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NIOSOMES: AN APPROACH TOWARDS TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

For better drug delivery into the body the drug is incorporated into the liposomes or niosomes. Niosomes are non ionic surfactant vesicles (nisomes or NSVs) which are widely investigated as alternative vesicles and are reported to mimic liposomes in several respects. Niosomes can be used as carriers of amphiphilic and lipophilic drugs. Niosomes have more penetrating capability than the previous preparations of emulsion.They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable.

INTRODUCTION

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes [1].

This review provides a brief overview of issues related to niosomes by explaining their chemical composition, structure, advantages, and applications, makes general remarks on niosomes as percutaneous permeation enhancers, and discusses the findings of investigations done over the past 5 years on niosomal drug delivery systems for transdermal applications [2]. Niosomes behave ***in vivo*** like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability [3]. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency [4].

Niosomes are vesicular nanocarriers and have received much attention as potential drug delivery systems in the last 30 years due to their unique advantages. They have lamellar (bilayer) structures composed of amphiphilic molecules surrounded by an aqueous compartment. These amphiphilic molecules, known as surfactants, contain both hydrophobic groups (tails) and hydrophilic groups (heads) and show self-assembling properties, aggregating into a variety of shapes like micelles or into a planar lamellar bilayer [5]. Surfactants that could be used as potential drug delivery systems include sorbitan esters and analogs, sugar-based, polyoxyethylene-based, polyglycerol, or crown ether-based surfactants, sometimes in addition to membrane additives, such as cholesterol or its derivatives. Nonionic surfactants are preferred because they have less potential to cause irritation, which decreases in order of cationic > anionic > nonionic [6].

The unique structures of niosomes as vesicular systems make them capable of encapsulating both hydrophilic and lipophilic substances. Hydrophilic drugs are usually encapsulated in the inner

aqueous core or adsorbed on the bilayer surfaces, while lipophilic substances are entrapped by their partitioning into the lipophilic domain of the bilayers (Figure 1).

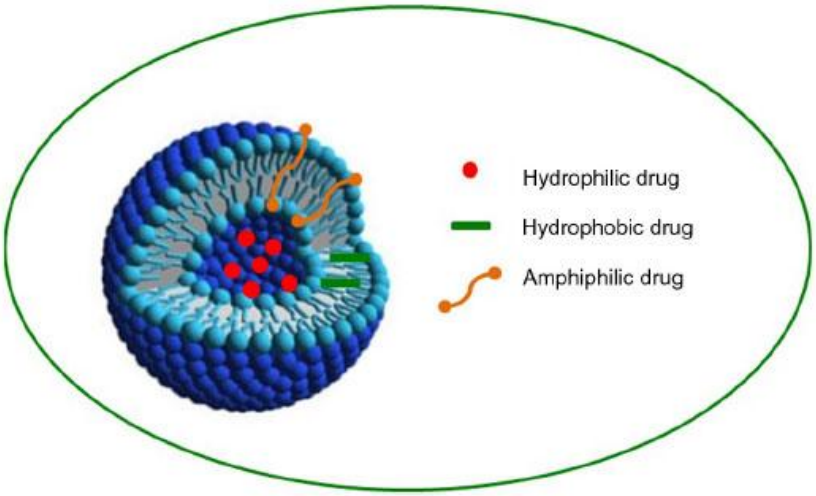

Figure 1: Schematic representation of a niosomal vesicle

The formation of vesicular assemblies requires the input of some form of energy, and all the experimental methods investigated involve hydration of a mixture of surfactants above the gel to liquid phase transition temperature of the system, followed by optional size reduction to obtain a colloidal dispersion [7]. Because of their potential ability to carry a variety of therapeutics, these vesicles have been widely used as drug delivery systems to achieve drug targeting, controlled release, and permeation enhancement [8]. In fact, niosomes can act as therapeutic reservoirs for delivery of a drug in a controlled manner to enhance bioavailability, obtaining a therapeutic effect over a longer period of time, and can be modified by altering the composition, concentration of various additives, and surface charge of vesicle components and membrane additives [9]. Moreover, drug ionization has been found to modulate the physicochemical properties of the vesicles and their percutaneous permeation profiles [10]. In recent decades, niosomes have been investigated in-depth as potential carriers for sustained and targeted drug delivery, since they are easily derivatized to enhance vesicles versatility to improve the affinity for the target site [11].

Definition of Niosomes

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

nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids.They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells.

Components of Niosomes

Surfactant: Non-ionic surfactants are used; they considered the important structural component. They act as Vesicle Forming Agents. The nature of vesicles formed depends upon HLB value in addition, phase transition temperature. HLB value is a good indicator to predict the vesicle formation and entrapment efficiency. HLB number in between 4 and 8 is compatible with vesicle formation. Another important parameter is the phase transition temperature, higher T^{o}C are more likely in the ordered gel form forming less leaky bilayer, thus having higher entrapment efficiency, while surfactants of lower T° C are more likely in the less ordered liquid form.

Cholesterol: Cholesterol acts as "vesicular cement" in the molecular space that formed by the aggregation of monomer to form the bilayer. Thereby increasing the rigidity decreases the permeability drug through the membrane and hence improves the entrapment efficiency. However, beyond certain concentration cholesterol will compete with the drug for the space within the bilayer, thereby excluding drug and can disrupt the regular linear structure of vesicular membrane. In addition to this, it can also act stabilizing agent.

Solvents: The solvent can act as penetration enhancer and in turn affect the vesicular size formation. Solvents commonly used are alcohols, mainly, ethanol, propanol, butanol, isopropanol. Researchers have reported that ethanol showed larger vesicular size due to the slow phase separation as it has greater solubility in water, whereas due to the branching of isopropanol it showed smaller vesicular size.In addition, reports suggest that the drug penetration is maximal for isopropanol due to the reason that the branched structure will act as co-surfactant and might loosen the bilayer packing resulting into the increased release of drug.

Structure of Niosomes

Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures, however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself.

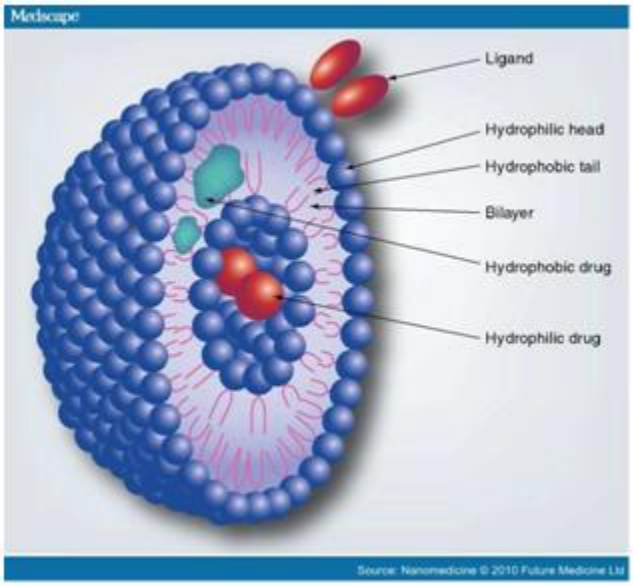

Figure 2: Structure of Niosomes

A typical niosome vesicle would consist of a vesicle forming ampiphile 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 diacetyl phosphate, which also helps in stabilizing the vesicle.

Advantages and disadvantages of niosomal carriers

Niosomes combine several advantages with respect to other nanocarriers [12].

- Surfactants used to prepare niosomes are biodegradable, biocompatible, and not immunogenic
- The method used for routine and large-scale production of niosomes does not involve use of unacceptable solvents
- Due to the chemical stability of their structural composition, the handling and storage of niosomes does not require any special conditions
- The physicochemical properties of niosomes, such as their shape, fluidity, and size, can be easily controlled by changing their structural composition and the method of production
- Niosomes are able to encapsulate a large amount of material in a small vesicular volume
- The structure of niosomes protect drug ingredients from heterogeneous factors present both inside and outside the body, so niosomes can be used for the delivery of labile and sensitive drugs
- Niosomes improve the therapeutic performance of drug molecules by delaying clearance from the circulation and restricting effects to target cells
- Niosomes can be administered via different routes, such as oral, parenteral, and topical, and using different dosage forms such as powders, suspensions, and semisolids, improving the oral bioavailability of poorly soluble drugs and also enhancing the permeability of drugs through the skin when applied topically
- The aqueous vehicle-based suspension formulation results in better patient compliance when compared with oily dosage forms; in addition, niosomal dispersion, being aqueous, can be emulsified in a nonaqueous phase to regulate the drug release rate
- Niosomes have been reported to achieve better patient adherence and satisfaction and also better effectiveness than conventional oily formulations.

At the same time, niosomes have some disadvantages, which may decrease their shelf life, and include physical and chemical instability, aggregation, fusion of vesicles, and leaking or hydrolysis of the encapsulated drug. Moreover, the methods required for preparation of multilamellar vesicles, such as extrusion or sonication, are time-consuming and may require specialized equipment for processing [13].

Niosomes versus liposomes

Niosomes and liposomes are functionally the same, with similar physicochemical properties depending on the composition of the bilayer and the preparation methods used (Table 1). They act as amphiphilic vesicles, and both can be used for targeted and sustained drug delivery.

Table 1: Niosomes versus liposomes: a summary

	Niosomes	Liposomes
Components	Surfactants	Phospholipids
Component availability	High	Low
Component purity	Good	Variable
Preparation and storage	No special conditions required	Inert atmosphere and low temperature
Stability	Very good	Low
Cost	Low	High

Several authors have reported that the function of niosomes in vivo is similar to that of liposomes [14]. Niosomal and liposomal vesicular systems have similar applications in the pharmaceutical and cosmetic field, but differ chemically in their structure units; niosomes are made of surfactants whereas liposomes are based on phospholipids, meaning that niosomes have greater stability and lack many of the disadvantages associated with liposomes, ie, high cost, low availability, and the variable purity problems associated with phospholipids. Niosomes do not require special conditions such as low temperature or an inert atmosphere during preparation and storage; these features make niosomes more attractive for industrial manufacturing [15]. On the other hand, niosomes offer several advantages over liposomes, such as intrinsic skin penetration-enhancing properties [16].

Recent advances in niosomal formulations for transdermal drug targeting

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 (ie, ethanol) provide vesicles with elastic characteristics, which allow them to penetrate more easily into the deeper layers of the skin [17]. 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 [18]. Niosomal gels were found to enhance retention of therapeutics by the skin and to provide high and sustained drug concentrations in the skin [19]. 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 [20]. A summary of the findings of investigations over the past 5 years for transdermal niosomal drug delivery systems is given in Table 2.

Table 2: Different types of non-ionic surfactants

Type of non-ionic surfactant	Examples
Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetostearyl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

Methods of Preparation

Niosomes are prepared by different methods based on the sizes of the vesicles and their distribution, number of double layers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane.

Preparation of small unilamellar vesicles

Sonication

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial [21]. The mixture is homogenised using a sonic probe at 60°C for 3 minutes. The vesicles are small and uniform in size.

Micro fluidisation

Two fluidised streams move forward through precisely defined micro channel and interact at ultra-high velocities within the interaction chamber [22]. Here, a common gateway is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility.

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique)

In the hand shaking method, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform or methanol in a rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask. The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation.

Trans-membrane pH gradient (inside acidic) drug uptake process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to obtain a thin film on the wall of the round-bottom flask [23]. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed three times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to produce the desired multilamellar vesicles.

Preparation of large unilamellar vesicles

Reverse phase evaporation technique (REV)

In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform [24]. 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. The organic phase is removed at 40°C under low pressure. The

resulting viscous niosome suspension is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min to yield niosomes.

Ether injection method

The ether injection method is essentially based on slow injection of niosomal ingredients in ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C [25]. The probable reason behind the formation of larger unilamellar vesicles is that the slow vapourisation of solvent results in an ether gradient extending towards the interface of aqueous-nonaqueous interface. The former may be responsible for the formation of the bilayer structure. The disadvantages of this method are that a small amount of ether is frequently present in the vesicles suspension and is difficult to remove.

In vitro **Release Study**

A method of ***in vitro*** release rate study was reported with the help of dialysis tubing [26]. A dialysis sac was washed and soaked in distilled water. The vesicle suspension was pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles was then placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer was analysed for the drug content by an appropriate assay method. In another method, isoniazid-encapsulated niosomes were separated by gel filtration on Sephadex G- 50 powder kept in double distilled water for 48 h for swelling [27]. At first, 1 ml of prepared niosome suspension was placed on the top of the column and elution was carried out using normal saline. Niosomes encapsulated isoniazid elutes out first as a slightly dense, white opalescent suspension followed by free drug. Separated niosomes were filled in a dialysis tube to which a sigma dialysis sac was attached to one end. The dialysis tube was suspended in phosphate buffer of pH (7.4), stirred with a magnetic stirrer, and samples were withdrawn at specific time intervals and analysed using high-performance liquid chromatography (HPLC) method.

In vivo Release Study

Albino rats were used for this study. These rats were subdivided with groups. Niosomal suspension used for ***in vivo*** study was injected intravenously (through tail vein) using appropriate disposal syringe.

Stability of Niosomes

Vesicles are stabilized based upon formation of 4 different forces:

1. van der Waals forces among surfactant molecules;
2. repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules;
3. entropic repulsive forces of the head groups of surfactants;
4. Short-acting repulsive forces.

Electrostatic repulsive forces are formed among vesicles upon addition of charged surfactants to the double layer, enhancing the stability of the system.

Biological stability of the niosomes prepared with alkyl glycosides were investigated which reported that niosomes were not stable enough in plasma. This may be due to single-chain alkyl surfactants. SUVs were found to be more stable.

Niosomes in the form of liquid crystal and gel can remain stable at both room temperature and 4°C for 2 months. No significant difference has been observed between the stability of these two types of niosomes with respect to leakage. Even though no correlation between storage temperature and stability has been found, it is recommended that niosomes should be stored at 4°C. Ideally these systems should be stored dry for reconstitution by nursing staff or by the patient and when rehydrated should exhibit dispersion characteristics that are similar to the original dispersion. Simulation studies conducted to investigate physical stability of these niosomes during transportation to the end-user revealed that mechanical forces didn't have an influence on physical stability. It is assumed that the reason behind the stability of niosomes may be due to the prevention of aggregation caused by steric interactions among large polar head groups of surfactants.

Applications of Niosomes

Niosomes were introduced for use in the cosmetic industry. The first report on surfactant vesicles came from the cosmetic applications devised by L'Oreal [28]. Phospholipids and nonionic surfactant have been reported to act as penetration enhancers that can overcome the barrier of transdermal drug delivery [29]. Since then, there has been increasing interest in the use of niosomes in the pharmaceutical, cosmetic, and food industries, leading to the publication of more than 1,200 research articles, about 200 patents, and six clinical trials from 1980 onwards. Most of these publications make reference to the importance of characterization of nanovectors.

Niosomal carriers are suitable for the delivery of numerous pharmacological and diagnostic agents, including antioxidants, anticancer, anti-inflammatory, antiasthma, antimicrobial, anti-

Alzheimer's, and antibacterial molecules, oligonucleotides, and others [30]. Depending on the type of drug, surfactant, disease, and anatomical site involved, various routes of administration exist for niosomal drugs, ie, intravenous, intramuscular, oral, ocular, subcutaneous, pulmonary, and transdermal [31]. Several other routes have been used to administer niosomal drugs, including the intraperitoneal and vaginal routes. Niosomes have been used for successful targeting of drugs to various organs like the liver and brain or to pathological districts such as tumor, enhancing drugs pharmacological activities while reducing side effects [32]. In particular, targeted niosomal systems have been designed with different mechanisms of action, including active, passive, and magnetic targeting, leading to more advanced and specific macromolecular drug carriers [33].

Mechanisms of action of Niosomes

There is no single mechanism that can sufficiently explain the ability of niosomes to increase drug transfer through the skin, and several mechanisms have been proposed, including: alteration of the barrier function of the stratum corneum, as a result of reversible perturbation of lipid organization [34]; reduction of transepidermal water loss, which increases hydration of the stratum corneum and loosens its closely-packed cellular structure [35] and adsorption and/or fusion of niosomes on the surface of the skin, as revealed by freeze fracture electron microscopy and small angle X-ray scattering, leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of a drug [36].

Adsorption of niosomes onto the cell surface occurs with little or no internalization of either aqueous or lipid components; it may take place either as a result of attracting physical forces or as a result of binding by specific receptors to ligands on the vesicle membrane and transfer of drug directly from vesicles to the skin. On the other hand, niosomes may fuse with the cell membrane, resulting in complete mixing of the niosomal contents with the cytoplasm. Finally, niosomes may be engulfed by the cell (endocytosis), with lysozymes present in the cytoplasm degrading or digesting the membranous structure of the niosome, thereby releasing the entrapped material into the medium [37, 38].

Conclusions

Niosomes have been proven to be useful controlled drug delivery systems for transdermal, parenteral, oral, and ophthalmic routes. They can be used to encapsulate anti-infective agents, anti-cancer agents, anti-inflammatory agents and fairly recently as vaccine adjuvants. Recent

advancements in the field of scientific research have resulted in the endorsement of small molecules such as proteins and vaccines as a major class of therapeutic agents. These, however, pose numerous drug-associated challenges such as poor bioavailability, suitable route of drug delivery, physical and chemical instability and potentially serious side effects. Opinions of the usefulness of niosomes in the delivery of proteins and biologicals can be unsubstantiated with a wide scope in encapsulating toxic drugs such as anti-AIDS drugs, anti-cancer drugs, and anti-viral drugs. It provides a promising carrier system in comparison with ionic drug carriers, which are relatively toxic and unsuitable. However, the technology utilised in niosomes is still in its infancy. Hence, researches are going on to develop a suitable technology for large production because it is a promising targeted drug delivery system.

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