A REVIEW ON COMPREHENSIVE NIOSOMES

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Abstract:

In the last one-decade numbers of review and research, articles have been published on niosomes. This shows the interest of researchers in niosomes because of the advantages offered by them over other vesicular carrier systems Niosomes are a novel drug delivery system (NDDS), in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. NDDS has an object to deliver the drug at a rate directed by the needs of the body during the period of treatment of a disease, and reach the active ingredient to the site of action.

The amphiphilic nature of niosomes promotes its efficiency in encapsulating lipophilic or hydrophilic drugs. Other additives, like cholesterol, are often want to maintain the rigidity of the niosomes structure. Niosomes potential for drug delivery are often improved using new ideas like proniosomes, discomes, and

as pasome . Niosomes also are useful for diagnostic testing and as a lively ingredient to the vaccine. Such areas, therefore, need additional study and development to products available within the market niosomal preparations.

Keywords : : Niosomes, NDDS, Vesicles, Systemic circulation, Controlled drug release, Compositions, Methods of Preparation, Surfactants.

Introduction

History : In 1909, Paul Ehrlich started the development of targeted drug delivery. 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.

Non-ionic surfactant vesicles niosomes were first discovered by Loreal for cosmatics application in (1975) patented.

• There are very small and microscopic in size that lies in the nanometric scale actually similar to liposome, they offer several -advantages over them.

Niosomes have recently been shown to greatly increase transdermal drug delivery and also in targeted drug delivery. They are vesicular systems similar to liposomes. that can be used as carrier of hydrophilic and lipophilic drug. Niosomes overcome the disadvantages associated with liposomes such as; chemical instability. Chemical instability of liposomes is due to their predisposition to oxidative degradation and variable purity of phospholipids. The main purpose of developing niosomal system is chemical stability, biodegradability, biocompatibility, through various routes such as oral, parenteral and topical. It is less toxic and improves the therapeutic Index of drug by restricting its action to target cells. Development of new drug improving safely and efficacy of existing drug is difficult expensive and time consuming. It delivers

drug directly to the site of action. leading to reduction of drug toxicity with no adverse effect.

Niosomes are amphiphilic in nature, in which the medication is encapsulated in a vesicle which is made by non-ionic surfactant vesicles and hence the name niosomes. Their size is very small and microscopic. In the presence of proper mixtures of surfactants and charge inducing agents from the thermodynamically stable vesicles

Most of the surfactants yield micellar structures on immersing in water; while, some of them yield bilayer vesicles, i.e., niosomes. Niosomes are either unilamellar of multilamellar, depending on their preparation method. They are classified based on the number of bilayer (e.g., (MLVs) multi lamellar vesicles and (SUVs) small unilamellar vesicles), on their size (e.g., LUVs and SUVS), and on their preparation method (e.g., REVs and DRVs). Niosomes are structurally similar to liposomes and hence represent alternative vesicular systems with respect to liposomes, due to their ability to encapsulate different drugs in their multi-environmental structure.

Type of Niosomes

Niosomes are defined as either a variable of bilayer number (e.g. MLV, SUV) or size function. (LUV, SUV, for example) or as a component

of the preparing technique (REV, DRV, for example).

1.Multilamellar vesicles (mlv)

It consists of the many bilayers, which correspond to the aqueous lipid compartment separately. Such vesicles are approximately 0.5-10 µm in size. Multilamellar vesicles were the foremost commonly used niosomes. All such vesicles are suitable for lipophilic substances as a drug transporter.

2.Unilamellar Vesicles (LUV)

The sort of niosomes features a high percentage of the aqueous / lipid container, and perhaps during a somewhat economical got to

have membrane lipids, larger quantities of bioactive substances could be obtained.

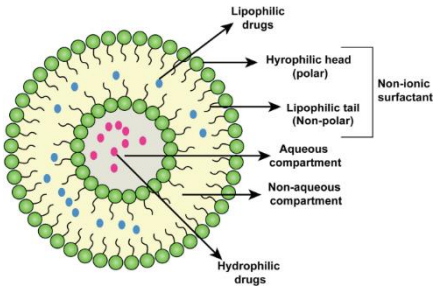
3.Small Unilamellar Vesicles (SUV)

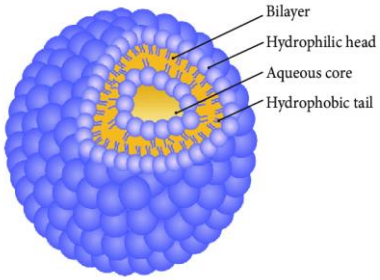
Such Small Unilamellar Vesicles are often formed by sonication approach through multilamellar vesicles. At an equivalent time, the

electrostatic stabilisation of French press deformation is that the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) charged niosomes supported Span 60.

STRUCTURE OF NIOSOME

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





The two major components used for the preparation of niosomes are,

1.Cholesterol 2.Non-ionic surfactants

1.Cholesterol

Cholesterol may be a steroid derivative, which is employed to supply rigidity and proper shape, conformation to the niosomes preparations.

2.Non-ionic surfactants

The following non-ionic surfactants are generally used for the preparation of niosomes.

e.g.Spans (span 60, 40, 20, 85, 80)

Tweens (tween 20, 40, 60, 80)

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

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.

Advantages of niosomes

1) Niosomes can accommodate a variety of drug moieties such as hydrophilic, lipophilic as well as ampiphilic drugs.

2) vesicle charecteristics can be controlled by altering the composition of vesicles, sixe lamellanty, surface charge, tapped volume and concentration

3) The drug can controlled release in the sustained/ manner

4) No special conditions required for handling and Storage of Surfactants

5) Due to the depot formulation Controlled release of the drug it allows

6) Poorly soluble drugs have increased 6> bioavailability- aral

7) surfactant non-toxic posses biodegradable biocompatible and non-immunogenic response.

8) They can protect the active moiety from biological circulation

9) Drug protection from enzyme metabolism

10) Improve the Stability of entrapped drug

11) They can enhance through the Skin the permeation of drug through the skin

12) They improve the therapeutic profile of drug molecule due to delayed clearance from the circulation.

13) Niosomal dispersion in an aqueous phase can be emulsified in a non- aqueous phase to regulate the delivery rate of drug and administer vesicle in external non-aqueous phase.

14) Niosomes have water base, thus having great patent compliance over oily dosage forms.

Disadvantages of niosomes

1 may exhibit fusion. leaching or hydrolysis. of entrapped drug which limits the shelf life.

2) physical instability.

3) Aggregation

4) Leaking of entrapped drug leakage of entrapped drug from the polymer system will affect the intended properties of niosomes.

5) Time consuming

6) specialized equipment required for manufacture

7) insufficient drug loading capacity

Method of preparation

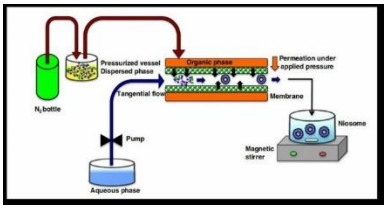
A. Passive Trapping Techniques - This category includes most of the techniques used in preparation of niosomes in

which drug is incorporated during the preparation of niosomes i.e. during their formation.

1. Sonication –

Mixture of drug solution in the buffer, surfactant and cholesterol

Sonicated with a titanium probe sonicator at 60°C for 3 minutes to yield niosomes



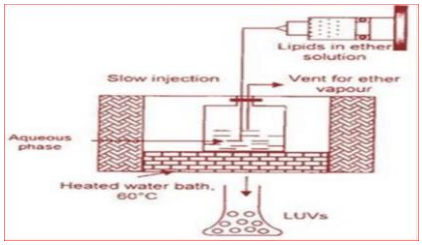
2. Ether Injection Method –

Niosomes by slowly introduce in a solution of surfactant dissolve in diethyl ether into warm water maintain at 60 C

Mixture in ether is injected through 14-gauge needle into an aqueous solution of material

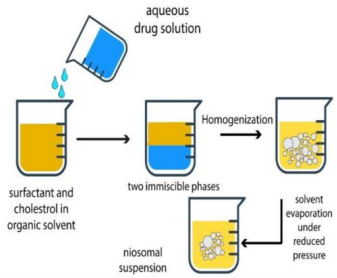
Vaporization of ether leads to the formation of the single layer vesicles

Diameter of the vesicle range from 50 to 1000 nm depends upon the conditions use



3. Reverse Phase Evaporation Technique
Cholesterol and surfactant (ratio of 1:1) dissolves in the mixture of organic solvent (ether and chloroform). Addition of the aqueous drug solution to this and water in oil emulsion is formed; two phases are sonicated at 4-5ºC. The emulsion is dried in a rotary evaporator at 40°C to form a semisolid gel of large vesicles. Small amounts of phosphate buffered saline (PBS) are added to the clear gel and sonicate again. The organic phase is removed at 40ºC and lower pressure. Viscous niosomal suspension is further diluted with phosphate buffered saline, then

heat on a water bath at 60ºC for 10 min to form niosomes



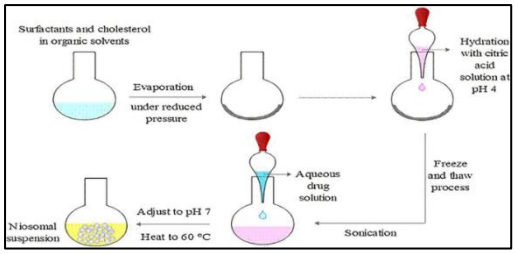
4. The "Bubble" Method

Bubbling unit involves round-bottomed flask with three neck position in water bath to control the temperature

Water-cool reflux is positioned in the first neck and thermometer is positioned in the second neck and nitrogen supply through the third neck

Cholesterol and surfactant are dispersed in the buffer (pH 7.4) at 70°C Dispersion mixing for 15 seconds with high shear homogenizer

"Bubbled" at 70°C using nitrogen gas



5. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator) –

The mixing ingredients - surfactant and cholesterol and charge inducer

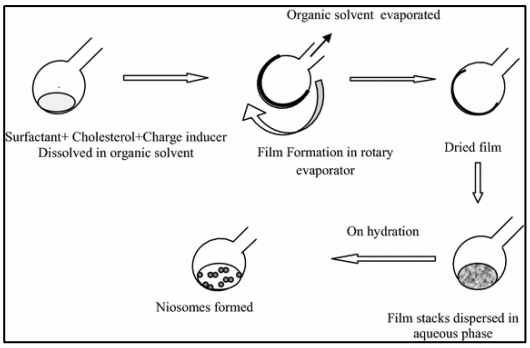
Dissolves in a volatile organic solvent (chloroform, diethyl ether or methanol) in a round bottom flask

By using a rotary evaporator organic solvent is evaporated at room temperature 20°C

Forming a thin layer of solid mixture

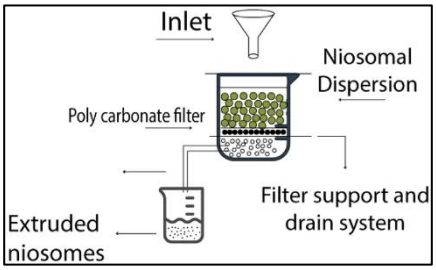
The dry surfactant film can be re-hydrated with an aqueous phase at 0-60°C with gentle agitation

Formation of niosomes



6. Multiple Membrane Extrusion Method

-Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform forms thin film by rotary evaporator. The film hydrates with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through polycarbonate membrane and placed in series for up to 8 passages. It is a good method for niosome size control



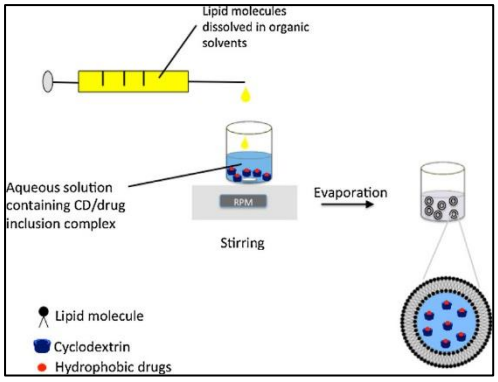
7. Ethanol Injection Method

An ethanol solution of surfactant is injected rapidly through a fine needle

Into excess of saline or other aqueous medium

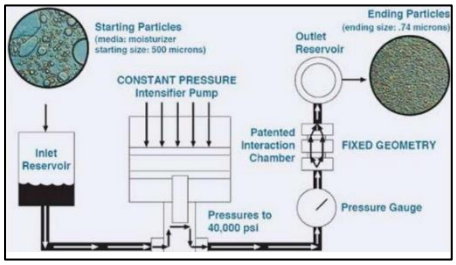
Vaporization of ethanol

Formation of vesicles



8. Micro Fluidization –

In this technique the principle involves is submerged jet principle in which two fluidized streams interact with each other at ultra high velocities and in the micro channels within the interaction chamber. Thin liquid sheet impingements along with common front are arranged such as that the energy supplies remain same within the area of niosomes formation, formation of niosomal vesicles of greater uniformity, smaller size and better reproducibility



This includes the loading of the drug after the formation of niosomes. The niosomes are prepared and then the drug is load of maintaining a pH gradient or ion gradients to facilitate uptake of drug into niosomes. Various advantages of noisome form are 100% entrapment, high drug lipid ratios, absence of leakage, cost effectiveness and suitability for labile drugs.

1. Trans Membrane pH Gradient Drug Uptake Process

In remote loading process surfactants and cholesterol are dissolved in organic solvent (chloroform)

Solvent evaporates under reduced pressure to get a thin film on the wall of the round bottom flask

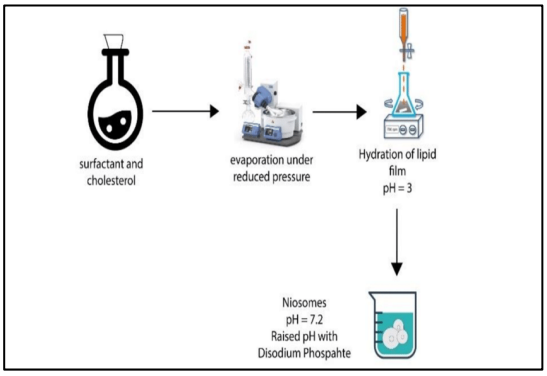
Film hydrates with 300 mM citric acid (pH4.0) by vortex mixing

Multilamellar vesicles are frozen and thawed 3 times and later sonication

For niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortex

Sample pH is raises to 7.0-7.2 with 1M disodium phosphate

The mixture is later heated at 60°C for 10 minutes to yield niosomes

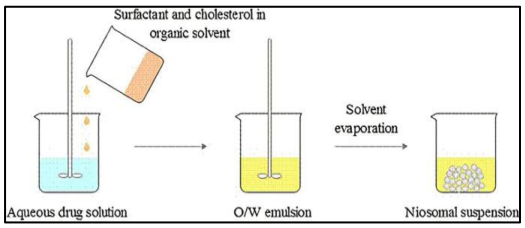


C. Miscellanous Methods –

1. Emulsion Method:

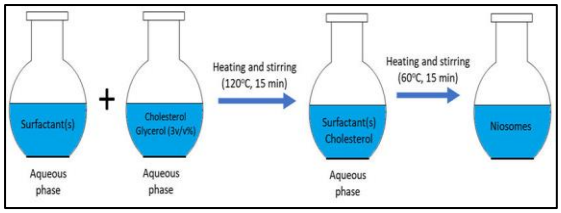
This is a simple method to form niosome in which oil in water (o/w) emulsion is prepared from an organic solution of

surfactant, cholesterol, and an aqueous solution of the drug. Finally, the organic solvent is evaporated leaving niosomes dispersed in the aqueous phase



2. Heating Method:

This method is in one-step, scalable and non-toxic and also based on the patentprocedure. A suitable aqueous medium such as buffer distilled water, etc. in which mixtures of non-ionic surfactants, cholesterol and/or charge inducing molecules are added in the presence of the polyol like as glycerol. The mixture is heated with (at low shear forces) until the vesicles were form

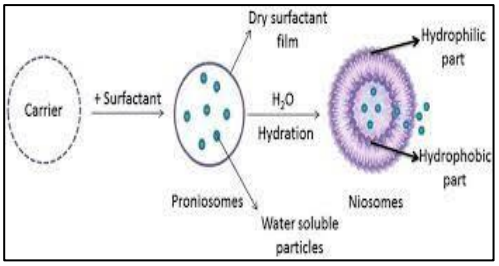


3. Formation of Niosomes from Proniosomes:

Proniosome is a dry formulation in which each water-soluble particle are covered with a thin film of dry surfactant. The niosomes are recognizing by the adding aqueous phase at T > Tm with brief agitation. T is the Temperature and Tm is the mean phase transition temperature

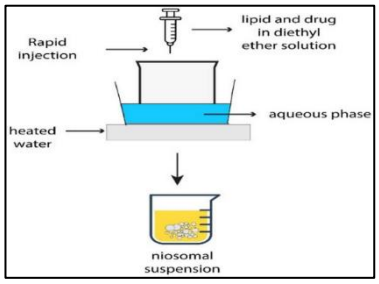
Carrier + surfactant = proniosomes,

Proniosomes + water = niosomes.



4. Lipid Injection Method:

This method does not require expensive organic phase. Mixture of lipids and surfactant is first melted and then injected into a highly agitate heated aqueous phase contains the dissolved drug. Drug dissolves in molten lipid and the mixture will be injected into agitate, heat aqueous phase containing surfactant.



 # Method of separation of unentrapped drug from niosomes:

Centrifugation: 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.

Gel Filtration: Unentrapped drug is separated by gel filtration of niosomal dispersion through a Sephadex- G-50 column and eluted with suitable mobile phase and analyzed with suitable analytical techniques.

Dialysis: The aqueous niosomal suspensions dialyzed in dialysis tubing against suitable dissolution medium at

room temperature. The samples are withdrawn from the medium at suitable time intervals, centrifuged and analyzed for drug content using U.V spectroscopy.

Comparison of niosomes with liposomes:

Niosomes are now being researched as an alternative to liposomes. Liposomes have several drawbacks: they are expensive, their constituents, such as phospholipids, are chemically unstable due to their proclivity for oxidative breakdown, they require particular storage and handling, and the purity of natural phospholipids varies. Niosomes are not affected by any of these issues. Furthermore, because niosomes are formed of uncharged single-chain surfactant molecules rather than neutral or charged double chained phospholipids, their structure differs from that of liposomes. However, in terms of functionality, niosomes are identical to liposomes. Niosomes, like liposomes, increase medication bioavailability while decreasing clearance. Niosomes, like liposomes, can be employed for targeted medication delivery.

Carrier system	**Size range**	**Features**	**Method of preparation**	**Application**
Liposomes	25-100 nm	Microscopic layer consist of one or more concentric bilayers separated by water or aqueous buffer compartment	Mechanical dispersion, Solvent dispersion, detergent removal etc.	In cancer, malaria AIDS, In therapies as immune diagnostic carrier.
Niosomes	10-1000nm	Nonionic surfactant vesicles are bilayered structures	Ether injection Reverse phase evaporation Microfludization Thin film hydration	Targeting of bioactive agent Delivery of peptides drug in diseases like neoplasia, Leishmaniasis.

Table No: 1 comparison of niosomes with liposomes

#Application of Niosomes

Niosomes used as drug targeting: One of the most useful features of niosomes is their ability to target drugs at site of action. It is used to target drugs to the reticulo-endothelial system (RES). The reticuloendothelial system (RES) particularly takes up niosome vesicles. Niosomes is controlled and uptake by circulating serum factors called opsonins. Opsonins are the mark of niosome for clearance. Such localization of drugs is

applied to treat tumors in animals known to metastasize to the liver and spleen. Localization of drugs used for treating parasitic infections of the liver. It can also be used for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosome) to target them to specific organs.

Pulmonary Delivery: Inhalation therapy is commonly used in asthmatic patients but is limited by poor permeation of drug through hydrophilic mucus. To overcome by developing polysorbate 20 niosomes containing beclomethasone dipropionate for pulmonary delivery to patients with COPD (chronic obstructive pulmonary disease). Helps to improved permeation of mucus and better therapeutic effect and also provided sustained and targeted delivery.

Used for hemoglobin carrier: It can be used as a carrier for hemoglobin. The vesicles are permeable to oxygen and could be modified to produce a hemoglobin dissociation curve similar to that of non-encapsulated hemoglobin. In addition, a niosomal suspension showed a visible spectrum super imposable onto that of free hemoglobin.

For treatment of HIV-AIDS: Zidovudine is commonly used to treat patients with AIDS but is limited by its toxicity and low potency. By using niosome formulation that may overcome these drawbacks and Zidovudine loaded niosomes would provide sustained delivery of drug and a more effective AIDS therapy.

Niosomes used in Cancer chemotherapy: Niosomes are very effective for targeting delivery of anticancer drugs to tumors. Example to developed niosomes containing 5- fluorouracil to treat skin cancer. Niosomes of doxorubicin prepared from C16 monoalkyl glycerol ether with and without cholesterol. Compared to simple drug solution, methotrexate loaded niosomes produced increased antitumor activity against tumors in serum and lung but not in liver and spleen.

Vaccine and antigen delivery by niosomes: A number of surfactants have immune stimulatory properties41 and have been used as vaccine adjuvants. The adjuvanticity of niosomes prepared from 1-monopalmitoyl glycerol: cholesterol: diacetyl phosphate (5:4:1) was demonstrated in mice administered a subcutaneous injection of ovalbumin or a synthetic peptide containing a known T-cell epitope and bovine serum albumin. Intraperitoneal administration of the same niosome formulation was also shown to act as a vaccine adjuvant in immune reconstituted SCID-human mice.

Niosomes used in Transdermal delivery: The delivery of NSAIDs by Trans dermally is the best way to avoid gastric disturbances. Elastic niosomes and transferosomes are novel types of vesicles for transdermal delivery with the latter having the advantage of low cost of manufacturing. Example novel elastic niosomes containing Diclofenacdiethyl ammonium for topical use. They concluded that the niosomal gel was superior to a conventional gel formulation because niosomes are penetrate into the deeper layers of the skin. However, for transdermal delivery of other drugs, penetration of

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Leishmaniasis therapy: Leishmaniasis is a disease caused by parasite genus Leishmania which invades the cells of the liver and spleen. Most Commonly prescribed drugs for the treatment are the derivatives of antimony which, in higher concentrations can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to administer the drug at high levels without the triggering the side effects, and thus showed greater efficacy in treatment. Antibiotics: The feasibility of using non-ionic surfactant vesicles (niosomes) as carriers for the ophthalmic controlled delivery of a water soluble local antibiotic gentamicin sulphate was investigated and the results demonstrated niosomes to be promising ophthalmic Carriers for the topical application of gentamicin sulphate.

Ophthalmic drug delivery: From ocular dosage form like ophthalmic solution, suspension and Ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, nonproductive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug.

4. Niosomes as Transdermal drug delivery: [24,25,26]

During recent years, transdermal drug delivery from niosomes has been studied in a number of disease models, and current efforts are focused on optimization of procedures, new compositions, and final formulations. For example, new highly flexible niosomes, known as elastic vesicles, have been proposed and are reported to be effective at delivering molecules through the skin, since edge activators (i.e. Ethanol) provide vesicles with elastic characteristics, which allow them to penetrate more easily into the deeper layers of the skin. Moreover, the major limitation of niosomes is the liquid nature of the preparation, because when applied they may leak from the application site. This challenge can be overcome by incorporation of niosomes in an adequate vehicle, which can be achieved by adding gelling agents to niosomal dispersions, thereby forming a niosomal gel. Niosomal gels were found to enhance retention of therapeutics by the skin and to provide high and sustained drug concentrations in the skin. A further evolution of niosomes is represented by proniosomes or dry niosomes, which have been proposed as niosomal formulations; these need to be

hydrated before use, and hydration results in formation of an aqueous niosomal dispersion. Proniosomes decrease the aggregation, leakage, and fusion problems associated with traditional niosomes and offer a versatile transdermal drug delivery system because, upon application to the skin, they become hydrated with water from the skin under occlusion. A summary of the findings of investigations over the past 5 years for transdermal niosomal drug delivery systems is given in table.

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