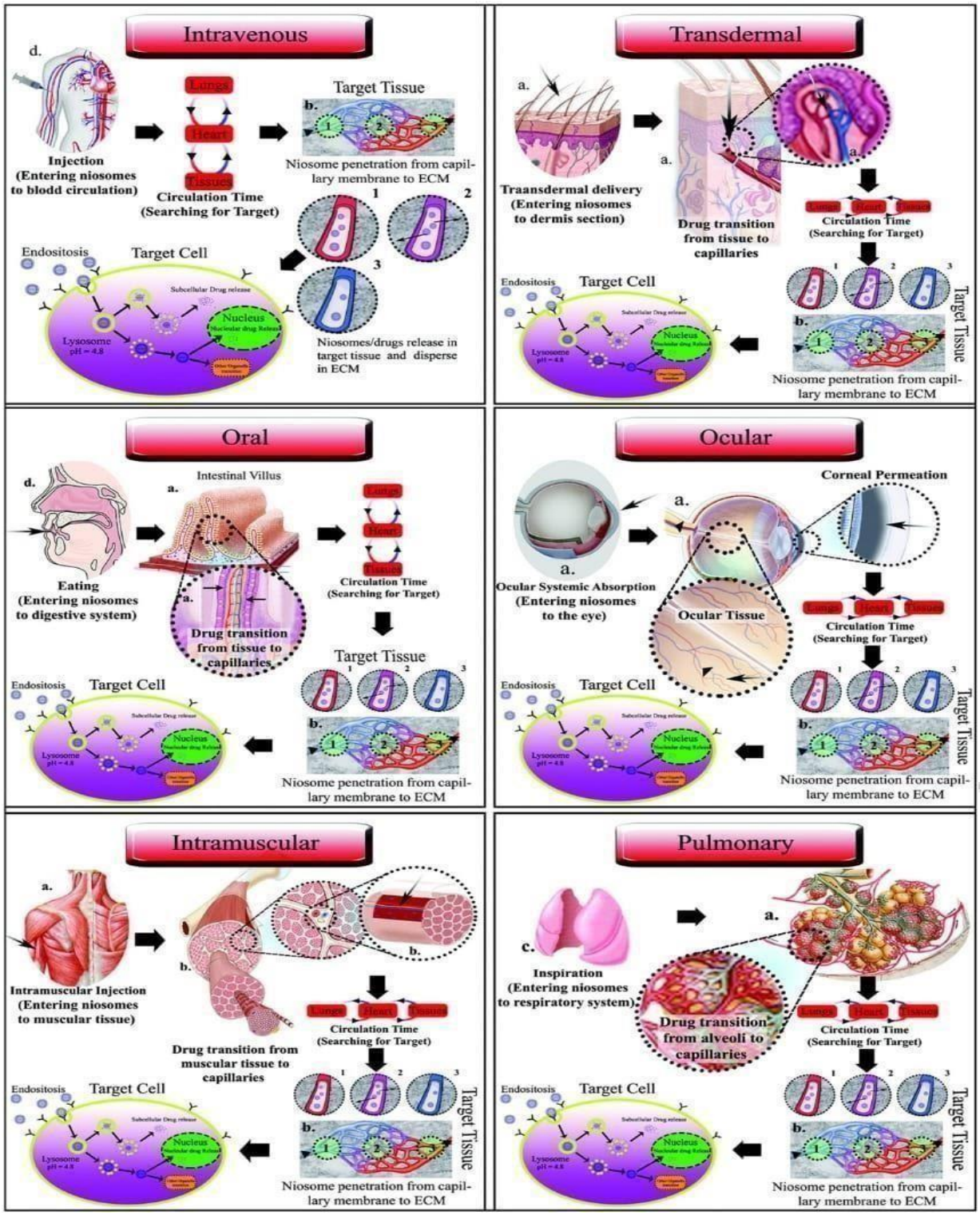

Fig . 4 The whole process and routes of administration [5]

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• Applications of niosomes :

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various disease . Few of their therapeutic applications are as follows :

1)Drug Targeting :

One of the most useful aspects of niosomes is their ability to target drugs . Niosomes can be used to target drugs to the reticuloendothelial system or other than reticuloendothelial system.

a)To reticuloendothelial system (RES) : The vesicles occupy preferentially to the cells of RES . It is due to circulating serum factors known as opsonins . These opsonins mark the niosome for clearance . Such localization of drugs is utilized to treat tumors in animal know to metastasis to the liver and spleen . This localisation of drugs can also be for treating parasitic infections of the liver [8,11] .

b)To organs other than reticuloendothelial system : By use of antibodies , carrier system can be directed to specific sites in the body . Immunoglobulins seem to have affection to the lipid surface, thus providing a convenient means for targeting of drug carrier . Many cells have the intrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells [8, 11] .

2) Niosomes as carriers for haemoglobin :

Niosomes can be used as a carrier for haemoglobin . Niosomal suspension shows a visible spectrum superimposable which is likely to be or ,onto that of free haemoglobin . Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non- encapsulated haemoglobin . Anti-neoplastic Treatment most antineoplastic drugs cause several side effects . Niosomes can alter the metabolism ; prolong circulation and half life of the drug , thus decreasing the side effects of the drugs . Niosomes are decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination [7,8,11,12] .

3]Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide : Radiolabelled (I125) VIP- loaded glucose bearing niosomes were injected intravenously to mice . Encapsulated VIP within glucose- bearing niosomes exhibit higher VIP brain uptake as compared to control [8,11] .

4) Transdermal delivery of drugs by niosomes :

Those drug have slow penetration of medicament through skin is the major drawback of transdermal Route of delivery . An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes . From the above discussed studies , and confocal microscopy ,it was seen that Non-ionic vesicles could be formulated to target pilosebaceous glands . Topical niosomes may serve as solubilization matrix , as a local depot for sustained release of dermally active compounds , as penetration enhancers , or as rate- limiting membrane barrier for the modulation of systemic absorption of drugs [7,8,11] .

5)Cosmetic delivery :

The first report of Non-ionic surfactant Vesicles came from the cosmetic application devised by L'Oreal . Niosomes were developed and patented by L'Oreal in the 1970s and 80s . The first product 'Niosomes' was introduced in 1987 by Lancome . The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs , improved bioavailability of poorly absorbed ingredients and skin penetration [3] .

6) protein and peptide delivery :

Protein delivery after oral administration was restricted via several factors that include proteolytic enzymes , pH , and little epithelial permeability . Niosomes were applied to effectively keep the peptides from gastrointestinal collapse . Presented that the oral administration of rh-a rh-insulin as niosomal construction based on polyoxyethylene alkyl ether was secure in contradiction with proteolytic action of chymotrypsin , trypsin , and pepsin . The drug release kinetics was defined by the Baker and Lonsdale equation indicating a diffusion-based delivery mechanism . Niosomes can be established as sustained release oral formulae for transport of peptides and proteins [7] . In vitro study conducted by oral drug delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide [11] .

7)Gene delivery :

Gene therapy , as a new modality for the treatment of disease , has emerged as a powerful tool in recent years . But delivery remains a problem for clinical applications . Non-viral gene carriers which are mainly based on polymers and lipids are employed as two approaches for the delivery of gene materials . Lipoplex is a widely-used gene delivery carrier which may cause toxicity and non-specific attachment during the circulation in vivo . A method to deliver pCMSEGFP plasmid to the retina using niosomes . They formulated the niosomes based on cationic lipid 2,3di(teradecyloxy)propan-1-amine , aqualene and polysorbate 80 by a method of solvent emulsification-evaporation . The results proved that niosomes could protect DNA from degradation and help the gene materials to enter cells [13] .

8) Sustained release :

Sustained release action of niosomes can be applied to drugs which have low therapeutic index and have low water solubility since those could be maintained in the circulation via niosomal encapsulation . The role of liver as a depot for methotrexate after niosomes are taken up by liver cells [8, 11] .

9)Localized drug action :

To achieve Localized drug action , niosomal dosage form is one of the approaches because of the size of niosomes and their low penetrability through epithelium and connective tissue the drug Localized at the site of administration . This results in enhancement of efficacy and potency of the drug and also reduces its systemic toxic effects e.g Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug , increase in potency and hence decrease both in dose and toxicity [8] .

10) Leishmaniasis therapy :

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen . Derivatives of Antimony are most commonly prescribed drugs for the treatment of Leishmaniasis . These drugs in higher concentrations – can cause liver , cardiac and kidney damage . Use of niosomes as a drug carrier showed that it is possible to overcome the side effects at higher concentration also and thus showed greater efficacy in treatment [3 ,8,11] .

11) Neoplasia :

Numerous attempts have been made to enhance the selectivity of antineoplastic agents by linking them to a cancer moiety . Novel vesicular systems , niosomes containing anticancer drugs if suitably designed will be expected to accumulate within tumors. Niosomal formulations of paclitaxel , an antineoplastic agent , were prepared using different surfactants by film hydration method . Paclitaxel was successfully entrapped in all of the formulations . The slow release observed from these formulations might be beneficial for reducing the toxic side effects of paclitaxel . The efficiency of niosomes to protect paclitaxel against gastrointestinal enzymes (trypsin , chymotrypsin and pepsin) was also evaluated for paclitaxel oral delivery . Among all formulations , gastrointestinal stability of paclitaxel was well preserved with Span 40 niosomes
[3] .

Table .2 : Recent studies in drug delivery using niosomes [7] .

Application	Drug	Routes of Administration
Pulmonary delivery	Ciprofloxacin Clarithromycin Rifampicin	Inheler Inheler Intratracheal
Protein delivery	Insulin N-acetyl glucosamine Bovine serum albumin	Oral Topical Oral
Cancer chemotherapy	Cisplatin 5-Flourouracil Curcumin 5 -Flourouracil	Topical Intravenous
for haemoglobin	Haemoglobin	Intravenous

Treatment of HIV-AIDS	Lamivudine Stavudine Zidovudine	Intravenous
Vaccine and antigen delivery	Tetanus toxoid Newcastle disease vaccine Ovalbumin Bovine serum albumin	Parenteral Topical vaccine

•Conclusion:

Niosomal drug delivery system is one of the example of the great evolution in in novel drug delivery technologies . The concept of drug incorporation in the niosomes and to target the niosomes to the specific site .They represent alternative vesicular system with respect to liposomes also having various advantages over liposomes such as , good chemical and physical stability ,low cost and easy formulation . They may prove to be an alternative to liposomes and attract extensive attention in field of pharmaceutics . more work may be undertaken in the fields below to yield more information for niosome development : 1) Development of multifunctional niosome- based target delivery systems by surface modification . Target molecules could be selected and immobilized on the surface of the niosomes .2) Studies to investigate the toxicity , especially long term trials to evaluate the safety for their clinical application development and scale up studies to investigate the applications of niosomes in industrialization .

•References :

1) Patrick J. Sinko : Martin's Physical Pharmacy & Pharmaceutical Sciences.7th ed. New Delhi; published by Wolters Kluwer: 2016 . P. 642-694

2)Kazi Masud Karim, Asim Sattwa Mandal, Nikhil Biswas, Arijit Guha, Sugata Chatterjee, Mamata Behera, & Ketousetuo Kuotsu : Niosome : A future of targeted drug delivery systems . J. Adv. Pharm. Tech. Res,2011,(62),122. P. 374-380

3)Ali Nasir ,Harikumar SL & Amanpreet : Niosomes ; An excellent tool for delivery . Int. J. Of Res. In pharmacy and chemistry 2012 ; 2(2) ; P. 479-487 .

4)Namdeo. A ,& N. K. Jain : Niosomes as drug carriers .Indian J. Pharm. Sci. ,1996, 52(2) P.4146

5)Moghassemi. S ,& Hadjizadeh. A :Nano-niosomes as nanoscale drug delivery system : An illustrated review . J. of Controlled Release (2014) ;185, P. 22-36.

6). Tarekegn, Nisha. M. Joseph, S. Palani , A. Zacharia , & Zelalem Ayenew : Niosomes in targeted drug delivery: Some recent advances .Int. J. Of pharm . Sci. & Res.(2010) ; vol.1(9) : 1-8

7)M. Gharbavi , J. Amani , H. Kheiri-Manjili , H. Danafar , & A. Sharafi : Niosome : A promising nanocarrier for natural drug delivery through Blood- Brain Barrier . Advanced in pharmacological sci. (2018) ;

8)Lohumi Ashutosh, Rawat Suman, Sarkar Sidhyartha, Sipai Altaf bhai., & Yadav M. Vandana : A novel drug delivery system : Niosomes review . J. Of Drug Delivery & Therapeutics; (2012) , 2(5), p.120-135.

9) R. Bartelds, M.H. Nematollahi, T. Pols, Marc C. A. Stuart, A. Pardakhty, G. Asadikaram, B. Poolman : Niosomes, an alternative for liposomal delivery . PLoS ONE (2018),13(4): e0194179

10)R. Muzzalupo & L. Tavano : Niosomal drug delivery for transdermal targeting : recent advances. J. Of Res.& Reports in Transdermal Drug Delivery ; (2015): 4,P.23-333

11)Sharma, D. Ali, A. A. E. & Aate, J. R : Niosome as novel drug delivery system (2018) ; PharmaTutor , 63(3),P. 58-65

12)G. P. Kumar & P. Rajeshwarrao : Nonionic surfactant vesicular for effective drug delivery – An overview .Acta. Pharm. Sin. B (2011) ; Vol.1 , no. 4 , P. 208-219.

13)Xuemei He. , Minyan Wei , Suna He & Wei-En Yuan : Advances of Non-ionic surfactant vesicles (Niosomes) and Their Application in Drug Delivery . J. Pharmaceutics (2019) , 11, 55.