Review Article

Niosomes As A Potential Drug Delivery System

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ABSTRACT

A non-ionic vesicle dependent on surfactants is a niosome. Niosomes are mainly formed as an excipient by non-ionic surfactant and cholesterol incorporation. Various excipients can also be used. Niosomes have a greater penetrating potential than previous emulsion preparations. There are various methods of manufacturing niosomes like thin film hydration, microfluidization, sonication, bubble method to name a few. The fact that niosomes are amphiphillic molecules makes them a flexible carrier of drugs, as both hydrophilic and lipophillic drugs can be trapped. Applications of niosomes in the pharmaceutical industry are many, some of the most important ones being as cosmoceuticals, gene delivery carriers, carriers for vaccine delivery and also in medical imaging. The main object of this review the appliance of niosome technology is employed to treat variety of diseases, niosome have good opportunity in research and beneficial for researcher and pharma industries. As niosome is stable and economical, niosome seems to be a well-preferred drug delivery mechanism over liposome.

Keywords: Niosomes, Surfactant, Liposomes, targeted delivery.

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INTRODUCTION

The Novel Drug Delivery System (NDDS) refers to the methods, formulations, technologies and systems needed to safely achieve the desired therapeutic effects for delivering a pharmaceutical compound into the body. The solubility and stability of natural pharmaceutical molecules can be enhanced by niosomes (nonionic surfactant vesicles), considered to be novel drug delivery systems. They are designed to provide natural pharmaceutical compounds with targeting and controlled release. Among these carriers, niosomes are one of the strongest. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Microscopic lamellar structures formed by combining non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class with cholesterol are niosomes obtained from hydration. Based on its amphiphilic nature, the non-ionic surfactants form a closed bilayer vesicle in aqueous media using some energy, such as heat and physical agitation, to form this structure.[1]

Hydrophobic parts are orientated away from the aqueous solvent in the bilayer structure, whereas the hydrophilic heads remain in contact with the aqueous solvent. Through varying the vesicle composition, size, lamellarity, tapped volume, surface charge and concentration, the properties of the vesicles can be changed. Inside the vesicle, various forces act, e.g., van der Waals forces between surfactant molecules, repulsive forces emerging from electrostatic interactions between charged groups of surfactant molecules, entropic repulsive forces of surfactant head groups, repulsive forces of short-acting, etc. These forces are responsible for preserving the structure of niosomes in the vesicles. The stability of niosomes, however, is affected by the type of surfactant, the nature of the encapsulated drug, the temperature of storage, the use of detergents, the use of membrane spanning lipids, the interfacial polymerisation of in situ surfactant monomers, and the inclusion of charged molecules. They can accommodate drug molecules with a wide range of solubility of drug molecules due to the presence of hydrophilic, amphiphilic and lipophilic moieties in the structure. These can act as a depot, in a controlled manner, releasing the drug. It is also possible to improve the therapeutic performance of drug molecules by delaying clearance from circulation, protecting the drug from the biological environment and limiting the effects on target cells.[2]

NIOSOMES

Niosomes are vesicles consisting predominantly of non-ionic hydrated surfactants, in addition to cholesterol (CHOL) or its derivatives in certain instances. It is capable of encapsulating both hydrophilic and lipophilic compounds via the special structures of niosomes. This can

be accomplished by trapping or adsorbing hydrophilic in vesicular aqueous core on the bilayer surfaces while the lipophilic compounds are encapsulated in the bilayer lipophilic domain by their partitioning. Thin lipid films or lipid cakes are hydrated and liquid crystalline bilayer stacks become liquid, swelling and liposome-forming. Agitation allows the hydrated lipid sheets isolate and self-associate to create vesicles, stopping water from communicating with the bilayer's hydrocarbon center on the sides. The development of niosomes was first initiated in the cosmetic industry, then possible applications of niosomes in drug delivery were investigated.[2] Niosomes were one of the illustrious vesicles in all vesicular systems (Fig.1) [3] As possible drug delivery systems for various routes of administration, in recent years, they have been the subject of great interest. This is thanks to the very fact that niosomes don't have the various disadvantages that others have and are a really useful drug delivery system with numerous applications; Niosomes have the power of entrapping various sorts of drugs, genes, proteins and vaccines.

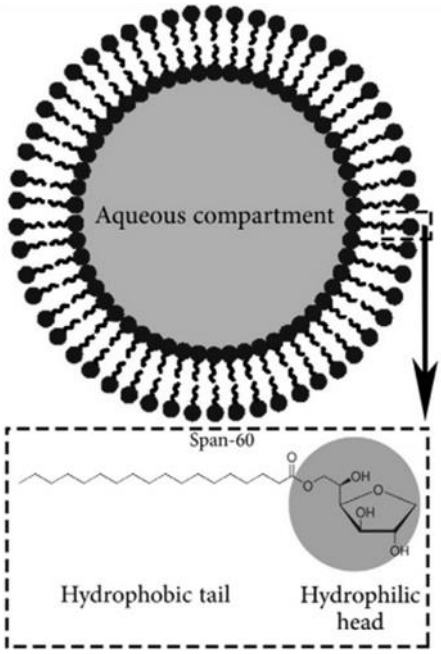

Figure 1: Schematic representation of niosome prepared by sorbitan monostearate (Span-60).

STRUCTURE AND COMPONENTS OF NIOSOME

Non-ionic surfactants, hydration media, and lipids such as cholesterol are the key components of niosomes. Self-assembly in aqueous media of non-ionic surfactants leads to closed bilayer structures (Fig.1). They are associated with a strong interfacial surface tension between water and, thus, the hydrophobic tails of the amphiphile. Between the top groups of non-ionic surfactants, the steric and hydrophilic repulsion ensures that hydrophilic termini point outward and are in contact with water. In general, assembly into closed bilayers requires some energy input, such as mechanical or heat. In three classes compatible with their sizes and bilayers, niosomes are also classified. Small unilamellar vesicles (SUV) (10-100 nm), big unilamellar vesicles (LUV) (100-3000 nm), and multilamellar vesicles (MLV) in which there is a single bilayer.

Structure of Niosome

Surfactants

Non-ionic surfactants are a class of surfactants that in their hydrophilic heads do not have any charged groups. Compared to their anionic, amplified, or cationic counterparts, they are more stable and biocompatible and less toxic. They are therefore favored for in vitro and in vivo applications for the formation of stable niosomes. Amphiphilic molecules containing two distinct regions are nonionic surfactants: one of them is hydrophilic (water-soluble) and, thus, the other is hydrophobic (organic soluble). The major non-ionic surfactant groups used for the processing of niosomes are alkyl ethers, alkyl esters, alkyl amides and fatty acids. The hydrophilic-lipophilic balance (HLB) and important packing parameter (CPP) values play a critical role within the choice of surfactant molecules for niosome preparation.[4]

Hydrophilic-Lipophilic Balance (HLB)

HLB may be a dimensionless parameter, which is that the indication of the solubility of the surfactant molecule. The HLB value describes the balance between the hydrophilic portion to the lipophilic portion of the non-ionic surfactant. The HLB range is from 0 to 20 for non-ionic surfactants. The lower HLB refers to more lipophilic surfactant and therefore the higher HLB to more hydrophilic surfactant. Surfactants with an HLB of 4 to 8 can be used for vesicle preparation.5 Due to their high aqueous solubility, hydrophilic surfactants with an HLB value starting from 14 to 17 are not suitable for creating a bilayer membrane.6

However, niosomes are actually formed from polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7) with the addition of an optimum cholesterol level.7,8 In the presence of equimolar cholesterol concentration, Tween 20 forms a stable niosome. The interaction takes place between the hydrophobic part of the next-to-go amphiphile group and therefore the equimolar ratio of the 3-OH cholesterol group, and this interaction could explain the impact of cholesterol on the formation and hydration behavior of Tween 20 niosomal membranes.9,10

Critical Packing Parameter (CPP)

The geometry of the vesicle during the niosomal preparation depends on the critical packing parameter. The shape of nanostructures formed by self-assembly of amphiphilic molecules is often predicted by the concept of the CPP of a surfactant. The critical packing parameter depends on the surfactant's symmetry and can be described using the equation below.[11,12]

CPP = V lc × a_o

where V is hydrophobic group volume, lc is that the critical hydrophobic group length, and $a0$ is that the world of

hydrophilic head group. If CPP ≤ 1/3 corresponding, for instance, to a bulky head group, small hydrophobic tail spherical micelles may form. Nonspherical micelles may form if 1/3 ≤ CPP ≤ 1/2, and bilayer vesicles can occur if 1/2 ≤ CPP ≤ 1. Inverted micelles form if CPP ≥ 1 When a voluminous tail and a small hydrophobic tail are composed of the surfactant.[10] CPP may be used as a tool for the self-assembled structure and its morphological transformation in amphiphilic solutions to be realized, rationalized, and projected.[13]

Cholesterol

In the bilayer structure of niosomes, cholesterol forms hydrogen bonds with hydrophilic head of a surfactant.[14,15] Cholesterol content of niosomes thereby influences the structures of niosomes and physical properties like entrapment efficiency, while stability, release of payload, and biostability.[16,17] Cholesterol improves the rigidity of vesicles and stabilizes niosomes towards destabilizing effects induced by plasma and serum components and reduces the permeability of vesicles for entrapped molecules thus inhibiting leakage.[18]

Charged Molecules

Charged molecules increase the steadiness of the vesicles by the addition of charged groups to the bilayer of vesicles. They increase surface charge density and thereby prevent vesicles aggregation. Dicetyl phosphate and phosphatidic acid are most used charged molecules for niosome preparation and, similarly, stearyl amine and stearyl pyridinium chloride are well-known charged molecules utilized in niosomal preparations. Normally, the charged molecule is added in niosomal formulation in an amount of two. 5-5 mol%. However increasing the amount of charged molecules can inhibit niosome formation.[19]

METHODS OF PREPARATION

Preparation of niosomes begins with the hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional niosome size reduction so on get a sol.[20] There are several well-studied standard methods for the preparation of niosomes. Ether injection, hand shaking, sonication, and microfluidization methods are a few examples.[21,22,23] Subsequently, the unentrapped drug is separated from the entrapped drug by centrifugation, gel filtration, or dialysis.[20]

The first step in niosome production by ether injection is through the dissolution of surfactant in ether. The solution is then injected through a 14-gauge needle into a solution of drug maintained at 60°C. Subsequently, single-layer vesicles with diameters ranging from 50 to 1000 nm are formed because of the vaporization of ether.24However, a small amount of residual ether frequently persists in the niosomal suspension.[22]

In the hand-shaking method, also mentioned as thin-film hydration technique, surfactant and cholesterol are dissolved during a volatile organic solvent and transferred to a rotary evaporator. After evaporation, a skinny layer of solid mixture is deposited on the wall of the flask. The dried layer is then hydrated with an aqueous phase containing the drug of interest. This process may be carried out at room temperature with gentle agitation.[23,25]

Niosomes can also be produced through sonicating a mixture of surfactant, cholesterol, and aqueous phase containing the drug at 60°C for 3 min. The vesicles produced through this method are usually small and uniform in size.[22,25] Micro-fluidization is another reproducible technique that achieves this size uniformity. Operationally, 2 fluidized streams move forward through a precisely defined micro-channel, and these 2 streams interact with each other at an ultrahigh velocity.[22,24,26]

Alternative methods have since been defined for the preparation of niosomes. The multiple membrane extrusion method uses surfactant, cholesterol, and dicetyl phosphate in chloroform, and thus the mixture is evaporated to provide a thin film. The film is then hydrated with aqueous drug solution, and therefore the suspension produced is extruded through polycarbonate membranes, which are placed serial for up to eight passages.[22,24,27]

The reverse-phase evaporation technique uses a mix containing surfactant and cholesterol during a 1:1 ratio, additionally to ether and chloroform. An aqueous phase containing the target drug is added to the mixture followed by sonication at 4-5°C. Sonication is sustained after adding a little amount of phosphate-buffered saline to the mixture. The organic solvent is removed at 40°C under a low pressure, and the remaining suspension is diluted with phosphate-buffered saline. After heating the mixture at 60°C for 10 min, the last word product of niosomes is obtained.[22,24,28] The preparation of niosomes using the reverse-phase evaporation technique is illustrated in fig.no 2.

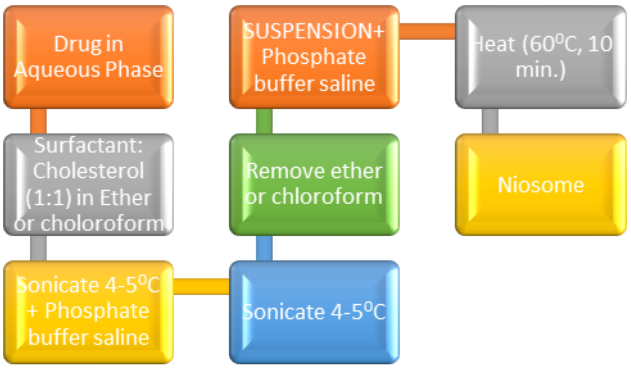

Figure 2: Schematic diagram of preparation of niosomes using the reverse-phase evaporation technique

Niosomes are often produced without the utilization of organic solvents using the "bubble" method. A "bubbling unit" consists of a round-bottomed flask with 3 necks positioned during a water bath; a water-cooled condenser and thermometer are positioned within the first and second necks, respectively, while nitrogen is abounding through the third neck. Surfactant and cholesterol that are varied at 70°C in a buffer are homogenized and "bubbled"

at 70°C using the "bubbling unit".[24,29] The preparation of niosomes using this system is illustrated in Fig. No.3

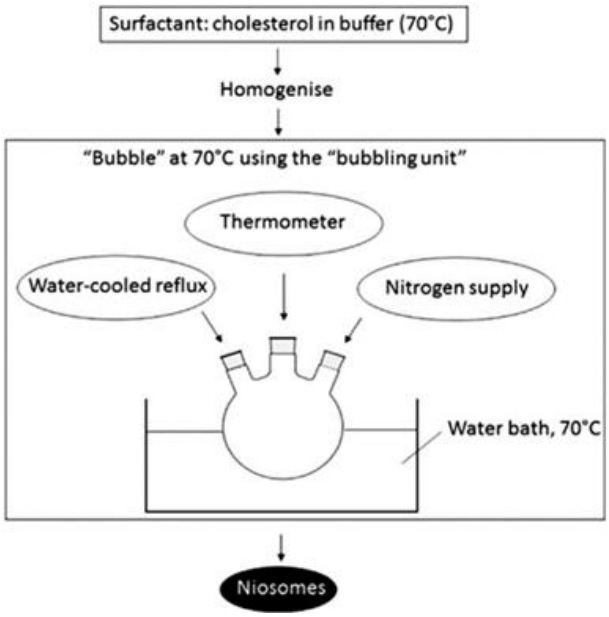

Figure 3: Schematic diagram of preparation of niosomes using the "bubble" method

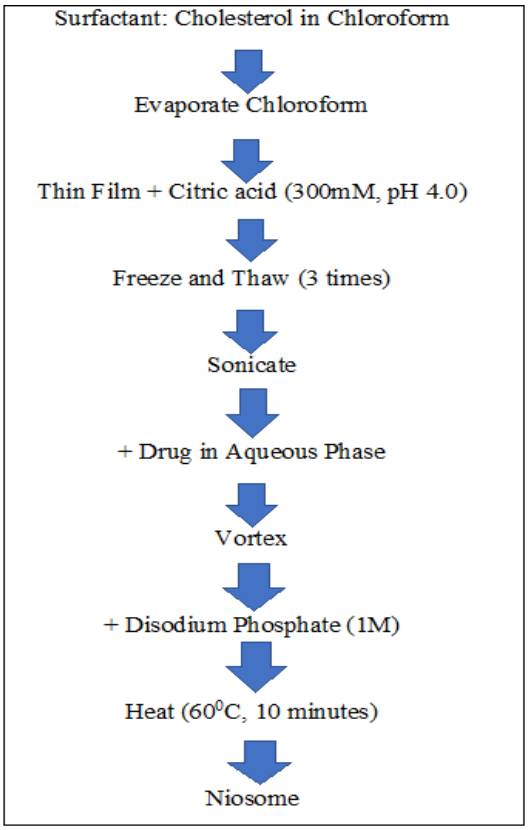

Figure 4: Schematic diagram of preparation of niosomes by transmembrane pH gradient (inside acidic) drug uptake process.

In another variation of preparation of niosomes, a thin film resulting from evaporation of surfactant and cholesterol dissolved in chloroform is hydrated with 300 mM acid (pH 4.0). Then, the suspension is subjected to three successive freeze–thaw cycles. After sonication, the solution containing the drug is added to the suspension and vortexed. Disodium phosphate (1 M) is added to the mixture to extend the pH to 7.0-7.2. This mixture is later heated at 60°C for 10 min to supply niosomes. This method is recognised as the "transmembrane pH gradient (inside acidic) drug uptake process".[22,24,30] Niosomes obtained by this method showed better entrapment efficiency and retention of drugs.[31,32] Fig. 4 shows the steps for the preparation of niosomes using this method.

The emulsion method, which uses an oil-in-water emulsion prepared from an organic solution of surfactant, cholesterol, and a solution of drug, is another technique for preparation of niosomes. The organic solvent is evaporated to obtain the final product.[22,33,34] By contrast, a mixture of lipids and surfactant is melted and injected into a heated aqueous phase containing the drug in the lipid injection method.[22]

LIPOSOME VERSUS NIOSOME

The differences between liposome and niosome are described in Table No. 1

Liposome	Niosome
• More expensive	• Less expensive
•Phospholipids are prone to oxidative degradation	• But non-ionic surfactants are stable toward this
•Required special method for storage, handling and purification	• No special methods are required for such formulations comparatively phospholipids
• Phospholipids may be neutral or charged • Non-ionic surfactants are uncharged	• Non-ionic surfactants are uncharged

Similarities between Liposome and Niosome[36]

1) The liposomes and niosomes are functionally same.

2) Both can be used in targeted and sustained drug delivery system.

3) Property of both depends upon composition of the bilayer and methods of their preparation.

4) Both Liposome and Niosome increase bioavailability and reduce the body clearance.

APPROACHES OF NIOSOMES

The administration of niosomes by various routes has been reported and it's clear that the route is vital in designing a vesicular formulation. Oral Route Delivery Niosomes are often proposed as a possible oral delivery system for the effective delivery of medicine. The delivery of biopharmaceuticals to the circulation through oral administration is hindered by numerous barriers, including pH gradients, proteolytic enzymes and low epithelial

permeability. The oral delivery of recombinant human insulin using niosomal formulations was demonstrated by a study involving poly-oxy ethylene alkyl ethers based niosomes. Entrapment of insulin in bilayer structure of niosomes endangered it against proteolytic activity of α-chymotrypsin, trypsin and pepsin in vitro. Significantly higher protection activity was seen in Brij 92/cholesterol (7:3 molar ratios) in which only 26.3±3.98% of entrapped insulin was released during 24 h in simulated intestinal fluid (SIF).[37]Encapsulation of Ganciclovir in lipophilic vesicular structure could even be estimated to strengthen the oral absorption and prolong the existence of the drug within the circulation. Niosomes were prepared from Span40, Span60, and Cholesterol using reverse evaporation method.

Transdermal Delivery

Slow penetration of drug through skin is that the major drawback of transdermal route of delivery. An increase within the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Niosomes of terbinafine hydrochloride was formulated by thin film hydration method using different ratios of non-ionic surfactants (Tween 20, 40, 60, and 80) and cholesterol with constant drug concentration. Niosomal preparations were tested for in-vitro antifungal activity using the strain Aspergillus niger and compared with pure drug solution (as standard). All the niosomal formulations showed gradual increase in zone of inhibition due to the controlled release of medicament.[38]

Leishmaniasis

Niosomes are often used for targeting of drug within the treatment of diseases during which the infecting organism resides within the organ of reticulo-endothelial system. Leishmaniasis is such a disease during which parasite invades cells of liver and spleen. The commonly prescription drugs are antimonials, which are associated with arsenic, and at high concentration they damage the guts, liver and kidney. Liver and serum concentrations of antimony within the mouse are determined after administration of sodium stibogluconate within the free, liposomal and niosomal form. High liver and low serum values were attained by the use of both vesicular formulations.39.[39]

Hormone delivery

The in-vitro permeation of estradiol from vesicular formulations through human stratum corneum was studied. The vesicles were composed of non-ionic n-alkyl poly-oxyethylene ether surfactants (CnEOm). Two mechanisms are proposed to play an important role in vesicle–skin interactions, i.e., the penetration enhancing effect of surfactant molecules and the effect of the vesicular structures caused by their adsorption at the stratum corneum– suspension interface.[40]

Cosmetic delivery

The first report of non-ionic surfactant vesicles came from the cosmetic applications developed by L'Oreal. Niosomes were developed and patented by L'Oréal within the 1970s and 80s. The first product 'Niosome' was introduced in 1987 by Lancôme. The advantages of using niosomes in cosmetic and skin care applications include their ability to extend the steadiness of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration.[41]

APPLICATIONS OF NIOSOMES

To Improve the Stability and Physical Properties of the Drugs

To Increase Oral Bioavailability: Ismail A. *et al.,* reported that with the formulation of niosomes, the oral bioavailability of the acyclovir as well as griseofulvin was increased as compared to the drug alone. Similarly, the absorptivity of poorly absorbed peptide and ergot alkaloid are often increased by the administration within the common bile duct of rats when administered as micellar solution along side the POE-24- cholesteryl ester.[42, 43]

To Modify the Physicochemical Properties of Drugs: Cable C. *et al.,* studied that non ionic surfactant can be used to improve the physicochemical properties of drug free niosomes as well as drug loaded niosomes.[43]

For Improvement of Stability of Peptide Drugs: The stability of peptide drugs can be increased significantly by using niosomes e.g. 8-arginin vasopressin, 9-glycinamidew etc.[44] Also, the in vitro release of insulin from niosomes formulated by span 40 and span 60 in simulated intestinal fluid was lower than the niosomes formulated by span 20 and span 80. Niosomes prepared by the span 60 has high resistance against proteolytic enzyme and exhibit good stability in storage temperature and in presence of sodium deoxycholate.[45]

To Promote Transdermal Delivery of Drugs: Many drugs such as lidocaine, estradiol, cyclosporine etc. are used for topical and transdermal drug delivery system by formulating them as niosomes.[46, 47]

For Controlled Release of Drugs

To Prolong the Release Rate: The release rate of drugs like withaferin and gliclazide from the niosomes was found slower as compared to withaferin without incorporating in niosomes.[48]

In Ophthalamic Drug Delivery: Experimental results of the water soluble antibiotic gentamicin sulphate showed a substantial change in the release rate. Beside this, the percent entrapment efficiency of gentamicin sulphate was altered when administered as niosomes.[49]

For Targeting and Retention of Drug in Blood Circulation:

For Increased Uptake by A431 Cells For targeting purpose, chitosan based vesicles incorporating transferrin and glucose as ligand have been reported.These vesicles bind

CoA (co-A) to their surface. Chitosan containing vesicles are then taken up by A431 cells and the uptake was found to be enhanced by transferrin.[50]

For Liver Targeting Methotrexate was reported to be selectively taken up by liver cells after administration as a niosomal drug delivery system.[51]

2In Treatment of Localized Psoriasis Methotrexate, a drug used in psoriasis has limited applications due to its formulation problem. In the treatment of localized psoriasis, niosomes of methotrexate taking chitosan as polymer have shown promising results.[52]

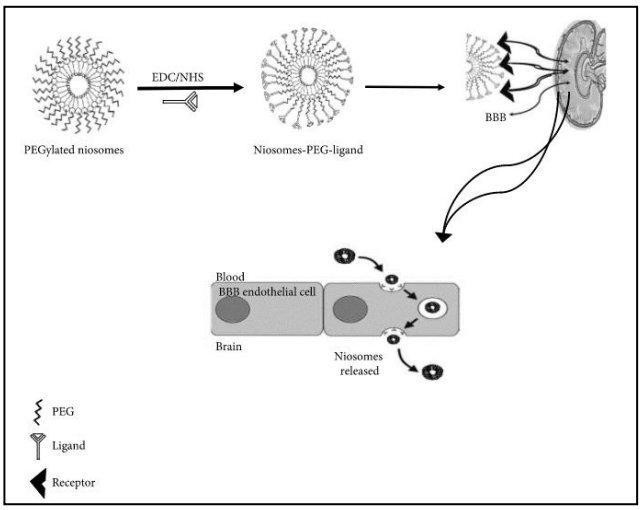

Figure 5: Schematic conjugation of targeting ligand to PEGylated niosomes delivery to BBB.

CONCLUSION

Niosomes drug delivery system is an efficient approach towards novel drug delivery. Niosomes are composed mainly of non-ionic surfactants and cholesterol. Niosomes offer various advantages over other drug delivery devices and have found applicability in pharmaceutical field. There are several well-studied standard methods for the preparation of niosomes. Niosomes are very effective drug delivery tools for incorporation/targeting of varied therapeutically active moieties and therefore the onus lies on future scientists to effectively harness its potential in diverse application areas for the advantage of mankind. It improve the Stability and Physical Properties of the Drugs and found to be effective for Controlled Release of Drugs.

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