CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://zenodo.org/records/10887368

https://www.iajps.com/volumes/volume11-march-2024/16-issue-03-march-24/

Available online at: http://www.iajps.com *Review Article*

PRONIOSOMES OF NOVEL DRUG DELIVERY SYSTEM

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Abstract:
The present article depicts an elaborative study of proniosomes as specialized drug delivery system. Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. Provesicular systems, such as proniosomes which is one of the advancement in nanotechnology minimize problems of vesicular systems such as aggregation, fusion and leakage of drug and provide additional convenience in transportation, distribution, storage and dosing. Conventional vesicular systems such as liposomes and niosomes are particulate in nature and face stability related difficulty. The review article provides an insight about these approaches along with a novel vesicular approach known as proniosomes. This new emerging concept has demonstrated the potential in improving the oral bioavailability, targeting drugs to the specific site and also permeation of drugs across the stratum corneum. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity. The goal of this study is to introduce and explore proniosomes as a carrier system for various pharmaceutical and cosmeceutical applications

Key words: *Proliposomes , Cosmeceutical , Bioavailability ,Permeation , Conventional vescicular system , Nanotechnology.*

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Please cite this article in press A.Anusha et al., ***Proniosomes Of Novel Drug Delivery System****., Indo Am. J. P. Sci, 2024; 11 (03).*

INTRODUCTION:

DEFINITION: [1]

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals.

- Drug delivery refers to the technology utilized to present the drug to the desired body site for drug release and absorption, or the subsequent transport of the active ingredients across the biological membranes to the site of action.
- As a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of drugs in the body.

DIFFERENT DRUG DELIVERY METHODS:

- Buccal drug delivery
- Nasal drug delivery
- Ocular drug delivery
- Oral drug delivery
- Pulmonary drug delivery
- Sublingual drug delivery
- Transdermal drug delivery
- Vaginal drug delivery
- Novel drug delivery

NIOSOMES

INTRODUCTION :[2]

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle, composed of a bilayer of non-ionic surface-active agents. Hence the name niosomes. The niosomes are very small and microscopic in size. Their size lies in the nanometric scale.

- Developing of new drugs and improving the safety and efficacy of existing drugs is difficult, expensive and time-consuming.
- At present, no available drug delivery system behaves ideally achieving all the lofty goals.
- Encapsulation of the drug in vesicular structures is one of the promising systems.
- Such as liposomes, niosomes, transferosomes, ethosomes and pharmacosomes etc.
- It delivers drugs directly to the site of action, leading to a reduction of drug toxicity with no adverse effects
- Vesicular drug delivery reduces the cost of therapy by improving the bioavailability of medication and also solves the problems of drug insolubility, instability and rapid degradation.

DEFINITION OF NIOSOMES:[3]

Niosomes are synthetic microscopic vesicles consisting of an aqueous core enclosed in a bi-layer consisting of cholesterol and one or more nonionic surfactants. Vesicles are prepared from the self-assembly of hydrated non-ionic surfactant molecules.

ADVANTAGES OF NIOSOMES:

- Targeted drug delivery can be achieved using niosomes; the drug is delivered directly to the body part where the therapeutic effect is required.
- A reduced dose is required to achieve the desired effect.
- Subsequent decrease in the side effects.
- The therapeutic efficacy of the drugs is improved by reducing the clearance rate, targeting the specific site and protecting the encapsulated drug.
- Niosomes are amphiphilic i.e., both hydrophilic and lipophilic in nature and can accommodate a large number of drugs with a wide range of solubilities.
- Improve the oral bioavailability of poorly soluble drugs.
- Enhance the skin permeability of drugs when applied topically to provide advantage of usage through various routes viz. oral, parenteral, topical, ocular etc.
- The bilayers of the niosomes protect the enclosed Active pharmaceutical ingredient from the various factors present both inside and outside the body.
- The surfactants used and the prepared niosomes are biodegradable, biocompatible, and non-immunogenic.
- They are osmotically active and stable.

DISADVANTAGES OF NIOSOMES:

- Aqueous suspension of noisome may exhibit fusion, aggregation leaching or hydrolysis of the entrapped drug, thus limiting the shelf life of noisome dispersion.
- Time consuming.
- Requires specialized equipment.
- Inefficient drug loading.

- Aggregation.
- Fusion.
- Leaking of entrapped drugs.
- Hydrolysis of encapsulated drugs limits the shelf life of the dispersion.
- Physically unstable.
- Specialized equipment is required for manufacture
- Expensive.

STRUCTURE OF NIOSOMES:[4]

Niosomes are microscopic lamellar structures.

Basic structural components are:

- Non-ionic surfactant.
- Cholesterol.
- Charge inducing molecule.

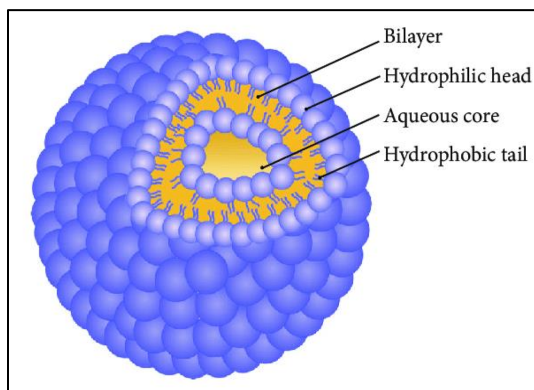


Fig.1 Structure of noisome.

NON-IONIC SURFACTANTS:

1. Surfactants are Amphiphilic molecules (hydrophilic & hydrophobic).
2. Lipophilic chains are made of alkanes, fluorocarbons, aromatic or other non-polar groups.
3. The head group involves highly solvated hydrophilic functionalities such as sulfonates, carboxylates, phosphonates & ammonium derivatives.
4. Non-ionic surfactant has no charge group in its head.
5. If the head charge is positive, it is called cationic surfactant (irritant & toxic).
6. If the head has two oppositely charged groups it termed amphoteric (ZWITTERIONIC) surfactant.

CHOLESTEROL:

1. Steroids are important components of the cell membrane and their presence in the membrane affects the bilayer fluidity and permeability
2. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of the bilayer, its importance in the formation of niosomes and manipulation of layer characteristics cannot be discarded.
3. In general, incorporation of cholesterol affects properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze-dried niosomes and their toxicity.
4. It prevents vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that lead to the transition from the gel to the liquid phase in noisome systems. As a result of this, the noisome becomes less leaky in nature.

CHARGE INDUCING MOLECULE:

- Some charged molecules are added to niosomes to increase the stability of niosomes by electrostatic repulsion which prevents aggregation and coalescence.
- The negatively charged molecules used are diacetyl phosphate (DCP) and phosphatidic acid.
- Similarly, stearyl amine (STR) and stearyl pyridinium chloride are the well-known positively charged molecules used in niosomal preparations.
- Only a 2.5-5 mol % concentration of charged molecules is tolerable because a high concentration can inhibit the noisome formation.

TYPES OF NIOSOMES:[5]

The three factors of niosomes are classified as a function of the amount of bilayer or as a function of size or as a function of the tactic of preparation. The various types of niosomes are described below:

1. Multi lamellar vesicles (MLV)
2. Large unilamellar vesicles (LUV)
3. Small unilamellar vesicles (SUV)

1.MULTILAMELLAR VESICLES: (MLV)

It consists of several bilayers surrounding the aqueous lipid compartment separately. The approximate size of those vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the foremost widely used niosomes. This type of vesicle is highly suitable as a drug carrier for lipophilic compounds.

2.LARGE UNILAMELLAR VESICLES: (LUV)

Niosomes of this sort have a high aqueous/lipid compartment ratio, in order that larger volumes of bio-active materials are often entrapped with a really economical use of membrane lipids.

3. SMALL UNILAMELLAR VESICLES: (SUV)

The approximate size of this vesicle are 10-100 nm and this types of vesicle is prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization in that the inclusion of diacetyl phosphate in 5-carboxyfluorescein loaded Span based niosomes.

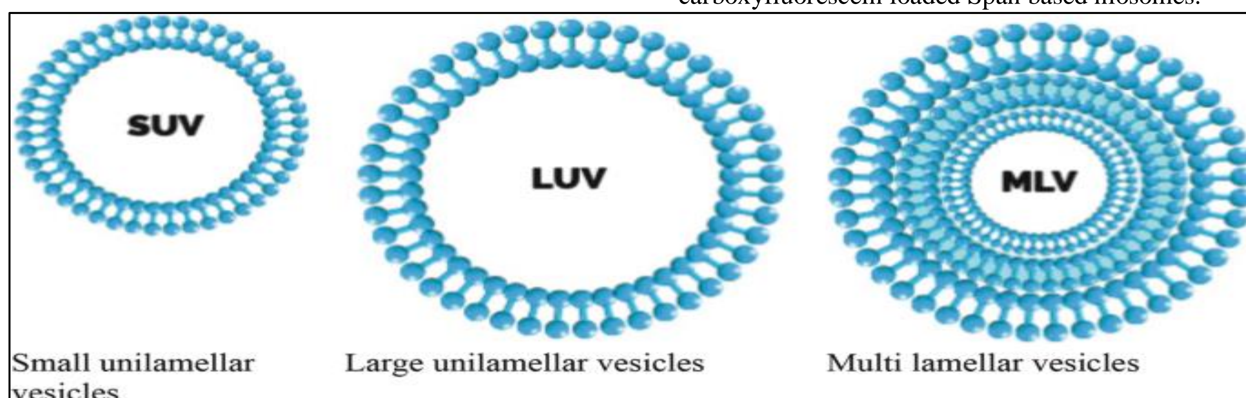


Fig.2 Sizes of niosomes.

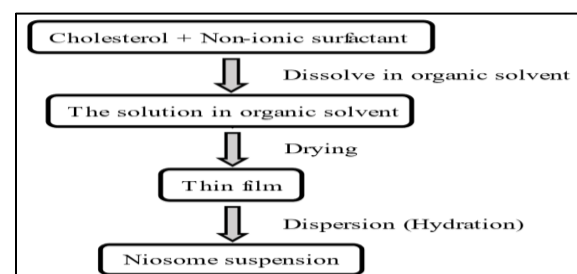
METHODS OF PREPARATION:

- Ether Injection (LUV)
- Hand Shaking Method (MLV)
- The "Bubble" Method.
- Reverse Phase Evaporation (LUV).
- Sonication (SUV).
- Multiple membrane extrusion methods.
- Transmembrane pH Gradient Drug uptake Process (remote loading) (MLV).
- Micro fluidization method (SUV).
- Formation of niosomes from proniosomes.

GENERAL STEPS INVOLVED IN PREPARATION:

- Hydration of mixture of surfactant/lipid at elevated temperature.
- Sizing of niosomes.
- Removal of entrapped material from vesicles.

COMMON STAGES OF ALL METHODS OF PREPARATION OF NIOSOMES:



ETHER INJECTION METHOD:

- **This method is based on slow injection of surfactant:** cholesterol solution in ether through a 14-gauge needle into a preheated aqueous phase maintained at 60°C.
- Vaporization of ether resulting into a formation of ether gradient at ether-water interface which leads to formation of single layered vesicles.
- Depending upon the conditions used, the diameter of the vesicle ranges from 50 to 1000 nm.

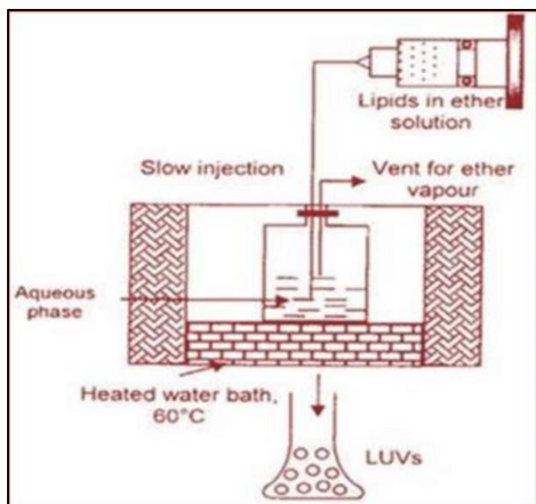


Fig.3 Diagrammatic representation of ether injection method.

HAND SHAKING METHOD: (Thin film hydration technique)

- Surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask.
- The organic solvent is removed under vacuum at room temperature using a rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask.
- The dried surfactant film can be rehydrated with aqueous phase at temperature slightly above the phase transition temperature of the surfactant used, with gentle agitation.
- This process forms large multilamellar niosomes.

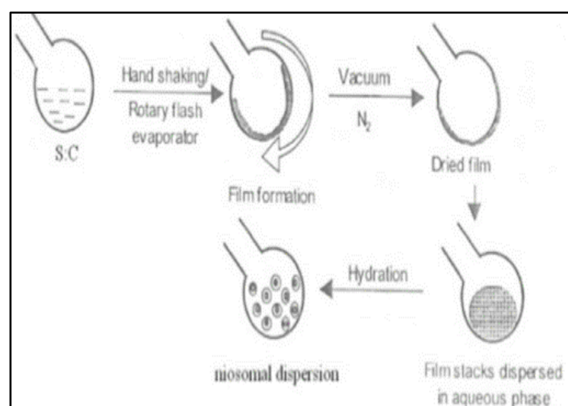


Fig.4 Diagrammatic representation of hand shaking method.

THE BUBBLE METHOD:

1. It is a novel technique for the one-step preparation of liposomes and niosomes without the use of organic solvents
2. The bubbling unit consists of round-bottom flasks with three necks positioned in a water bath to control the temperature.
3. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply is through the third neck.
4. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4)at 70°C, the dispersion is mixed for 15 seconds with a high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

REVERSE PHASE EVAPORATION TECHNIQUE:

1. Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform.
2. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS)
3. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

SONICATION:

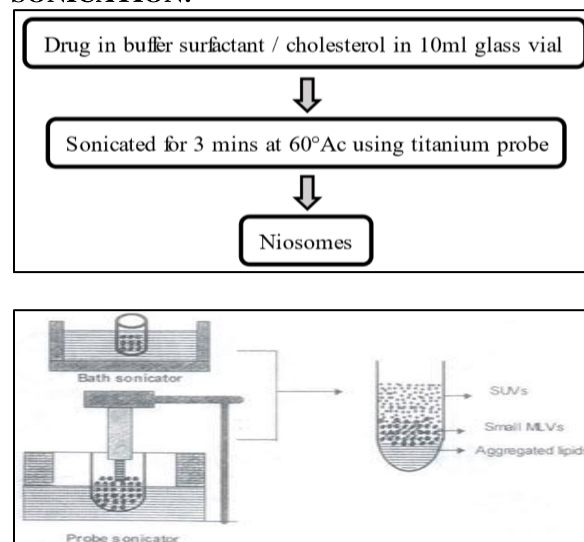
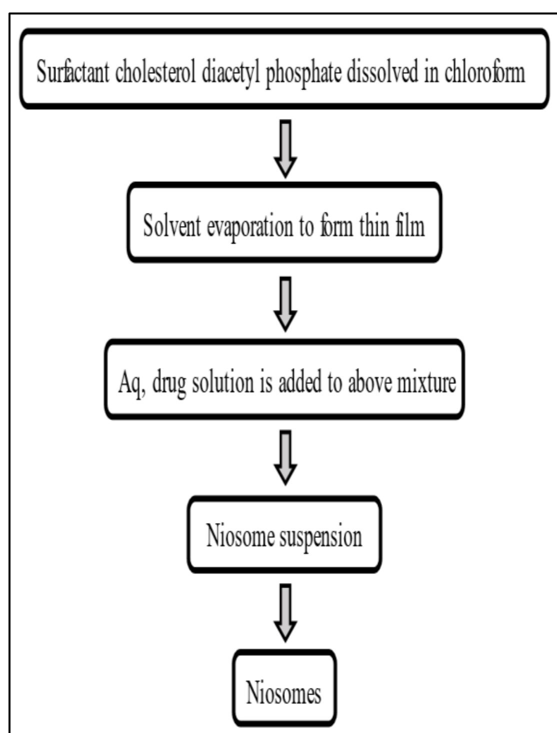


Fig.5 diagrammatic representation of sonication.

MULTIPLE MEMBRANE EXTRUSION METHOD:



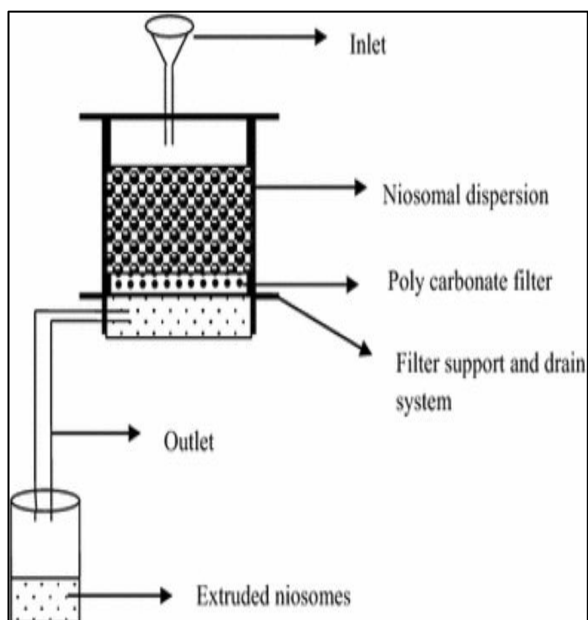
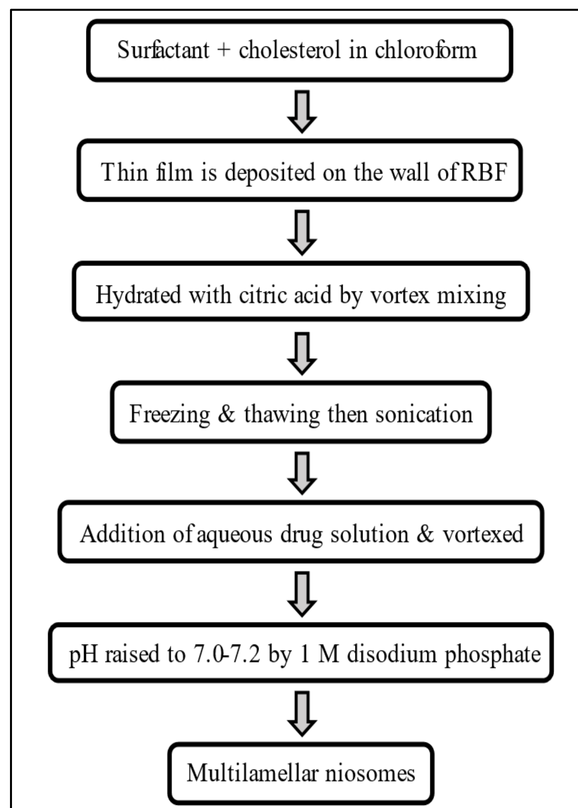
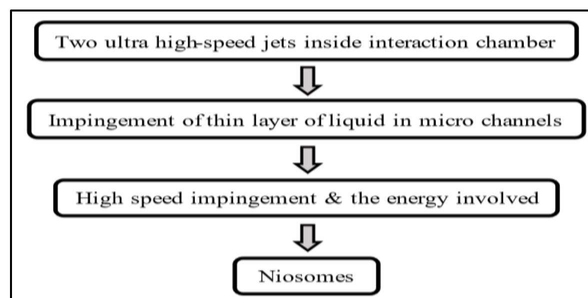


Fig 6 Diagrammatic representation of multiple membrane extrusion method.

TRANSMEMBRANE PH GRADIENT DRUG UPTAKE PROCESS: (remote loading)



MICROFLUIDIZATION METHOD:



FORMATION OF NIOSOMES FROM PRONIOSOMES:

1. Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant.
2. 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".

3. The Niosomes are formed by the addition of aqueous phase at T >Tm and brief agitation. T = Temperature, Tm = mean phase transition temperature.

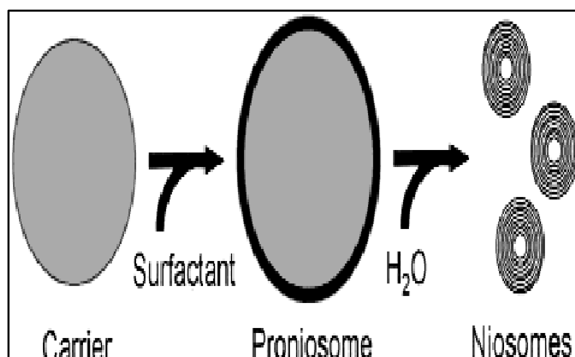


Fig 7. Formation of niosomes from proniosomes.

PRONIOSOMES

INTRODUCTION:[6]

- Niosomes are water-soluble carrier particles, and these are dried to form a niosomal dispersion on brief agitation in hot aqueous media. This dehydrated product is called proniosomes.
- To achieve targeted and controlled drug distribution, new drug delivery systems have arisen that incorporate diverse routes of administration. One such route is the vesicular route of drug delivery.
- Many vehicles have been used as a carrier to have better result. But all of them have shown some instabilities. To overcome that one of the carriers used are Proniosomes.
- Proniosomes are a new formulation that is used in the pro vesicular system of the type of delivery
- They are formulated as dry particles that are soluble in water coated with a surfactant and are further dehydrated to create noisome dispersion by using the media which is hot and easily converted to its niosomes.
- The formed niosomes are considered to be the same as that of the original noisome, except they are smaller and more homogeneous.
- In the vesicular route, drug-encapsulated vesicles are the main important part of the system that aids in the prolongation of drug action in the systemic circulation.
- By selective absorption, it reduces toxicity and circulates the amount of medication required by the body.
- As a result, many of the vesicles have been developed which include liposomes, Niosomes, and Proniosomes. Among them are liposomes made up of spheroid structures.
- Proniosomes have unique encapsulation efficiency and diffusion mechanism which helps in enhancing the bioavailability of drug.

Proniosomes formulations can be:

- Proniosomes are dry formulations of water-soluble carrier particles that are coated with surfactant.
- Proniosomes are physically stable during storage and transport.
- These proniosomes-derived niosomes are as good as or even better than conventional niosomes.
- Proniosomes are a versatile delivery system because of the ease of distribution, measuring, transfer and storage.
- To overcome the demerits of niosomes, proniosomes are prepared and reconstituted to produce niosomes
- Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both polar and non - polar or hydrophobic or hydrophilic drugs.
- It can provide optimal flexibility metered unit dosing in capsules & stability.
- Proniosomes minimize problems of niosomes like aggregation, fusion, leaking and transportation, storage, dosing problems

STRUCTURE OF PRONIOSOMES:

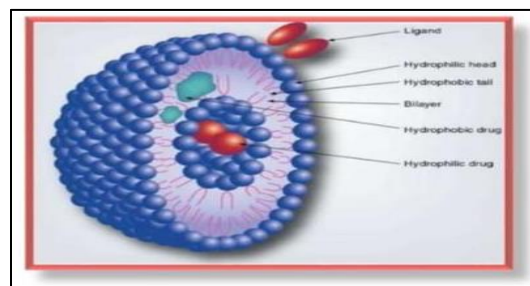


Fig 8. Proniosomes structure .

ACTION OF PRONIOSOMES:

- Proniosomes show their action after they are converted to niosomes on hydration. Hydration may occur by the addition of aqueous solvents.
- Hydration of proniosomes into niosomes and hydrophilic and hydrophobic regions of niosome.

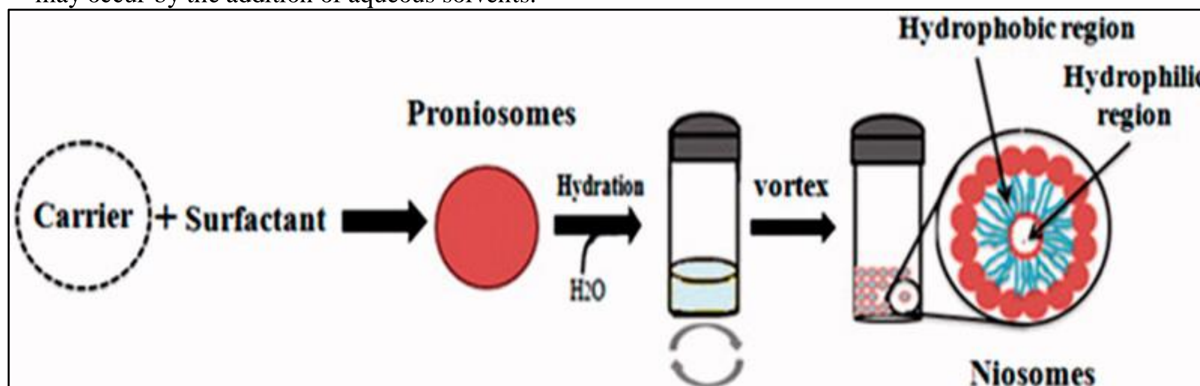


Fig 9. Action of proniosomes.

ADVANTAGES:

- Both the non-ionic surfactant and phospholipids in proniosomes can act as a penetration enhancer and help in the diffusion of the drug.
- Proniosomes have higher advantages such as additional convenience of dosing, storage, transportation, and distribution.
- Proniosomes avoid degradation by hydrolysis or oxidation as well as sedimentation, aggregation, or fusion during storage.
- Proniosomes also could enhance the recovery rate of the skin barrier.
- Improve bioavailability & minimize side effects.
- Easy to handle.
- Storage of surfactants requires no special conditions.
- Transportation is easy.
- Avoid the encapsulation of hydrolysis drugs which is limiting the shelf - life of the dispersion.
- Unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrices.
- It is biodegradable, biocompatible and non - immunogenic to the body.
- The shape, size, composition, fluidity of niosomes can be controlled when required.
- The storage makes proniosomes a versatile delivery system with potential for use, with a wide range of active compounds.

DISADVANTAGES:

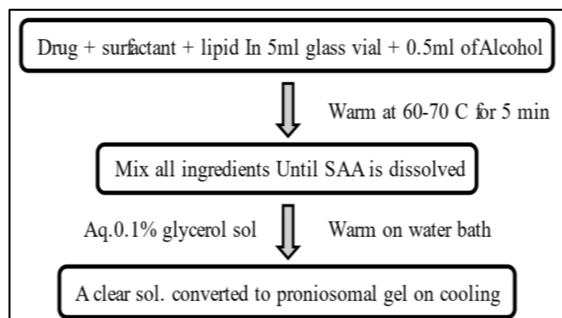
- During hydration to niosomes, complete drug entrapment may not be possible, sometimes hence the amount of the unentrapped drug should be analyzed.
- Complex process.
- Time consuming.
- Requires specialized equipment.
- Insufficient drug loading.
- High production cost.
- Leakage of drugs.
- Fusion of vehicles.
- Aggregation.

PREPARATION OF PRONIOSOMES:

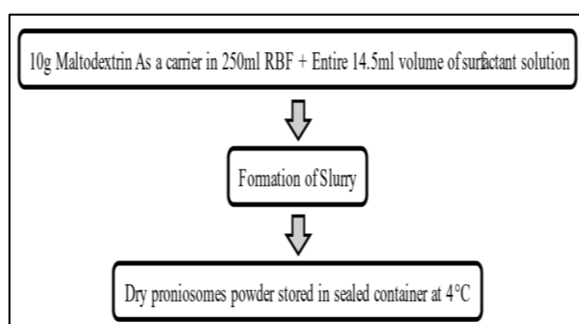
The proniosomes consist of a number of ingredients such as the non-ionic surfactant, cholesterol or lecithin being the main ingredient. Some of the methods, which were reported for the preparation of proniosomes are as follows:

1. Coacervation Phase Separation Method.
2. Slurry method.
3. Slow spray coating method.

COACERVATION PHASE SEPARATION METHOD:[7]



SLURRY METHOD:[8]



SLOW SPRAYING COATING METHOD:[9]

- This method involves preparation of proniosomes by spraying surfactant in organic solvent onto sorbitol powder and then evaporating.
- The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles as the carrier dissolves.
- The resulting niosomes are very similar to the conventional niosomes but are more uniformly distributed.

METHODS FOR EVALUATION OF PRONIOSOMES:

Optical Microscopy:

- For the number of vesicles formed after hydration the proniosomal powder was evaluated with Phosphate buffer (Ph 7.4).
- The proniosomal powder was subjected to hydration & the formed Niosomes counted by the optical microscope using the haemocytometer.
- The niosomes are mounted On the glass slides & viewed under the microscope with the magnification of 1200X for the Morphological observation after the suitable dilution.
- By using the digital SLR camera the Photomicrograph of the preparation is also obtained from the microscope.

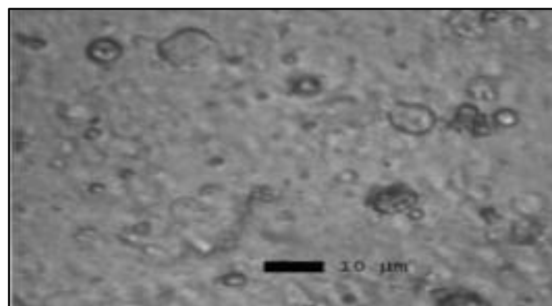


Fig 10 Vesicle size determination by optical microscopy.

A. Drug content :

In the standard flask the proniosomal formulation equivalent to 250mg of drug was taken & they Were mixed with 50mL of the propanol by shaking & 1mL of the mixture was then diluted with the Phosphate buffer (Ph 7.4). By spectroscopically at 281 nm the absorbance was measured & drug Content was calculated from calibration curve.

B. Vesicle Morphology:

It involves the measurement of shape & size of proniosomal vesicles. In 2 conditions the size of The proniosomal vesicles can be measured by the dynamic light scattering method these two Conditions are: with agitation & without agitation. The hydration without agitation results in largest Vesicle size.

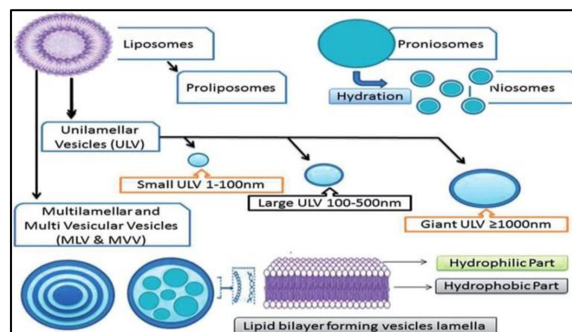


Fig 11. Vesicle Morphology.

C. Penetration and permeation studies : By CLSM (confocal laser scanning microscopy) the depth of penetration in the proniosomes can be Visualized.

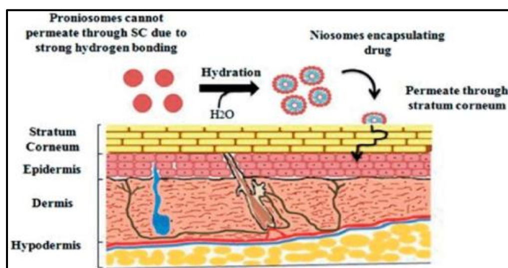


Fig 12 Penetration and permeation studies.

D. Transmission electron microscopy:

1. By using TEM (transmission electron microscopy) the morphology of the hydrated niosome dispersion is determined. A drop of the niosome dispersion is diluted 10-fold using the deionized Water.
2. To the carbon coated 300 mesh copper grid a drop of the diluted niosome dispersion is applied & is left for 1 minute to allow some of the niosomes to adhere to a carbon substrate.
3. By adsorbing the drop with the corner of the piece of the filter paper the remaining dispersion is removed.
4. A drop of 2 percent aqueous solution of uranyl acetate is applied for 1 second, after twice rinsing the grid (deionized water for 3-5 seconds).
5. By absorbing the liquid with the tip of a piece of filter paper the Remaining solution is removed & the sample is air dried. At 80 kv the sample is observed.

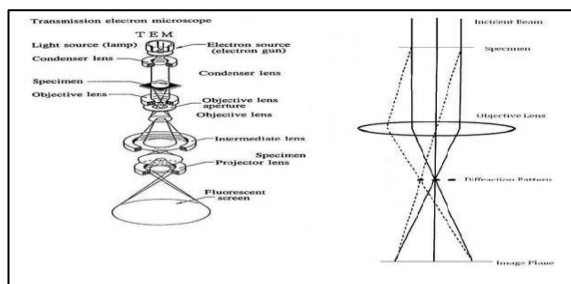


Fig 13. Transmission electron microscopy.

E. Encapsulation efficiency:

After separation of the unentrapped drug the encapsulation efficiency of the proniosomes is Determined.

1. By the following techniques the separation of unentrapped drug is done;

A. Dialysis :

Tubing against the suitable dissolution medium the aqueous niosomal dispersion is dialyzed at room Temperature then the samples are withdrawn from the medium at the suitable time interval Centrifuged & by using UV spectroscopy analyzed for drug content.

B. Gel filtration :

By gel filtration of niosomal dispersion through a sephadex G50 column the free drug is removed & Separated with the suitable mobile phase & with analytical techniques they are analyzed.

C. Centrifugation:

The niosomal suspension is centrifuged & the surfactant is separated. To obtain the niosomal Suspension free from unentrapped drug the pellet is washed & then resuspended.

2. Determination of entrapment efficiency of proniosomes ;

- After removal of the unentrapped drug by dialysis the vesicles are obtained which are then Resuspended in 30% v/v of the PEG 200 & 1 ml of the 0.1% v/v triton x-100 solution was added to Solubilize vesicles.
- The resulted clear solution is then filtered & analyzed for the drug content. The Percentage of the drug entrapped is calculated by using the following formula:

$$Percent\ Entrapment = \frac{Amount\ of\ drug\ entrapped}{total} X\ 100$$

F. Shape and surface morphology:

It is studied by SEM (scanning electron microscopy), TEM (transmission electron microscopy) & Optical microscopy. The surface morphology means smoothness, roundness & aggregation Formation.

G. In-Vitro method for assessment of drug release from proniosomes :

1. Dialysis tubing :

In this the apparatus has prewashed dialysis tubing which can be sealed hermetically. Against the Suitable dissolution medium the dialysis sac is then dialyzed at room temperature; at suitable Intervals the samples are

withdrawn from the medium then centrifuged and analyze for the drug Content using suitable method [HPLC, UV spectroscopy, etc]. The sink condition's maintenance is Essential.

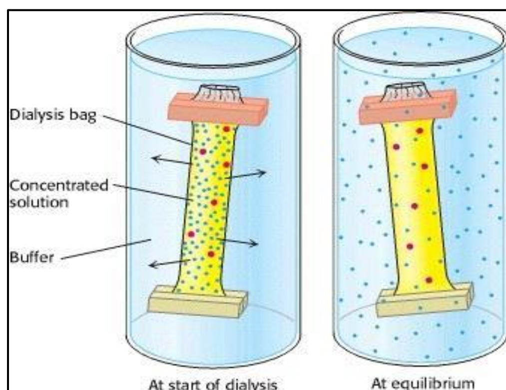


Fig 14. Dialysis tubing.

2. Reverse dialysis:

A number of small dialysis tubes containing 1 ml of dissolution medium are placed In this technique. Into the dissolution medium the proniosomes are then displaced. With this method the direct dilution Of the proniosomes is possible however by using this method the rapid release cannot be quantified.

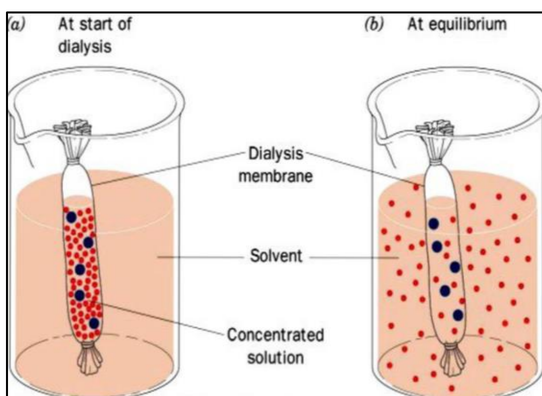


Fig 15. Dialysis bag method reverse dialysis.

3. Franz diffusion cell :

By using Franz diffusion cell the in-vitro studies can be performed. The proniosomes are placed in The donor chamber of a Franz diffusion cell fitted with the cellophane membrane. Against the Suitable dissolution medium the proniosomes is then dialyzed at room temperature, At suitable Intervals, the samples are withdrawn from the medium & analyzed for the drug content by using Suitable method (HPLC, UV spectroscopy etc.). The sink condition's maintenance is essential.

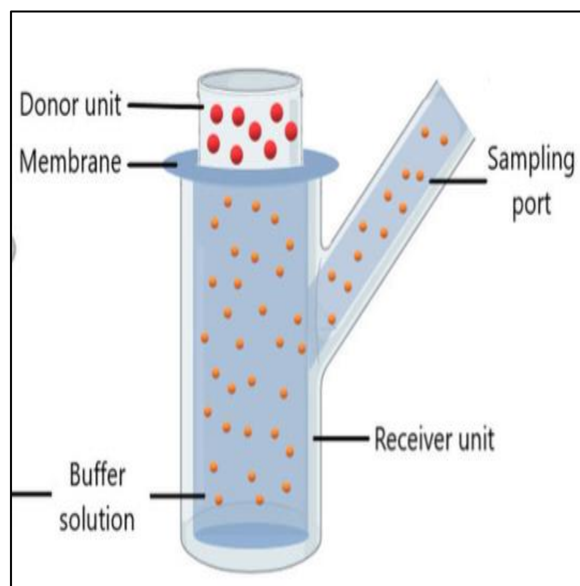


Fig 16. Franz diffusion cell method.

4. Zeta potential analysis :

For determining the colloidal properties of the prepared formulations the zeta potential analysis is Done. By using zeta potential analyzer based on the electrophorectic light scattering & laser Doppler Velocimetery method the suitably diluted proniosomes derived niosome dispersion is determined. At 25°CThe temperature is set. Directly from the measurement the charge on vesicles & their mean Zeta potential values with the standard deviation of 5 measurements are obtained.

H. Scanning electron microscopy :

- The proniosomes can be easily visualized by using SEM (Scanning Electron Microscopy), TEMb (Transmission Electron Microscopy) & by Optical Microscopy.
- On to the double-sided tape that is To be affixed on aluminum stubs, the proniosomes are sprinkled In the vacuum chamber of a scanning Electron microscope the aluminum stub is placed.
- By using a gaseous secondary electron detector (working pressure: 0.8 tor, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands), the Samples are observed for the morphological characterization

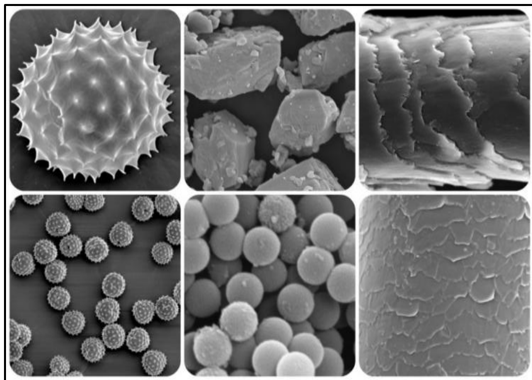


Fig 17. Scanning electron microscopy.

I. Measurement of angle of repose:

a. Cylinder Method :

Into the cylinder the proniosomal powder was poured which was fixed at the position 10cm above The leveled surface, the powder is flowed down in the cylinder to form the cone on a surface & by Measuring the height of the cone & the diameter of its base the angle of repose was then calculated

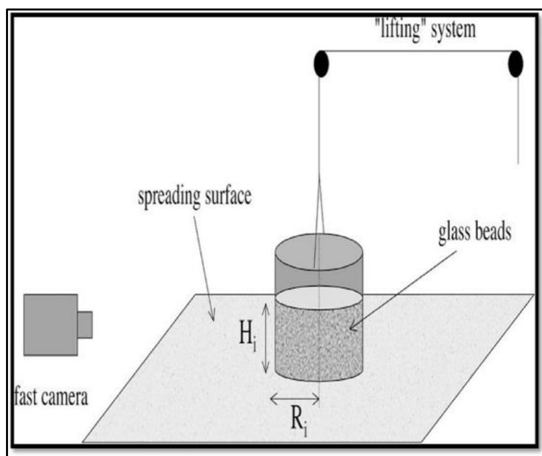


Fig 18. Measurement of angle of repose for cylinder method.

b. Funnel Method :

The proniosomal powder was poured into the funnel which was fixed at the position 10cm above The level surface & from funnel the powder is flowed down to form the cone on the surface. By Measuring the height of the cone & the diameter of its base the angle of repose was calculated Angle Of repose is calculated by the following equation.

Angle of repose = Tan-1 [h/r]

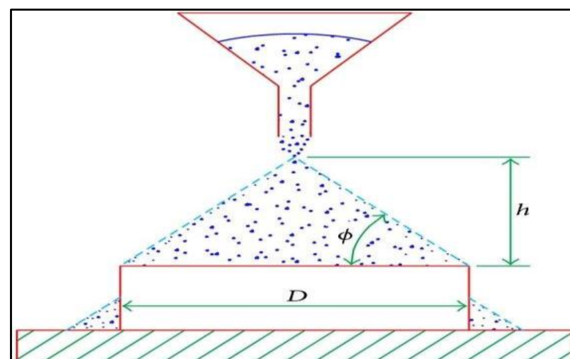


Fig 19. measurement of angle of repose for funnel method.

J . Drug Release Kinetics and Data Analysis:

The result of the in-vitro drug release study of noisome are fitted with the various kinetic equations, In order to understand the kinetics & mechanism of drug release:

1. **The Zero order, as cumulative % release vs. time,**

C = K0t

Where,
k0 = zero order constant expressed in units of concentration
t = time in hours.

2. **The Higuchi's model, as cumulative % drug release vs. square root of time.**

Q = KHt1/2

Where,
KH = higuchi's square root of time kinetic drug release constant.
N = release exponent indicative of the drug release mechanism If the exponent n= 0.5 or near, then, the drug release mechanism is Fickian diffusion, & if n have near 1.0 then it is Non Fickian diffusion.

K. Stability Studies:[10]

- By storing the prepared proniosomes at various temperature conditions like refrigeration (2°-8°C), Room temperature (25°± 0.5°C) & elevated temperature (45°C ± 0.5°C) from a period of one month to three months the studies are carried out to determine stability of proniosomes.

- The drug content & variation in the average vesicle diameter are periodically monitored.
- The ICH guidelines suggest Stability studies for the dry proniosomes powder meant for the reconstitution should be studied for the accelerated stability at 75% relative humidity as per international climatic zones & the climatic Conditions.

MARKET FORMULATION:

Using their in-depth knowledge of cellular organisation, Lancôme laboratories have created multi – tension technology, to strengthen the skin natural protein network, there by promoting firmness and elasticity for immediate results.

APPLICATIONS OF PRONIOSOMES :

- **In Studying Immune Response:[11]**
Due to their greater stability, immunological selectivity & low toxicity the proniosomes are used to Study the immune response. To study the nature of the immune response provoked by antigens the niosomes are being used.
- **In Delivery of Peptide Drugs:[12]**
The oral peptide drug delivery has long been faced with the challenge of bypassing a enzymes which Breakdown the peptide. The use of proniosomes intended to protect the peptides breakdown Successfully from gastrointestinal tract. In the study the oral delivery of the vasopressin derivative Entrapped in the proniosomes showed the highest entrapment of a drug & significant increase in the Stability of the peptide which are incorporated.
- **In Anti-neoplastic treatment:[13]**
Most of the antineoplastic drugs cause severe side effects. Niosome can alter the metabolism, Prolong circulation & half-life of a drug thus decreasing the side effects of the drugs. The niosome Entrapment of the doxorubicin & methotrexate [in two separate studies] showed the beneficial effects Over the entrapped drugs such as the decreased rate of the proliferation of the tumor & the higher Plasma levels accompanied by the slower elimination. The podophyllotoxin-Dipalmitoyl phosphatidyl choline proliposomes for the improvement of the stability.
- **In NSAID application:[14]**
The NSAID (Non-steroidal anti-inflammatory drug) like KT (Ketorolac tromethamine) when Administered intramuscularly & orally in divided multiple doses for the short-term management of The postoperative pain. Hence, an alternative noninvasive mode of delivery of the drug is needed, so That the transdermal route of delivery is an unconditionally an attractive route of administration to Maintain the drug blood levels of the Ketorolac tromethamine for an extended period of time.
- **In Hormonal Therapy:[15]**
The proniosome based transdermal drug delivery system of LN [Levonorgestrel] was developed & Widely characterized both in vivo & in vitro. The biological assay for the progestational activity Included the inhibition & endometrial assay with the formation of corpora lutea
- **The proniosomes as Carriers for Haemoglobin:[16]**
By using the photo initiator such as eosin & visible light. These hydrogel are constrained to the Surgical sites nearby to the light source as they form with difficulty after injection into body. For the Number of polymers Ion-mediated gelation has been described for e.g. alginates/calcium ions or Chitosan/phosphate ions. For cross-linking of the above mentioned polymers the concentrations of The counter ion available under physiological situations are usually lacking. There are 2 important Factors which limit the use of calcium-alginate. Which are as follows:
1. Potential immunogenicity
2. Longer time in-vivo degradability.

- **In Drug Targeting:[17]**
The ability to target the drugs is one of the most useful aspects of the proniosomes. The Proniosomes Can be used to target the drugs to the reticule-endothelial system. The RES [reticule-endothelial System] preferentially takes up the

proniosomes vesicles. By circulating serum factors called Poisonings the uptake of proniosomes is controlled. These poisonings mark the proniosomes for the Clearance. Such localization of drugs is utilized to treat the tumors in the animals known to Metastasize to the liver & spleen. For treating the parasitic infections of the liver this localization of Drugs can also be used. The proniosomes can also be utilized for targeting the drugs to the organs Other than the reticule-endothelial system. The carrier system [such as antibodies] can be attached To the proniosomes [as the immunoglobulin binds readily to the lipid surface of the niosome] to Target them to the specific organs

- **The proniosomes used in Cardiac Disorders:[18]**
  The proniosomal carrier system that is used for the treatment of hypertension, for example captopril Which is capable of efficiently delivering the entrapped drug over an extended period of time.
- **In sustained release drug delivery:[19]**
  To the drugs with low therapeutic index and low water solubility the sustained release action of Proniosomes can be applied since those could be maintained in the circulation via proniosomal Encapsulation. To achieve localized drug actionTo achieve the localized drug action the drug delivery through the proniosomes is one of the Approaches. The localized drug action results in the enhancement of efficacy of the drug & at the Same time it will reduces its systemic toxic effects.
- **In Leishmaniasis:[20]**
  The leishmaniasis is an illness which is caused by the parasite of the genus leishmania invades the Cells of the liver & spleen. The commonly prescribed drugs that are used for the treatment of Leishmaniasis is derivatives of antimony [antimonials] which in higher concentrations can cause the Liver, cardiac & kidney damage. The use of proniosome in assessments conducted showed that it Was possible to administer higher levels of the drug.

CONCLUSION:

For the future the proniosomes are promising drug carriers, with greater physical & chemical stability & potentially scalable for commercial viability. Different types of drug deliveries can be possible by using proniosomes based niosomes like targeting, topical, ophthalmic, oral vaccine, parenteral, etc. The proniosomes derived niosomes represent the promising drug delivery module.

Mostly they are known to avoid many of the problems associated with aqueous niosome dispersion as problems of physical stability such as leakage, aggregation & fusion. They provide additional convenience of dosing, transportation, storage & distribution.

WHY WE NEED PRONIOSOMES:

Proniosomes are physically stable during storage and transport. Drug encapsulated in the vesicular structure of proniosomes prolong the existence of drug in the systemic circulation and enhances the penetration into target tissue and reduce toxicity.

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