



Niosomes: A Promising Drug Delivery System in Transdermal Drug Delivery (TDDS)

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Infectious disease treatment and immunisation have undergone a transformative change in recent years. With the advancement of biotechnology and genetic engineering, a large number of disease-specific biological have been created, as well as a focus on delivering these biological effectively. Niosomes are vesicular Nano carriers that are gaining popularity as a potential transdermal drug delivery system due to properties like enhanced drug penetration, a local depot for sustained drug release, and a rate-limiting membrane for modulating systemic absorption of drugs through the skin. Niosomes are non-ionic surfactant-based vesicles that are biodegradable, relatively nontoxic, more stable, and less expensive than liposomes. This analysis gives a high-level overview of niosomes, including their chemical composition, structure, benefits, and applications, as well as some general observations on niosomes as percutaneous permeation enhancers.

Keywords: Niosomes; drug delivery system; transdermal drug delivery.

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1. INTRODUCTION

Targeted drug delivery is a concept that aims to concentrate a drug in the tissues of interest while lowering the relative concentration. As a result, the drug is localised at the desired location. As a result, the medication has no effect on the underlying tissues. Synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes have all been targeted using various carriers [1]. Niosomes are vesicular Nano carriers that have gotten a lot of attention because of their unique properties. They have amphiphilic molecules in a lamellar (bilayer) structure surrounded by an aqueous compartment. Contain both hydrophobic (tails) and hydrophilic (heads) classes and are self-assembling, aggregating into a variety of shapes like micelles or into a planar lamellar bilayer [2].

In the bilayer structure are oriented away from the aqueous solvent, while the hydrophilic heads remain in contact with it. The composition of the vesicles, size, lamellarity, tapped volume, surface charge, and concentration can all be modified. Various forces act within the molecules, including repulsive forces arising from electrostatic interactions between charged groups of surfactant molecules, entropic repulsive forces, and so on. The vesicular structure of niosomes is held in place by these powers. However, the form of surfactant, temperature, detergents, membrane spanning lipids, in situ interfacial polymerisation of surfactant monomers, and the presence of a charged molecule all influence the stability of niosomes. Drug molecules with a wide range of solubility can be accommodated by lipophilic moieties in the structure [3].

Many pharmacological agents may benefit from niosomal drug delivery for their action against various diseases. It can also be used to distribute medications. It improves bioavailability by crossing the gastrointestinal tract's anatomical barrier through transcytosis of Peyer's 1 M cells of a payer's patches in the intestinal lymphatic tissues [4].

1.1 Niosome Structure and Components

Because of their peculiar structure as vesicular systems, niosomes can encapsulate both hydrophilic and lipophilic substances. Lipophilic substances are entrapped by partitioning into the lipophilic domain of the bilayers, whereas hydrophilic substances are adsorbed on the bilayer surfaces (Fig. 1).

1.2 Non-ionic Surfactants

Non-ionic surfactants are a form of surfactant with no charged groups in their hydrophilic heads. As compared to anionic, amphoteric, or cationic equivalents, they are more stable, biocompatible, and less toxic [5]. As a result, they are favoured for the in vitro and in vivo development of stable niosomes. Non-ionic surfactants are amphiphilic molecules with two distinct regions: one is hydrophilic (water-soluble) and the other is hydrophobic (water-insoluble) (organic-soluble). The major non-ionic surfactant groups used in niosome processing are alkyl ethers, alkyl esters, alkyl amides, and fatty acids. In the selection of surfactant molecules for niosome preparation, the hydrophilic-lipophilic balance (HLB) and essential packing parameter (CPP) values are crucial. HLB (Hydrophilic-Lipophilic Balance) is a term used to describe the balance between hydrophilic and lipophilic substances.

1.3 Hydrophilic-Lipophilic Balance (HLB)

The solubility of the surfactant molecule is indicated by HLB, a dimensionless parameter. The HLB value defines the balance between the non-ionic surfactant's hydrophilic and lipophilic portions. For non-ionic surfactants, the HLB range is 0 to 20. The lower the HLB, the more lipophilic the surfactant, and the higher the HLB, the more hydrophilic. Surfactants with an HLB of 4 to 8 can be used in vesicle preparation [6]. Owing to their high aqueous solubility, hydrophilic surfactants with an HLB value of 14 to 17 are not ideal for forming a bilayer membrane [7]. Polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7) do, however, form niosomes when an optimal amount of cholesterol is added [8,9].

1.4 Charged Molecule

Certain charged molecules are attached to niosomes to improve their stability and prevent coalescence by electrostatic repulsion. Diacetyl phosphate (DCP) and Phosphotidic acid are the negatively charged molecules used. Similarly, positively charged molecules such as stearyl amine (STR) and stearyl pyridinium chloride are commonly used in niosomal preparations. Since higher concentrations can obstruct niosomal formation, a concentration of 2.5-5 mole percentage of charged molecules is tolerable [10].

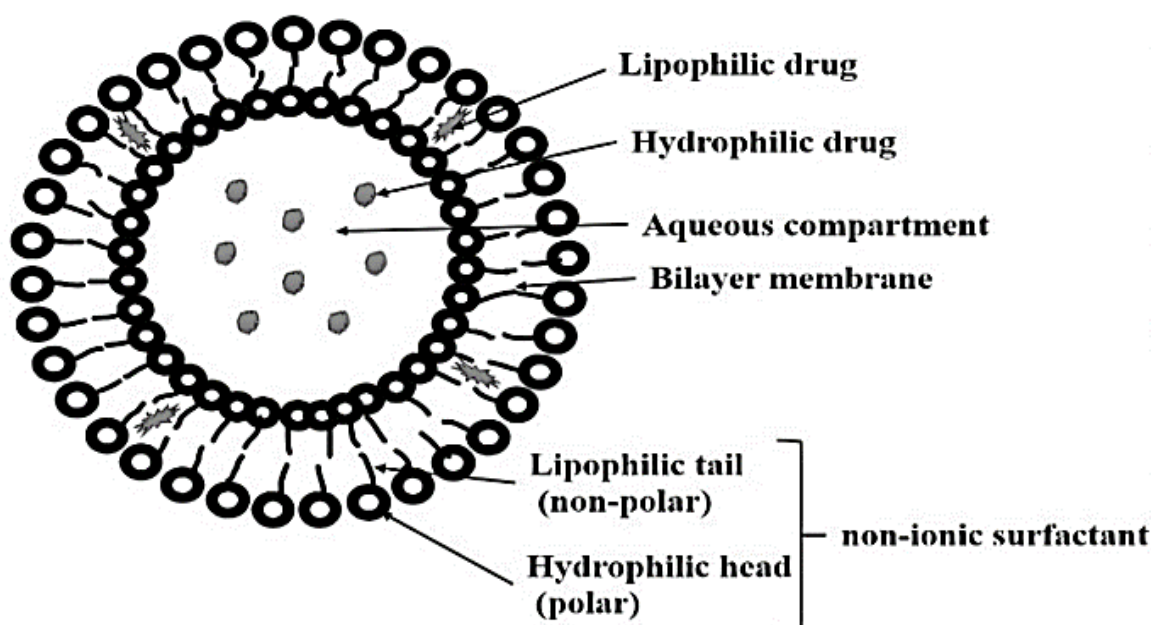


Fig. 1. Structure of niosome [5]

1.5 Cholesterol

Cholesterol forms hydrogen bonds with the hydrophilic head of a surfactant in the bilayer structure of niosomes [11]. The amount of cholesterol in niosomes affects their structure as well as physical properties including entrapment performance, long-term stability, payload release, and biostability [12]. Cholesterol increases vesicle rigidity and stabilises niosomes against destabilising effects caused by plasma and serum materials, as well as lowering vesicle permeability for entrapped molecules, preventing leakage [13].

2. TYPES OF NIOSOME

Niosomes are classified into three classes based on their vesicle size.

2.1 Small Unilamellar Vesicles

Small unilamellar vesicles are most generated by sonication and French Press systems. SUVs can be prepared using ultrasonic electro capillary emulsification or a solvent dilution technique. These vesicles have an approximate size of 0.025-0.05 μ m.

2.2 Multilamellar Vesicles

This type of vesicle is made up of many bilayers that surround the aqueous lipid compartment

separately, displaying increased trapped volume and equilibrium solute distribution and requiring the hand-shaking process. They denote different lipid compositions. These vesicles have an approximate diameter of 0.5-10 μ m.

2.3 Large Unilamellar Vesicles

Lipids solubilized in an organic solvent can be infused into an aqueous buffer to cause spontaneous LUV growth. The best way to prepare LUV is to use reverse phase evaporation or the detergent solubilisation process. These rough vesicles can grow to be more than 0.10 μ m in diameter [14].

3. NIOSOME ADVANTAGES AND DISADVANTAGES

3.1 Niosome Advantages

1. Cosmetics contain niosomes.
2. They have a stable osmotic activity.
3. They improve the entrapped drug's stability.
4. Surfactants do not need any special handling or storage conditions.
5. They can improve drug bioavailability in the mouth.
6. Niosomes improve drug penetration through the skin.
7. They may be used for oral, parenteral, and topical administration.

8. The surfactants are non-immunogenic, biodegradable, and biocompatible.
9. Improve the drug's therapeutic performance by shielding it from the biological environment and limiting its effects to target cells, lowering the drug's clearance.
10. In an aqueous phase, niosomal dispersions may be emulsified in a non-aqueous phase to monitor the drug's release rate and administer normal vesicles in an external non-aqueous phase [15-18].

3.2 Niosome Disadvantages

1. In rare situations, a non-ionic surfactant interacts with other device elements, resulting in a homogeneous formulation or the absence of precipitates.
2. Preparation methods take a long time.
3. Can necessitate the use of specialised equipment.
4. Expensive to produce.
5. Inadequate drug loading.
6. Instability in terms of both physical and chemical properties.
7. Drug spillage.
8. Drug entrapment in aqueous suspension of niosomes can result in fusion, aggregation, leaching, or hydrolysis, reducing the shelf life of niosome dispersion [19].

4. NIOSOMES PREPARATION METHODS

Niosome preparation starts with the hydration of a surfactant and lipid mixture at high

temperatures, accompanied by optional niosome size reduction to produce a colloidal suspension [20]. The dissolution of surfactant in diethyl ether is the first step in ether injection niosome formation. After that, the solution is injected into a 60°C aqueous drug solution using a 14-gauge needle. As a result of the vaporisation of ether, single-layer vesicles with diameters ranging from 50 to 1000 nm are formed [21]. A small amount of residual ether, on the other hand, is commonly found in the niosomal suspension [22].

4.1 Hand-Shaking Method

Surfactant and cholesterol are dissolved in a volatile organic solvent and transferred to a rotary evaporator in the hand-shaking process, also known as thin-film hydration technique. A thin layer of solid mixture is accumulated on the flask wall during evaporation. After that, an aqueous phase containing the drug of interest is used to hydrate the dried layer. At room temperature, with gentle agitation, this process can be carried out [23].

4.2 Bubble Method

Niosomes can also be made by sonicating a surfactant, cholesterol, and aqueous phase containing the drug for 3 minutes at 60°C. This method produces vesicles that are usually small and uniform in size. Micro fluidization is another method for achieving size Uniformity that is repeatable. In terms of operation, two fluidized streams pass forward through a specifically specified micro-channel, and these two streams interact at a high rate [24].

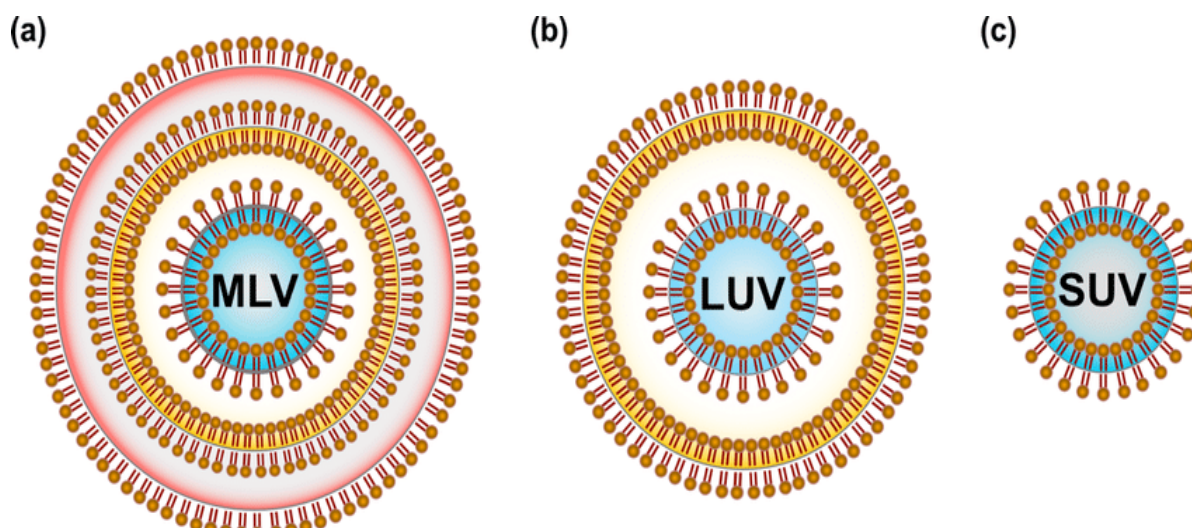


Fig. 2. Types of niosomes [14]

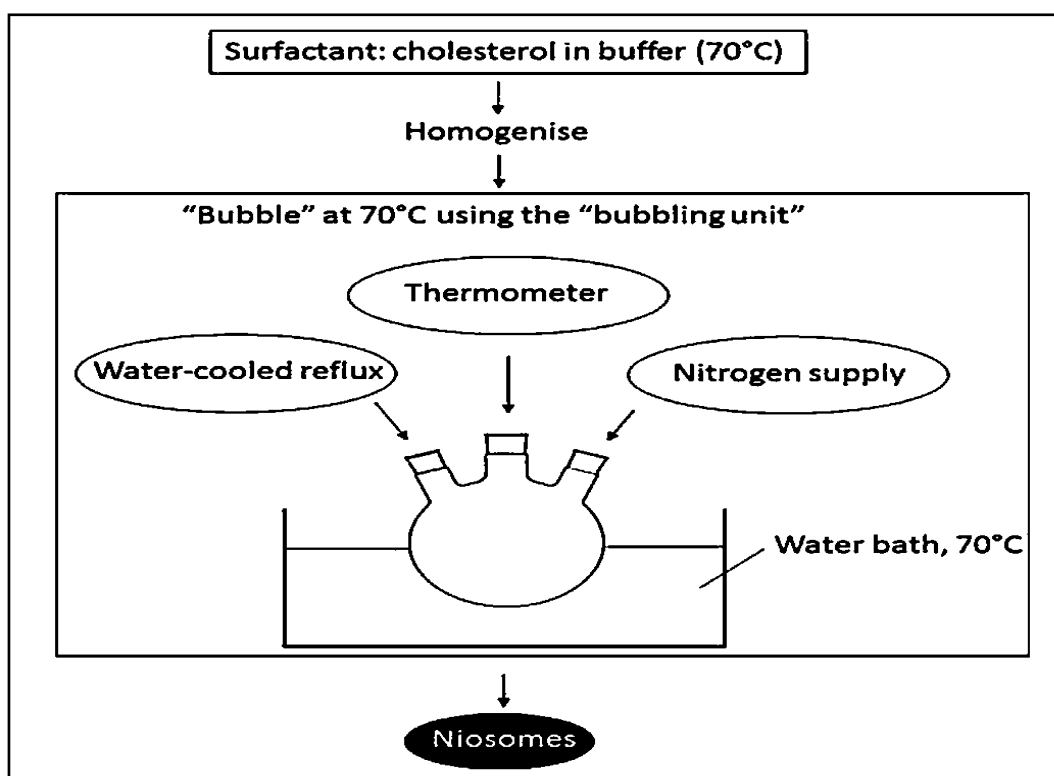


Fig. 3. Schematic diagram of preparation of niosomes using the "bubble" method [24]

4.3 The Reverse-Phase Evaporation Technique

It uses a mixture containing surfactant and cholesterol in a 1:1 ratio, in addition 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 continued after adding a small 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 final product of niosomes is obtained [25].

5. THE ROLE OF NIOSOMES IN TRANSDERMAL DRUG DELIVERY

Niosomes can be used to transdermally distribute both hydrophobic and hydrophilic drugs. While niosomes have been tried for a variety of routes, they are most commonly used for the transdermal route (Novasome Products Such as 30 percent Petrolatum Novasomes and 10 percent Salicylic Acid Novasomes). Studies have shown that encapsulating drugs in niosomes improves drug delivery. Niosomes help drugs penetrate the skin and may serve as a

local depot for the long-term release of dermally active compounds. When non-ionic surfactants are mixed into niosomes, the skin tolerates them much better than when they are used in an emulsion. Various bio-active agents, such as Cyclosporin – A, Lidocaine, Estradiol, Erythromycin, and Alpha – interferon, Diclofenac sodium, Nimesulide, Enoxacin, Miconazole nitrate, Ketoconazole, Tretionin, Metronidazole, have been tried via transdermal route as niosomal drug delivery method [26] (Table 1).

6. TRANSDERMAL DRUG TARGETING WITH NIOSOMAL FORMULATIONS

Niosomal formulations are said to have significant advantages over traditional topical formulations, including increased solubility, bioavailability, toxicity resistance, pharmacological activity enhancement, and stability enhancement. Transdermal drug delivery from niosomes has been studied in many disease models in recent years, with existing efforts focusing on protocol optimization, novel compositions, and final Transdermal drug delivery from niosomes has been studied in many disease models in recent years, with existing efforts focusing on protocol optimization, novel compositions, and final formulations.

6.1 Elastic Vesicle Gel

New highly flexible niosomes known as elastic vesicles, for example, have been proposed and confirmed to be effective at transporting molecules through the skin, since edge activators (such as ethanol) give vesicles elastic properties, allowing them to reach deeper layers of the skin more easily [50].

6.2 Niosomal Electrophoresis

The liquid nature of niosomes is a major drawback, as they can leak from the application site when applied. This problem can be solved by incorporating niosomes into an appropriate vehicle, which can be accomplished by applying

gelling agents to niosomal dispersions, resulting in a niosomal gel [51]. Niosomal gels have been found to improve therapeutic retention by the skin and provide high and sustained drug concentrations in the skin [52]. Proniosomal or "dry niosomes," which have been proposed as niosomal formulations, reflect a further development of niosomes; these must be hydrated before use, and hydration results in the formation of an aqueous niosomal dispersion. Since they become hydrated with water from the skin under occlusion, proniosomes reduce the accumulation, leakage, and fusion problems associated with conventional niosomes and provide a flexible transdermal drug delivery method [53].

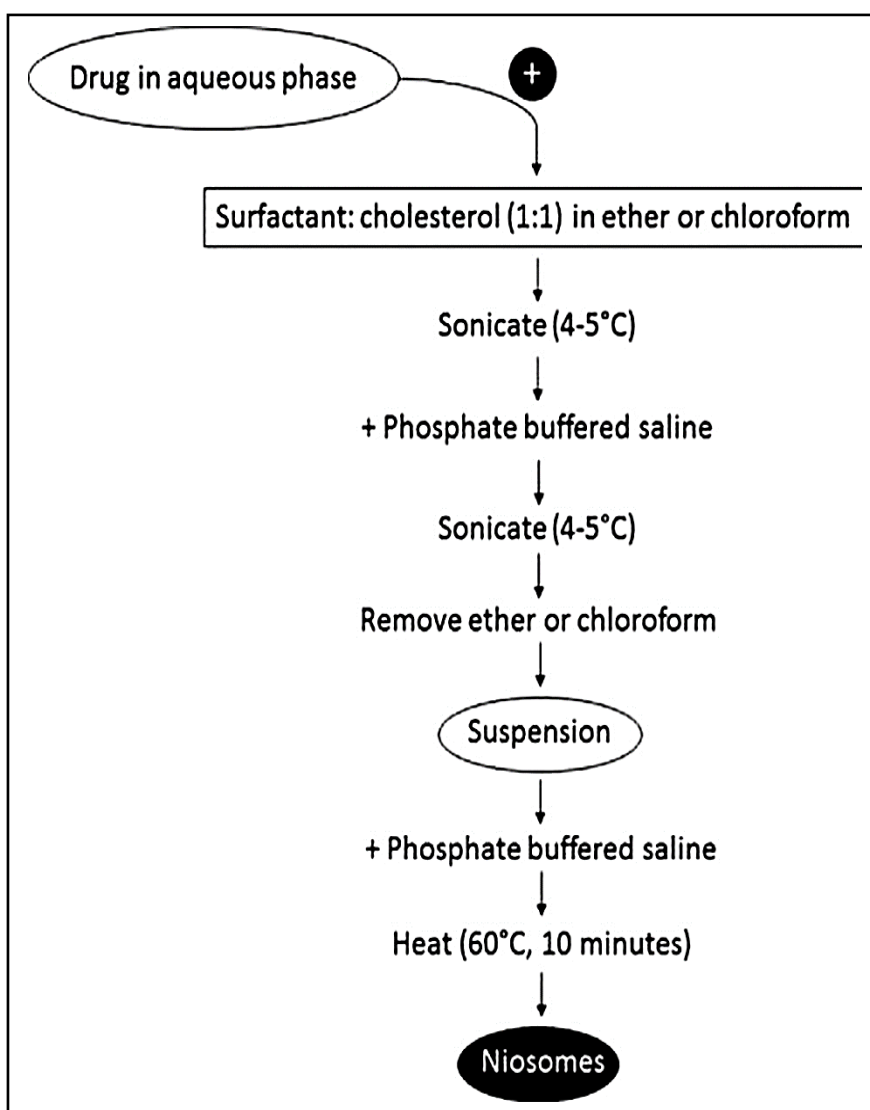


Fig. 4. Schematic diagram of preparation of niosomes using the reverse-phase evaporation technique [25]

Table 1. Summary of recent niosomal formulations developed for drug transdermal delivery [26]

TDDS	Drug	References
Niosomes	Aceclofenac	[27]
	Diclofenac sodium	[28]
	Ketoprofen	[29]
	Baclofen	[30]
	Salidroside	[31]
	Capsaicin	[32]
	Resveratrol, alpha tocopherol, Curcumin	[33]
	Alpha-tocopherol	[34]
Niosomal gel	Aceclofenac	[35]
	Meloxicam	[36,37]
	Rofecoxib	[38]
	Simvastatin	[39]
	Sulfadiazine sodium, propranolol hydrochloride, tyrosol	[40]
	Lopinavir	[41]
Proniosomes	Vinpocetine	[38]
	Simvastatin	[42]
	Nisoldipine	[43]
	Nifedipine	[44]
Proniosomal gel	Tenoxicam	[45]
	Flurbiprofen	[46]
Elastic vesicle gel	Diclofenac diethylammonium	[47]
	Papain	[48]
Elastic vesicles	Sulfadiazine sodium	[49]

Abbreviation: TDDS, transdermal drug delivery systems.

6.3 Niosomal Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Different groups of researchers have produced niosomes containing Nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs can cause local mucosal irritation and, after oral administration, undergo first-pass metabolism in the liver, resulting in partial inactivation. As a result, about half of the medication enters the market. For long-term use of this medication, particularly when treating rheumatic symptoms, topical dosage forms are preferred. The ability of topical NSAIDs to penetrate the skin is critical to their efficacy [54].

6.3.1 Aceclofenac

Aceclofenac is a Nonsteroidal anti-inflammatory drug (NSAID). Aceclofenac is used for the treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis [55]. The rat paw edoema technique was used to test the anti-inflammatory activity of aceclofenac vesicles. By varying the cholesterol content, the type of surfactant used, and the type of charge, the researchers

were able to manipulate the entrapment efficiency and in vitro release of aceclofenac from the vesicles. After incorporation into a carbopol gel, aceclofenac niosomes were prepared using Span 60 and cholesterol at various molar ratios for topical use [56]. When compared to the simple gel formulation, data from Solanki et al. [56] showed that the gel increases drug penetration and therapeutic efficacy in all niosomal gel preparations.

6.3.2 Sodium diclofenac

Tavano et al. [57] investigated the impact of diclofenac sodium compartmentalization on the physicochemical properties of niosomal vesicles used as transdermal carriers in 2014. The findings revealed that all niosomes were spherical and uniform in shape. Their size was discovered to be based on the surfactant mixture's hydrophile-lipophile balance, i.e., an increase in hydrophobicity resulted in smaller vesicles. Drug integration resulted in a large difference in vesicle size, which was determined by whether the drug was in the aqueous or bilayer compartment.

6.3.3 Capsaicin

Topical application of capsaicin results in rapid absorption from the skin. Several capsaicin-based creams and patches are available over the counter and are widely used for pain relief. They typically contain the drug in amounts ranging from 0.025 percent to 1%. Capsaicin transmission via the skin has been suggested using niosomal carriers. To obtain systems with a specific hydrophile-lipophile balance (10, 12, and 14), vesicles were prepared using a given ratio of Span 80 and Tween 80 and characterised in terms of dimension, morphology, and drug entrapment performance [58].

6.4 Proniosome Gel

Ammar et al. [44], who engineered a promising proniosome gel formulation intended to minimise the daily dose of medication that needed to be administered in order to increase patient compliance, produced a new transdermal formulation of tenoxicam, characterised by enhanced safety and high therapeutic efficacy. Flurbiprofen was created as a Proniosomal transdermal gel with a high drug loading (55.4 percent, w/w) and cholesterol using a sequence of non-ionic surfactants (Span 20, Span 40, and Span 60) [59].

7. NIOSOMAL DRUG ADMINISTRATION ROUTES

Depending on the medication, surfactant, illness, and anatomical site involved, various routes of administration for niosomal drugs exist, including intravenous, intramuscular, dental, ocular, subcutaneous, pulmonary, and transdermal [60]. Niosomal drugs have been administered through a number of routes in addition to intraperitoneal and vaginal routes.

Table 2. Drugs used in niosomal delivery

Route of administration	Examples of drug
Nasal Rout	Sumatriptan
Transdermal Rout	Piroxicam, Nimesulide, Estradiol
Intravenous Rout	Doxorubicin, Insulin, Rifampicin
Ocular Rout	Cyclopentol

7.1 Oral Route Delivery

Oral drugs are not suitable for emergencies due to their slow absorption and the different layers of

barriers they must overcome. Due to the harsh conditions in the gastrointestinal tract, which may degrade/denature active antigens, oral vaccines are not commonly available, despite being the most appropriate administration method for small therapeutic molecules [61]. The lower GI tract includes the remainder of the small intestine (jejunum and ileum), as well as the divisions cecum, colon, and rectum [62,63]. Environmental factors that influence drug integrity and absorption include segment duration, pH, mucus thickness, residence drug, and bacterial diversity/population in different segments [64-66]. There are two types of oral administration issues: procedural challenges and technical challenges. Any biological factors that denature or prevent drugs from meeting their intended absorption target when taken orally are referred to as biological barriers. Technical difficulties, on the other hand, apply to any issues that arise during the development of the oral delivery system.

7.2 Transdermal Delivery

Niosomes have been proposed as a potential drug delivery method via transdermal delivery. Some of the major advantages provided by transdermal drugs include enhanced bioavailability, more uniform plasma levels, longer time of action resulting in a reduction in dosing frequency and decreased and improved therapy due to the retention of plasma levels up to the end of the dosing period compared to a drop in plasma levels with conventional types [67]. The penetration rate of a drug embedded in niosome was improved by transdermal delivery. Thin film hydration of Terbinafine hydrochloride with varying ratios of non-ionic surfactants (Tween 20, 40, 60, and 80) and cholesterol yielded Terbinafine hydrochloride niosomes with constant drug concentration. The antifungal activity of the preparations was tested in vitro using the *Aspergillus Niger* strain, and the findings were compared to a pure drug solution (as standard). Both formulations showed a steady increase in the zone of inhibition due to the regulated release of the medicament. Total gels have the highest zone of inhibition (12 mm) at first, followed by sustained release (12mm16mm) as compared to gels containing drug entrapped in pure drug and sold preparations [68]. While transdermal patches are successful in the same way that oral dosage forms are, they have a few advantages over oral dosage forms. In comparison to the oral route, transdermal administration has a first pass metabolic effect. Transdermal administration

improves bioavailability as a result. Second, transdermal administration allows for a longer release of certain medications, which can make it easier for patients to adhere to their medications. Finally, medication peak concentrations are reduced when drugs are administered transdermally [69,70].

8. CONCLUSION

Niosomes are a novel drug delivery system that outperforms all conventional and vesicular delivery systems. This comprehensive guide covers the chemical composition, structure, advantages, and applications of niosomes, as well as their use in percutaneous permeation and recent applications as drug delivery systems for transdermal drug targeting. Niosomes have been designed to treat a wide range of chronic diseases with less side effects and improved patient compliance. As a result, niosomes seem to be a therapeutic method with a wide range of applications.

9. FUTURE PROSPECTS

The ability of niosomes can be improved using innovative preparation, loading, and adjustment methods. In these areas, further research and development of commercially available niosomal preparations is needed. Researchers should be aware of the importance of using appropriate surfactants for the preparation of niosomes, as the type of surfactant used determines their toxicity, stability, and potential applications.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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