Niosomal-Based Transdermal Drug Delivery System for Effective Management of Rheumatoid Arthritis

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Abstract

Chronic inflammatory disorders such as arthritis, psoriasis, eczema, and inflammatory skin diseases require long-term pharmacotherapy, often associated with systemic adverse effects and poor patient compliance. Topical and transdermal drug delivery systems offer localized drug action with reduced systemic exposure; however, their therapeutic effectiveness is frequently limited by the barrier properties of the stratum corneum. Conventional topical formulations such as creams, ointments, and gels often fail to deliver adequate drug concentrations to deeper skin layers, resulting in suboptimal therapeutic outcomes.

Niosome-loaded gels have emerged as an advanced vesicular drug delivery system capable of overcoming these limitations. Niosomes are non-ionic surfactant-based vesicles that enhance drug stability, encapsulation efficiency, and controlled drug release. Incorporation of niosomes into gel matrices combines the advantages of vesicular carriers with improved viscosity, spreadability, and residence time at the application site. This review comprehensively discusses the formulation strategies, components, preparation methods, and evaluation parameters of niosome-loaded topical and transdermal gels. Furthermore, their therapeutic applications in chronic inflammatory disorders, including arthritis and inflammatory dermatoses, are critically highlighted. Overall, niosomal gels represent a promising and patient-friendly platform for effective management of chronic inflammatory conditions.

Keywords:
Niosomes; Topical drug delivery; Transdermal gels; Chronic inflammatory disorders; Vesicular systems; Controlled drug release

1. INTRODUCTION

1.1 CHRONIC INFLAMMATORY DISORDERS: OVERVIEW AND THERAPEUTIC CHALLENGES

Chronic inflammatory disorders encompass a wide range of conditions including rheumatoid arthritis, osteoarthritis, psoriasis, eczema, dermatitis, and inflammatory musculoskeletal diseases. These disorders are characterized by persistent inflammation, pain, tissue damage,

and functional impairment, significantly affecting patient quality of life. Long-term pharmacological management using non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunomodulatory agents is often required [1,2].

Systemic administration of anti-inflammatory drugs is associated with several adverse effects such as gastrointestinal irritation, hepatotoxicity, cardiovascular risks, and immunosuppression. These limitations necessitate the development of safer and more effective localized drug delivery approaches [3].

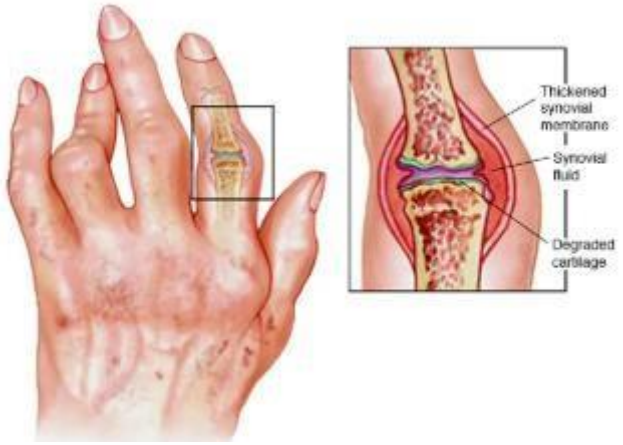

Fig.1.1 Rheumatoid Arthritis

1.2 TOPICAL AND TRANSUNGUAL DRUG DELIVERY SYSTEMS

Topical and transdermal drug delivery systems deliver drugs directly through the skin to achieve localized or systemic therapeutic effects. These systems offer advantages such as avoidance of first-pass metabolism, reduced systemic toxicity, improved patient compliance, and sustained drug release [4].

Despite these advantages, conventional topical formulations often show limited drug penetration due to the strong barrier function of the stratum corneum, particularly for hydrophilic and high-molecular-weight drugs [5].

1.3 BARRIERS TO EFFECTIVE SKIN DELIVERY

The stratum corneum is the primary barrier to percutaneous drug absorption. It consists of corneocytes embedded in a lipid matrix, restricting drug diffusion based on molecular size, lipophilicity, and formulation characteristics. In chronic inflammatory disorders, deeper skin penetration is essential for effective therapy, which conventional gels and creams often fail to achieve [6].

1.4 NEED FOR ADVANCED VESICULAR DRUG DELIVERY SYSTEMS

To overcome the limitations of conventional topical formulations, advanced vesicular carriers such as liposomes, niosomes, transfersomes, and ethosomes have been developed. Among these, niosomes have gained significant attention due to their chemical stability, costeffectiveness, and ability to encapsulate both hydrophilic and lipophilic drugs [7].

2. NIOSOME-LOADED GELS: CONCEPT, COMPOSITION, AND ADVANTAGES

2.1 CONCEPT OF NIOSOME-LOADED GELS

Niosome-loaded gels are hybrid delivery systems formed by incorporating niosomal vesicles into a suitable gel base. Niosomes are microscopic lamellar vesicles composed of non-ionic surfactants and cholesterol, capable of encapsulating drugs and releasing them in a controlled manner [8].

The gel matrix improves formulation stability, viscosity, and residence time at the site of application, enhancing therapeutic efficacy [9].

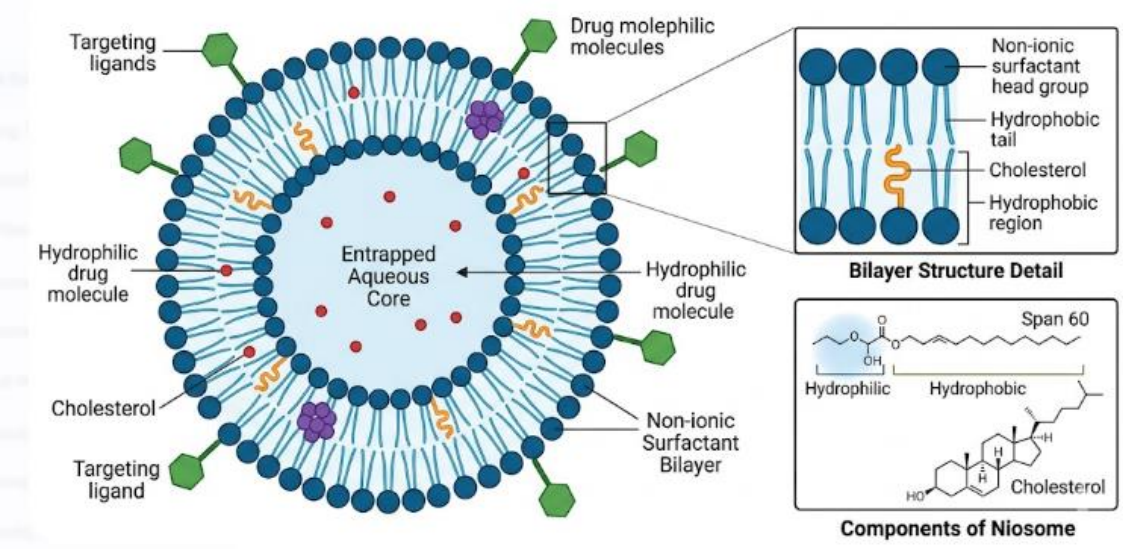

Fig.no. 2.1 Structure of Niosomes

2.2 COMPOSITION OF NIOSOME-LOADED GELS

2.2.1 Non-ionic Surfactants

Non-ionic surfactants such as Span (Span 20, Span 60) and Tween series are the primary components responsible for the formation of niosomal vesicles. Due to their amphiphilic nature, they form bilayer structures capable of encapsulating both hydrophilic and lipophilic drugs. The hydrophilic–lipophilic balance (HLB) of surfactants plays a crucial role in determining vesicle size, entrapment efficiency, and permeability characteristics [8,9].

2.2.2 Cholesterol

Cholesterol is an essential component that imparts rigidity and stability to the niosomal bilayer. It reduces membrane permeability, prevents drug leakage, and enhances vesicle integrity. The ratio of surfactant to cholesterol significantly influences the stability, fluidity, and overall performance of niosomes [9,12].

2.2.3 Drug Substance

The drug incorporated into niosomes may be either hydrophilic or lipophilic. Hydrophilic drugs are entrapped within the aqueous core, whereas lipophilic drugs are incorporated into the bilayer membrane. This dual encapsulation ability makes niosomes versatile carriers for various therapeutic agents used in inflammatory conditions [8,11].

2.2.4 Aqueous Phase

The aqueous phase is required for hydration during vesicle formation and serves as the medium for encapsulating hydrophilic drugs. Its composition, pH, and ionic strength can influence drug solubility, vesicle formation, and stability of the formulation [10].

2.2.5 Gelling Agents

Gelling agents such as Carbopol, hydroxypropyl methylcellulose (HPMC), and xanthan gum are used to convert niosomal dispersions into semisolid gels. These agents enhance viscosity, spreadability, and residence time at the site of application, thereby improving drug retention and therapeutic effectiveness. Carbopol is widely preferred due to its excellent bioadhesive and rheological properties [10,14].

2.3 ADVANTAGES OF NIOSOME-LOADED GELS

2.3.1 Enhanced Skin Penetration and Drug Localization

Niosome-loaded gels improve drug permeation across the stratum corneum by altering the lipid structure of the skin barrier. The vesicular nature of niosomes facilitates deeper drug penetration and ensures targeted drug localization at the site of inflammation, thereby enhancing therapeutic effectiveness [8,11].

2.3.2 Controlled and Sustained Drug Release

Niosomal vesicles act as drug reservoirs, allowing gradual and prolonged release of the encapsulated drug. This controlled release profile helps maintain therapeutic drug levels for an extended period, which is particularly beneficial in chronic inflammatory conditions [9,12].

2.3.3 Improved Drug Stability

Encapsulation of drugs within niosomal vesicles protects them from chemical degradation, enzymatic breakdown, and environmental factors such as light and oxidation. This leads to improved stability and shelf-life of the formulation [10,11].

2.3.4 Reduced Dosing Frequency

Due to sustained drug release and prolonged residence time at the application site, niosome-loaded gels reduce the need for frequent drug application. This improves patient convenience and treatment adherence [9,13].

2.3.5 Enhanced Patient Compliance

The gel formulation provides better spreadability, non-greasy texture, and ease of application compared to conventional ointments and creams. These characteristics improve patient acceptability and compliance, especially in long-term therapies [10,14].

2.3.6 Reduced Systemic Toxicity

By delivering drugs locally at the site of action and minimizing systemic absorption, niosomal gels significantly reduce systemic side effects commonly associated with oral or parenteral drug administration [11,12].

3. FORMULATION STRATEGIES FOR NIOSOMAL GELS

3.1 SELECTION OF SURFACTANTS

Non-ionic surfactants such as Span 60 and Tween 80 are widely used due to their low toxicity and ability to form stable vesicles. Surfactant selection significantly influences vesicle size and entrapment efficiency [12].

3.2 ROLE OF CHOLESTEROL

Cholesterol provides rigidity and stability to the niosomal bilayer, preventing vesicle leakage and improving drug retention [13].

3.3 SELECTION OF GELLING AGENTS

Gelling agents such as Carbopol 934/940 and HPMC are commonly used to convert niosomal dispersions into gels. Carbopol is preferred due to its excellent rheological properties and bioadhesiveness [14].

3.4 METHODS OF PREPARATION

Niosomes are prepared using techniques such as thin-film hydration, ether injection, and reverse-phase evaporation. The optimized niosomal suspension is then incorporated into a preformed gel base under gentle stirring to obtain a uniform niosomal gel [15].

3.4.1 Thin Film Hydration Method

The thin film hydration technique is the most commonly employed method for the preparation of niosomes due to its simplicity and reproducibility. In this method, non-ionic surfactant and cholesterol are dissolved in a volatile organic solvent such as chloroform or methanol. The solvent is then removed under reduced pressure using a rotary evaporator to form a thin lipid film on the inner wall of the flask. The dried film is hydrated with an aqueous drug solution under controlled temperature with gentle agitation, resulting in the formation of multilamellar niosomal vesicles.

This method offers high drug entrapment efficiency and is particularly suitable for lipophilic and amphiphilic drugs used in chronic inflammatory disorders **[15,16]**.

3.4.2 Ether Injection Method

In the ether injection method, a solution of surfactant, cholesterol, and drug dissolved in diethyl ether is slowly injected into a heated aqueous phase. Upon injection, the organic solvent evaporates rapidly, leading to the spontaneous formation of niosomal vesicles.

Although this method produces relatively uniform vesicles, its use is limited due to the involvement of organic solvents and difficulties in complete solvent removal [17].

3.4.3 Reverse Phase Evaporation Method

The reverse phase evaporation method involves the formation of a water-in-oil emulsion by sonication of an aqueous drug solution with surfactant and cholesterol dissolved in organic solvents. Subsequent removal of the solvent under reduced pressure results in the formation of unilamellar niosomes with high aqueous core volume.

This method is particularly advantageous for encapsulating hydrophilic anti-inflammatory drugs; however, it requires careful control of processing parameters to ensure vesicle stability [18].

3.4.4 Sonication and Size Reduction Techniques

Post-preparation size reduction techniques such as probe sonication, bath sonication, or extrusion are often employed to obtain niosomes with nanoscale size and narrow size distribution. Vesicle size reduction enhances skin permeation and improves drug deposition in deeper skin layers, which is essential for effective management of chronic inflammatory conditions **[19]**.

3.4.5 Optimization of Niosomal Formulation

Optimization of niosomal formulations is carried out by evaluating critical parameters such as vesicle size, polydispersity index, zeta potential, entrapment efficiency, and physical stability. Factorial design and response surface methodology are often used to optimize surfactant-tocholesterol ratio, hydration volume, and processing conditions **[20]**.

3.4.6 Incorporation of Niosomes into Gel Base

The optimized niosomal dispersion is incorporated into a pre-formulated gel base prepared using suitable gelling agents such as Carbopol 934/940 or HPMC. The gel base is prepared by dispersing the gelling agent in purified water followed by neutralization using triethanolamine (in the case of Carbopol) to achieve the desired pH and viscosity.

The niosomal dispersion is added slowly to the gel base under gentle stirring to ensure uniform distribution without disrupting vesicle integrity. This step enhances formulation stability and prolongs drug residence time at the site of application [21].

3.4.7 Role of Processing Parameters

Processing parameters such as hydration temperature, stirring speed, sonication time, and order of addition play a crucial role in determining vesicle characteristics and gel consistency. Improper control may result in vesicle aggregation, leakage, or loss of drug content. Therefore, careful optimization is essential to obtain reproducible and stable niosomal gels [22].

3.4.8 Scale-Up and Industrial Considerations

For large-scale production, methods such as thin film hydration combined with high-pressure homogenization are preferred due to better reproducibility and scalability. Industrial translation requires strict control of batch-to-batch consistency, sterility, and regulatory compliance. Selection of pharmaceutically acceptable excipients and solvents is critical to ensure safety and regulatory approval [23].

4. EVALUATION OF NIOSOMAL GEL

4.1. PHYSIOCHEMICAL EVALUATION

4.1.1 Vesicle Size and Polydispersity Index (PDI)

Vesicle size is a critical parameter influencing drug permeation, stability, and therapeutic efficacy of niosomal gels. Smaller vesicles exhibit enhanced skin penetration and improved drug deposition in deeper skin layers. Vesicle size is commonly measured using dynamic light scattering (DLS) techniques.

The polydispersity index (PDI) indicates the uniformity of vesicle size distribution. A PDI value below 0.3 suggests a homogeneous and stable formulation, whereas higher values indicate a broad size distribution and potential instability [16,19].

4.1.2 Zeta Potential

Zeta potential is an important indicator of the surface charge and stability of niosomal vesicles. It reflects the degree of electrostatic repulsion between particles in a dispersion. Higher absolute zeta potential values (either positive or negative) indicate better stability by preventing vesicle aggregation.

Zeta potential is measured using electrophoretic light scattering techniques and plays a crucial role in predicting the shelf-life and physical stability of the formulation [17,18].

4.1.3 pH of the Formulation

The pH of niosome-loaded gels is an essential parameter for ensuring skin compatibility and patient safety. Ideally, the pH of topical formulations should be in the range of 5.5–7 to match the physiological pH of the skin and avoid irritation.

pH is measured using a calibrated digital pH meter, and any deviation may affect drug stability, skin tolerance, and overall formulation performance [16].

4.1.4 Viscosity

Viscosity determines the flow behavior, spreadability, and retention of the gel on the skin surface. An optimal viscosity ensures that the formulation remains at the application site for a prolonged period without flowing off.

Viscosity is typically measured using a Brookfield viscometer, and it is influenced by the type and concentration of gelling agents such as Carbopol and HPMC [14,16].

4.1.5 Spreadability

Spreadability is a measure of how easily the gel can be applied over the skin. Good spreadability ensures uniform distribution of the formulation, which is essential for consistent drug delivery.

It is commonly evaluated by measuring the time required for two glass slides to slip apart under a certain load. Better spreadability enhances patient compliance and therapeutic effectiveness [14,17].

4.1.6 Homogeneity

Homogeneity refers to the uniform distribution of niosomes within the gel matrix. A homogeneous formulation ensures consistent drug content and uniform therapeutic response.

It is evaluated visually by checking for the presence of lumps, phase separation, or aggregation. A good niosomal gel should appear smooth, uniform, and free from any particulate matter [16].

4.2. ENTRAPMENT EFFICIENCY

Entrapment efficiency is determined by separating unentrapped drug and quantifying the drug content within niosomes [17].

4.3 IN VITRO DRUG RELEASE STUDIES

In vitro drug release studies are performed to evaluate the release behavior and diffusion characteristics of drugs from niosome-loaded gels. These studies are commonly carried out using Franz diffusion cells with a suitable membrane (e.g., dialysis or cellulose acetate), where the formulation is applied to the donor compartment and the receptor compartment contains phosphate buffer maintained at skin-simulating conditions (≈32 °C) [18].

Samples are withdrawn at predetermined time intervals and analyzed using UV–Visible spectrophotometry or HPLC to determine cumulative drug release. Niosomal gels typically exhibit a biphasic release pattern, characterized by an initial burst release followed by sustained drug release due to diffusion from the vesicular bilayer and gel matrix [18,19].

Release data are further fitted into kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to understand the mechanism of drug release, which is generally diffusion-controlled or anomalous transport [20].

5. APPLICATION IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

5.1.1 Rheumatoid Arthritis and Osteoarthritis

Niosome-loaded gels provide an effective localized drug delivery approach for rheumatoid arthritis (RA) and osteoarthritis (OA). They enhance drug penetration into joint tissues and maintain sustained drug release, resulting in prolonged anti-inflammatory action.

Common NSAIDs such as diclofenac, aceclofenac, and ibuprofen have shown improved therapeutic efficacy in niosomal formulations with reduced systemic side effects compared to oral therapy [20–22].

5.1.2 Application in Inflammatory Skin Disorders

Niosomal gels are widely used in the treatment of inflammatory skin conditions such as psoriasis, eczema, and dermatitis. They enhance drug localization within the epidermal and dermal layers while minimizing systemic absorption.

Drugs like corticosteroids and immunosuppressants demonstrate improved efficacy and reduced side effects due to controlled drug release and better skin penetration [21–23].

5.1.3 Transdermal Delivery of Anti-inflammatory and Analgesic Drugs

Niosome-loaded gels also facilitate transdermal delivery by overcoming the barrier properties of the stratum corneum. They act as penetration enhancers and drug reservoirs, enabling sustained systemic drug delivery.

Drugs such as diclofenac, piroxicam, and ketorolac have shown improved bioavailability and prolonged therapeutic action when delivered through niosomal gels [22–24].

6. CHALLENGES AND FUTURE PERSPECTIVES

6.1 FORMULATION AND STABILITY CHALLNEGES

One of the primary challenges associated with niosomal gel formulations is maintaining longterm physical and chemical stability. Niosomes are thermodynamically unstable vesicular systems and may undergo aggregation, fusion, leakage of encapsulated drug, or changes in vesicle size during storage. These stability issues can compromise drug content uniformity, release profile, and therapeutic efficacy.

The surfactant-to-cholesterol ratio plays a crucial role in vesicle stability. Excess surfactant may cause vesicle disruption and skin irritation, whereas insufficient surfactant can result in poor vesicle formation and low drug entrapment efficiency. Additionally, interactions between niosomes and gelling agents may alter vesicle integrity and drug release characteristics. Therefore, careful optimization of formulation components is essential to achieve stable and reproducible niosomal gels.

6.2 SKIN IRRITATION AND TOXICITY CONCERNS

Although non-ionic surfactants used in niosomal formulations are generally considered safe, prolonged topical application may lead to skin irritation, sensitization, or allergic reactions, particularly in patients with compromised skin barriers. High surfactant concentrations required for vesicle formation may disrupt skin lipids, leading to dryness or erythema.

Comprehensive dermatological safety evaluation, including skin irritation, sensitization, and repeated-dose toxicity studies, is essential before clinical application. The use of

biocompatible, biodegradable, and natural surfactants may help mitigate these concerns in future formulations.

6.3 MANUFACTURING AND SCALE – UP LIMITATIONS

Laboratory-scale preparation techniques such as thin film hydration and sonication are often difficult to scale up for industrial production due to batch-to-batch variability, high energy consumption, and limited reproducibility. Achieving uniform vesicle size and consistent drug entrapment on a large scale remains a major challenge.

Advanced manufacturing techniques such as high-pressure homogenization, microfluidization, and continuous manufacturing processes may offer better scalability and reproducibility. However, these methods require specialized equipment and rigorous process validation, which can increase production costs.

6.4 REGULATORY AND QUALITY CONTROL ISSUES

The regulatory approval of niosome-loaded gels is complicated by the lack of well-defined regulatory guidelines specific to vesicular and nanotechnology-based topical drug delivery systems. Regulatory agencies require extensive characterization of vesicle size, distribution, stability, skin penetration behavior, and long-term safety.

Quality control parameters such as vesicle morphology, drug loading efficiency, and release kinetics must be standardized to ensure consistent product performance. Establishing harmonized regulatory frameworks and standardized testing protocols will be crucial for facilitating clinical translation and commercialization.

6.5 CLINICAL TRANSLATION AND PATIENT-RELATED CHALLENGES

While preclinical studies have demonstrated promising results, limited clinical data are available on the long-term efficacy and safety of niosome-loaded gels in chronic inflammatory disorders. Variability in skin physiology, disease severity, and patient adherence can influence therapeutic outcomes.

Additionally, patient acceptance of novel topical formulations depends on factors such as texture, odor, ease of application, and cosmetic appeal. Formulations must be optimized not only for therapeutic efficacy but also for patient comfort and usability to ensure long-term compliance**.**

6.6 FUTURE PERSPECTIVES

Future research on niosome-loaded gels should focus on the development of next-generation formulations with enhanced functionality and clinical relevance. Promising future directions include:

- Stimuli-responsive niosomes capable of releasing drugs in response to pH, temperature, or enzymatic activity associated with inflammation
- Targeted niosomal systems using ligands or antibodies to improve site-specific drug delivery

- Combination therapy by co-encapsulation of anti-inflammatory drugs with antioxidants or disease-modifying agents
- Use of natural and biodegradable surfactants to improve biocompatibility and safety
- Integration of physical enhancement techniques such as microneedles or iontophoresis to further improve skin penetration.

7. CONCLUSION

Niosome-loaded topical and transdermal gels represent a highly promising and versatile drug delivery platform for the effective management of chronic inflammatory disorders. By integrating the unique advantages of non-ionic surfactant–based vesicular carriers with the patient-friendly characteristics of gel formulations, these systems successfully address many of the limitations associated with conventional topical and systemic therapies.

The ability of niosomes to encapsulate both hydrophilic and lipophilic drugs, protect labile drug molecules, and provide controlled and sustained drug release significantly enhances therapeutic outcomes. Incorporation of niosomes into gel matrices further improves formulation stability, skin adhesion, spreadability, and residence time at the site of application. These attributes collectively result in enhanced drug penetration across the stratum corneum, improved drug localization within inflamed tissues, and prolonged anti-inflammatory action.

Extensive preclinical investigations have demonstrated that niosome-loaded gels offer superior anti-inflammatory efficacy compared to conventional gels, creams, and ointments, while simultaneously reducing systemic drug exposure and associated adverse effects. Such benefits are particularly valuable in chronic inflammatory conditions, including rheumatoid arthritis, osteoarthritis, and inflammatory skin disorders, where long-term therapy is required and patient compliance plays a critical role in treatment success.

Despite the encouraging progress, challenges related to formulation stability, large-scale manufacturing, regulatory approval, and clinical validation remain. Addressing these challenges through systematic formulation optimization, adoption of scalable manufacturing technologies, and development of standardized regulatory guidelines will be essential for successful clinical translation.

Overall, with continued advancements in vesicular drug delivery technology, improved understanding of skin biology, and increased emphasis on patient-centric formulation design, niosome-loaded topical and transdermal gels hold significant potential to emerge as nextgeneration therapeutic systems for chronic inflammatory disorders. Future research and welldesigned clinical studies are expected to further establish their role in modern pharmaceutical and clinical practice.

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