

## NIOSOMES A PROMISSING NANOCARRIER: A REVIEW

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### ABSTRACT

There are numerous traditional methods for applying medications to the skin. Transdermal has become a popular method of drug delivery in recent years for a variety of medications that are difficult to administer in other ways. Transdermal drug delivery has a number of advantages, the most important of which is the prevention of first-pass metabolism and the stomach environment, which would render the drug inactive. In addition to discussing in depth the various formulation techniques and permeability enhancement for improved therapeutic efficacy, a transdermal patch allows for the controlled release of medication into the patient, typically through membrane pores that house a reserve of medication or over body heat that melts thin layers of medication entrenched in the adhesive.

The drug molecules can permeate the skin and be administered in this manner. Niosomes are vesicles made of non-ionic surfactants that are more stable, biodegradable, and generally harmless. Because surfactants are more chemically stable than lipids, niosomes are ideal for liposomes. The main topics of this review study are the concept of niosome, its benefits and drawbacks, composition, various type of transdermal formulation, enhancers using in this delivery and novel transdermal drug delivery, variables influencing niosomes, characterization, and use of niosome. Niosomes can be used to carry both amphiphilic and lipophilic drugs. Niosomes have great potential in targeted drug delivery of anticancer and anti-infective agents. This review article represents the structure of Niosomes, its advantages and disadvantages, types of niosomes, applications, method of preparation of niosomes.

**Keywords:** Niosomes, Small unilamellar vesicle, Proniosomes, pH gradient method, Ether injection, Future perspectives

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### INTRODUCTION

The transdermal drug delivery route has significant advantages over the conventional oral route. It can provide more patient compliance, especially in patients with swallowing problems, more stable serum drug levels, pain-free drug administration, avoiding hepatic first-pass metabolism and drug degradation in the gastrointestinal tract, food-drug interaction, and reducing side effects. Moreover, transdermal drug delivery is suitable for long-term administration, especially for insulin and analgesic drugs [1]. However, the low skin permeability, which limits drug penetration and inconsequence affects drug bioavailability, represents the most challenging mission for delivering drugs across the skin layers. Transdermal drug delivery system one of the innovative drug delivery methods that is advancing the fastest is transdermal drug delivery [2]. This medication delivery system was made to distribute drugs under control through the skin into the bloodstream while preserving consistent efficacy and lowering the dose and associated side effects. The most popular route, oral administration, expedites patient satisfaction but is more likely to cause hepatic first-pass metabolism, necessitating a higher dose of medication [3]. The main barrier to the inclusion of surfactants in lipid-based formulations is additional

gastrointestinal irritability. The simultaneous dissemination of medicine throughout the body may result in unavoidable adverse effects. Therefore, the non-invasive, painless, and irritation-free topical delivery of definition may be a diverse strategy related to several benefits, counting the drug delivery to a particular location of activity with decreased systemic toxicity, evasion of first-pass metabolism and gastric irritation, increased release rate of the drug from formulation to induce superior percutaneous absorption, and for a minute topical application related to increasing bioavailability [4]. Also the limitation of niosomes having physical instability and aggregation also fusion of drug molecule and leaking of entrapped drug within formulation, hydrolysis of encapsulated drugs which limits the shelf life of the dispersion. Niosomal aqueous suspensions owe limited shelf life due to fusion. We can see aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs. The techniques involved in the niosomal formulation such as extrusion, sonication are time consuming and requires specialized equipment for processing. There are many transdermal delivery technologies on the market right now. However, the transdermal market is still only available for a few medications. The capacity which overcomes the problems related to penetration and skin irritation of the drug molecules will determine whether transdermal delivery technology [5].

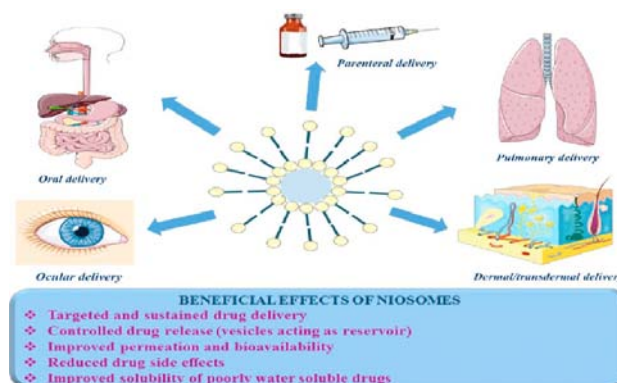


Fig. 1: Beneficial effect of niosomes on different organ system [6]

Typical transdermal formulations, such as ointments, creams, and lotions, have more drawbacks, including their pasty texture, poor spreadability, stability problems, etc., which eventually cause patient noncompliance. The topical medication delivery is made possible by targeting the skin directly. Both beauty products and pharmaceutical preparations now use semi-solid translucent gels. One of the many difficult areas for formulation scientists to work in is developing dosage forms for topical medication administration. Comparing the stratum corneum to the other epithelial barriers of the gastrointestinal, rectal, nasal, buccal and vaginal pathways, the stratum corneum is the supreme terrifying barrier because of its peculiar composition (proteins: lipids: water = 40:40:20%, respectively) and tight intercellular connections. Drugs are applied topically either for local or systemic effects, depending on their intended use [7].

### Niosomes

Targeted medicine delivery aims to concentrate a drug in the mark tissues while reducing the relative concentration. Medicine is thereby contained to the appropriate site. Because of this, the medicine has no impact on the primary tissues. There are several theories put out to explain how niosomes can encourage medication transfer through the skin [8]. This review points to supply a thorough collection of later studies for this intriguing field, with uncommon emphasis on methods utilized to maximise the potential of niosomes. Niosomal carriers are reasonable for the transdermal conveyance of a variety of pharmacological specialists, counting antioxidant, anti-inflammatory, anticancer, antimicrobial, and antibacterial molecules. Due to their distinct benefits, niosomes, vesicular nanocarriers, have gained much attention as probable drug delivery systems over the past 30 y. They have amphiphilic

molecule-based lamellar (bilayer) structures encased in an aqueous compartment. Surfactants are amphiphilic molecules with hydrophobic (tails) and hydrophilic (heads) groups that have the ability to self-assemble into a diversity of geometries [9]. Administration via the transdermal route increased the drug's ability to enter the skin when it was embedded in niosome. Terbinafine hydrochloride was thin-film hydrated using polysorbate 20, 40, 60, and 80 non-ionic surfactants and cholesterol to produce terbinafine hydrochloride niosomes with continuous drug concentration. *Aspergillus niger* strain was used to test the formulations' antifungal activity *in vitro*, along with the results were concomitant to a pure drug solution as standard [10]. Due to the medication's-controlled release, both formulations demonstrated a consistent inhibition zone expansion. Comparing gels having drug entrapped in pure drug and commercial formulations, whole gels have the maximum zone of inhibition (12 mm) at initially, subsequently sustained release (12–16 mm). While transdermal patches are equally effective as oral dose forms, they also have a few advantages over them. Transdermal delivery has a first-pass metabolic effect in comparison to the oral method. As a result, transdermal administration increases bioavailability. Second, transdermal administration allows a prolonged drug release, which may make it simpler for patients to take their drugs consistently. Finally, when medications are applied via transdermal route, their peak concentrations are decreased [11].

### Niosome structure

A niosomal vesicle typically consists of a vesicle-forming amphiphile, such as a non-ionic surfactant, cholesterol, and a little quantity of an anionic surfactant, such as diacetyl phosphate, which is also provided for vesicle stabilisation [12].

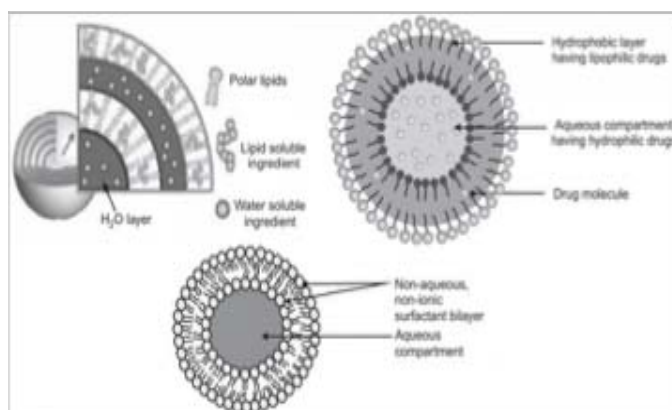


Fig. 2: Structure of Niosome [12]

The transdermal drug delivery system advantages, like avoids pre-systemic metabolism and the hazards and inconveniences during intravenous therapy, were avoided also the absorption conditions, such as pH variations, the existence of enzymes, and the rate at which the stomach empties. The capability of more targeted medicine delivery to a particular place. The disadvantages of transdermal drug delivery are some medications have low skin permeability and the irritation could result from touch with dermatitis [13].

### Types of niosomes

Types of niosomes are classified according to three factors: first, basis of function of niosomes size; second, the method of preparation; and third, based on the vesicle size. So, niosomes can be separated to three clusters including small unilamellar vesicles (SUVs, size = 0.025–0.05  $\mu\text{m}$ ), multilamellar vesicles (MLVs, size  $\geq 0.05 \mu\text{m}$ ), and large unilamellar vesicles (LUVs, size  $\geq 10 \mu\text{m}$ ), which are described in the following subsections (fig. 3).

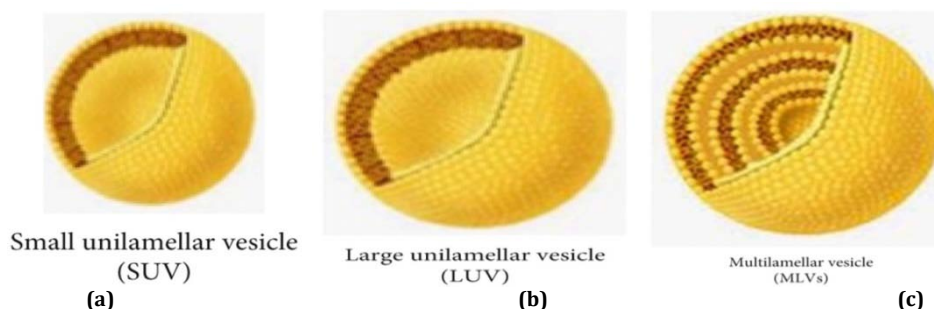


Fig. 3: Schematic typical vesicle size of niosomes [14]

### Multilamellar vesicles (MLVs)

As shown in fig. 3, MLVs are formed from some bilayers adjacent to the aqueous lipid section individually. The estimated dimensions of these vesicles stay between 100 and 1000 nm in diameter. Multilamellar vesicles, because of simple preparation, are reflexively stable upon keeping for extend phases, and appropriate for lipophilic agents, are widely used [15].

### Large unilamellar vesicles (LUVs)

The approximate sizes of these vesicles are 100–250 nm in diameter. LUV has a high aqueous part to lipid section proportion, so that the bioactive resources can be captured by membrane lipids [16].

### Small unilamellar vesicles (SUVs)

The approximate sizes of small unilamellar vesicles are 10-100 nm. Small unilamellar vesicles are consisted of several procedures,

such as sonication, high-pressure homogenization, and extrusion methods [17].

### Surfactant containing niosomes

In these kinds of niosomes, bola-surfactant compounds require two hydrophilic heads, which can link by one or two long lipophilic spacers. The surfactant use in bola-surfactant containing niosomes is prepared of omega hexadecyl-bis-(1-aza-18 crown-6) (bola surfactant): span-80/cholesterol in 2:3:1 molar percentage [18].

### Proniosomes

As shown in fig. 4, proniosomes are the niosomes formation that consists of water-soluble carriers and surfactants. The proniosomes are dehydrated niosomes constructions, which would be hydrated for earlier usage. Proniosomes can decrease niosomes problems, for example, aggregation, fusion, and leakage of medication in after a while [19].

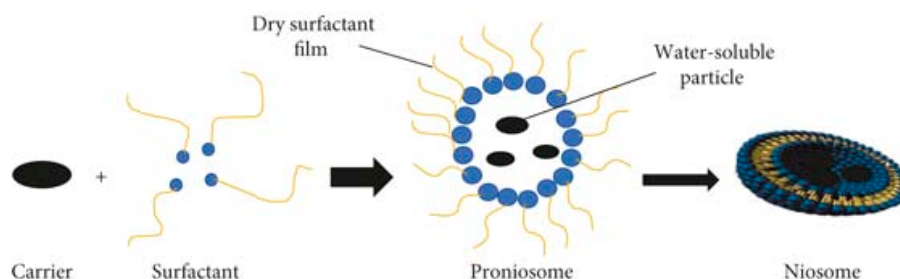


Fig. 4: Schematic proniosome and niosomes formation process [20]

### Apsasome

Apsasome includes cholesterol, ascorbyl palmitate, and highly charged lipid such as dihexadecyl phosphate (DCP). It is hydrated by water solvent and sonicated to produce the final product. Apsasome can improve the transdermal drug-delivery systems and decrease the disorders which triggered using reactive oxygen species [21].

### Discome

Large disk-shaped structures or discomes have low cholesterol concentration. It was reported that niosomes were prepared from incubating in cholesteryl poly-24-oxyethylene ether (Solulan C24) at 75 °C for 1 h to obtain spherical niosomes. This has caused in the construction of large size, approximately 11–60  $\mu\text{m}$  and multilayered vesicular structures. Discomes act as potential drug delivery carriers as sustained release system at the ocular site [22].

### Elastic niosomes

This type of niosomes could be supple, lacking destroying construction, so they have the ability to permit from side-to-side pores in smaller their size. These vesicles have nonionic surfactants, water, and ethanol. This flexible structure can be used to increase the penetration intact skin layers [23].

### Polyhedral niosomes

This type of niosomes are created by hexadecyl diglycerol ether ( $\text{C}_{16}\text{G}_2$ ), replacing with any of the nonionic surfactants and polyoxyethylene 24 cholesteryl ether ( $\text{C}_{24}$ ), without cholesterol. These vesicles have unconventional structures which can entrap water-soluble particles. Accumulation of an equimolar volume of cholesterol to the definite surfactant upsurges the curving of the membranes. These conditions result in the formation of spherical vesicles and tubules [24].

### Vesicles in water and oil system (V/W/O)

Vesicles in water and oil system contain niosomes in water in oil (as external phase) emulsion (v/w/o). This phenomenon is formed by the suspension of niosomes figured from a blend of sorbitol monostearate, cholesterol, and solulan C24 (poly-24-oxyethylene

cholesteryl ether) to oil phase at 60 °C. This results in the formation of vesicle in water in oil (v/w/o) emulsion using cooling to room temperature forming vesicle in water in oil gel (v/w/o gel). This type of niosomes were hired for protein drug delivery and protection from enzymatic degradation after oral administration and controlled release [25].

### Niosomes in carbopol gel

In this system, niosomes were prepared from the drug, nonionic surfactant, and cholesterol; then, it is combined in carbopol-934 gel (%1 w/w) base comprising propylene glycol (%10 w/w) and glycerol (%30 w/w) [26].

### Preparation methods of niosomes

The general method of niosomes preparation is by hydration of nonionic surfactants using a hydration medium. However, they are prepared by several techniques, such as, transmembrane pH gradient method, lipid layer hydration, reversed-phase evaporation, EER injection, bubbling of nitrogen, sonication, the enzymatic method, the single-pass technique, and microfluidization which are defined here in depth [27].

### Transmembrane pH gradient method

Surfactant and cholesterol are ready in chloroform and evaporated under reduced pressure and stream of  $\text{N}_2$  to yield a tinny lipid film on the wall of a round-bottomed bottle. The obtained lipid film is hydrated with an acidic compound (usually citric acid). The resulting preparation (multilamellar vesicles) is exposed to freeze-thaw cycles. The pH of the sample is then elevated to 7.2 (fig. 5). Bhaskaran and Lakshmi reported that niosomes can be made by this process (entrapment efficiency (EE) = 87.5%) [28].

### Lipid layer hydration

As shown in fig. 5, surfactant and cholesterol are dissolved in chloroform and evaporated under reduced pressure to produce a thin lipid film on the wall of a round-bottomed flask. The obtained film was hydrated with an aqueous solution of drug at a temperature slightly above the phase transition temperature of the surfactants under moderate shaking conditions. Several variables were

validated that comprise the mass per batch, angle of evaporation, rotation speed of the vacuum rotary evaporator, and the hydration procedure. The latter variable was developed by various solvents (water, phosphate buffer (PB), and PB/drug) and hydration

temperature below and above the gel transition temperature. Sathali and Rajalakshmi prepared terbinafine niosomes by thin film hydration and settled this procedure, which, upon sonication, produced small unilamellar niosomes (EE = 85%) [30].

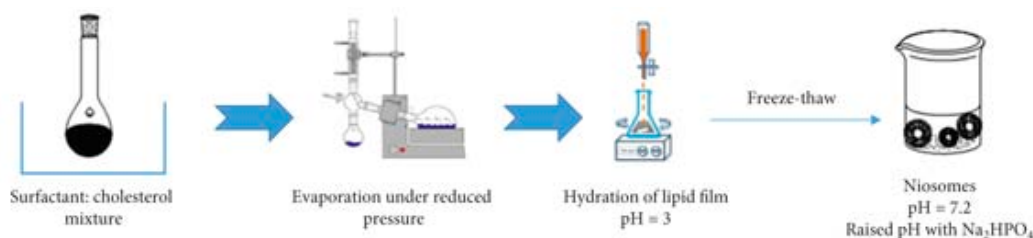


Fig. 5: Schematic nonionic surfactant vesicles (niosomes) formation by transdermal pH gradient method [29]

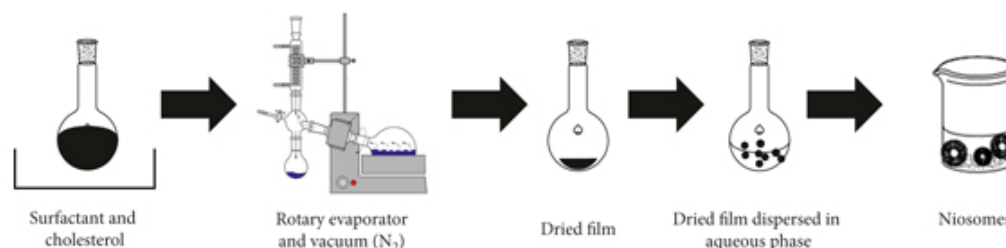


Fig. 6: Schematic nonionic surfactant vesicles (niosomes) formation by lipid layer hydration method [31]

#### Reversed-phase evaporation

The surfactants are dissolved in a mixture of ether and chloroform and added into water phase, having the medication emulsified to get w/o emulsion. The resulting mixture is homogenized, and then organic phase is evaporated. The lipid or surfactant forms a gel first and then hydrates to form spherical stable uniform vesicles [32].

#### Ether injection

The mix of surfactant, cholesterol and drug is dissolved in diethyl ether and, over a gauze needle, injected gradually into an aqueous phase. The ether solution is evaporated by a rotary evaporator above the boiling point of the organic solvent. The large unilamellar vesicles, after evaporation of the organic solvent, are

additionally exposed to decrease the size to give single-layered vesicles [33].

#### Bubbling of nitrogen

This method is a new procedure for the one-step establishment of niosomes lacking the usage of any organic solvents. Using this buffer, cholesterol and surfactant are spread together (pH 7.4) at 70 °C conditions. It presumed by a round-bottomed flask with three necks. The first two necks are placed in water-cooled reflux to control the temperature. Due to the sample (cholesterol and surfactant) of homogenized nitrogen gas was passed from the third neck. Thereby, large unilamellar vesicles were produced. A continuous stream of nitrogen gas bubbles is made and introduced through the dispersion and to give small unilamellar vesicles (fig. 7) [34].

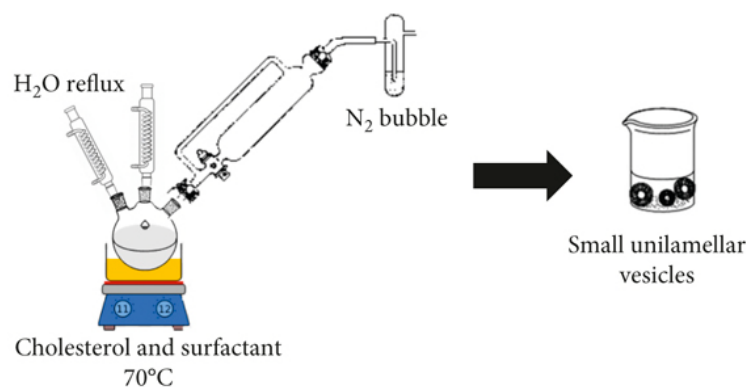


Fig. 7: Schematic small unilamellar vesicles (niosomes) formation by bubbling of nitrogen method [35, 36]

#### The single-pass method

It is a patented method including an incessant procedure which contains the extrusion of a solution or suspension of lipids that concluded a porous device and subsequently through a nozzle. It associates homogenization and high-pressure extrusion to provide niosomes with a narrow size supply in the range 50–500 nm [37].

#### Applications

##### Delivery of ophthalmic drugs

Drug release from niosomes designed for ocular use is prolonged. An *in vitro* comparison of gentamicin Niosomes and gentamicin solution revealed that those consisting of Tween 60, cholesterol, and DCP

were the most effective gentamicin Niosomes for prolonged drug release from the ocular delivery system [37].

### Drug transdermal delivery

When made into Niosomes, medications like lidocaine and oestrogen derivatives like estradiol, cyclosporine, etc. are employed for topical application and transdermal drug delivery systems [38].

### Delivery of antiviral medication

Numerous antiviral medications are delivered by niosomes. Zidovudine-containing niosomes were made by Ruckmani and Sankar, who also assessed the effectiveness of drug entrapment and the durability of drug release. Cholesterol, Tween 80, and Span 60 made up the niosomes.

Zidovudine was more effectively trapped inside niosomes made with Tween 80. Dicetyl phosphate was added to niosomes, which improved the drug release over time [39].

### Delivery of cancer drugs

The current method of treating cancer is chemotherapy. The therapeutic effectiveness of many anti-cancer medications is constrained by poor tissue penetration and adverse effects on other healthy cells. One of the many strategies used to get over these restrictions is the use of niosomes as a unique medication delivery mechanism [40].

### Future perspectives

Small molecules like proteins and vaccines are now recognized as a serious class of therapeutic agents thanks to recent developments in the research project. One of the many examples of significant progress in drug delivery technology is the niosomal drug delivery system. They can be created using a variety of methods, which alter the process and, consequently the medication's features, including the amount of cholesterol and the types, structures, and surfactant concentrations. The drug's metabolism, tissue distribution, plasma clearance kinetics, and cellular contact are all changed by non-ionic surfactant vesicles. Researchers and academicians generally agree with the idea of putting the drug into or niosomes for a much better targeting of the drug to the appropriate tissue destination.

### CONCLUSION

The systems for transdermal medicine distribution have been employed as reliable means of delivering medications. The scientists with high rates of accomplishment are utilizing their potential in a controlled release on a worldwide scale. Many fresh studies are being conducted today to incorporate newer medications via the system due to the TDDS's many benefits. For the regulated percutaneous administration of both hydrophilic as well as lipophilic medicines, niosomes have been shown to be promising. Niosomes potential can be increased by employing fresh formulation, drug loading, along with modification techniques. To create niosomal formulations that can be sold commercially, these areas require additional investigation and study. The simple elements of a niosomal transdermal patch, such as drug reservoirs, liners, adherents, permeation enhancers, plasticizers, backing laminates and solvents, are crucial to the drug's release through the skin. Niosomes are used to modify the drug release profile, drug absorption, distribution and elimination for the benefit of improving product efficacy and safety and improving patient convenience and compliance. They are very small and microscopic. Although they are structurally similar to liposomes, they offer several advantages over them. Niosomes are stable, less toxic and less expensive than liposomes.

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Nil

### AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

### CONFLICT OF INTERESTS

Declare that there is no conflict of interest regarding the publications of this paper.

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