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NIOSOMES: AN ADVANCEMENT IN NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

This review article focuses on the niosomal drug delivery system by preparing the niosomes by using different types of preparation methods such as ether injection method, thin film hydration method, multiple membrane extrusion, reverse phase evaporation method, sonication method, microfludization method, lipid injection method, transmembrane pH gradient method. We have also studied in this review article about the components of niosomes and the types of components such as non-ionic surfactants, cholesterol and active pharmaceutical ingredients. We had also studied about the various types of niosomes such as aspasomes, deformable niosomes, proniosomes, etc.

KEYWORDS:- Niosomes, Non-ionic surfactants, Cholesterol, Proniosomes, Aspasomes, etc.

INTRODUCTION

There are severe issues that can take place by using Conventional Drug Delivery System and New DrugDelivery System are as follows-

- Due to the RES (reticulo-endothelial system), there is an early drug degradation.
- Low efficacy of the drug due to in efficient drug uptake at targeted site.
- Undesired side effect can be caused due to the unfavourable bio-distribution and

pharmacokinetics.

In this scenario the nano- carriers drug delivery system offers an enhanced dose delivery at the targeted site of action and also having carboprotection. The Nano Drug Delivery System is a new and innovative approach for drug delivery system. The human body is a complex structure which deals with several chronic and severe diseases, in which many in vivo drug treatments becomes ineffective, for this purpose, the biological functional nano- carrier were developed which helps the selective targeted specific cells to bindup and incorporate with drugs. For enhancing the efficacy, there are different patterns of nano-carriers were designed and several attempts are made to evaluate their function. Still, there are few numbers of nano- carriers that produces the significant clinical activity.

Due to the, novel characteristics of the NSVs (Non-ionic surfactant vesicle), we studied that, how these nano doses forms are going to be a good therapeutic agents. As we can see, there is a rapid growth in the field of nano- technology, now we are able to needful modification in the drug delivery system. We can convert the drugs in the nano- materials forms and encapsulate them in the vesicles. Like this, there are numbers of nano- carriers are present in the form of vesicle and produce their effect on the targeted site.[1]

Niosomes

Somehow, the niosomes are same as liposome, but there is a specification that, as phospholipids are used in the liposomes, on its place the non-ionic surfactants are used in the niosomes. So, we can say that, **Niosomes** are defined as the multilameller vesicular structure of the non-ionic surfactants.[2,3] Now a days, the alternative options of the liposomes are niosomes which are currently a wide topic to study. In niosomes, the hydrophobic or hydrophilic solute particles are retained and entrapped in the non-ionic surfactants. There are various types of surfactants that are used in the formulation of vesicles[2-4] There are two main constituents are present in the niosomes are as follows-

- The additives.
- The non-ionic surfactants.

The charged molecules and the cholesterol are the additives and non-ionic surfactants in the vesicular layers are used in the formulation of niosomes.[4] The cholesterol which is present in the steroidal system is responsible for providing rigidity to the bilayer system. The cholesterol is an important substance for the cell membrane and the bilayer permeability and

fluidity of the cell membrane were affected by the presence of cholesterol. The premature degradation of the drug molecule can be avoided by using these nano- carrier system. It can also protect the inactivation of the drug molecule due to the undesired pharmacological and immunological effects.[5] For the delivery of the drugs as hormones, antigens and other bioactive agents, the potency of the niosomes as a nono-carrier have been studied in the recent years. For avoiding the rapid degradation of drugs, insolubility and instability, the niosomes are more widely used.[6]

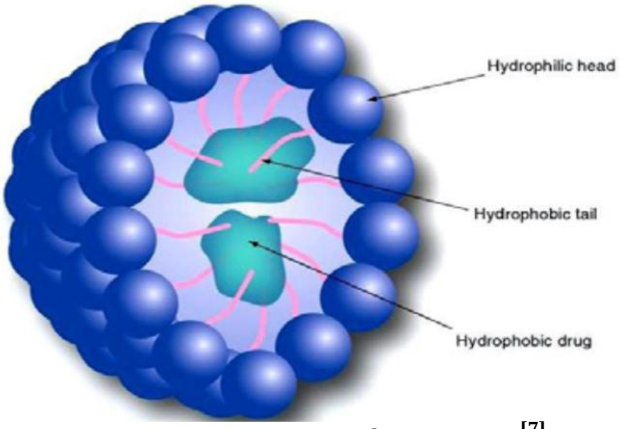

Figure 1: Structure of niosomes.[7]

Salient features of niosomes[8,9,10]

- The Niosomes are active and stable osmotically.
- Niosomes entered in the body as a warehouse medication because, noisome release the drug in a controlled manner via bilayer which provides help at the entry of the enclosed drug.
- The solutes particles are entrapped in the niosomes.
- The drugs entrapped in the niosomes, had a wide criteria for the dissolvability, as niosomes arecomposed of hydrophilic and hydrophilic part.
- The drug which are entrapped and retained in the niosomes, there stability were enhanced.
- The drug components performance can be enhanced by using niosomes.
- Niosomes protects the drug from the biological environment of the body and produce betteravailability at the targeted site.
- According to the circumstances, the niosomes can be designed and exhibits flexibility in theircomposition, size and fluidity.
- Niosomes when applied topically, it enhances the permeability of drugs on the skin, it also enhancesthe oral bioavailability and solubility of the drugs which are poorly soluble.

- The niosomes can specifically used to the body part, at the targeted site where the remedies impact isrequired, to enhance the targeted modification system.

Advantages[11,12]

- In external non-equeous phase, the normal vesicles increase the rate of administration of drug.
- The entrapped drug molecule stability were enhanced and the niosomes are osmotically stable and active.
- The niosomes can be made to intake from different routes of administration and increase the rate ofto reach the site of action such as parentral, topical and oral routes.
- There are no special conditions are required for the storage and handling of surfactants.
- The skin penetration of drug can be increased, and the oral bioavailability also improved of drugs which are poorly soluble by using niosomes.
- To regulate the delivery of the drug in a non- aqueous phase, the niosomal dispersion in an aqueous phase can be emulsified.
- The bioavailability can be improved by using niosomes. In gastro- intestinal tract, the niosomesvesicles store the drug and protect it from the enzymatic and acidic degradation in the vesicles due to which the bioavailability will increase of the drug.
- The niosomes elevate the drug particles restorative execution by delay of flexibility from the distribution, protection of the drug from the environmental condition and due to which targeted cells get affected.

Components of niosomes

The niosomes consists of the various components are as follows-

- **Non-ionic surfactants**

In niosomes, the non- ionic surfactants are present in the bilayer frameworks, where the hydrophobichead (hydrocarbon segments) are present in the pattern that there are less option to interact with the water while hydrophilic heads are present in the pattern that faces towards the bulky medium. Thebilayers of the membrane continuously fold itself to attain the thermodynamic stability due to which vesicles are formed.

There are chiefly four types of non- ionic surfactants are used in the formulation of niosomes are mentioned below-

- **Alkyl ethers**

There are some specific surfactants which are used in the formulation of niosomes which

consist of thedrugs or any other chemicals, were described by the L' Oreal are as follows-

- **Surfactant- I:-** Surfactant- I with a mean of three glycerol units is a C16 monoalkyl glycerolether having molecular weight 473 g/ mol.
- **Surfactant- II:-** Surfactant- II with a mean of seven glycerol units is a diglycerol ether havingthe molecular weight 972 g/ mol.
- **Surfactant- III:-** Surfactant- III is a surfactant that is linked with ester compounds having themolecular weight 393 g/ mol.

For the preparation of niosomes, rather than alkyl glycosides, alkyl glycerol and alkyl ethers which consistof head groups are also utilised.

- **Alkyl esters**

If we talk about this category of surfactants, than sorbitan esters are preferred most among all other surfactants for the formulation of niosomes.[13,14] In the comparison of other surfactant vesicles, the surfactants vesicles which are made up of polyoxyethylene sorbitan monolaurate are more solubilityproperty.[15] We can explore this more by taking some examples, such as, for the encapsulation of Diclofenac sodium polyoxyethylene (polysorbate 60) has been used.[16] For the transdermal deliveryof Cyclosporine- A, a mixture of polyoxyethylene-10- stearyl ether: glyceryl laurate: cholesterol (27:15: 57) has been utilized.[17,18]

- **Alkyl amides**

For the production of niosomal vesicles various alkyl amides are used such as glucosides and galactosides.[19]

- **Fatty Acid and Amino acid compounds**

In formulation of some specific niosomes the moieties of amino acids and some long fatty acids chains are used.[20]

- **Cholesterol**

The existence of the steroids chiefly affects the bilayer permeability and bilayer fluidity of the cell membrane. For the preparation of niosomes the cholesterol were used which is the derivative of the steroid.As such, it is not involved in the formation of the bilayer, but it is responsible for influencing the propertiesof the bilayers and also plays an important role in the formulation of niosomes. The characteristics such as, the toxicity of the niosomes, the rigidity of the membrane of the niosomes, encapsulation efficiency of the niosomes, freeze

dried niosomes due to the simple rehydration and permeability of the membrane of the niosomescan be affected by the incorporation of the cholesterol in the niosomes. In the niosomes system, by adding such types of molecules of the cholesterol that prevents aggregation of the vesicles, this is due to the molecules stables against the preparation of aggregates with the help of electrostatic forces that results as the conversion of the gel in the liquid phase. Due to this effect, there is less chance of leakage of the drug from the niosomes.[21]

- **Charged molecule**

For the prevention of conjoining of niosomes particles, some specific charged molecules were embedded in the niosomes due to which the stability of the niosomes will be enhanced by the aid of electrostatic repulsion. Such as Phosphotidic acid and Diacetyl phosphate were used as charged molecules which are negatively charged. While, Stearyl pyridinium chloride and Stearyl amine were used as charged molecules which are positively charged. The aggregation in the niosomes preparation can also be prevented by usi ngthis charged molecules.[22] There is a limitation in the percentage concentration of the charged molecules used in the formulation of the niosomes due to the high concentration inhibition , so only 2.5 to 5 mole percentage concentration charged particles were used.[23]

Types of niosomes[24,25]

- **Bola surfactant containing niosomes**

The Bola surfactant containing niosomes are the types of niosomes, in which its composition is in 2: 3: 1 molar ratio in which Omega hexadecylbis- (1- aza- 18 crown- 6) bola surfactant: span- 80: cholesterol were used.

- **Proniosomes**

The proniosomes are the pre phase of the niosomes. It is prepared by using the surfactant solution mixture and the carrier. After that, the proniosomes are passed through the process of the hydration and then, the niosomes are formulated in this type.

- **Aspasomes**

The aspasomes aree the types of niosomes that are manufactured by making the mixture of the exceptionally charged lipid diacetyl phosphate molecules, cholesterol and acorbypalmitate which stimulates the formulation of the niosomes vesicles. By using the process of sonication, the aspasomes niosomes were prepare, firstly the aspasomes were

hydrated by using the arrangement of fluid/ water and then sonication were performed for the formation of aspasomes. To permeate the drugs transdermally, theaspasomes were used. As aspasomes having the innate cell reinforcement characteristics, it is also used for the reduction of scattering produced by the responsive oxygen species.

- **Niosomes in carbopolgel**

The carbopol-934 gel (1% w/w) they consist of glycerol (30% w/w) and propylene glycol (10% w/w) were incorporated after the formulation of niosomes which is composed of drugs, spans and cholesterol.

- **Vesicles in Water and Oil system (v/w/o)**

In this strategy, the aqueous niosomes into an oil stage frame vesicle in water in oil emulsion (v/w/o). This can be set up by expansion of niosomes suspension figured from blend of sorbitol monostearate, cholesterol and solulan C24 (Poly-24-Oxyethylene cholesteryl ether) to oil stage at 60 0C.Thisresult in the formation of vesicle in water in oil (v/w/o)emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel). The v/w/o gel thus obtained can entrap proteins/ proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release.

- **Niosomes of hydroxyl propyl methyl cellulose**

In this type of niosomes, before the preparation of noisome, the base will be prepared which contains 10 % of glycerine of hydroxyl propyl methyl cellulose and then it will be incorporated in formulated niosomes.

- **Deformable niosomes**

The deformable niosomes were formulated by using the mixture ethanol, water and non-ionic surfactant. The penetration effect can be enhanced due to the smaller vesciles of the deformable noisome which can pass through the force of stratum corneum easily. The deformable niosomes were prepared mostly for topical use.[26,27]

- The niosomes are also classified according to the number and size of bilayer which is as follows,

➢ **Multi Lamellar Vesicles (MLV):** Multilamellar vesicles are the most widely used niosomes. It consists of a number of bilayer. The approximate size of vesicles is 0.5-10 μm diameter .It is simple to make and are mechanically stable upon storage for long

periods.

- **Large Unilamellar Vesicles (LUV):** These are the large unilamellar vesicles which having a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped.
- **Small Unilamellar Vesicles (SUV):** These small unilamellar vesicles are mostly prepared from multilamellarvesicles by sonication method, French press and extrusion method.

Methods of peparation of niosomes

- **Ether injection method**

The drug and lipid (**Figure 2**) are added to diethyl ether and gradually to the aqueous phase through a 14- gauge needle at 0.25 ml/min, which is maintained at 60°C. When the organic solvent is heated above theboiling point, large unilamellarniosomes are produced, which can be further treated to obtain reduced niosomes in size. Using the ether injection method[28] were successful in the preparation of salbutamol niosomes with an entrapment efficiency of 67.7%.

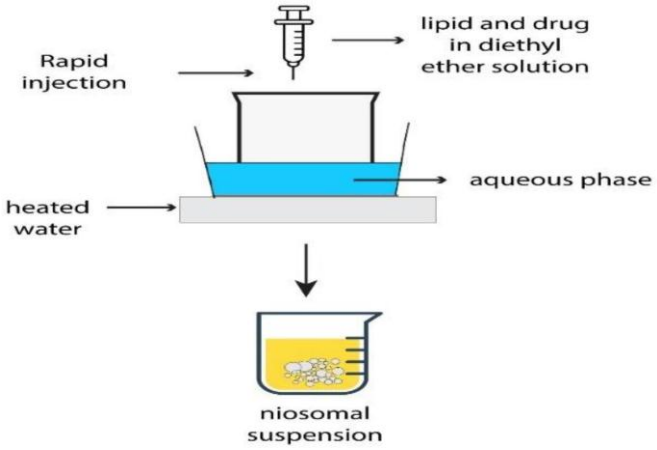

Figure 2: Illustrative depiction of the preparation of niosomes with the ether injection method.[29]

- **Thin film hydration method (Hand shaking)**

The thin-film hydration method (**Figure 3**) is the most widely used, repeatable, and studied technique to produce multilayer vesicles (MLV). After dissolving surfactant and cholesterol in a volatile solvent such as diethyl ether, chloroform, or methanol in a round bottom flask, dissolve the niosomes by thinlayer hydration, then remove the organic solvent by a rotary evaporator at room temperature (20°C). This creates a thin layerof solid mixture on the wall

of the flask. While stirring gently, the dried surfactant can be hydrated with the aqueous phase including the drug at 0-60°C. Fig.3. This process forms typical multilamellarniosomes.[30,31] Imran Khan et al.[32] synthesized diaceteine containing niosomes to treat joint disease by thin layer hydration.

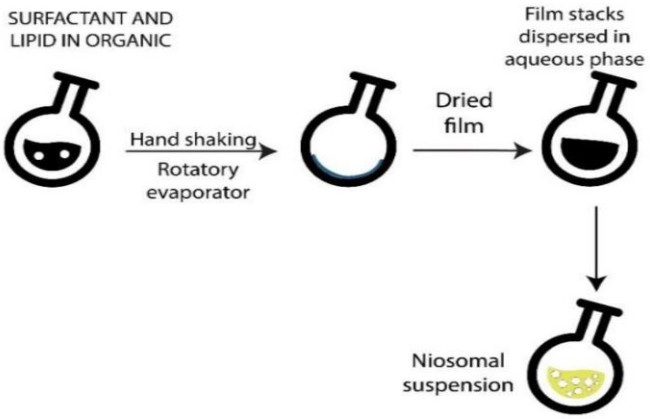

Figure 3: Illustrative depiction of the preparation of niosomes with the thin film hydration (handshaking) method.[33]

- **Multiple membrane extrusion method**

This is an acceptable way to control the size of niosomes. With a mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform, a thin layer is produced by evaporation. This product is hydrated with an aqueous medicinal solution (**Figure 4**).[34] The suspension is extruded through polycarbonate membranes and then placed in up to 8 passages.[35]

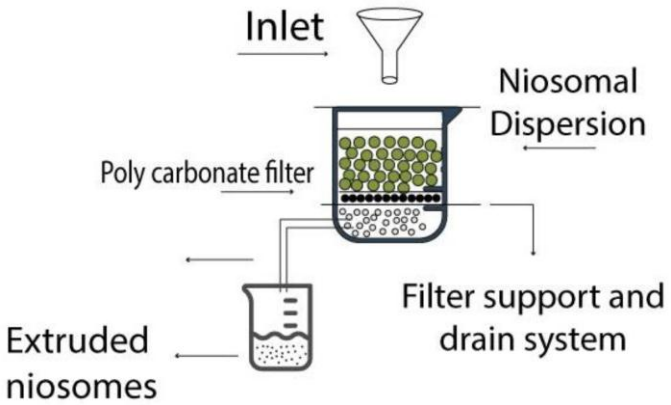

Figure 4: Illustrative depiction of the preparation of niosomes with the multiple membrane extrusionmethod.[36]

- **Reverse phase evaporation method**

Surfactant and cholesterol are dissolved in chloroform and ether. An aqueous phase including the drug is added to the mixture and then ultrasound is performed at 4-5 ° C. A

small proportion of buffer saltis then included in the compound, producing a more sonic gel. The organic solvent is withdrawn at 40° C under low pressure. After diluting the resultant suspension with PBS, we heated the mixture in a water bath at 60 ° C for 10 minutes to form large monolayers (**Figure 5**). *Guinedi et al*[37] produced acetazolamide niosomes with REV for the treatment of glaucoma with a 65.71% ± 1.09 encapsulation efficiency.[38]

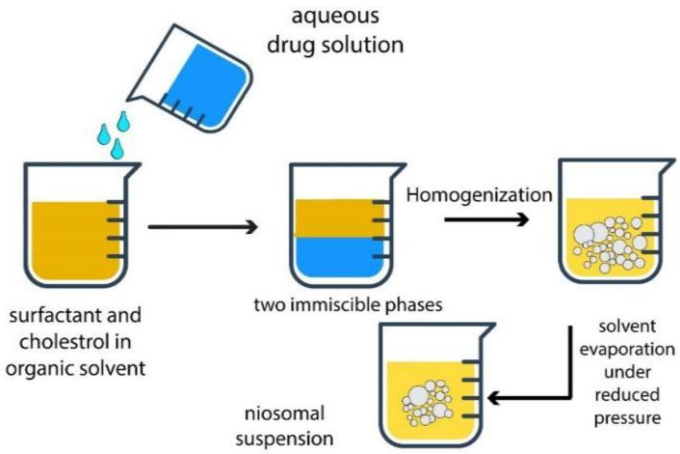

Figure 5: Illustrative depiction of the preparation of niosomes with the reverse phase evaporationmethod.[39]

- **Sonication method**

A standard method of producing vesicles is the ultrasound technique. An aqueous phase containing the active agent in the buffer is included in a mixture (cholesterol/surfactant) in a 10 ml glass vial. For 3 minutes, sonication in a sonic titanium probe is applied to the mixture at 60°C, yielding small and uniformniosomes in size. Niosomes loaded with rifampicin were produced using the probe sonication method as a drug model for low-soluble drugs[40,41,42] (**Figure 6**).

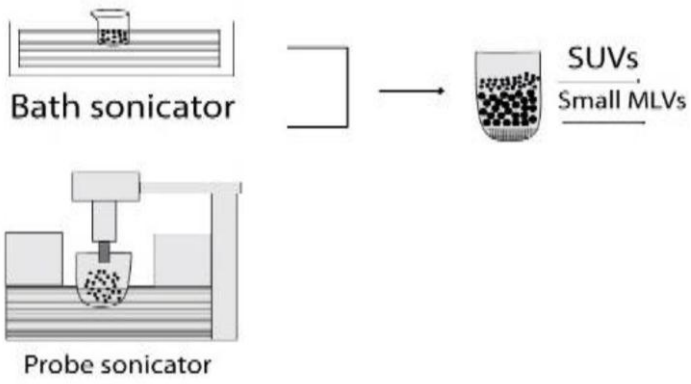

Figure 6: Illustrative depiction of the preparation of niosomes with the sonication method.[43]

- **Micro fluidization**

Micro-fluidization (**Figure 7**) is a current approach to prepare niosomes by specified size distribution. This method is formed on the jet principle. That is to say, mix two different fluids, namely water and alcohol, in the microchannel. The surfactant solution and the drug are pumped under tank pressure through ice-filled interactions. The mixture is then passed through a cooling ring to withdraw the heat generated in the course of micro-fluidization. The recirculation or removal happens when the solution reinterns the reservoir. This is repeated to obtain the proper size of the size of the vesicle.[44] Obeid et al.[45] prepared siRNA-containing niosomes in the treatment of cancer cells. The niosomes were monodisperse and small (less than 60 nm), considered an efficient size range for drug delivery systems.

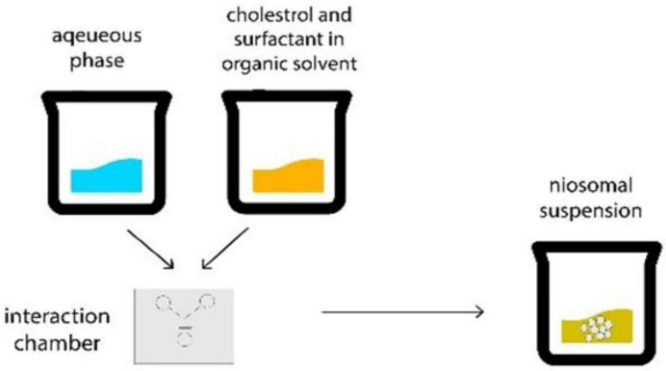

Figure 7: Illustrative depiction of the preparation of niosomes with Microfluidization method.[46]

- **Lipid injection method**

In this method, there are no organic solvents involved, which are both expensive and highly toxic for in vivo use. The molten surfactant and cholesterol are added to a heated aqueous phase, including dissolved drug molecules, resulting in niosomes formation(**Figure 8**).[47]

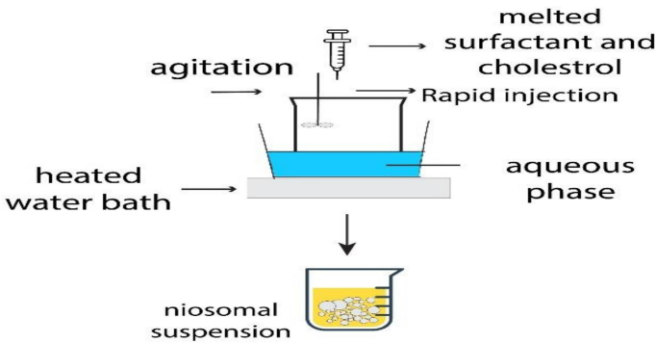

Figure 8: Illustrative depiction of the preparation of niosomes with the lipid injection method.[48]

- **Transmembrane pH gradient method**

In this method, the same amount of cholesterol and surfactant is added to chloroform. Under low pressure, the evaporated solvent forms a thin film on the wall of the round bottom flask. The resulting film is hydrated with 300 ml of citric acid (pH 4.0) using a vortex mixer. The following vesicular particles undergo freezing and thawing cycles. After adding an aqueous solution to the mixture, the pH of the sample increases to 2.7-7.2 by adding a solution of sodium hydrogen phosphate. (**Figure 9**) The suspension is then heated to 60°C to form multilayeredniosomes for 10 minutes.[49]

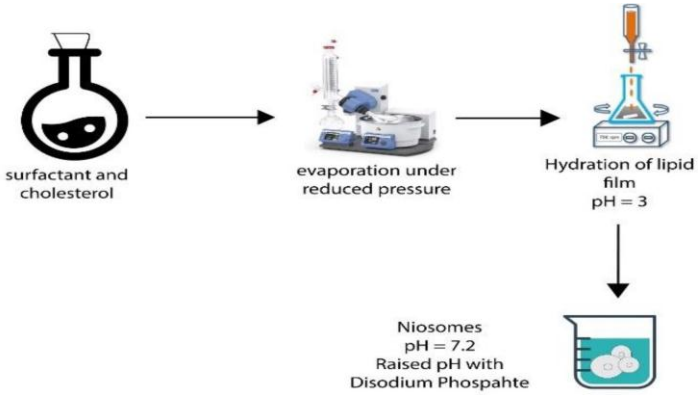

Figure 9: Schematic diagram of the preparation of niosomes via trans membrane pH gradient.[50]

CONCLUSION

When we talk about the novel drug delivery system, the niosomes drug delivery system is an effective approach in this sector. Generally, the difference types of non-ionic surfactants and cholesterol are mixed together with the medicament to formulate the niosomes. There are various methods are used to formulate the niosomes such as reverse phase evaporation method hand shaking method, ether injection method etc. We can conclude from this review article that the niosomes are very important drug delivery tool which is used for incorporation or targeting of drug for various therapeutic activities and provides various advantages over other drug delivery tools. The niosomes will be proved as a great reward for the future perspective.

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