Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1339-1344
DoI-10.004687/1000-9035.2025.178

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Development of Proniosomal Formulation for Enhanced Anti-Inflammatory Therapeutic Efficacy

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Article Information
Received: 21-10-2025
Revised: 15-11-2025
Accepted: 02-12-2025
Published: 24-12-2025

Keywords
Diclofenac Sodium, Anti-Inflammatory, Proniosomal-Loaded Gel, Topical Formulation.

ABSTRACT
Topical administration of anti-inflammatory drugs at the site of inflammation can overcome their systemic negative effects and increase their therapeutic activity. Proniosomal gels have earlier been reported to increase the topical distribution. Proniosomal gels are the formulations that, on in situ hydration with water from the skin, are transformed into niosomes. Proniosomal gels overcome niosomes' vesicular instability. The medicine in the niosomal vesicles penetrates the skin more quickly than the free drug. Given the proniosomal gel's topical delivery potential, the current study developed a diclofenac sodium-loaded proniosomal gel-based formulation. The coacervation phase separation approach was used to create diclofenac sodium-based proniosomal gels that were not ionic surfactants. The prepared systems were characterized for encapsulation efficiency, shape, size, and in vitro drug release. A stability study was carried out to investigate the leaching of drug from the proniosomal system during storage. The results showed that diclofenac in all the formulations was successfully entrapped, and a substantial change in release rate and an alteration in the encapsulation efficiency of diclofenac from proniosomes were observed upon varying the type of surfactant and cholesterol content.

INTRODUCTION:

Among the medications that are most frequently used to lessen pain and inflammation are non-steroidal anti-inflammatory medicines (NSAIDs). NSAIDs have an anti-inflammatory effect by inhibiting the cyclooxygenase 2 enzyme system, and they can cause stomach discomfort when they inhibit the Cox-1 enzyme system. The development of gastrointestinal (GI) adverse effects, which can range from dyspepsia to significant life-threatening episodes, is the primary issue restricting the oral use of NSAIDs. polymer, and ceramic. Microspheres that are both solid and hollow have vastly varying densities, making them suitable for various uses. Topical NSAIDs are useful in treating both acute and chronic soft tissue disorders, according to several studies. An NSAID with analgesic and antipyretic qualities, naproxen sodium [(S)-6-methoxy-alphamethyl-2naphthaleneacetic acid sodium salt] is used to treat musculoskeletal problems that have suboptimal skin delivery characteristics. NSAIDs gels have a therapeutic benefit over their oral counterparts, and they also greatly reduce the possibility of systemic adverse effects. Because topical treatment achieves plasma concentrations between 1 and 10% of those attained by oral medication, the danger of potentially harmful side effects is greatly decreased. Proniosomal gels can control drug release, conform to the contour of the treated area, and withstand physiological stress brought on by skin flexion and mucociliary movement. Proniosomes, a dry substance in gel form, can reduce issues with physical stability and avoid many of the issues with aqueous niosomes dispersions.

Topical delivery system

The phrase "topical delivery system" refers to a way of treating localized ailments by applying the formulation to the skin, eyes, nose, and vagina.

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When a medication is administered topically, it does not experience the variations in stomach pH, hepatic first-pass metabolism, or plasma level fluctuations that are common with oral drug delivery. Further research on topical medicine delivery to the skin's surface is required for the local therapy of a variety of diseases. Most foreign compounds (drugs/active moieties) exhibit resistance to permeability, which poses a significant design issue for topical drug delivery systems. Furthermore, because illness states change the permeability and barrier characteristics of skin, creating an effective topical delivery method is difficult.

Benefits of the topical route of drug administration

1. Alternative to Oral Medicine Administration
2. Low Chance of Drug Abuse
3. Minimal Chance of Digestive Issues
4. Extremely Simple Administrative Procedure

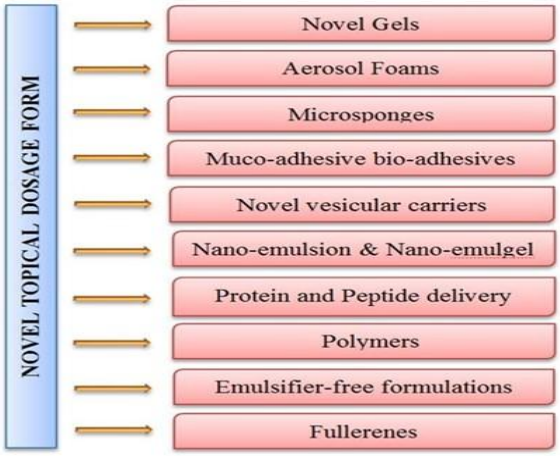

Figure 1: Branches of Topical Drug Innovation

Proniosomes:

Recent advancements in drug delivery research have emphasized the development of vesicular carrier systems to enhance therapeutic efficacy, improve bioavailability, and minimize drug-related toxicity. Among these systems, proniosomes have emerged as a promising alternative to conventional vesicular formulations such as liposomes and niosomes. Proniosomes are dry, free-flowing, or semisolid formulations that are readily converted into niosomal vesicles upon hydration. These systems are primarily composed of non-ionic surfactants, cholesterol, and aqueous phase components, enabling the encapsulation of both hydrophilic and lipophilic drugs. The primary objective of developing proniosomal drug delivery systems is to overcome the stability issues associated with niosomes, including vesicle aggregation, fusion, and drug leakage during storage. Owing to their enhanced stability, ease of handling, and extended shelf life, proniosomes have gained considerable attention as efficient drug carriers for various routes of administration.

Proniosomes are coated with a surfactant and are a dry formulation of water-soluble carrier particles. Before being used on agitation in heated aqueous media, they are quickly rehydrated to form niosomal dispersion in a matter of minutes. Proniosomes do not physically change while being transported or stored. A medication enclosed in a proniosomes vesicular structure increases the drug's penetration into the target tissue, decreases toxicity, and prolongs its existence in the systemic circulation.

Rationale and Need for Proniosomal Systems:

Conventional drug delivery systems sometimes have drawbacks such as poor drug solubility, fast drug degradation, frequent dosage, and low patient compliance. Vesicular technologies, such as niosomes, have showed promise in meeting these issues; nevertheless, their practical applicability is limited due to physical instability during long-term storage. Proniosomes overcome these limitations by remaining stable and dehydrated and generating niosomal vesicles only at the time of delivery. This feature improves formulation stability while simplifying transit and storage.

Structure:

Proniosomes are tiny structures that resemble lamellae. They mix cholesterol with a non-ionic surfactant belonging to the alkyl or dialkyl polyglycerol ether class, and then they hydrate in aqueous media. To form the bilayer, the hydrophilic ends of the non-ionic surfactant orient outward, while the hydrophobic ends are oriented in the opposite direction. Proniosomes can be either unilamellar or multilamellar depending on the preparation method. The niosomes is composed of a bilayer of surfactants, the hydrophobic chains of which face one another within the bilayer, and the hydrophilic ends of which are exposed both inside and outside of the vesicles. As a result, hydrophobic medications are embedded in the bilayer, while hydrophilic drugs are held within the vesicle's enclosed space.

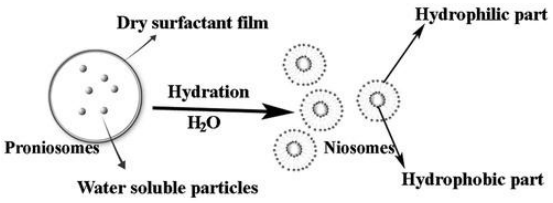

Figure 2: Diagrammatic depiction of proniosomes

Proniosomal Drug Release Pathway

Niosomal Vesicles Formed After Hydration
↓

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Drug Entrapped in Bilayer / Core
↓
Diffusion Through Vesicle Membrane
↓
Vesicle Erosion / Fusion with Cells
↓
Sustained Drug Release
↓
Therapeutic Response

METHODOLOGY:

Material:

A diclofenac sodium sample was obtained from Carbanio: B2B Chemical Marketplace, and other analytical-grade chemicals and reagents were used from the laboratories.

Method:

Method of Preparation of Diclofenac-Loaded Proniosomal Gel Using Coacervation-Phase Separation Technique:

A coacervation-phase separation process was used to prepare proniosomal gel. A clean and dry wide-mouthed glass vial with a capacity of 5.0 ml was filled with precisely weighed amounts of surfactant, lecithin, cholesterol, and medication, followed by 1.0 ml of alcohol. After warming, all the materials were thoroughly mixed with a glass rod; the open end of the glass bottle was sealed with a lid to prevent solvent loss, and it was warmed over a water bath at 60-70°C for about 5 minutes, or until the surfactant combination was entirely dissolved. The aqueous phase (phosphate buffer saline pH 7.4) was then added and warmed on a water bath until a clear solution formed, which cooled to form proniosomal gel. The resulting gel was stored in the same glass bottle under dark conditions for characterization. The compositions of proniosomal gel formulations are shown in Table 1.

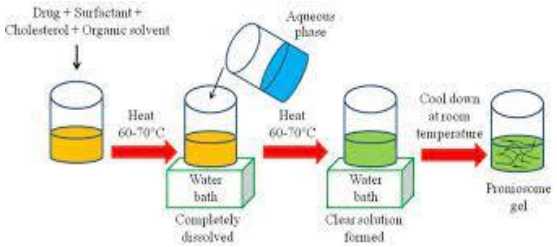

Figure 3: Method of Preparation of Proniosomal Gel

Table 1: Composition of different formulation codes

Formulation code	Drug (mg)	Non-ionic surfactants	Ratio (mg)	Lecithin (mg)	Cholestrol (mg)	Ethanol (ml)	PBS pH 7.4 (ml)
PN1	10	Span 20	1000	100	100	1.0	0.5
PN2	10	Span 40	1000	100	100	1.0	0.5
PN3	10	Span 60	1000	100	100	1.0	0.5
PN4	10	Span 20:Span 40	500:500	100	100	1.0	0.5
PN5	10	Span 40: Span 60	500:500	100	100	1.0	0.5
PN6	10	Span 20: Span 60	500:500	100	100	1.0	0.5

EVALUATION:

1. Physical appearance:

The created gel was examined with the naked eye to determine its color and physical state. Each formula's appearance, such as color, consistency, and fluidity, was assessed and compared to one another.

2. pH:

The pH of the proniosomal gels was evaluated using a digital pH meter. One gram of gel was dissolved in 25 ml of distilled water, and the electrode was immersed in the gel solution for 30 minutes until a consistent reading was obtained. Constant reading was also reported. The pH readings of each formulation were repeated two times.

3. Vesicle Size Analysis:

Size and Size Distribution Niosomes were generated using proniosome hydration with and without agitation. Size analysis was performed by adding 0.9% saline solution to 100 mg of proniosomal gel in a tiny glass vial and shaking it occasionally for 10 minutes. After hydration, the dispersion of niosomes was examined with an optical microscope (Olympus) at 100, 40, and 10x magnifications. The diameters of 150-200 vesicles were measured with a calibrated ocular and stage micrometer attached to the optical microscope.

4. % Encapsulation Efficiency:

The concentration of drug entrapped was calculated by weighing 0.2 g of proniosomal gel in a glass tube and adding 10 ml of pH 7.4 phosphate buffer. An aqueous solution was sonicated in a sonicator bath. Centrifugation at 18000 rpm and 5°C for 40 minutes separated the drug-containing niosomes from the untrapped drugs. The clear supernatant fraction was employed to determine free drug levels and drug content.

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5. Data Analysis via Drug Release Kinetics Study

The results of the in vitro release profile obtained for all of the formulations were shown in kinetic models as follows: cumulative drug released versus time (zero-order kinetic model) and log cumulative percent of drug remaining to be absorbed versus time (first-order model).

6. Stability Studies:

Stability testing of drug products is part of the drug development process and finishes with the commercial product. Stability studies were conducted to examine the stability of the medication and its formulation. A stability study will be conducted to determine the most suitable formulation. The optimal formulation will be stored in a glass vial at 30 ± 2°C and 40 ± 2°C at RH 65 ± 5 and 75 ± 5 RH for two months. After one and two months, the samples were examined for drug content and an in vitro diffusion investigation. Antimicrobial effects of volatile aromatic oils derived from plants have been known since antiquity.

RESULT & DISCUSSION:

1. Physical appearance

Formulation Code	Colour	Physical State
PN1	Brown	Liquid
PN2	White	Semi-solid
PN3	White	Semi-solid
PN4	Light-brown	Gel
PN5	Light brown	Gel
PN6	Light-brown	Gel

2. pH

FORMULATION	pH
PN1	6.4
PN2	6.9
PN3	7.3
PN4	6.8
PN5	7.5
PN6	6.7

3. Vesicle Size:

Formulation code	Mean vesicle size before shaking (µm)	Mean vesiclesize after shaking (µm)
PN1	4.23	1.91
PN2	3.87	1.75
PN3	3.05	1.43
PN4	4.09	1.97
PN5	3.20	1.66
PN6	4.15	2.12

4. % Encapsulation Efficiency:

Formulation	% Encapsulation Efficiency
PN1	65.22
PN2	77.56
PN3	78.81
PN4	71.16
PN5	84.61
PN6	74.11

5. Drug Release Kinetics Study:

Formulation code	Correlation coefficient of model fitting (R^2)				'n' values for Peppas	Best-fit model
	Zero order	First order	Higuchi matrix	Peppas kinetics		
NP1	0.9903	0.9627	0.9508	0.9759	2.2538	Zero Order
NP2	0.9814	0.8855	0.9298	0.9797	2.2386	Zero Order
NP3	0.9676	0.8844	0.9044	0.9673	2.2864	Zero Order
NP4	0.9544	0.8968	0.8822	0.9701	2.2167	Peppas Model
NP5	0.9497	0.8921	0.8754	0.9668	2.2109	Peppas Model
NP6	0.9186	0.8467	0.8317	0.9666	2.1168	Peppas Model

Future Aspects Of Proniosomal Drug Delivery System:

The proniosomal drug delivery system is a diverse and growing platform with great promise for future pharmaceutical and biological applications. Because of their improved stability, simplicity of storage, and capacity to improve drug bioavailability, proniosomes are likely to play an increasingly prominent role in next-generation drug delivery techniques. Future research and development in this subject will most likely focus on formulation optimization, enhanced targeting techniques, large-scale production, and clinical translation. The proniosomal drug delivery system is a diverse and growing platform with great promise for future pharmaceutical and biological applications. Because of their improved stability, simplicity of storage, and capacity to improve drug bioavailability, proniosomes are likely to play an increasingly prominent role in next-generation drug delivery techniques.

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1. Advanced Targeted Drug Delivery:
Future improvements in proniosomal systems will focus on site-specific and targeted medication delivery. Surface modification of proniosomes with ligands including antibodies, peptides, aptamers, and sugars allows for receptor-mediated targeting of specific tissues or disease areas, such as tumors, inflamed tissues, and infected cells. Such ligand-functionalized proniosomes may improve therapeutic outcomes by boosting medication concentration at the target site while reducing systemic negative effects.

2. Application in Gene and Nucleic Acid Delivery:
Proniosomes can be created to carry genetic resources such plasmid DNA, siRNA, mRNA, and CRISPR components. Their capacity to preserve labile biomolecules from enzymatic degradation while still facilitating cellular absorption makes them potential carriers for gene therapy and RNA-based therapies. Future study could focus on using cationic surfactants or polymers to improve nucleic acid binding and transfection efficiency.

3. Integration with Nanotechnology:
The amalgamation of proniosomal systems and nanotechnology is predicted to greatly increase their applications. Nano-sized proniosomes can be engineered to increase cellular absorption, improve penetration across biological barriers, and allow fine control over drug release kinetics. Smart proniosomal systems that respond to stimuli such as pH, temperature, enzymes, or redox conditions could allow for on-demand drug release at the illness site.

4. Personalized and Precision Medicine:
With a rising emphasis on customized treatment, proniosomes may be modified to patient-specific parameters such as genetic profile, disease condition, and drug metabolism. Customized proniosomal formulations may provide dose individualization, controlled release patterns, and enhanced patient adherence, especially in chronic illness treatment.

5. Improved Transdermal and Mucosal Delivery:
Future improvements are expected to improve the utilization of proniosomes in transdermal and mucosal medication delivery systems. Proniosomes can more efficiently cross biological barriers including the stratum corneum, nasal mucosa, and ocular tissues by introducing penetration enhancers or altering surfactant composition. This will enable non-invasive delivery of medications with low oral bioavailability.

6. Clinical Translation and Regulatory Acceptance:
Despite promising preclinical results, there are currently few clinical studies on proniosomal formulations. Future research should include complete pharmacokinetic, pharmacodynamic, and toxicological investigations to determine safety and efficacy. Clear regulatory criteria and quality control standards will be critical to clinical approval and widespread adoption.

7. Delivery of Biopharmaceuticals and Vaccines:
Proniosomes may be effective transporters for peptides, proteins, and vaccines, preserving them from breakdown and boosting immune responses. Their use in vaccine delivery, particularly mucosal and transdermal immunization, is a promising field for future research.

8. Combination Therapy and Multidrug Delivery:
Proniosomal systems can be used to co-encapsulate several medicines with distinct physicochemical features. This property could be used for combination therapy in cancer, infectious illnesses, and metabolic disorders, where synergistic medication action is needed.

CONCLUSION:
The purpose of this study was to create and evaluate diclofenac sodium proniosomal gels utilizing the coacervation-phase separation method for treating degenerative and inflammatory musculoskeletal conditions. A thorough analysis of the literature on the vesicle and pro-vesicle systems, their production procedures, and various excipients was done to develop a stable proniosomal formulation of diclofenac sodium with good anti-inflammatory action and several hours of drug release. The transdermal proniosomal gels showed signs of regulated drug release. The current study's findings indicate that Naproxen proniosomal gel, which is used to treat specific disorders, creates a 12-hour sustained release of medication when it combines surfactants such as span 20, 40, and 60 with lecithin and cholesterol.

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