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Review Paper

Recent Advances in Novasomal Transdermal Patches for Enhanced Skin Permeation.

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ABSTRACT

Novasomes have recently gained attention as promising nanovesicular carriers for transdermal drug delivery systems due to their enhanced structural stability and high drug encapsulation capability. These vesicles are composed of non-ionic surfactants, free fatty acids, and cholesterol, forming multi-lamellar structures that facilitate both hydrophilic and lipophilic drug incorporation. In transdermal patch applications, novasomes improve drug permeation across the stratum corneum by fluidizing skin lipids and promoting sustained drug release. Their nano-sized architecture enhances surface contact with the skin, thereby increasing drug retention and systemic absorption while minimizing first-pass metabolism. Compared to conventional transdermal formulations, novasomal patches offer advantages such as controlled release profiles, improved bioavailability, reduced dosing frequency, and better patient compliance. Recent formulation strategies, including optimization through design-based approaches, have further improved vesicle size distribution, entrapment efficiency, and stability. Despite encouraging in vitro and ex vivo permeation results, challenges related to scale-up production, long-term stability, and clinical validation require further investigation. This review highlights the formulation principles, mechanisms of skin permeation, evaluation parameters, and future prospects of novasome-based transdermal patches

INTRODUCTION

Novasomes are advanced non-ionic surfactant-based vesicular drug delivery systems developed to overcome limitations associated with conventional carriers such as liposomes and niosomes. These multi-lamellar vesicles are composed primarily of non-ionic surfactants, cholesterol, and free fatty acids, forming stable bilayered structures capable of encapsulating both hydrophilic and lipophilic therapeutic agents. Due to their unique architecture, enhanced drug loading capacity, and improved membrane permeability characteristics, novasomes have gained increasing attention in pharmaceutical research for topical,

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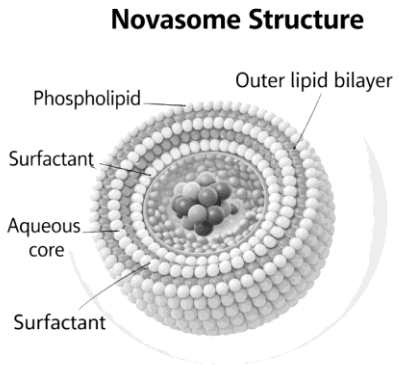
transdermal, ocular, nasal, and systemic drug delivery applications.

The growing demand for targeted and controlled drug delivery systems has accelerated research into nanocarriers that can improve bioavailability, reduce dosing frequency, minimize systemic toxicity, and enhance patient compliance. Within this context, novasomes represent a promising platform offering structural flexibility, formulation adaptability, and enhanced physicochemical stability.

1 Structure of Novasome



The illustrated structure represents a typical novasome, a multi-lamellar vesicular system composed primarily of non-ionic surfactants, cholesterol, and fatty acid components arranged in concentric lipid bilayers. The outer lipid bilayer forms a protective boundary that stabilizes the vesicle and regulates interaction with biological membranes. Beneath this layer, multiple surfactant-based bilayers surround a central aqueous core, allowing simultaneous encapsulation of both hydrophilic drugs (within the aqueous core) and lipophilic drugs (within the lipid bilayers). The amphiphilic nature of the surfactants facilitates vesicle self-assembly and enhances membrane permeability. This multilayered architecture contributes to high drug-loading capacity, improved structural stability, and sustained drug release characteristics, making novasomes suitable for advanced drug delivery applications, particularly in transdermal and topical systems.

1.2 Mechanism of Action of Novasomal Transdermal Patch

Novasomal transdermal systems enhance drug delivery through a combination of vesicular transport and reversible modulation of the stratum corneum barrier. After application, the occlusive patch increases skin hydration, which loosens the tightly packed lipid structure of the outermost skin layer. The non-ionic surfactants present in novasomes interact with intercellular lipids, increasing membrane fluidity and temporarily reducing barrier resistance. Simultaneously, the multilamellar vesicles adhere to and partially fuse with skin lipids, facilitating drug partitioning into the epidermis. The encapsulated drug is released in a controlled manner from the vesicular bilayers, creating a sustained concentration gradient that promotes diffusion across deeper skin layers and into systemic circulation. This dual action of permeation enhancement and controlled release results in improved bioavailability and prolonged therapeutic effect.

2. Materials and Preparation Method of Novasomal Transdermal Patch

2.1 Materials

The development of a novasomal transdermal patch involves the strategic selection of vesicle-forming constituents, polymeric matrix materials, and auxiliary excipients to ensure vesicle stability, effective drug encapsulation, controlled release, and adequate mechanical strength of the final patch system. The choice of materials significantly influences vesicle characteristics, permeation efficiency, and therapeutic performance.

2.2 Vesicle-Forming Components (Novasomes)

Novasomes are typically composed of amphiphilic molecules capable of self-assembling into multilamellar vesicular structures. The principal components include:

a. **Non-ionic surfactants** (such as Span 60, Span 80, and Tween series) serve as the primary structural elements responsible for vesicle formation. Their amphiphilic nature facilitates bilayer assembly and contributes to enhanced drug permeation through interaction with stratum corneum lipids.
b. **Cholesterol** is incorporated as a membrane stabilizer to improve bilayer rigidity, reduce permeability, and prevent drug leakage. It enhances vesicular stability by modulating membrane fluidity and mechanical strength.
c. **Free fatty acids** (e.g., stearic acid, oleic acid) act as bilayer modifiers that regulate membrane flexibility and influence vesicle integrity. These components also contribute to permeation enhancement by interacting with skin lipids.
d. **Drug candidate** may be either hydrophilic or lipophilic in nature. Hydrophilic drugs are typically entrapped within the aqueous core, while lipophilic drugs are incorporated within the lipid bilayers.
e. **Organic solvents** such as chloroform, methanol, or ethanol are utilized during lipid phase preparation to dissolve surfactants, cholesterol, fatty acids, and lipophilic drugs prior to thin film formation.
f. **Hydration medium**, commonly phosphate buffer saline or distilled water, is employed to hydrate the dry lipid film and facilitate vesicle formation during the hydration stage.

2.3 Polymeric Matrix Components (Patch Base)

a. Following vesicle preparation, novasomes are incorporated into a polymeric film matrix to fabricate the transdermal patch system. The polymeric base ensures structural integrity and controlled drug diffusion.
b. **Film-forming polymers**, such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), Eudragit, or ethyl cellulose, are selected based on their film-forming capacity, biocompatibility, mechanical strength, and drug release characteristics.
c. **Plasticizers**, including propylene glycol, polyethylene glycol 400 (PEG 400), or glycerol, are added to enhance flexibility, reduce brittleness, and improve tensile properties of the film. Plasticizers also influence drug diffusion by modifying polymer chain mobility.
d. **Permeation enhancers** may optionally be incorporated to further improve transdermal flux. Agents such as terpenes, alcohols, or glycols act by temporarily altering the lipid structure of the stratum corneum.
e. **Backing membrane** is an impermeable layer that prevents drug loss from the outer surface of the patch and provides structural support.

3. Preparation Method of Novasomal Transdermal Patch

Novasomes are vesicular drug delivery systems composed of non-ionic surfactants, cholesterol, and fatty acids that enhance drug permeation through the skin. The preparation of a novasomal transdermal formulation generally involves the **thin-film hydration technique**, which is widely used for the fabrication of lipid-based vesicular carriers. Initially, the required components such as the drug (e.g., Fingolimod), cholesterol, fatty acid (such as stearic acid or oleic acid), and a non-ionic surfactant like Span 60 are selected. These components are dissolved in an organic solvent mixture, typically chloroform and ethanol in an appropriate ratio, to obtain a homogeneous lipid solution. The organic solvent is then removed

using a rotary evaporator under reduced pressure at a controlled temperature, generally around 55–60 °C, which results in the formation of a thin and uniform lipid film on the inner wall of the round-bottom flask. Subsequently, the dried lipid film is hydrated with an aqueous phase such as phosphate buffer of suitable pH while maintaining gentle agitation at an elevated temperature. Hydration of the lipid layer leads to the formation of multilamellar vesicles containing the drug within the lipid bilayers. To obtain vesicles of smaller size and narrow size distribution, the dispersion is further subjected to probe or bath sonication, which converts the multilamellar structures into nanosized novasomes. For the development of a transdermal delivery system, the prepared novasomal dispersion is incorporated into a suitable polymeric matrix. Polymers such as hydroxypropyl methylcellulose (HPMC) or carbopol are commonly used to form the patch matrix, while plasticizers such as polyethylene glycol or propylene glycol are added to improve flexibility and film-forming properties. The final formulation is cast and allowed to dry to produce a stable novasomal transdermal patch capable of providing controlled drug release through the skin.

3.1 Materials Used in Novasomal Transdermal Patch

1. **Drug (Active Pharmaceutical Ingredient)**
   The therapeutic drug intended for transdermal delivery (e.g., fingolimod or other lipophilic drugs).
2. **Non-ionic Surfactant (Span 60)**
   Acts as a vesicle-forming agent and stabilizes the novasomal structure.
3. **Cholesterol**
   Provides rigidity and stability to the lipid bilayer of novasomes.
4. **Fatty Acid (Oleic Acid / Stearic Acid)**
   Functions as a membrane component and penetration enhancer to improve skin permeation.
5. **Organic Solvents (Chloroform and Ethanol)**
   Used for dissolving lipids and drug during the initial stage of formulation.
6. **Hydration Medium (Phosphate Buffer pH 6.8)**
   Helps in hydration of the thin lipid film to form novasomal vesicles.
7. **Polymer for Patch Formation (Carbopol / HPMC)**
   Forms the polymeric matrix of the transdermal patch.
8. **Plasticizers (Propylene Glycol / PEG)**
   Improve flexibility, elasticity, and mechanical strength of the patch.

3.2 Preparation Methods of Novasomal Transdermal Patch

3.1 Thin Film Hydration Method

The thin film hydration technique is one of the most commonly used methods for the preparation of novasomes. In this method, the drug, non-ionic surfactants (such as Span series), fatty acids, and cholesterol are dissolved in a mixture of organic solvents like chloroform and ethanol. The solvent is then evaporated under reduced pressure using a rotary evaporator, resulting in the formation of a thin lipid film on the wall of a round-bottom flask. This dry film is subsequently hydrated with an aqueous phase while continuously rotating the flask. Hydration causes the lipid layers to swell and detach, leading to the formation of multilamellar novasomal vesicles. Further size reduction can be achieved by sonication or extrusion to obtain uniform vesicles suitable for transdermal delivery.

3.2 Ethanol Injection Method

In the ethanol injection method, the lipid components including surfactants, fatty acids, cholesterol, and the drug are dissolved in ethanol to form an organic phase. This organic solution is slowly injected into an aqueous phase under continuous stirring. As ethanol diffuses rapidly into the aqueous medium, the lipids spontaneously assemble to form novasomal vesicles. The formation of vesicles occurs due to the reduction in solvent polarity which promotes self-assembly of amphiphilic molecules. This method is relatively simple and does not require complex equipment, making it suitable for the preparation of nanosized vesicular systems for transdermal applications.

3.3 Reverse Phase Evaporation Method

The reverse phase evaporation technique involves the formation of a water-in-oil emulsion. In this method, lipids and surfactants are first dissolved in an organic solvent such as chloroform or diethyl ether. An aqueous phase containing the drug is then added to the organic phase and emulsified using sonication or mechanical agitation. The organic solvent is gradually removed under reduced pressure, leading to the formation of vesicles with a large aqueous core. This method generally produces novasomes with high drug entrapment efficiency and is particularly useful for encapsulating hydrophilic drugs.

3.4 Preparation of Novasomal Transdermal Patch (Solvent Casting Method)

After the preparation of novasomal dispersion, it is incorporated into a polymeric matrix to form a transdermal patch. In the solvent casting method, suitable polymers such as HPMC, PVA, or ethyl cellulose are dissolved in an appropriate solvent system. Plasticizers like propylene glycol or PEG are added to improve flexibility of the film. The prepared novasomal suspension is then mixed with the polymeric solution to obtain a uniform mixture. This mixture is poured onto a flat surface or casting plate and allowed to dry at controlled temperature to form a thin film. After complete drying, the film is carefully removed and cut into patches of desired size for transdermal drug delivery.

4. Characterization of Novasomal Transdermal Patch

4.1 Particle Size and Size Distribution

Particle size and polydispersity index (PDI) of novasomes are determined using **Dynamic Light Scattering (DLS)** with a particle size analyzer. The analysis is generally performed at controlled temperature (around 25 °C). The mean particle size indicates the vesicle diameter, while the **PDI value** represents the uniformity of the vesicle population. A PDI value below **0.3** indicates a homogeneous and stable dispersion. Smaller particle size improves skin penetration and drug delivery efficiency.

4.2. Morphology Study (Transmission Electron Microscopy – TEM)

The structural morphology of novasomes is examined using **Transmission Electron Microscopy (TEM)**. A drop of the hydrated novasomal dispersion is placed on a **carbon-coated copper grid** and stained with a contrast agent such as **phosphotungstic acid**. After drying, the sample is observed under the electron microscope. TEM images provide information about **vesicle shape, lamellarity, and surface morphology**, confirming the spherical structure of novasomes.

4.3 Entrapment Efficiency (%EE)

Entrapment efficiency is an important parameter used to determine the amount of drug successfully

encapsulated within the vesicular structure of novasomes. It indicates the loading capacity of the carrier system and helps in assessing the effectiveness of the formulation process.

Methods Used:

Several techniques can be employed to separate the free (unentrapped) drug from the drug incorporated inside the vesicles:

- **Ultracentrifugation method:** The novasomal dispersion is centrifuged at high speed to sediment the vesicles. The free drug remains in the supernatant, while the entrapped drug is present in the pellet.
- **Dialysis method:** The dispersion is placed in a dialysis membrane and immersed in an appropriate buffer solution. The free drug diffuses through the membrane, whereas the encapsulated drug remains inside the vesicles.
- **Gel filtration (size exclusion chromatography):** This technique separates the vesicles from the free drug using a column packed with gel beads based on molecular size differences.

After separation, the vesicles are disrupted using a suitable solvent and the drug content is quantified.

Formula:

$$\%EE = \frac{\text{Amount of Entrapped Drug}}{\text{Total Amount of Drug Added}} \times 100$$

Higher entrapment efficiency generally indicates better drug incorporation and improved therapeutic potential of the novasomal system.

4.4 Drug Content Uniformity

Drug content uniformity is evaluated to ensure that the drug is evenly distributed throughout the novasomal formulation. Uniform distribution is necessary to maintain consistent dosing and therapeutic efficacy.

Method:

A measured quantity of the novasomal formulation is taken and disrupted using a suitable solvent to release the entrapped drug. The resulting solution is filtered and analyzed.

Analytical Technique:

The drug concentration is commonly determined using **UV–Visible spectrophotometry** at the specific wavelength corresponding to the maximum absorbance (λmax) of the drug. The obtained absorbance is compared with a calibration curve to calculate the drug content.

Uniform drug distribution indicates proper formulation and stability of the vesicular system.

4.5 In-Vitro Drug Release Study

The in-vitro drug release study is performed to evaluate the rate and extent of drug release from the novasomal formulation. It helps in predicting the release behavior and therapeutic performance of the transdermal system.

Method:

The **dialysis membrane diffusion technique** is widely used for this purpose. The novasomal formulation is placed inside a dialysis membrane, which acts as a semi-permeable barrier.

Experimental Conditions:

1. **Release medium:** Phosphate buffer solution (pH 5.5 or pH 7.4), simulating skin or physiological conditions.
2. **Temperature:** Maintained at **32 ± 0.5°C**, which corresponds to the normal surface temperature of human skin.
3. **Procedure:** The dialysis bag containing the formulation is immersed in the release medium with continuous stirring. At predetermined time intervals, samples are withdrawn and replaced with fresh buffer to maintain sink conditions.

The collected samples are analyzed using **UV–Visible spectrophotometry** to determine the amount of drug released over time.

This study provides valuable information about the **drug release kinetics, diffusion characteristics, and sustained release behavior** of the novasomal transdermal formulation.

CONCLUSION

The study demonstrated that vesicular systems based on non-ionic surfactants can significantly improve the transdermal delivery of hydrophilic drugs. Niosomes prepared from different surfactants were successfully characterized in terms of vesicle size, morphology, and drug encapsulation efficiency, showing stable and uniformly distributed vesicles. Permeation studies revealed that drug-loaded niosomes produced a markedly higher transdermal flux compared to drug solutions or surfactant sub-micellar systems. In contrast, pretreatment of the skin with surfactant solutions or empty vesicles did not enhance drug permeation. These findings suggest that the improved permeation is mainly associated with the organized vesicular structure of niosomes rather than the surfactant molecules alone. Therefore, niosomal systems can be considered promising carriers for enhancing transdermal drug delivery and improving the therapeutic effectiveness of hydrophilic drugs.

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