International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 30-11-2025, Accepted: 30-12-2025, Published: 14-01-2026
Volume 11, Issue 1, 2026, Page No. 1-6

Emerging trends in Niosomal sublingual film drug delivery system

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Abstract
Sublingual Niosomal films represent a promising drug-delivery platform designed to enhance the bioavailability and therapeutic performance of molecules with poor oral absorption or extensive first-pass metabolism. In this study, niosomes were prepared using non-ionic surfactants and cholesterol via the thin-film hydration technique and subsequently incorporated into fast-dissolving polymeric sublingual films. The films were evaluated for physicochemical properties, including thickness, folding endurance, surface pH, disintegration time and drug content uniformity. Entrapment efficiency, particle size and zeta potential of the niosomes were also characterized to confirm vesicular stability and suitability for transmucosal delivery. Ex *vivo* permeation studies demonstrated significantly enhanced drug flux across sublingual mucosa when compared with conventional films, attributed to the vesicular structure that facilitates improved drug retention and diffusion. *In vitro* release profiling revealed sustained yet rapid-onset release behaviour, while stability studies confirmed the integrity of both film and niosomal vesicles over the test period. Overall, the developed sublingual niosomal films offer a robust, patient-friendly and efficient route for systemic drug delivery, making them a viable alternative for drugs requiring rapid action and improved bioavailability.

Keywords: Niosomes, compositions, methods of preparation, Sublingual film formulation

Introduction
The oral route remains the most commonly used and preferred approach for drug administration owing to its high patient compliance, which is attributed to its convenience, safety and ease of use. Consequently, oral bioavailability is a critical parameter in drug discovery and development, as it depends on the fraction of the administered dose that survives gastrointestinal degradation, escapes intestinal metabolism and avoids hepatic first-pass elimination. Factors affecting oral bioavailability can be broadly classified into physiological, physicochemical and biopharmaceutical aspects. Among these, the physicochemical characteristics of the drug are particularly important, as they significantly influence oral absorption and metabolic behavior [1].

The pharmaceutical industry has recently become more interested in fast-dissolving sublingual films because of their better patient compliance, precise dose, quick onset of action, pleasing taste, and ease of handling and administration. These films are made of thin oral strips made of hydrophilic polymers that dissolve quickly in the mouth to release the drug [2].

The sublingual film is a perfect intraoral fast-dissolving medication administration method that meets the market's unmet needs. One such innovative strategy to boost consumer acceptance is oral fast-dissolving film (FDF), which dissolves quickly and is self-administered without the need for chewing or water. is simple to handle and administer, has an easy-to-use container, reduces bad taste, and is easy to make. The film is positioned on the tongue's floor or top. It is held at the application site and quickly releases the active ingredient for systemic or local absorption. Due to patients' poor acceptance and adherence to current delivery regimens, the small market size of pharmaceutical companies and drug uses, and the high expense of illness management,
non-invasive delivery technologies remain necessary [3].

Fig 1: Oral thin film pictorial form

The use of drug delivery systems to increase the oral bioavailability of active drugs has drawn more attention in recent years; in particular, nanosized drug delivery systems (NDDSs) are becoming more popular in this area [5].

Drug carriers are biocompatible devices used in pharmaceutical, cosmetic, and nutraceutical applications to carry molecules.
Conventional vesicles used as drug carriers can be categorized into two major kinds based on the carrier substance.

1. **Microparticulate system**
- Microspheres
- Nanospheres
- Solid lipid nanoparticles
- Microcapsules

2. **Vesicular systems**
- Liposomes
- Niosomes
- Ethosomes
- Transferosomes [6]

Niosomes
Niosomes are spherical vesicular systems composed of a bilayer formed by non-ionic surfactants in different combinations and molar ratios. Their formulation typically includes alkyl ethers, cholesterol and a charge-inducing agent. The non-ionic surfactant molecules are amphiphilic, containing a hydrophilic head and a hydrophobic tail, which help enhance permeability and solubility. Niosomes offer similar advantages to phospholipid vesicles (liposomes), as they can encapsulate both hydrophilic and lipophilic drug molecules and provide controlled drug release, making them versatile carriers for various drug delivery applications. Compared to liposomes, niosomes exhibit several benefits, including higher surfactant and chemical stability, easier formulation, simple and cost-effective synthesis methods, the ability to be prepared and stored under ambient conditions and convenient scaling without issues related to purity [7].

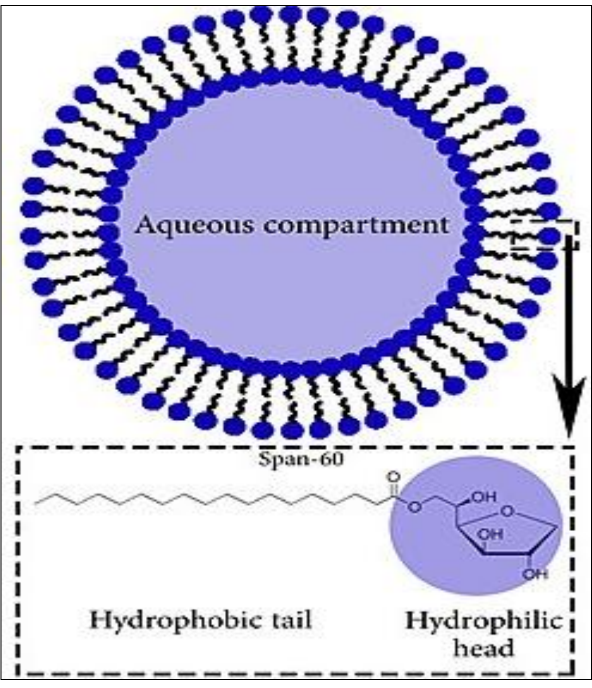

Fig 2: Structure of niosomes [8]

Composition of niosomes
The two major components used for the preparation of niosomes are,
1. Cholesterol.
2. Nonionic surfactants.

- **Cholesterol**

Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes preparation

- **Non-ionic surfactant [9]**

The role surfactants play a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes.
E.g.
- Spans (span 60, 40, 20, 85, 80)
- Tweens (tween 20, 40, 60, 80)
- Brijs (brij 30, 35, 52, 58, 72, 76). The non-ionic surfactants possess a hydrophilic head and a hydrophobic tail.

Advantages [10]
1. Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as amphiphilic drugs.
2. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
3. The drug can release in the sustained/controlled manner.
4. No special conditions required for handling and storage of surfactants.
5. The drug's regulated release is made possible by the depot formulation.
6. Poorly soluble drugs have increased oral bioavailability.
7. Surfactants possess following response biodegradable, biocompatible, non-toxic and nonimmunogenic.
8. They can protect the active moiety from biological circulation.
9. Drug protection from enzyme metabolism.

10. They can enhance the permeation of drugs through the skin.
11. They improve the therapeutic profile of the drug molecules due to delayed clearance from the circulation.

Limitations of Niosomes [9]

1. Physical instability: niosomes aqueous suspensions have a limited shelf life
2. Aggregation
3. Fusion
4. Leaking of entrapped drug: After over time drug leaking
5. Hydrolysis of encapsulated drugs which limits the shelf life of the dispersion.

Table 1: Difference between niosomes and liposomes [11]

Niosomes Vs. Liposome

Liposomes	Niosomes
Vesicles made up of concentric bilayer of phospholipids	Vesicles made up of surfactants with or without incorporation of cholesterol.
Size ranges from 10-3000nm	Size ranges from 10-100nm
Comparatively expensive	Inexpensive
Special storage condition are required	No such special requirement
Phospholipids used are unstable	Non-ionic surfactants are stable
Comparatively more toxic	Less toxic

Methods of preparation

1. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator)

Chloroform and ethanol (1:2), two volatile organic solvents, were used to dissolve the mixture of vesicle-forming materials, such as cholesterol and surfactant, in a round-bottom flask. A small coating of solid mixture was left on the flask wall after the organic solvent was extracted using a rotary evaporator above the lipid transition temperature.
Ten milliliters of aqueous phase (pH 7.4 buffer) could be used to rehydrate the dried surfactant film at temperatures between 0 and 60 degrees Celsius while gently stirring. Typical multilamellar niosomes were created by this procedure [9].

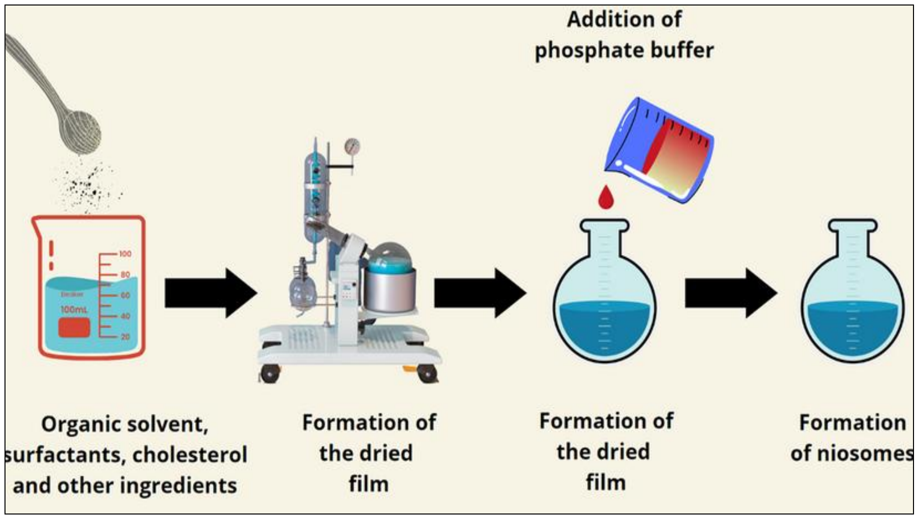

Fig 3: Hand Shaking Method

2. Ether injection method

By gradually adding a solution of surfactant dissolved in diethyl ether to warm water kept at 60°C, this technique offers a way to create niosomes. A 14-gauge needle is used to inject the surfactant mixture in ether into a material's aqueous solution. Single-layered

vesicles are created when ether vaporizes. The vesicle's diameter ranges from 50 to 1000 nm, depending on the conditions [10].

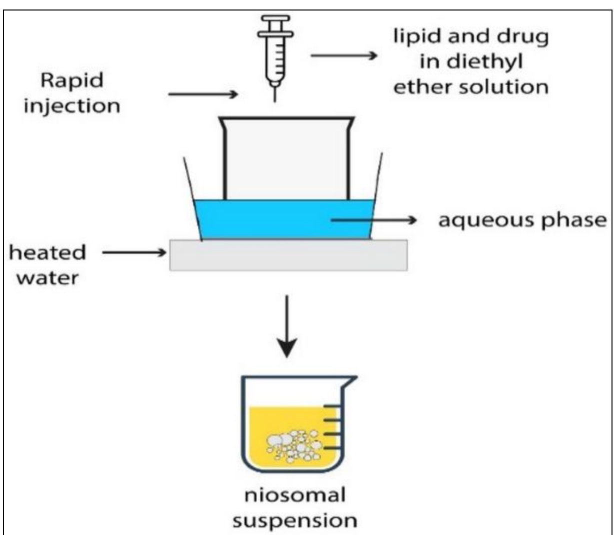

Fig 4: Ether injection method

3. Sonication

In a scintillation vial, the surfactant and cholesterol mixture are usually combined with the aqueous phase. It is then homogenized with a sonic probe. Niosomes of the small unilamellar (SUV) type are the resulting vesicles (Baillie *et al*., 1986). SUV niosomes are larger than SUV liposomes; that is, their diameter is greater than 100 nm, whereas that of SUV liposomes is less than that. By sonicating MLV-type vesicles, such as those produced by the previously described film technique, SUV niosomes can be produced. A bath type sonicator is better suitable for greater volume samples, whereas a probe type sonicator is employed for smaller volume samples [12].

4. Reveres phase evaporation technique

Ether and chloroform are used to dissolve cholesterol and surfactant (1:1). After adding a drug-containing aqueous phase, the two phases are sonicated at 485°C. A tiny amount of phosphate buffered saline (PBS) is added, and the resulting transparent gel is further sonicated. At 40°C and low pressure, the organic phase is eliminated. Niosomes are produced by diluting the resulting viscous noisome suspension with PBS and heating it to 60°C for 10 minutes in a water bath [13].

Characterization of Niosomes

- **Drug content**

Niosomal suspension equivalent to 10mg taken in a volumetric flask of 100 ml and volume was made up by phosphate buffer pH7.4 after that 1ml of this mixture was diluted to10ml by phosphate buffer pH 7.4 and the percentage dug content was observed at 275nm using uv spectrophotometer [14].

- **Determination of vesicle size & shape**

This is performed for characterization of vesicle’s size and shape. Vesicle size of niosomes were determined by using optical microscopy method using calibrated optical microscope [15]

- **PH**

2.5 g of gel were accurately weighed and dispersed in 25 ml of distilled water. The pH of the dispersion was measured by using a digital pH meter [16].

- **Entrapment efficiency**

Entrapment efficiency of niosomes was determined by exhaustive dialysis method [15]

$$\text{Percent entrapment} = \frac{total\ drug - diffused}{total\ drug} 100$$

- **Stability studies**

It can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM [16].

- **Preparation of sublingual Niosomal film.**

Following processes can be used to manufacture fast dissolving films:

1. Solvent casting
2. Semi solid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

1. Solvent casting method

The solvent casting process involves dissolving water-soluble polymers in water and dissolving the medicine and other excipients in a suitable solvent. The two solutions are then combined, agitated, and cast into a Petri plate that has been dried and cut to uniform dimensions [17].

2. Semisolid casting

A homogenous viscous solution is created by combining a solution of an acid-insoluble polymer with a solution of a water-soluble film-forming polymer. 1:4 is the ideal ratio. For instance, cellulose acetate butyrate and cellulose acetate phthalate. After that, it is sonicated and applied to casting film that hasn't been treated [18].

3. Solid dispersion extrusion

This process creates solid dispersions by extruding immiscible components with the medication. Lastly, dies are used to mold the solid dispersions into films.

4. Rolling method

The rolling method involves rolling a drug-containing solution or suspension on a carrier. Water and a combination of water and alcohol make up the majority of the solvent. The film is cut into the appropriate shapes and sizes after being dried on the rollers [17].

- **Evaluation Parameters**

1. Thickness

The patch's thickness was measured using a digital Vernier Calliper with a minimum count of 0.01mm at various locations on the film. The patch's thickness was measured at three different locations and an average and standard deviation were calculated [19].

2. Weight variation

Three (2 cm × 2 cm) films from each batch of the formulation were weighed separately to assess the weight variation of the films, and the average weight was computed. For this, an electronic balance was utilized. The

average weight and the individual weight shouldn't differ substantially [20].

3. Folding endurance
Folding endurance was measured by repeatedly folding the film in the same spot until the strip broke. The folding endurance value was calculated as the number of times the film was folded without breaking [19].

4. Tensile strength
The highest stress that may be applied to a strip specimen until it breaks is known as its tensile strength. It is computed using the following formula: the applied load at rupture divided by the strip's cross-sectional area [21].

5. Percentage elongation
The amount that a substance stretches under stress is referred to as strain. Strain is essentially calculated by dividing the distortion of the film by the initial dimension of the substrate. Generally speaking, the longer the film, the more plasticizer it contains [22]. The calculation formula is

$$\text{Strain} = \frac{\text{Change in length (elongation)}}{\text{Original length (gauge length)}}$$

6. Drug content uniformity
The film (2cm x 2cm) was cut at three different places with nominal drug content. Each film was dissolved in 100ml of phosphate buffer pH 6.8 (stimulated saliva fluid) for 20 minutes with continuous shaking to obtain a homogenous solution. 10ml of the above solution was filtered to remove polymer residues if any and the filtrate obtained was made up to 100ml with phosphate buffer pH 6.8 in a volumetric flask and the absorbance was measured using UV visible spectrophotometer [23].

7. Surface pH
A 4 cm2 part of the film was cut, and it was placed in distilled water for an hour in a glass tube to swell to measure the surface pH of the film. The combined glass electrode of the pH meter was then brought close to the film's surface and it was given a minute to acclimatize before measuring the surface pH. The average values of the three replicated experiments were recorded [24].

8. *In vitro* diffusion studies
The release studies of sublingual niosomal film were carried out using Franz diffusion Cell [19].

Conclusions
The developed sublingual niosomal films successfully combined the advantages of vesicular drug delivery with the rapid absorption potential of the sublingual route. Incorporation of niosomes into polymeric films improved drug entrapment, stability and permeation across the sublingual mucosa, resulting in enhanced bioavailability compared with conventional formulations. The films demonstrated favorable mechanical properties, fast disintegration and consistent drug release, confirming their suitability for patient-friendly, non-invasive systemic delivery. Overall, sublingual niosomal films represent an effective and innovative platform for delivering drugs that require rapid onset of action or avoidance of first-pass metabolism and they hold strong potential for future clinical application.

Acknowledgment
Our appreciation extends to the SJM college of pharmacy and library that provided access to relevant literature. We express our sincere gratitude to our mentor and college for their valuable guidance and insightful discussions throughout the preparation of this review article.

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