Int. J. Pharm. Investigation, 2024; 14(3):616-632.
https://www.jpionline.org

Review Article

Advancement and Characteristics of Non-Ionic Surfactant Vesicles (Niosome) and their Application for Analgesics

Prachi Pandey*, Rahul Pal, Vinay Kumar Rao Khadam, Himmat Singh Chawra, Ravindra Pal Singh

Department of Pharmaceutics, Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur, Rajasthan, INDIA.

ABSTRACT

Targeted drug delivery systems are employed to administer pharmaceutical medication, facilitating the precise delivery of drugs to specific diseased areas. Several drug delivery systems utilise carriers such as antibodies, transdermal patches, biodegradable polymers, Nanoparticles (NPs), liposomes, niosomes, and microspheres. Niosomes, on the other hand, represent a promising and innovative category of vesicular systems. Non-ionic surfactant vesicles commonly referred to as niosomes, have garnered significant attention within the pharmaceutical industry due to their remarkable capacity to versatility in encapsulation for both hydrophilic and hydrophobic drugs. Recent studies have demonstrated the potential of these vesicles to enhance the bioavailability of drugs, making them a promising strategy for delivering various therapeutic agents such as gene materials, protein therapeutics, and chemical pharmaceuticals. This approach offers minimal toxicity and desirable targeting effectiveness. Niosomes has non-immunogenic properties and can be designed as a controlled release drug that payload slowly and steadily, reducing the risk of side effects and improving therapeutic efficacy. Niosomes are substantially more stable during the preparation and storage procedure than liposomes. Liposomes are generally less stable than niosomes due to their susceptibility to enzymatic degradation and leakage of encapsulated materials. The desired pharmacokinetics property can be attained through the optimization of constituents or surface modifications. This novel method of distribution is also facile to establish and expand while maintaining cost-effective manufacturing expenses. This review article elucidates the fundamentals of niosomes as non-ionic surfactant vesicles, including their structure and components, as well as various formulation methods. Additionally, the article explores the diverse applications of niosomal in analgesics.

Keywords: Niosome, Analgesics, Non-ionic vesicles, Formulation, Characteristics, Thin film hydration, Nano-carriers.

Correspondence:
Ms. Prachi Pandey
Department of Pharmaceutics, Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur-303121, Rajasthan, INDIA.
Email: pandeyprachi167@gmail.com

Received: 06-02-2024;
Revised: 09-04-2024;
Accepted: 30-04-2024.

INTRODUCTION

Targeted Drug Delivery (TDD) is intended to establish the medication in certain tissues of interest, with a reduced concentration on other tissues. Therefore, the drug is targeted to its designated site. Therefore, the drug does not have any adverse effects on the surrounding tissues. Furthermore, the drug remains localized, preventing any loss, thereby ensuring maximum efficacy of the medication.[1] The various vehicles, such as synthetic polymers, immunoglobulin, serum proteins, liposomes, niosomes, microspheres, and erythrocytes, have been employed for targeted drug delivery. Amongst, Niosomes are considered to be the improved vehicle to enhance bioavailability and therapeutic efficiency by acting as a trusted approach for disease treatment and minimizing the side effects.[2,3]

In recent years, research efforts have concentrated on the development of alternative drug delivery systems, with the goal of overcoming the constraints of traditional dosage forms and ensuring enhanced bioavailability, fewer side effects, controlled drug release, and targeted administration. Niosomes demonstrate pharmacologically acceptable characteristics, including the potential for enhanced drug bioavailability, stability, sustained action, biodegradability, alteration of drug distribution and non-toxicity.[2-4] Niosomes are nano-sized layered structures ranging from 10 to 1000 nm in size. The central component of these structures is composed of substances that are both environmentally friendly and non-reactive towards the human immune system.

Polymersomes, liposomes, polymer-based vesicles, micelles, and niosomes are examples of nano-carriers that can be used to transport therapeutic drugs to disease-specific locations.[4] Nanocarriers have garnered significant attention from researchers due to their numerous advantages, including the capacity to prolong the serum half-life of medications, impede absorption by Reticulo-Endothelial Systems (RESs), and minimizing

OPEN ACCESS

EPUBL editing. publishing. technology

DOI: 10.5530/ijpi.14.3.74

Publishing Partner : EManuscript Tech. [www.emanuscript.in]

non-specific adsorption by optimizing their constituents or generating a multifunctional surface. It can safeguard the medicine during *in vivo* circulation and storage.[1-5] Nano vesicles are often utilised as vehicle for chemical pharmaceuticals, protein therapeutics, and gene therapies. Niosomes exhibit a higher degree of stability in comparison to lipids due to the inherent stability of their constituent elements, namely non-ionic surfactants, which possess superior chemical and physical stability characteristics.[5] Improved stability of the niosomes made formulation processing considerably easier. According to these advancements and the benefits of niosomes, this study introduces the structure, components, and formulation processes, as well as their prospective therapeutic uses.

The structure and composition of niosome

The Structure of the Niosome

The identification of the fundamental structural constituents of niosomes is of paramount importance as it has a significant impact on the selection of chemicals that can be employed in the formation of niosomes, as well as the packing mechanism of pharmaceuticals for delivery. Niosomes, akin to liposomes, are vesicles composed of non-ionic surfactants that exhibit a bilayer structure (Figure 1). Aqueous fluids have polar heads, while organic solutions have hydrophobic heads.[9] Bilayer vesicles are classified as unilamellar or multilamellar (Figure 2).[8-10] Multilamellar vesicles (Figure 2, 2.1, 2.2 and 2.3) are concentric rings formed by at least two bilayer vesicles or a big vesicle containing more than one tiny carrier. As a result of this, multilamellar vesicles often have greater particle sizes than unilamellar vesicles. Niosomes are typically sub-micron (colloidal) in size. Niosomes, which resemble liposomes, are stable colloidal particles prepared through the self-assembly of non-ionic surfactants and a hydrating mixture of cholesterol in an aqueous environment.

The Small Unilamellar Vesicles (SUVs) exhibited particle dimensions ranging from 10 to 100 nm, while the Large Unilamellar Vesicles (LUVs) displayed particle sizes within the range of 100 to 3000 nm. On the other hand, the Multi-Lamellar Vesicles (MLVs) possessed particle sizes exceeding 5 µm, with a limited number of "giant" vesicles measuring greater than 15 µm being documented.[11] The schematic representation of niosome vesicular on their sizes discussed in Table 1.

Small Lamellar Vesicles (SUVs)

Small Unilamellar Vesicles (SUVs) are vesicles that have a single membrane layer and a diameter of about 20 to 100 nanometers. They are typically formed by sonication or extrusion of a lipid solution. Niosomes are vesicles that are made from non-ionic surfactants instead of lipids.[9-11] SUVs niosomes are a type of niosome that has a small unilamellar structure.

Large Lamellar Vesicles (LUVs)

Large Unilamellar Vesicles (LUVs) are vesicles that have a single membrane layer and a diameter of about 100 to 1000 nanometers. They are typically formed by sonication or extrusion of a lipid solution. Niosomes are vesicles that are made from non-ionic surfactants instead of lipids.

LUV niosomes are a type of niosome that has a large unilamellar structure. LUV niosomes have several advantages over other types of niosomes. They are more stable and have a higher drug-loading capacity.[12] They are also less likely to aggregate and can be easily formulated into different dosage forms.

Multilamellar Vesicles (MLVs)

The structure comprises multiple bilayers that enclose the aqueous compartment individually. The vesicles exhibit diameters ranging from 0.05 to 10 µm. Among various types of niosomes, multilamellar vesicles have garnered significant attention in research. These vesicles are relatively easy to fabricate and possess remarkable mechanical stability; enabling prolonged storage durations.[10-12] These vesicles are greatly suitable for drug vehicle for hydrophobic compounds.

The composition of the Niosome

Niosome is composed of cholesterol or its imitative, non-ionic surfactants, and occasionally, ionic amphiphiles with the desired drug. Unlike liposomes, which are primarily composed of phospholipids, non-ionic surfactants serve as the primary

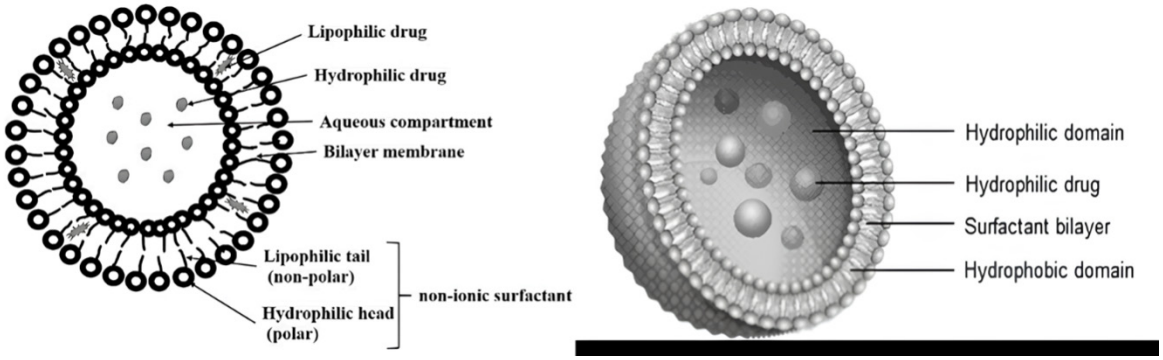

Figure 1: The schematic representation of niosome structure.

constituent of niosomes. Niosomes have the capability to encapsulate drugs that possess both hydrophilic and lipophilic properties. Hydrophilic medications are accommodated within the core of the niosomes, while lipophilic pharmaceuticals are confined within the lipophilic region of the bilayer. To achieve the utmost stability in the formulation, an optimal amount of cholesterol is incorporated into the niosomes, owing to its interaction with non-ionic surfactants.[13] Cholesterol can only produce the bilayer structure, but it may get mixed in the bilayer membrane, managing the shape and flexibility of the membrane as a reliable buffer.

Amphipathic non-ionic surfactants that are used for niosomes include polysorbates,[14] Spans,[15] alkyl oxyethylenes[16] (often from C12 to C18), and others. Additionally, cholesterol as membrane stabilizer. The utilization of the niosomal vehicle (consisting of Tween 60, Span 60, and cholesterol) has been found to substantially enhance the entrapment efficiency of drugs. This improvement can be attributed to the interaction occurring between the the acyl chains of Span 60 and drugs, as supported by previous studies.[13-15]

In addition, certain charged molecules, namely phosphatidic acid and dicetyl phosphate (DCP) (negatively charged molecules), cetylpyridinium chloride and stearylamine (SA) (positively charged molecules), are employed in niosomes are three particular objectives: drug encapsulation, efficacy augmentation, and ICH based strength improvement.[12-16]

Niosomes are a type of vesicular drug delivery system composed of non-ionic surfactants. Liposomes are structurally similar, made from amphiphilic non-ionic surfactants in place of phospholipids. Niosomes can encapsulate both hydrophilic and lipophilic pharmaceuticals, giving them an adaptable drug delivery system. There are mainly four components (Figure 3) used for the preparation of niosome:

Non-Ionic Surfactant

Surfactants are essential in the preparation of niosomes. Non-ionic surfactants such as Tweens (tween20,40,60,80), Spans

Table 1: **The niosome diameter of various sizes with their types.**

Sl. No.	Types of Niosome	Size diameter of Niosome
1.	Small Unilamellar Vesicles (SUVs)	Range=0.025-0.05 µm (25-50 nm)
2.	Multilamellar Vesicles (MLVs)	Range=less than 0.05 µm (50 nm)
3.	Large Unilamellar Vesicles (LUVs)	Range=less than 0.10 µm (100 nm).[11-13]

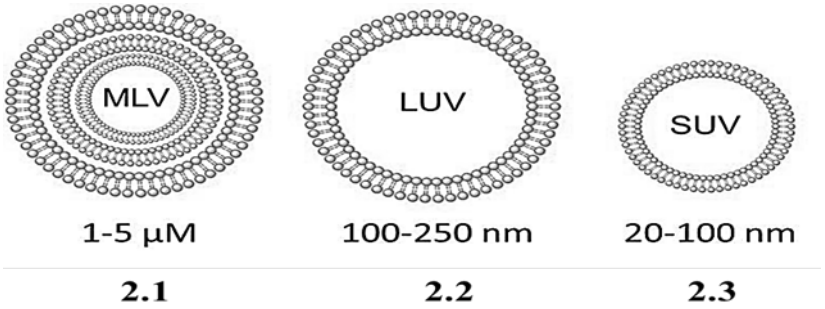

Figure 2: The schematic representation of niosome vesicular size: 2.1 the Multi-Lamellar Vesicles (MLVs), 2.2 the Large Unilamellar Vesicles (LUVs), 2.3 Small Unilamellar Vesicles (SUVs).

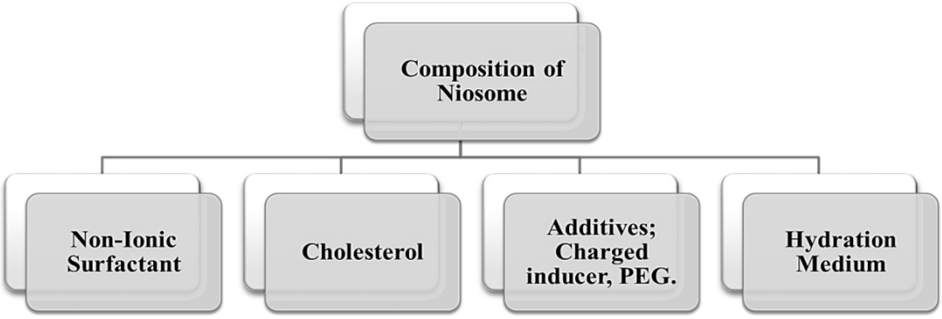

Figure 3: The structural composition of Niosome formulation.

Table 2: **The list of non-ionic surfactants according to their hydrophilic and lipophilic nature of drug medicament.**

Nature of Non-Ionic Surfactant	Types of Non-Ionic Surfactant	Drug Choice in niosome formulation
Lipophilic HLB (4-8)	Sorbitan Monolaurate. Sorbitan monopalmitate. Sorbitan stearate. Sorbitan trioleate.	Hydrophilic drugs, ex: ibuprofen,[18] naproxen,[19] ACE inhibitors,[20] and Anti-histamine.[21]
Hydrophilic HLB (8-14)	Polyoxyethylene (20) sorbitan Monolaurate. Polyoxyethylene (20) sorbitan monopalmitate. Polyoxyethylene (20) sorbitan stearate Polyoxyethylene (20) sorbitan monooleate.	Lipophilic drug, ex: acyclovir, paclitaxel, doxorubicin and piroxicam, meloxicam[22-26] etc.
Amphiphilic HLB (9.7-18)	Brij (polyoxyethylene (20) alkyl ether) 30,35,52,58,72,76. Lauryl (C12), cetyl (C16), Stearyl (C18), oleyl (C18:1), lauryl (C12), and cetyl (C16) respectively.	Both Hydrophilic and Lipophilic drugs ex: tetracycline and erythromycin and itraconazole[27-29] etc.

Table 3: **The list of charge inducers in niosome formulation.**

Charge Inducers in Niosome Formulation		
Positive (+ Ve)	Stearyl Amine (SA)	Stearyl Pyridinium Chloride.[40]
Negative (- Ve)	Dicetyl Phosphate (DCP)	Phosphotidic acid.[15,16]

(span60,40,20,60,85,80), and Brij (Brij 30,35,52,58,72,76) are usually utilised in the formation of niosomes. The hydrophilic head of the non-ionic surfactants is followed by a lipophilic tail. The selection of a non-ionic surfactant is illustrated by the Hydrophilic and Lipophilic Balance (HLB), critical packing of amphiphiles and Critical Micellar Concentration (CMC).[14-16] The non-ionic surfactant employed to produce niosomes has the potential to influence their size, stability, and drug-loading capability. Non-ionic surfactants with longer alkyl chains tend to form larger niosomes with higher drug loading capacity.[17]

Cholesterol

Cholesterol is one of the most critical components of niosome. In the bilayer structure, it creates a hydrogen bond with the surfactant's hydrophilic head. It can affect several crucial carriers with features including Entrapment Efficiency (%EE) as well as improve stability. It also improves bilayer surface stability by changing the gel liquid transition temperature. If surfactants, HLB >6 is required to form bilayer vesicles, and adding cholesterol improves stability at lower HLB values.[38] Its composition also influences loading capacity, which is a crucial aspect in niosomal formulation. It has also been demonstrated that in the case of more lipophilic surfactants, the inclusion of cholesterol aids in the inhibition of aggregation and the creation of vesicles.[13-15] To increase niosome stability and drug loading capability, cholesterol can be added. Cholesterol, on the other hand, can cause niosomes to grow in size.

Additives

Charge Inducers

The primary goal of adding charged groups to the bilayer surface is to enhance stability. Dicetyl phosphate is primarily utilised as a charged molecule that imparts negatively charged molecules on the bilayer surface. It is primarily used to promote vesicle stability and avoid aggregation by supplying charged groups over the bilayer surface. The Dicetyl phosphate is a charged chemical that adds a negative charge to the bilayer surface. Generally, in the range of 2.5-5 mol. percentage. Enhancing the quantity of charge molecule, however, inhibits niosome production.[14-16] The list of charge inducer depending on their charges as below followings in Table 3.

Cationic/Helper Lipids Elaboration of Niosomes

Niosomes are vesicular systems that are similar to liposomes in structure and function. They can be used to encapsulate a variety of drugs and other bioactive agents, including genes. Cationic/helper lipids are a type of lipid that can be used to enhance the gene delivery efficiency of niosomes. Cationic/helper lipids work by interacting with the negatively charged cell membrane and promoting the re-uptake of the niosomes into the cell.[14] There are a number of different cationic/helper lipids that can be used to elaborate niosomes as a gene delivery platform. Some of the most common cationic/helper lipids include:

- Dioctadecyldimethylammonium bromide (DOTMA).
- Dioleoylphosphatidylethanolamine-N-[3-(2-hydroxyethyl) proprionamide] (DOPE).
- Stearyltrimethylammonium bromide (STAB).

Table 4: The list of some common hydration media used in niosome formulation.

Hydration medium	Advantages	Disadvantages
Water	Simple to use and cost-effective.	Can lead to the formation of niosomes with a wide range of sizes.
Buffered Saline (PBS)	Maintains the pH of the niosomal dispersion, which can improve the stability of the niosome.	Can increase the cost of the formulation.
Phosphate buffer	Can be used to optimize the size and charge of the niosome.	Can increase the complexity of the formulation process.
Glycerol solution	Can be used to decrease the freezing point of the niosomal dispersion, which can improve the stability.	Can increase the viscosity of the niosomal dispersion, which can make it difficult to administer.[12-17]

Table 5: The common objective of the composition of Niosome formulation.

Niosome Components	Specified objectives
Surfactants	The vesicle membrane and control its properties, such as size, stability, and drug loading capacity.
Cholesterol	Stabilizes the vesicle membrane and prevents it from aggregating.
Charged Molecule	To prevent the aggregation of molecules of vesicles.
Drugs	The API that is encapsulated in the niosomes.
Hydration Medium	Use to hydrate the vesicle formulation.[7,13,14,17]

Cholesterol

Cationic/helper lipids can be incorporated into niosomes using a variety of methods, including the melt method, micelle solution method, and enzymatic method. The improved method to use will be based on the type of cationic/helper lipid being used and the desired properties of the niosomes.

Polyethylene Glycol (PEG)

Polyethylene Glycol (PEG) is a non-ionic polymer that can be used to modify the surface of niosome. PEGylation of niosomes has a number of advantages, including:

Increased circulation time in the bloodstream

PEGylation can reduce the uptake of niosomes by the Reticuloendothelial System (RES), i.e., is a network of organs and tissues that removes foreign particles from the bloodstream. This can increase the circulation time of niosomes in the bloodstream and allow them to reach their target tissues.

Reduced immunogenicity and Increased stability[13-15]

PEG can be incorporated into niosomes using a variety of methods, including the melt method, micelle solution method, and enzymatic method.

Hydration Medium

In the preparation of niosome, the hydration medium, also known as the aqueous phase, is a crucial component that plays a significant key role in the formation of niosomal vesicles (Table 4). The hydration medium typically consists of water or an aqueous buffer solution. The choice of hydration medium can influence the characteristics of the resulting niosomes, including size, stability, and drug encapsulation efficiency. For example, a more polar hydration medium will tend to form smaller niosomes with a higher drug-loading capacity.[15-17] The hydration temperature is the temperature at which the niosomes are formed. It is important to control the hydration temperature because it can influence the size, drug loading capacity and stability of the niosomes. The various commonly used hydration media for niosomes include:

Each compound in the formulation of niosome having lots of merits in the niosome from initial to the formation and till their stability having different function. The common purpose of the composition of niosome formulation as shown in the give Table 5 below following discussion.

These above the main objective of all excipients involving in the niosomal formulation as well as the preparation. The composition

of the niosomal formulation is carefully designed to achieve the desired drug delivery profile. For example, the type of non-ionic surfactant as well as the quantity of cholesterol employed is going to alter the stability, rigidity, and drug loading capacity of the niosome. The aqueous phase may also be modified to improve the solubility of the drug or to enhance the targeting ability of the niosomes.

THE FORMULATION DEVELOPMENT AND EVALUATIONS OF NIOSOME

The fabrication and preparation of niosome Nano vesicles can be accomplished through various methodologies, each of which presents distinct advantages. It is worth highlighting that the production process significantly influences the ultimate characteristics of niosomes. An overview of the various techniques for niosome preparation is given in this section. Depending of the size the formulation methods will be summarized in Table 6:

Formulation methods of Niosome

Formulation of Niosome by TFH, Hand Shaking Method

Thin Film Hydration (TFH) is also known as hand shaking methods which is one of the most used methods for producing liposomes. This approach could also be used for producing niosomes. Initially, dissolve the non-ionic surfactant and cholesterol in such solvent chloroform or ethanol. The ratio of surfactant to cholesterol is typically 2:1, but this can be varied depending on the desired properties of the niosomes. Deposit the organic solution onto a round-bottom flask and rotate the flask under vacuum to evaporate the solvent. This will form a thin film of surfactant and cholesterol on the bottom of flask. As shown in the (Figure 4) after, add an aqueous phase to the round-bottom flask and gently shake the flask by hand to hydrate the lipid film. The aqueous phase can be water or a buffered saline solution. Sonicate the round-bottom flask for a few minutes to form the niosomes.[32]

Centrifuge the round-bottom flask to separate the niosomes from the aqueous phase. The niosomes can then be collected and used for further applications. Multilamellar Vesicles (MLV) are niosomes generated using the TFH method. This process is commonly used to create niosome containing pharmaceuticals like aceclofenac niosome and pro-niosome,[30,31] diclofenac sodium,[33] and naproxen.[34,35]

Ether Injection Method (EIM)

Surfactant along with additives are soluble in diethyl ether (organic solvent), and subsequently extruded with care via injection into an aqueous solution. This aqueous solution, which holds the desired medicament, is assisted at a consistent temperature of approximately 60°C. A rotary evaporator evaporates the organic solvent.[8] Surfactants play a pivotal aspect in the preparation of single-layered vesicles through the process of ether vaporization. The ether injection method yields SUVs and LUVs with a substantial encapsulated aqueous volume. The ultimate vesicle size might range from 50-1000 nm based on the conditions (Figure 5).

This Ether Injection Method (EMI) widely used in the formulation of Aspirin[36] and Nimesulide[37] etc.,

Table 6: The preparation method of niosome depending on their vesicular diameter.

	SUVs	LUVs	MLVs
Niosome Preparation methods	Sonication, Ethanol/Ether Injection (EI), Homogenization.	Extrusion	Thin Film Hydration (TFH) method.
	REV	Reverse Phase Evaporation (REV).	Solvent injection
	Micro emulsion.		Freeze-Drying (Lyophilization) and other.

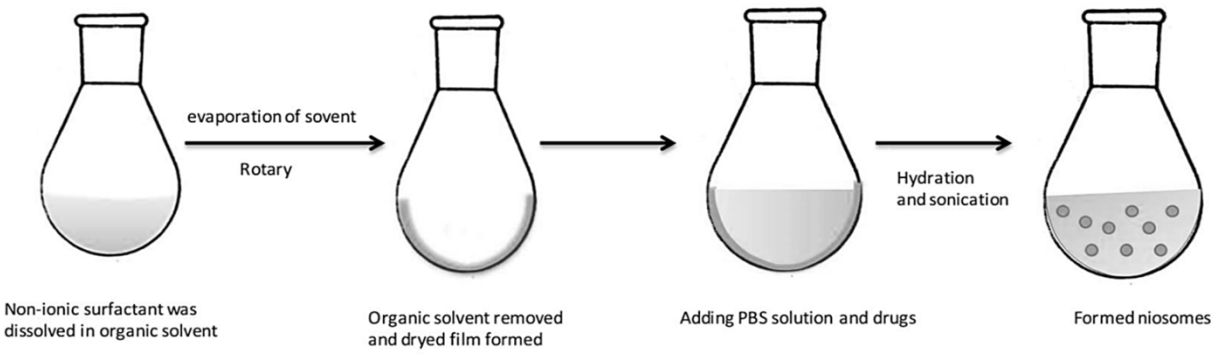

Figure 4: The formulation of niosomes via TFH method.

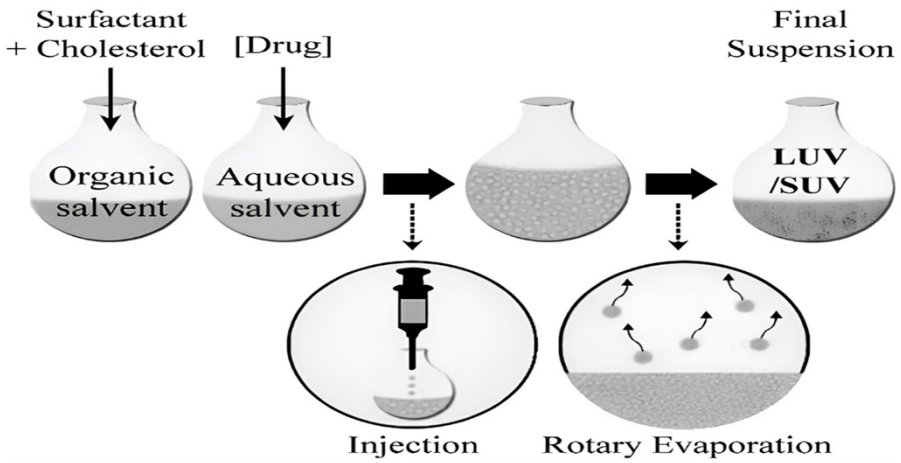

Figure 5: The niosomal preparation via ether injection method.

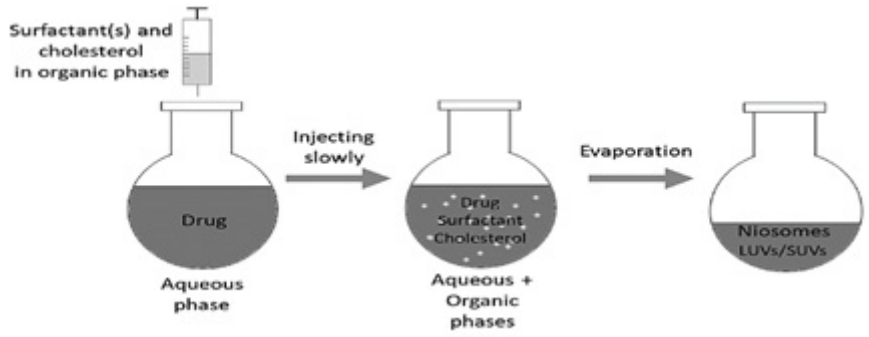

Figure 6: The niosomal formulation via SI method.

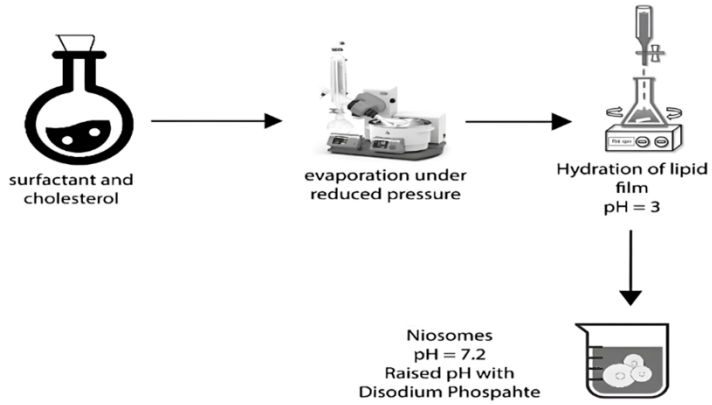

Figure 7: The schematic representation of niosomal formulation via pH gradient method.

Solvent Injection (SI) Method

Diethyl ether and ethanol are utilized in the solvent-induced technique (Figure 6) to dissolve surfactants and other additive. The resulting homogeneous solutions is subsequently loaded into a syringe pump and administered drop by drop through a needle into an aqueous solution containing the drug, which is maintained at a sustained temperature greater than the boiling point of the organic solvent. A rotating vacuum evaporator totally evaporates the residual organic solvent. Unilamellar vesicular niosomes of various sizes are generated during this evaporation process, and the encapsulated aqueous volume is substantially bigger than in previous approaches.[39,40] This approach is used to make elastic niosomes out of tween 80 and span 60 for the entrapment of the diclofenac sodium.[41] They employed ethanol as a solvent for span 60 and diclofenac sodium, and then injected the solution into an aqueous phase containing tween 80.

Transmembrane pH gradient method (Remote Loading Technique)

If the pH of the niosome vesicles is higher on the outside, the basic medication passes through the membrane barrier. Because of the decreased pH inside the niosome, the basic medication

becomes ionised and precipitates. As a result, after encapsulation, it is unable to leave the vesicle.[42] This process can be demonstrated experimentally by vortex mixing a thin coating of surfactant and cholesterol with acidic medium i.e., citric acid (pH 4.0). As a result, the MLVs (Figure 7) are frozen and thawed. The drugs are suspended in an aqueous solution and vortex. The pH is then elevated to 7.0-7.2 before being kept at a high temperature of 60°C for 10 min to produce niosomes.[43]

Probe Sonication Method

A widely accepted technique for the formulation of niosomes, which is both user-friendly and straightforward. The procedure includes the incorporation of a drug solution (in buffer) to a carefully selected blend of non-ionic surfactants, at an optimized ratio, followed by sonication at a predetermined temperature, frequency, and duration to achieve the optimum niosomes. It is an effective method for controlling the particle diameter of the niosomes (Figure 8). Sonication has been shown to reduce the size of niosomes with a restricted size distribution.[44,45] However, probe sonication uses a high energy, which can result in a fast increase in temperature and titanium shedding.

Pro Niosome or Dry Niosome

Proniosomes, alternatively referred to as dry niosomes, are dry formulations of non-ionic surfactant vesicles that can be rapidly converted into niosomes upon hydration. These formulations are increasingly employed in niosome formulation owing to their exceptional stability.[6-9] Proniosomes are non-ionic surfactant-coated water-soluble carriers that may be quickly hydrated into niosomes before usage (Figure 9). This approach presents several benefits, encompassing enhanced physically and chemically stability for extended storage, convenient transport, and scalability.[43] Moreover, this technique holds the potential to expand the manufacturing possibilities of niosomes into other forms, like as gels and tablets. Detailed research has demonstrated that proniosomes have shown promising potential for effective medication administration through various routes, such as periodontal and transdermal routes.[46-48]

This technique is highly efficient in decreasing the amount of water for niosomes, thereby enhancing their stability and offering a potential resolution for prolonged storage. It has been successfully employed in formulating Ketoprofen,[43] Ketorolac,[44] and Tenoxicam.[45]

The Bubble Method

A novel technique has been recently developed to facilitate the production of niosomes, eliminating the need for organic solvents. The process involves employing a specialized apparatus comprising a spherical bottom flask with three necks that was immersed in a water bath to ensure precise temperature. The first and second necks include a water-cooled reflux and thermometer, while the third neck is used to provide nitrogen (Figure 10). At a temperature of 70°C, a mixture of cholesterol and surfactant is uniformly distributed in a buffer solution with a pH of 7.4. Dispersion is subjected to a blending process at a duration of 15 seconds using a high shear homogenizer. Subsequently, the mixture is exposed to nitrogen gas at 70°C, resulting in the formation of niosomes.[49,50]

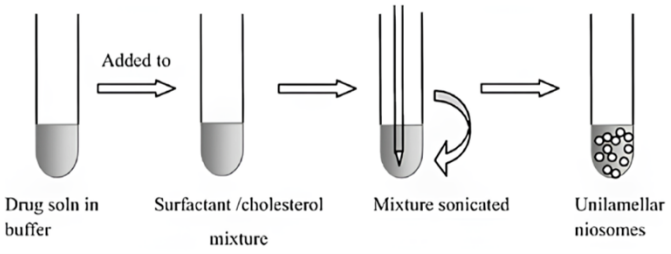

Figure 8: The schematic representation of niosomal formulation via sonication.

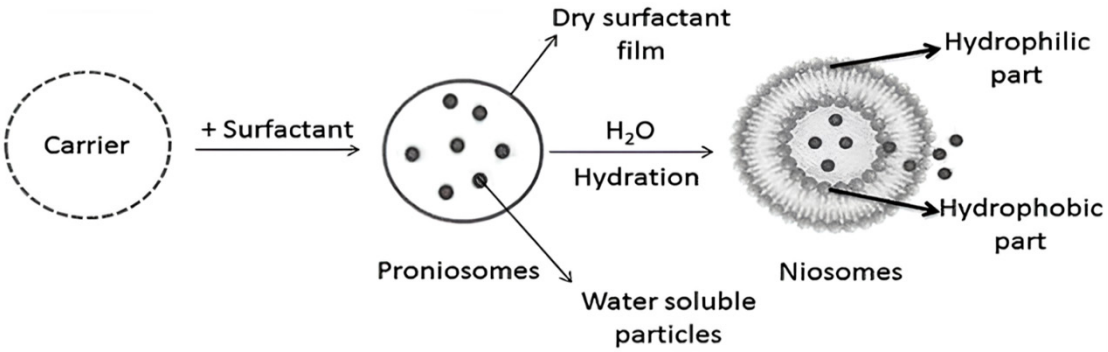

Figure 9: The preparation of niosomes via proniosomes method.

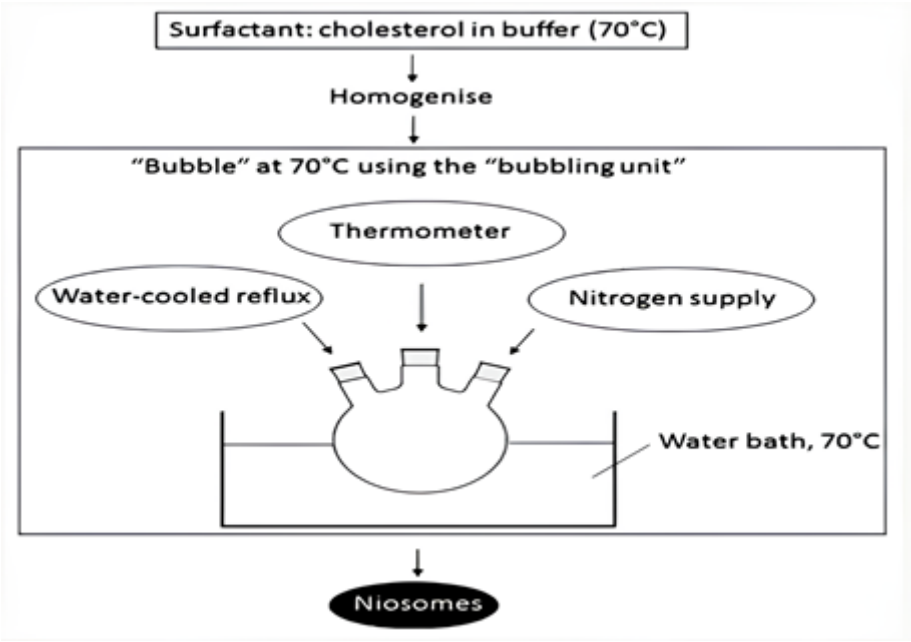

Figure 10: The bubble method in formulation of niosomal preparation.

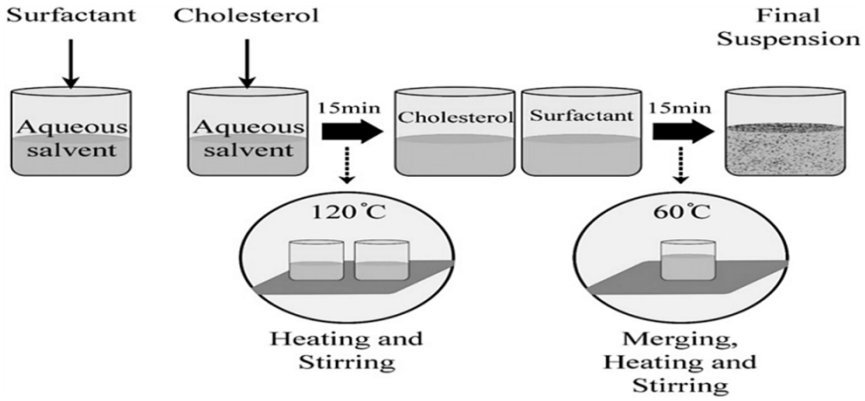

Figure 11: The systematic representation for niosome formulation through HM.

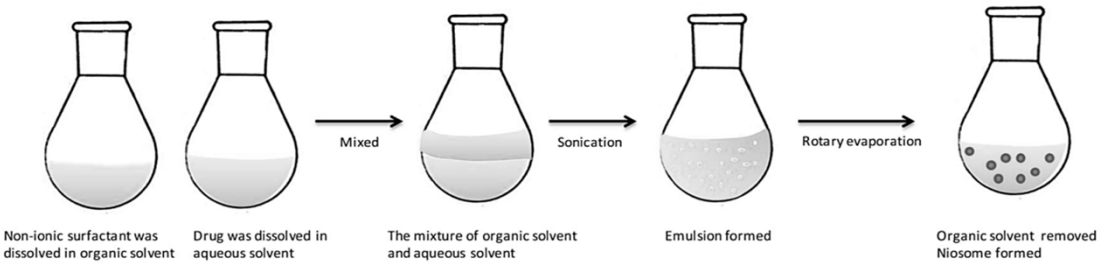

Figure 12: The formulation of niosomes Via REV method.

Heating Method (HM)

The various non-ionic surfactants and certain additives, such as cholesterol, hydrate with individually for one hour at room temperature in a nitrogen environment in PBS (pH=7.4). The solution is then heated on a hot-plate stirrer (about 120°C) for around 15-20 min to dissolve cholesterol. Following the reduction of temperature to 60°C, the supplementary constituents, namely surfactants and other additives, are introduced into the buffer solution that already contains the dissolved cholesterol. Subsequently, the mixture is subjected to continuous stirring for an additional duration of 15 min.[51] Niosomes produced at this stage are kept for 30 min at 4-5°C in a nitrogen surrounding before it is needed (Figure 11).[51,52]

Reverse Phase evaporation (REV) Method

As illustrated in Figure 12, the REV technique necessitates the dissolution of the non-ionic surfactant and cholesterol to an organic solvent. Prior to being subjected to sonication with the

organic phase to generate an emulsion, the loaded medication is solubilized to an aqueous solution, like PBS or water. The organic solvent is evaporated using a rotating vacuum evaporator with temperature of 40-60°C for the formation of niosomes. In contrast to the TFH technique, the REV method demonstrated the production of nanoparticles characterized by consistent size and unilamellar or oligolamellar structures. This REV process was employed in the development of diverse niosomal preparations for analgesic drugs, such as acetazolamide.[51]

Micro Fluidization Method

Dissolve the non-ionic surfactant with cholesterol to ethanol or isopropanol (organic solvent). Ratio for surfactant to cholesterol is typically 2:1, but this can be varied depending on the desired properties of the niosomes. Prepare an aqueous phase comprising of API or other molecule to be encapsulated. The aqueous phase can also contain other components, such as buffers, salts, and excipients. Load the organic and aqueous phases into the microfluidic device. Apply high pressure to the microfluidic device to mix the two phases. This will result in the preparation of niosome. Collect the niosomes from the outlet of the microfluidic device. The microfluidization method is a powerful tool for the formulation of niosomes (Figure 13).[52]

This technique holds the potential to generate niosomes possessing a diverse range of desired characteristics, including size, encapsulation efficiency, and release profile. Consequently, this approach is regarded as a favourable avenue for the production-based advancement of niosomes.

Others

Melt Method, the simplest and most commonly used method for preparing niosomes. It involves melting the surfactant and cholesterol at a temperature above their melting points. The aqueous phase is then added and the mixture is sonicated to form a dispersion of niosomes.[53] Micelle solution and enzymatic method, it involves dissolving surfactant and cholesterol in ethanol. Subsequently, the water-soluble phase is introduced and the amalgamation is agitated to generate a micellar solution. The micellar solution is subsequently subjected to sonication, resulting in the formation of a dispersion comprising niosomes. Enzymatic method, similar to the micelle solution method, but the micellar solution is treated with an enzyme such as phospholipase D to form a dispersion of niosomes.[54]

Characteristics and evaluations of niosome

Typically, the evaluation of niosomes encompasses an examination of their size distribution, surface morphology, drug loading efficiency, stability and zeta potential throughout the formulation as well as storage. These attributes hold significant importance for niosomes as they not only impact the stability, entrapment rate of the niosomes, in fact it also influences their *in vivo* performance.[52-54] As the field of detection technology continues to progress, an increasing number of methodologies are being devised to measure niosomes. Table 7 provides a comprehensive overview of commonly employed techniques for the characteristics of niosomes.

Vesicular Size diameter and Size distribution of Niosome

Niosomes are spherical in form, and their size may be evaluated using a variety of methods, as summarised in Table 10. Typically, their size distribution and polydispersity index are calculated. Niosomes exhibit a spherical morphology and their dimensions can be determined through various techniques, as outlined in Table 2. Laser scattering (DLS) particle size analyzers are commonly used to measure their size distribution and polydispersity index. TEM, SEM, AFM, and STC are utilised to regulate the morphology of the niosomes in order to better detect their sharpness. SEM and TEM pictures were used to examine the shape of blank niosomes and three types of medicines, Etodolac,[55] diclofenac diethyl ammonium,[56] diclofenac sodium,[57] and aspirin-loaded niosomes.[58]

The assembly of niosomal formulations may be influenced by various factors, including the structural characteristics of non-ionic surfactants, which can significantly impact the size,

Table 7: The characteristics and evaluation of niosome.

Characterization	Evaluation parameters
Vesicular Size diameter and Size distribution	CLS, SEM, STM, AFM, DLS.
Zeta potential	DLS, mobility.
Entrapment efficiency (%EE)	Entrapment Efficiency (%EE) =x 100 HPLC, UV/vis, and fluorescence are used to measure the quantity of the loaded medication.
Stability	DLS was employed to determine size and zeta potential under *in vivo* conditions (37°C or serum), while drug leakage was loaded.

DLS: Diameter laser scatter, SEM: Scanning electron microscope, AFM: Atomic Force Microscope, STM: Scanning Tunnelling Microscope, and HPLC: High-Performance Liquid Chromatography are other abbreviations.

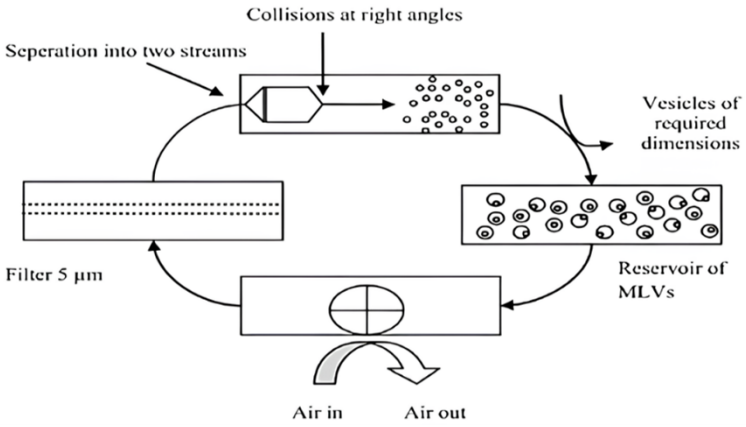

Figure 13: The schematic representation of niosomal formulation via micro-fluidization method.

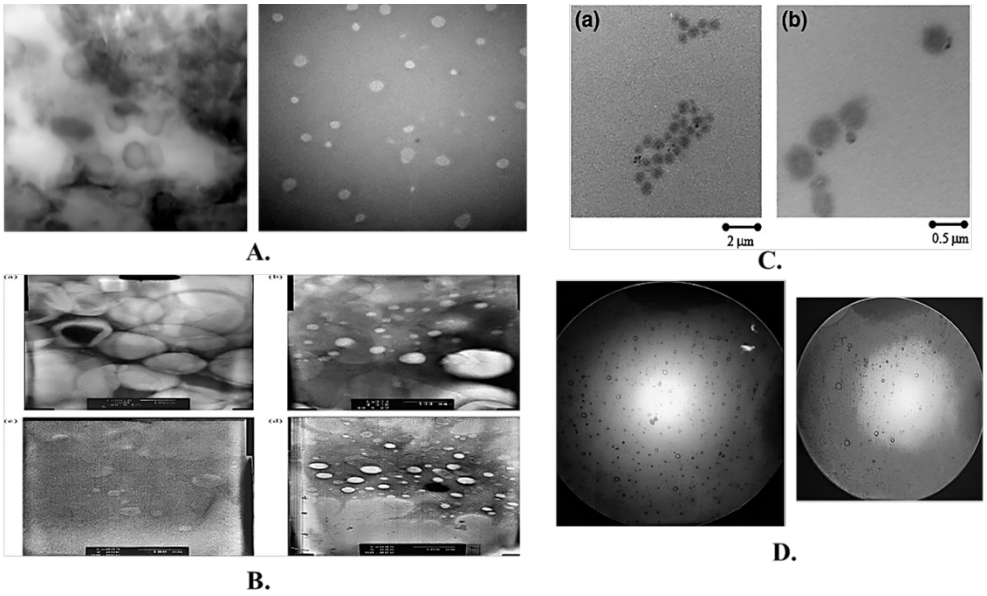

Figure 14: The schematic representation of (A)The SEM view of the Paracetamol Antidote, (B) The SEM view of Etodolac, (C) The TEM view of Diclofenac Gel and (D) Aspirin Optical View respectively

shape, and stability of niosomes. 1) The HLB of the surfactant is a key factor, as surfactants with a higher HLB tend to form smaller and more stable niosome. 2) Membrane additives is cholesterol used to improve the stability and rigidity of niosomes. 3) Type of encapsulated drug, can also affect the assembly of niosome. The lipophilic drug may tend to interact with the lipid bilayer, while water loving drug may remain in the aqueous core. This can affect the size, shape, and stability of the niosome. 4) Surfactant and lipid levels, in the niosome formulation are another important factor. A higher concentration of surfactant will generally result in the formation of smaller niosomes, while a higher concentration of lipids will increase the stability of the niosome. 5) Hydration temperature, in most non-ionic surfactants, the optimal hydration temperature is above the gel-to-liquid phase transition temperature. The diameters of the niosomes have been observed to range from roughly 20 nm to 50 m.[60-63] The zeta potential of niosomes in solution is critical for their stability in solution and may be evaluated using Zetasizer, microelectrophoresis, and DLS equipment. The SEM/TEM of some analgesic drugs are shown in Figure 14 and their diameters are mentioned in the Table. 10.

Zeta Potential of Niosomes

Zeta potential is a crucial parameter in niosomal characterization. It measures the surface charge of the niosomes. A high zeta potential (greater than +30 mV) indicates that the niosomes are stable and will not aggregate. A low zeta potential (less than -30 mV) indicates that the niosomes are unstable and may aggregate. Zeta potential is affected by a number of factors, including the type of surfactant used, the ratio of surfactant to cholesterol, the pH of the aqueous phase, and the presence of electrolytes. The optimal zeta potential may vary depending on the intended application of the niosomes.[56-58] As discussed in Table 8, the zeta potential of analgesic niosomal formulations can be evaluated through a range of techniques, including Zetasizer, mastersizers, microelectrophoresis, pH-sensitive fluorophores,

high-performance capillary electrophoresis, and DLS devices. These methods are effective in assessing the surface zeta potential of the formulations. The zeta potential of Lornoxicam,[60] Naproxen[61] and Diclofenac sodium.[33]

PDI of Niosome

The Polydispersity Index (PDI) serves as a quantitative indicator of the size distribution within a particle population. PDI value is determined as the standard deviation of the particle size distribution divided by the mean particle size. A PDI value with 0 signifies population where every particle is of identical size, whereas a PDI value of 1 signifies a highly heterogeneous population in terms of particle size. According to Table 8, Dynamic Light Scattering (DLS) particle size analyzer is applicable for evaluating the size distribution and Polydispersity Index (PDI) of niosomes. The PDI values for Meloxicam[59] and Lornoxicam[60] are provided in Table 8 in a comprehensive manner.

Entrapment Efficiency (%EE) of Niosomes

The ability of vesicles to effectively incorporate medicinal substances is quantified by the encapsulation efficiency of niosomes. The definition of niosome encapsulation efficiency is provided in Table 10 where the term "total weighed quantity" which refers to the number of pharmaceuticals utilized in the preparation. The efficacy of niosomes in encapsulating active ingredients is primarily influenced by the type of non-ionic surfactant employed, the production methodology, and other components incorporated during the formulation process, including cholesterol. Studies have demonstrated that entrapment efficiency can attain levels of 75%-90%, albeit typically falling within the range of 10%-40%.[61] The Entrapment Efficacy (%EE) of some niosomal preparations including aceclofenac niosome[30] and aceclofenac proniosome,[31] Nimesulide,[37] naproxen,[34] Etodolac[55] and diclofenac sodium[57] as analgesic niosomal formulation.

Stability of Niosomes

The stability of niosome is a crucial factor in their preparation, which is influenced by various factors such as the preparation process, loaded medications, and the type of membrane-forming materials used. To evaluate the stability of niosomes during storage, it is imperative to assess changes in particle size, zeta potential, shape, and the rate of loaded drug leakage. In accordance with the ICH Guidelines for Stability, as outlined in Table 9, an evaluation of niosome stability during circulation was conducted. The study considered three primary storage conditions, namely general storage, refrigeration, and freezer storage, to assess the stability of the niosomal formulation.[60-62]

All the above condition for the storage with the stability form can be performed according to the general case, refrigerator and freezer case so on. In order to evaluate the stability of these vesicles, an assessment is conducted on the diameters, zeta potential, and leakiness of the loaded medicines in niosomes over a specific duration of time. Niosomes are more stable than liposomes and have the potential for therapeutic applications.

Table 8: The list of zeta potential and PDI of analgesic medicament in the niosomal formulations.

Drug Name	Zeta Potential	PDI (Polydispersity Index)	References
Diclofenac sodium	-49.4 mv	--	33
Naproxen	-31.9 mV	--	34
Meloxicam	--	0.15-0.25	59
Lornoxicam	-69±7.4 mV	0.492-0.259	60

Table 9: The storage condition for the Niosomal formulation as per the general case, refrigerator and freezer stability condition.

Case of Stability parameter	Study	Storing climate	Least duration for data submission time
General Case	Long term*	25°C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH.	12 months
	Intermediate**	30°C±2°C/65% RH±5% RH.	6 months
	Accelerated	40°C±2°C/75% RH±5% RH.	6 months
Refrigerated Case	Long term	5°C±3°C	12 months
	Accelerated	25°C±2°C/60% RH±5% RH.	6 months
Freezer Case			
	Long term	-20°C±5°C	12 months
Storage below -20°C	API that are studied for storing temperatures below -20°C must be handled and evaluated individually, taking into consideration specific circumstances and requirements.[62]		

Table 10: Various characterization and evaluations of analgesics previously prepared with lots of methods.

Drug	Vesicular Size Diameter	% Drug Release (hr.)	% Entrapment Efficiency (%EE)	References
Meloxicam	107.2±0.6 nm	-	98%	26
Aceclofenac	4.22±0.47µm	87.21% in 72 hr.	96.07%±0.35	30
Aceclofenac proniosomes	136 µm to 236 µm	45% for 24 hr.	97.60±1.85	31
Naproxen	393.9 nm	88.9±0.71% in 12 hr.	95.86%,	34
Aspirin	--	45.5% drug release at 3rd hr.	80.8%	36
Nimesulide	13.4821 m	48.1% in 8 hr.	55.89%	37
Ketoprofen	5.24 m	64.69 in 12 hr.	82.68%	43
Ketorolac	4.4±0.21 m	203.1±1.6 g/cm^2 h^{-1}.	99.2±5.2%	44
Tenoxicam	-	0.61 mg/hr.	92%	45
Etodolac	2 m to 4 m	94.91% in 24 hr.	96.72%	55
Diclofenac diethyl ammonium	224.45±11.95 nm	32±2°C for 6 hr.	93%	56
Diclofenac sodium	436±28 nm	80% permeation rate.	75±6%	57
Aspirin	144.8±12.90 nm	96.99±1.57% for 24 hr.	49±0.15%	58
Meloxicam	70±5.5 nm	-	84.35±6.8%	59
Lornoxicam	295 nm to 1298 nm	25.5±4.32% for 24 hr.	More than 66%	60
Flurbiprofen	1.35±0.23 m	-	88±2.50%	64
Paracetamol	242.3±18.5 nm	80% in 8 hr.	27.74±4.20%	65
Piroxicam	4.81±1.1 m	49.38±1.4 g cm^{-2} h^{-1}.	91.7 ± 6.2%	66

In vitro Drug diffusion of Niosome

In vitro drug diffusion of niosomes can be measured using a variety of methods, including Franz diffusion cell, dialysis bag and spectrophotometry. Franz diffusion cells are a commonly used method for measuring the *in vitro* drug diffusion of niosomes.[34] The Franz diffusion cell consists of two chambers separated by a semipermeable membrane. The niosome formulation is placed in the donor chamber and the receptor chamber is packed with a buffer solution. The drug diffusion is measured by sampling the receptor solution at systemic intervals of time and analysing it for the drug concentration.

Franz diffusion cells are a good choice for measuring the *in vitro* drug diffusion of niosomes because they are relatively easy to use and provide reproducible results. Additionally, Franz diffusion cells[37] can be used to measure the drug diffusion of niosomes across a variety of semipermeable membranes, which can be useful for predicting the *in vivo* drug absorption of niosomes. The semipermeable membrane is located in the middle of donor and receptor chambers within the Franz diffusion cell.

To measure the *in vitro* drug diffusion of niosomes using a Franz diffusion cell, the following steps are typically followed:

The niosome formulation is located in the donor chamber.

The receptor chamber is packed with a buffer solution.

The Franz diffusion cell is assembled and placed in an incubator at a constant temperature.

At regular intervals, samples are taken from the receptor cell and analyzed for the drug concentration.

The drug diffusion is calculated from the alteration in the drug amount variation in the receptor solution over time.[37,57,60]

The various evaluation and characterization parameters of the several analgesic niosome previously prepared are shown in Table 10 as below:

Separation of Un-entrapped Drug

There are a number of methods that can be used to separate unentrapped drugs from niosomes, including dialysis, gel filtration chromatography, and centrifugation.

Dialysis

Process of separating molecules depending on their size. Niosomes are typically larger than un-entrapped drug molecules, so dialysis

Table 11: The list of niosomal formulations of analgesics drugs with including their components and methods involved.

Drug medicament	Methods of formulation	Components	Dosage form	References
Meloxicam	TFH Method	Span 60, Carboxy methylcellulose sodium.	Transdermal Gel-based Delivery.	26
Aceclofenac	EIM	Cholesterol, Span 20, Span 60, methanol, diethyl ether and PBS and pH 7.4.	Niosome	30
Aceclofenac proniosomes	Coacervation phase separation method.	Cholesterol, Span 20, Span 40, Span 60.	Gel	31
Naproxen	EIM	Span 60, Span 80, Tween 60, Tween 80.	Niosomes	34
Naproxen	Modified EIM	Tween 80, Brachystegia eurycoma gum, HPMC.	Topical Gel based Delivery.	35
Aspirin	EIM	Span 60, cholesterol, diethyl ether, ethanol, buffer.	Niosomes	36
Nimesulide	TFH Method and EIM.	Span 20, 40, 60, cholesterol, chloroform, methanol, PBS pH-7.4.	Niosomal formulation.	37
Ketoprofen	Modified literature method.	Span 80, soya lecithin, Oleic acid, Cholesterol.	Periodontal Proniosomes.	43
Ketorolac	Modified literature method.	Span 60, Tween 20, soya lecithin, Cholesterol.	Transdermal Gel based Proniosomes.	44
Tenoxicam	Modified literature method.	Span 20, Span 60, Span 80, Tween 20, Tween 60, Tween 80.	Transdermal Proniosomes.	45
Etodolac	THF Method	Span 60	Topical Niosomal Gel	55
Diclofenac diethyl ammonium	THF Method	Span 20, 80, Tween 20, 80, Cholesterol, Diethyl ether, chloroform and methanol.	Niosomal formulation	56
Diclofenac Sodium	TFH Method	Span 60, Tween 60 and Pluronic F127.	Transdermal niosomes.	57
Aspirin	Solvent- based co-precipitation method with a phase inversion technique.	Tween 20, PEG 6000, Ethanol, water.	Biomimetic Niosomal Nanoparticles (BNNs).	58
Meloxicam	Cold method	Span 60, Poloxamer, Chitosan, Carbopol	Transdermal Gel-based Delivery.	59
Lornoxicam	Thin film hydration technique	Span 40, Dicetyl Phosphate, Stearylamine (SA).	Transdermal Gel-based Delivery.	60
Flurbiprofen	THF Method	Span 60	Ocular gel	64
Paracetamol (PCM) Antidote	TFH	Span 60, Cholesterol, PEG.	PEGylated nano-niosome.s	65
Piroxicam	Slightly modified method	Span 20, 60, 80, Tween 20, Tween 60, Tween 80.	Transdermal Delivery.	66

can be used to separate them. To do this, the niosome dispersion is placed in a dialysis bag and the dialysis bag is immersed in a buffer solution. The unentrapped drug will diffuse through the pores of the dialysis bag into the buffer solution, while the niosomes will remain in the dialysis bag. The unentrapped drug can then be collected from the buffer solution.

Gel Filtration Chromatography (GFC)

GFC separates the molecules depending on their sizes. To separate the unentrapped drug from niosomes using gel filtration chromatography, the niosome dispersion is passed through a column filled with a porous material. The niosomes will elute from the column first, followed by the un-entrapped drug. The un-entrapped drug can then be collected from the eluate.

Centrifugation

Centrifugation is a process of separating particles based on their density. Niosomes are typically denser than un-entrapped drug molecules, so centrifugation can be used to separate them. To do this, the niosome dispersion is centrifuged at a high speed. The niosomes will pellet at the bottom of the centrifuge tube, while the un-entrapped drug will remain in the supernatant. The un-entrapped drug can then be collected from the supernatant.[65-67]

The applications of niosome for an analgesics

Analgesics play a vital role in niosomal formulations, as they can be used to relieve pain and inflammation at the targeted site of action. Niosomes are non-ionic surfactant vesicles that are similar to liposomes in structure and function but offer several advantages, such as greater stability, higher drug-loading capacity, and enhanced targeting ability. Analgesic drug niosomes are non-ionic surfactant vesicles that are loaded with analgesic drugs.[67] They are a promising drug delivery system for the treatment of pain and inflammation. Analgesic drug niosomes can be administered orally, ocular, dermal, periodontal or parenterally route. When administered orally, niosomes are absorbed in the intestine and enter the bloodstream. When administered rectally, niosomes are absorbed through the rectal mucosa and enter the bloodstream. When administered topically, niosomes are absorbed through the skin as they have a smaller size that makes the permeation easier which leads to Enhanced Permeation and Retention (EPR). When administered parentally, niosomes directly enters into the bloodstream and focus only on the targeted site of the drug.[68,69]

Niosome broadly used in the treatment in pain relieve of injury mainly focus on COX (Cyclooxygenase) inhibitors. Cyclooxygenase is involved in various chemical production within the body, one of them is prostaglandins. Prostaglandins is an active lipid-based compounds (eicosanoids) that is mostly concern with uterine contraction, pain, injury or post injury inflammatory within the body. Flurbiprofen (FBP) is a Non-Steroidal Anti-Inflammatory (NSAIDs) that inhibits cyclooxygenase that has currently gained a lot of attention in ocular based drug delivery system.[64] Diclofenac is an anti-inflammatory, antipyretic and analgesic drug. It blocks prostaglandin synthesis and also blocks COX-2 selectively. It is employed to treat bursitis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The drug has a short half-life of 2 hr. and 70-80% of dose is excreted via renal transport which makes the dosage frequency of Diclofenac more than once a day.[57] Tenoxicam is also an NSAID that is mostly used to treat rheumatologic disease and is distinguished by its enhanced efficacy and reduced side effects in contrast to supplementary NSAIDs.[45] Niosome formulation improve the permeability of the formulation and prolong as well as sustain the drug release with prolonging the retention time in at specific target area at therapeutic level.

The niosome formulation decreases the frequency of administration and increases patient compliance. They majorly decrease the side effects of particular drug interactions.

The main purpose of niosome formulation before the conventional dosage forms is poor bioavailability, 1st passes metabolism and rapid elimination. By using the niosome formulation these drawbacks are reduced and enhance the bioavailability of the drug, providing the localized drug delivery to ensure a targeted action of the drug.[66-68] Formulations have been made for analgesic drugs as Niosomal entrapped drug delivery systems. Aceclofenac via ether injection technique with compositions of cholesterol, Span 20, Span 60, Diethyl ether, methanol, and PBS of pH 7.4.[30] The present study investigated the efficacy of formulations of Aspirin via the ether injection method, utilizing a composition consisting of Span 60, cholesterol, diethyl ether, ethanol, and buffer.[36] Additionally, the study evaluated the effectiveness of Diclofenac Sodium as a transdermal niosomal drug delivery system, utilizing the hydration of lipidic film method and composition of Tween 60, Span 60, and Pluronic F127.[57] Furthermore, the study examined the potential of Flurbiprofen as an ocular gel, utilizing the TFH method and composition of Span 60, Carbopol, Carrageenan, and cholesterol.[64] The various niosomal formulations for analgesics with various excipients involved in it as below Table 11 following discussion.

These are the various drug prepared via niosomal formulation. Niosomal formulation has potentially benefits to various pharmacological agents for their action against several diseases. Some of their therapeutic benefits are as follows: Gene delivery, Antineoplastic treatment, Delivery of peptide drugs, Drug targeting, studying immune response, Carriers for haemoglobin, Transdermal drug delivery systems, Cosmetics preparations, Anti-Inflammatory (NSAIDs), Anti-Fungal Agents.[68,69]

Niosomes can deliver analgesics to the target site of action more effectively than traditional oral or injectable formulations. This is because niosomes can evade the body's natural defence

mechanisms and fuse with cell membranes, releasing the analgesic directly into the cells.

CONCLUSION

Niosomes are a relatively new drug delivery method comprised of two layers of non-ionic surfactants. Different medications can be put in niosomes by varying the experiment settings and the ratio of surfactant and cholesterol utilised. Furthermore, because niosomes are amphipathic, hydrophobic and hydrophilic medicines may be put into them. Niosomes also improve medication stability, decrease drug toxicity, and delay drug release. Nanoparticles have the potential to serve as a viable substitute for liposomes, thus garnering significant interest within the realm of pharmaceutics. Advanced niosomal formulations, designed for the purpose of theranostics, have the potential to provide valuable insights for diagnostics, treatment, and monitoring of patients' response to treatment. It is anticipated that the ongoing extensive research dedicated to pioneering niosome formulations will pave the way for the creation of novel pharmaceutical products, thereby enhancing the implementation of the "personalized medicine" approach in the near future. The main purpose of this review to indicate the niosomal preparation in analgesics with their all-descriptive data in previous literature.

ACKNOWLEDGEMENT

We would like to thanks Dr. Himmat Singh Chawra, Dr. Ravindra Pal Singh and other faculty members of department of Pharmaceutics, Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur, 303121, India for their collaboration in completion of work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TDDS: Targeted drug delivery system; **SUVs:** Small unilamellar vesicles; **LUVs:** Large unilamellar vesicles; **MLVs:** Multi-lamellar vesicles; **SA:** Stearylamine; **DCP:** Dicetyl phosphate; **CMC:** Critical micellar concentration; **%EE:** Entrapment efficacy; **HLB:** Hydrophilic and Lipophilic Balance; **PEG:** Polyethylene glycol; **TFH:** Thin film hydration; **EIM:** Ether injection method; **SI:** Solvent injection; **HM:** Heating method; **REV:** Reverse phase evaporation; **DLS:** Diameter laser scatter; **SEM:** Scanning electron microscope; **AFM:** Atomic Force Microscope; **STM:** Scanning Tunnelling Microscope; **HPLC:** High Performance Liquid Chromatography; **GFC:** Gel filtration chromatography.

REFERENCES

1. Moammeri A, Chegeni MM, Sahrayi H, Ghafelehbashi R, Memarzadeh F, Mansouri A, *et al*. Current advances in niosomes applications for drug delivery and cancer treatment. Materials Today Bio. 2023 Oct 21:100837. DOI: 10.1016/j.mtbio.2023.100837.
2. Yasamineh S, Yasamineh P, Kalajahi HG, Gholizadeh O, Yekanipour Z, Afkhami H, *et al*. A state-of-the-art review on the recent advances of niosomes as a targeted drug delivery system. International journal of pharmaceutics. 2022;624:121878. DOI: 10.1016/j.ijpharm.2022.121878
3. Masjedi M, Montahaei T. An illustrated review on nonionic surfactant vesicles (niosomes) as an approach in modern drug delivery: Fabrication, characterization, pharmaceutical, and cosmetic applications. Journal of Drug Delivery Science and Technology. 2021;61:102234. DOI: 10.1016/j.jddst.2020.102234
4. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. Journal of Drug Delivery Science and Technology. 2020;56:101581. DOI: 10.1016/j.jddst.2020.101581
5. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. European journal of pharmaceutics and biopharmaceutics. 2019;144:18-39. DOI: 10.1016/j.ejpb.2019.08.015
6. Khatoon M, Shah KU, Din FU, Shah SU, Rehman AU, Dilawar N, Khan AN. Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug delivery. 2017;24(2):56-69. DOI: 10.1080/10717544.2017.1384520
7. Awasthi R, Pant I, T Kulkarni G, Satiko Kikuchi I, de Jesus Andreoli Pinto T, Dua K, *et al*. Opportunities and challenges in nano-structure mediated drug delivery: where do we stand?. Current Nanomedicine (Formerly: Recent Patents on Nanomedicine). 2016;6(2):78-104.
8. Sahoo SK, Jain TK, Reddy MK, Labhasetwar V. Nano-sized carriers for drug delivery. NanoBioTechnology: BioInspired Devices and Materials of the Future. 2008:329-48. DOI: 10.1007/978-1-59745-218-2_13
9. Barenholz YC. Doxil®—The first FDA-approved nano-drug: Lessons learned. Journal of controlled release. 2012;160(2):117-34. DOI: 10.1016/j.jconrel.2012.03.020
10. Abdelkader H, Alani AW, Alany RG. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications and limitations. Drug delivery. 2014;21(2):87-100. DOI: 10.3109/10717544.2013.838077
11. Khan MI, Madni A, Peltonen L. Development and in-vitro characterization of sorbitan monolaurate and poloxamer 184 based niosomes for oral delivery of diacerein. European Journal of Pharmaceutical Sciences. 2016;95:88-95. DOI: 10.1016/j.ejps.2016.09.002
12. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014;185:22-36. DOI: 10.1016/j.jconrel.2014.04.015
13. Varshosaz J, Taymouri S, Pardakhty A, Asadi-Shekaari M, Babaee A. Niosomes of ascorbic acid and α-tocopherol in the cerebral ischemia-reperfusion model in male rats. Biomed research international. 2014;2014. DOI: 10.1155/2014/816103
14. Ritwiset A, Krongsuk S, Johns JR. Molecular structure and dynamical properties of niosome bilayers with and without cholesterol incorporation: A molecular dynamics simulation study. Applied Surface Science. 2016;380:23-31. DOI: 10.1016/j.apsusc.2016.02.092
15. Puras G, Mashal M, Zárate J, Agirre M, Ojeda E, Grijalvo S, *et al*. A novel cationic niosome formulation for gene delivery to the retina. Journal of Controlled Release. 2014;174:27-36. DOI: 10.1016/j.jconrel.2013.11.004
16. Primavera R, Palumbo P, Celia C, Cinque B, Carata E, Carafa M, Paolino D, Cifone MG, Di Marzio L. An insight of in vitro transport of PEGylated non-ionic surfactant vesicles (NSVs) across the intestinal polarized enterocyte monolayers. European Journal of Pharmaceutics and Biopharmaceutics. 2018;127:432-42. DOI: 10.1016/j.ejpb.2018.03.013
17. Barani M, Mirzaei M, Torkzadeh-Mahani M, Nematollahi MH. Lawsone-loaded Niosome and its antitumor activity in MCF-7 breast Cancer cell line: a Nano-herbal treatment for Cancer. DARU Journal of Pharmaceutical Sciences. 2018;26:11-7. DOI: 10.1007/s40199-018-0207-3
18. Berlepsch HV, Thota BN, Wyszogrodzka M, De Carlo S, Haag R, Böttcher C. Controlled self-assembly of stomatosomes by use of single-component fluorinated dendritic amphiphiles. Soft Matter. 2018;14(25):5256-69. DOI: 10.1039/C8SM00243F
19. Tavano L, Muzzalupo R, Mauro L, Pellegrino M, Andò S, Picci N. Transferrin-conjugated pluronic niosomes as a new drug delivery system for anticancer therapy. Langmuir. 2013;29(41):12638-46. DOI: 10.1021/la4021383
20. Mujeeb SA, Sailaja AK. Formulation of ibuprofen loaded niosomal gel by different techniques for treating rheumatoid arthritis. Journal of Bionanoscience. 2017;11(3):169-76. DOI: 10.1166/jbns.2017.1435
21. Yasam VR, Jakki SL, Natarajan J, Kuppusamy G. A review on novel vesicular drug delivery: proniosomes. Drug delivery. 2014;21(4):243-9. DOI: 10.3109/10717544.2013.841783
22. Sayyad N, Maji R, Omolo CA, Ibrahim UH, Pathan TK, Devnarain N, *et al*. Development of niosomes for encapsulating captopril-quercetin prodrug to combat hypertension. International Journal of Pharmaceutics. 2021;609:121191. DOI: 10.1016/j.ijpharm.2021.121191
23. Sun Z. Optimization of clobetasol propionate loaded niosomal gel for the treatment of psoriasis: *Ex vivo* and efficacy study. Journal of Dispersion Science and Technology. 2023;44(14):2599-609. DOI: 10.1080/01932691.2022.2110111
24. Jacob S, Nair AB, Al-Dhubiab BE. Preparation and evaluation of niosome gel containing acyclovir for enhanced dermal deposition. Journal of liposome research. 2017;27(4):283-92. DOI: 10.1080/08982104.2016.1224897
25. Suriyaprakash TN, Parthiban S, Prabu SL, Sumathi A. Formulation and evaluation of paclitaxel niosome for its improved anti-cancer activity. ACTA Pharmaceutica Sciencia. 2011;53(3).
26. Bragagni M, Mennini N, Ghelardini C, Mura P. Development and characterization of niosomal formulations of doxorubicin aimed at brain targeting. Journal of pharmacy & pharmaceutical sciences. 2012;15(1):184-96. DOI: 10.18433/J3230M
27. Gad S, Ahmed AM, Ghourab MM, Queshawy MK. Design, formulation, and evaluation of Piroxicam niosomal gel. Int. J. PharmTech. Res. 2014;6(1):185-95.

28. El-Menshawe SF, Hussein AK. Formulation and evaluation of meloxicam niosomes as vesicular carriers for enhanced skin delivery. Pharmaceutical Development and Technology. 2013;18(4):779-86. DOI: 10.3109/10837450.2011.598166
29. Tavano L, Picci N, Ioele G, Muzzalupo RJ. Tetracycline-niosomes versus tetracycline hydrochlo-ride-niosomes: how to modulate encapsulation and percutaneous permeation properties. J Drug. 2017;1(2):1-6. DOI: 10.24218/jod.2017.6
30. Jigar V, Puja V, Krutika S. Formulation and evaluation of topical niosomal gel of erythromycin. Int J Pharm Pharm Sci. 2011;3(1):123-6.
31. Kumar A, Dua JS. Formulation and evaluation of itraconazole niosomal gel. Asian Journal of Pharmaceutical Research and Development. 2018;6(5):76-80. DOI: 10.22270/ajprd.v6i5.425
32. Srinivas S, Kumar YA, Hemanth A, Anitha M. Preparation and evaluation of niosomes containing aceclofenac. Dig J Nanomater Bios. 2010;5(1):249-54.
33. Radha GV, Sastri KT, Prathyusha P, Bhanu P, Rajkumar J. Formulation and evaluation of aceclofenac proniosome loaded orabase for management of dental pain. Int J Appl Pharm. 2018;10(7):204-10. DOI: 10.22159/ijap.2018v10i6.29143
34. Umbarkar M, Thakare S, Surushe T, Giri A, Chopade V. Formulation and evaluation of liposome by thin film hydration method. Journal of drug delivery and therapeutics. 2021;11(1):72-6. DOI: 10.22270/jddt.v11i1.4677
35. Sreya M, Sailaja AK. Preparation and evaluation of diclofenac sodium niosomal formulations. Journal of Bionanoscience. 2017;11(6):489-96. DOI: 10.1166/jbns.2017.1486
36. Sailaja AK, Shreya M. Preparation and characterization of naproxen loaded niosomes by ether injection method. Nano Biomed. Eng. 2018;10(2):174-80. DOI: 10.5101/nbe.v10i2.p174-180
37. Okafo SE, Ordu JI, Ofagbor G, Agbamu E. Evaluation of physicochemical, *in vivo* analgesic and antiinflammatory activities of *Brachystegia eurycoma* gum-based naproxen loaded niosomal gels. German Journal of Pharmaceuticals and Biomaterials. 2023;2(1):26-37. DOI: 10.5530/gjpb.2023.1.3
38. John CR, Sailaja AK. A curcumin loaded niosomes as novel drug delivery system by ether injection method. Drug Discovery. 2023;17:e19dd1918. DOI: 10.23880/nnoa-16000237
39. Singh CH, Jain CP, Kumar BN. Formulation, characterization, stability and *in vitro* evaluation of nimesulide niosomes. Pharmacophore. 2011;2(3-2011):131-48.
40. Negi P, Aggarwal M, Sharma G, Rathore C, Sharma G, Singh B, Katare OP. Niosome-based hydrogel of resveratrol for topical applications: An effective therapy for pain related disorder (s). Biomedicine & Pharmacotherapy. 2017;88:480-7. DOI: 10.1016/j.biopha.2017.01.083
41. Ge X, Wei M, He S, Yuan WE. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics. 2019;11(2):55. DOI: 10.3390/pharmaceutics11020055
42. Sankhyan A, Pawar P. Recent Trends in Niosome as Vesicular DrugDelivery System. Journal of Applied Pharmaceutical Science. 2012(Issue):20-32. DOI: 10.7324/JAPS.2012.2625
43. Jothy MA, Shanmuganathan S. An overview on niosome as carrier in dermal drug delivery. Journal of pharmaceutical sciences and research. 2015;7(11):923.
44. Izhar MP, Hafeez A, Kushwaha P, Simrah. Drug Delivery Through Niosomes: A Comprehensive Review with Therapeutic Applications. Journal of Cluster Science. 2023;34(5):2257-73. DOI: 10.1007/s10876-023-02423-w
45. Yadav NK, Nanda S, Sharma G, Katare OP. Systematically optimized ketoprofen-loaded novel proniosomal formulation for periodontitis: *in vitro* characterization and *in vivo* pharmacodynamic evaluation. AAPS PharmSciTech. 2017;18:1863-80. DOI: 10.1208/s12249-016-0665-1
46. Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. European journal of pharmaceutics and biopharmaceutics. 2005;59(3):485-90. DOI: 10.1016/j.ejpb.2004.09.006
47. Ammar HO, Ghorab M, El-Nahhas SA, Higazy IM. Proniosomes as a carrier system for transdermal delivery of tenoxicam. International journal of pharmaceutics. 2011;405(1-2):142-52. DOI: 10.1016/j.ijpharm.2010.11.003
48. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. European journal of pharmaceutics and biopharmaceutics. 2019;144:18-39. DOI: 10.1016/j.ejpb.2019.08.015
49. Shahiwala, A. and Misra, A., Studies in topical application of niosomally entrapped nimesulide, J Pharm Pharm Sci. 2002;5(3):220-5.
50. Sahin NO. Niosomes as nanocarrier systems. Nanomaterials and nanosystems for biomedical applications. 2007:67-81. DOI: 10.1007/978-1-4020-6289-6_4
51. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. Journal of Drug Delivery Science and Technology. 2020;56:101581. DOI: 10.1016/j.jddst.2020.101581
52. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014;185:22-36. DOI: 10.1016/j.jconrel.2014.04.015
53. Guinedi AS, Mortada ND, Mansour S, Hathout RM. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. International journal of pharmaceutics. 2005;306(1-2):71-82. DOI: 10.1016/j.ijpharm.2005.09.023
54. Obeid MA, Khadra I, Mullen AB, Tate RJ, Ferro VA. The effects of hydration media on the characteristics of non-ionic surfactant vesicles (NISV) prepared by microfluidics. International journal of pharmaceutics. 2017;516(1-2):52-60. DOI: 10.1016/j.ijpharm.2016.11.015
55. Reddy KT, Gandla K. Novel Vesicular Drug Delivery Systems Proniosomes. Pharm Res. 2022;6(3):000272. DOI: 10.23880/oajpr-16000272
56. Elmowafy E, El-Derany MO, Biondo F, Tiboni M, Casettari L, Soliman ME. Quercetin loaded monolaurate sugar esters-based niosomes: Sustained release and mutual antioxidant—hepatoprotective interplay. Pharmaceutics. 2020;12(2):143. DOI: 10.3390/pharmaceutics12020143
57. Shilakari Asthana G, Asthana A, Singh D, Sharma PK. Etodolac containing topical niosomal gel: formulation development and evaluation. Journal of drug delivery. 2016;2016. DOI: 10.1155/2016/9324567
58. Manosroi A, Jantrawut P, Manosroi J. Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium. International journal of pharmaceutics. 2008;360(1-2):156-63. DOI: 10.1016/j.ijpharm.2008.04.033
59. Tavano L, de Cindio B, Picci N, Ioele G, Muzzalupo R. Drug compartmentalization as strategy to improve the physico-chemical properties of diclofenac sodium loaded niosomes for topical applications. Biomedical microdevices. 2014;16:851-8. DOI: 10.1007/s10544-014-9889-6
60. John CR, Sailaja AK. A curcumin loaded niosomes as novel drug delivery system by ether injection method. Drug Discovery. 2023;17:e19dd1918. DOI: 10.23880/nnoa-16000237
61. El-Badry M, Fetih G, Fathalla D, Shakeel F. Transdermal delivery of meloxicam using niosomal hydrogels: *in vitro* and pharmacodynamic evaluation. Pharmaceutical development and technology. 2015;20(7):820-6. DOI: 10.3109/10837450.2014.926919
62. El-Ridy MS, Yehia SA, Mohsen AM, El-Awdan SA, Darwish AB. Formulation of niosomal gel for enhanced transdermal lornoxicam delivery: *in vitro* and *in vivo* evaluation. Current Drug Delivery. 2018;15(1):122-33. DOI: 10.2174/1567201814666170224141548
63. Ge X, Wei M, He S, Yuan WE. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics. 2019;11(2):55. DOI: 10.3390/pharmaceutics11020055
64. Qumbar M, Imam SS, Ali J, Ahmad J, Ali A. Formulation and optimization of lacidipine loaded niosomal gel for transdermal delivery: *in vitro* characterization and *in vivo* activity. Biomedicine & Pharmacotherapy. 2017;93:255-66. DOI: 10.1016/j.biopha.2017.06.043
65. Rajeev J, Kamalasanan K, Sapa H, Sabitha M, Abhi C. Controlled release nanomedicine (CRNM) of aspirin using "biomimetic niosomal nanoparticles (BNNs)" for Covid-19 and cardiovascular treatment: DOE based optimization. OpenNano. 2023;9:100119. DOI: 10.1016/j.onano.2022.100119
66. El-Sayed MM, Hussein AK, Sarhan HA, Mansour HF. Flurbiprofen-loaded niosomes-in-gel system improves the ocular bioavailability of flurbiprofen in the aqueous humor. Drug development and industrial pharmacy. 2017;43(6):902-10. DOI: 10.1080/03639045.2016.1272120
67. Firozian F, Karami S, Ranjbar A, Azandaryani MT, Nili-Ahmadabadi A. Improvement of therapeutic potential N-acetylcysteine in acetaminophen hepatotoxicity by encapsulation in PEGylated nano-niosomes. Life Sciences. 2020;255:117832. DOI: 10.1016/j.lfs.2020.117832
68. Abou-Taleb HA, Khallaf RA, Abdel-Aleem JA. Intranasal niosomes of nefopam with improved bioavailability: preparation, optimization, and *in vivo* evaluation. Drug design, development and therapy. 2018:3501-16. DOI: 10.2147/DDDT.S177746
69. Muzzalupo R, Tavano L, Cassano R, Trombino S, Ferrarelli T, Picci N. A new approach for the evaluation of niosomes as effective transdermal drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics. 2011;79(1):28-35. DOI: 10.1016/j.ejpb.2011.01.020

Cite this article: Pandey P, Pal R, Khadam VKR, Tiwari A, Chawra HS, Singh RP. Advancement and Characteristics of Non-Ionic Surfactant Vesicles (Niosome) and their Application for Analgesics. Int. J. Pharm. Investigation. 2024;14(3):616-32.