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Original Article

GEL WITH PRONIOSOME- A PIONEERING APPROACH FOR DRUG RELEASE

Sagar Vaishnav, Dr. Praveen Khirwadkar, Dr. Narendra Mandoria, Dr. Kamlesh Dashora, Dr.Darshan Dubey, Dr.Tanu Bhargava

Institute of Pharmacy, Vikram University, Ujjain (M.P.) India

Abstract:- Vesicular systems, such as liposomes and niosomes, offer distinct advantages over conventional dosage forms due to their role as reservoirs for drug encapsulation. These systems can function both as carriers and as permeation enhancers, facilitating drugpenetration through the skin's stratum corneum. Additionally, they serve as controlled percutaneous drug delivery vehicles, capable of modifying particle composition or surface characteristics for targeted drug delivery.However, the potential of these vesicular systems is limited by challenges like stability issues, sedimentation, aggregation, fusion, and drug hydrolysis, all of which affect the shelf life of the dispersion. To address these concerns, proniosomes were developed. Proniosomes consist of dry formulations of water-soluble carrier particles coated with nonionic surfactant

Keywords- non- ionic, stabilizer, membrane, proniosomes, drug carrier.

Corresponding Author: Sagar Vaishnav†, Institute of Pharmacy, Vikram University, Ujjain (M.P.) India

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Introduction:

Vesicular systems, such as liposomes and niosomes, offer distinct advantages over conventional dosage forms due to their role as reservoirs for drug encapsulation. These systems can function both as carriers and as permeation enhancers, facilitating drugpenetration through the skin's stratum corneum. Additionally, they serve as controlled percutaneous drug delivery vehicles, capable of modifying particle composition or surface characteristics for targeted drug delivery.However, the potential of these vesicular systems is limited by challenges like stability issues, sedimentation, aggregation, fusion, and drug hydrolysis, all of which affect the shelf life of the dispersion. To address these concerns, proniosomes were developed. Proniosomes consist of dry formulations of water-soluble carrier particles coated with nonionic surfactants. These can be easily measured and rehydrated just before use by brief agitation in hot aqueous media. Proniosomal-derived niosomes exhibit significant improvements over conventional niosomes, boasting greater uniformity in size. This attribute provides flexibility, precise dosing, streamlined processing, and convenient packaging.The proniosomal approach effectively mitigates these challenges by introducing a dry, free-flowing product that remains stable during sterilization and storage. The ease of transfer, distribution, measurement, and storage positions proniosomes as a versatile delivery system with the potential for a wide range of active compounds. Although the number of studies on the preparation and evaluation of proniosomes remains limited, their potential impact is substantial.

Proniosomes

Vesicular systems, such as liposomes and niosomes, offer distinct advantages over conventional dosage forms due to their role as reservoirs for drug encapsulation. These systems can function both as carriers and as permeation enhancers, facilitating drugpenetration through the skin's stratum corneum. Additionally, they serve as controlled percutaneous drug delivery vehicles, capable of modifying particle composition or surface characteristics for targeted drug delivery.However, the potential of these vesicular systems is limited by challenges like stability issues, sedimentation, aggregation, fusion, and drug hydrolysis, all of which affect the shelf life of the dispersion. To address these concerns, proniosomes were developed. Proniosomes consist of dry formulations of water-soluble carrier particles coated with nonionic surfactants. These can be easily measured and rehydrated just before use by brief agitation in hot aqueous media. Proniosomal-derived niosomes exhibit significant improvements over conventional niosomes, boasting greater uniformity in size. This attribute provides flexibility, precise dosing, streamlined processing, and convenient packaging.The proniosomal approach effectively mitigates these challenges by introducing a dry, free-flowing product that remains stable during sterilization and storage. The ease of transfer, distribution, measurement, and storage positions proniosomes as a versatile delivery system with the potential for a wide range of active compounds. Although the number of studies on the preparation and evaluation of proniosomes remains limited, their potential impact is substantial.

1.3.1. Types of Proniosomes

Proniosomes can be classified into two main types: dry granular proniosomes and liquid crystalline proniosomes. This classification and description provide an overview of the various types of proniosomes and their applications, showcasing their adaptability in drug delivery systems.The classification of proniosomes is illustrated in Figure 3.

Dry Granular Proniosomes:

1. Sorbitol-Based Proniosomes: In this variation of proniosomes, sorbitol serves as the carrier material. The carrier is coated with non-ionic surfactants using a simple agitation technique in the presence of water. Notably, the size distribution of sorbitol-based proniosomes is notably uniform. This type of proniosome is created through the slow spraying method and is particularly beneficial for drugs that are susceptible to hydrolysis.

2. Maltodextrin-Based Proniosomes: These proniosomes are prepared using the fast slurry method, and the time required for their production remains consistent regardless of the ratio of surfactant solution employed. Maltodextrin-based proniosomes exhibit potential for delivering hydrophobic and amphiphilic drugs effectively.

Liquid crystalline proniosomes-The liquid crystalline proniosomes and proniosomes gel act as reservoir for transdermal drug delivery. This system may be formulated into transdermal patch containing a backing layer along with plastic sheet. Proniosomal gel is spread evenly on the sheet. Liquid crystalline proniosomes shows number of

advantages such as stability, high entrapment efficiency, no disruption of membrane properties of stratum corneum.

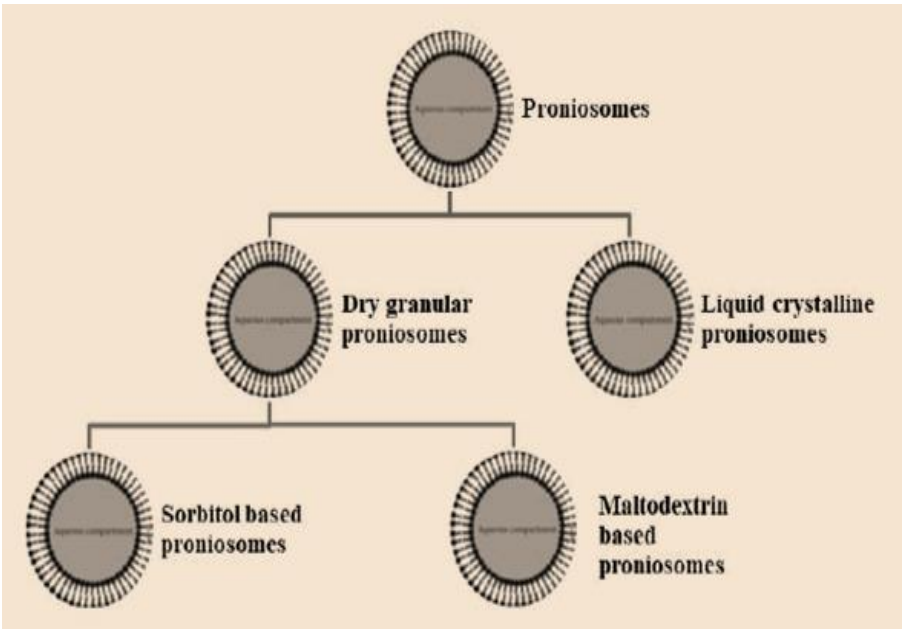

Fig 3: Classification of proniosomes

1.3.2. Advantages ofProniosomes

Convenient Handling: Proniosomes offer ease in transportation, sterilization, distribution, storage, and dosing.

Versatile Drug Compatibility: Proniosomes exhibit the ability to encapsulate both hydrophilic and hydrophobic drugs.

Enhanced Drug Stability: Proniosomes mitigate drug degradation caused by hydrolysis or oxidation, which is a common issue with liposomes.

Simple Storage and Handling: Proniosomes require no specialized conditions for storage and handling.

Enhanced Physical Stability: Issues such as sedimentation, aggregation, fusion, and leakage, often observed in other systems, are absent in proniosomes.

Controlled and Sustained Release: Proniosomes facilitate controlled and sustained drug release through depot formation.

Biocompatibility: Proniosomes are biodegradable, biocompatible, and non-immunogenic to the body.

Improved Bioavailability and Reduced Side Effects: Proniosomes elevate drug bioavailability while simultaneously minimizing adverse effects.

Niosome Conversion: Proniosomes can be transformed into niosomes upon hydration with a hot aqueous medium. The niosomes thus formed are characterized by a higher degree of size uniformity compared to conventional niosomes11.

1.3.3.Preaparation of Proniosomes 11:

Proniosomes Components and Formulation Methods:

Proniosomes comprise several essential components, with non-ionic surfactants and cholesterol, primarily lecithin, constituting the main ingredients. Carriers like maltodextrin, mannitol, and sorbitol are commonly employed, ensuring safety, non-toxicity, free flowability, and water solubility to facilitate hydration. Various carriers, non-ionic surfactants, and membrane stabilizers used in proniosomal formulation are outlined in Table 3 below:

Table 3: Commonly Used Materials for Proniosomal Formulation

Class	Example	Uses
Surfactants	Span 20, 40, 60, 80, 85 Tween 20, 40, 80	Enhance drug flux across the skin.
Stabilizers	Cholesterol, Soya lecithin,	Prevent leakage of drug formulation.
	Egg lecithin	Penetration enhancer.
Carriers	Maltodextrin	Offers flexibility in surfactant ratios.
	Sorbitol	Alters drug distribution.
	Alcohol (Ethanol, methanol, Isopropyl alcohol,	Softens vesicle membrane, acts as a
	Chloroform)	penetration enhancer.

The preparation of proniosomal formulations can be achieved through various methods:

a) Slurry Method:

In the slurry method, a stock solution of non-ionic surfactants and stabilizers is dissolved in a methanol: chloroform (1:2) solution. This mixture is added to a round-bottom flask containing the maltodextrin carrier. Additional stock solution and the drug are introduced into another flask containing the carrier. Solvent is evaporated using a rotary flash evaporator under controlled conditions. The resulting dry product, termed proniosomes, is stored in a closed container in a refrigerator for further evaluation.

b) Coacervation Phase Separation Method:

This method is employed for preparing proniosomal gel. Precise amounts of surfactant, lipid, and drug are mixed with alcohol in a glass vial. The mixture is warmed over a water bath until the surfactant dissolves. The aqueous phase is then added, and the solution is heated on a water bath until it forms a clear solution, which is subsequently transformed into proniosomal gel upon cooling. The gel is stored in a dark environment for further studies.

c) Slow Spray-Coating Method:

Ideal for hydrophobic drugs, the slow spray-coating method involves spraying a surfactant dissolved in an organic solvent onto sorbitol powder and evaporating the solvent. This process is repeated until the desired surfactant loading is achieved. As the sorbitol carrier dissolves, the thin surfactant coating hydrates, leading to the formation of multilamellar vesicles. This approach yields niosomes similar to those generated through conventional methods, with enhanced uniformity in size. The slow spray-coating method offers a viable solution for formulating hydrophobic drugs in a lipid suspension, circumventing concerns of instability or hydrolysis susceptibility.This comprehensive overview underscores the diverse components and formulation methods involved in the creation of proniosomes, highlighting their potential for addressing various drug delivery challenges.

REVIEW OF LITERATURE

S. No.	Author	Work Done
1	Radha *et al* 2013	proniosomes exhibit significant promise in the realms of cancer chemotherapy and anti-leishmanial therapy. They emerge as a viable alternative to conventional carrier systems like liposomes. The potential applications of proniosomes span targeted drug delivery, catering to both polar and nonpolar drugs. Their advantages are multifaceted, as they are user-friendly in terms of distribution, measurement, transfer, and storage. Notably, proniosomes boast qualities such as low toxicity, uncomplicated formulation, and straightforward preparation methods. This confluence of attributes positions proniosomes as a versatile and appealing choice in the realm of drug delivery and therapeutic interventions.
2	M. Wen *et al*	The primary objective of this research endeavor was to establish a transdermal drug delivery system

	2014	for mefenamic acid (MA) utilizing proniosomes as a carrier, all the while circumventing the necessity for penetration enhancers. The focus of the investigation encompassed various formulation parameters, including the inclusion of cholesterol, different types of lecithin, and various surfactants. These factors were scrutinized for their impact on crucial aspects such as entrapment efficiency, vesicle size, drug release kinetics, and the extent of skin permeation. By systematically exploring these formulation variables, the study aimed to optimize the proniosomal system for enhanced MA delivery through the skin, contributing to the advancement of effective transdermal drug administration..
3.	Bhargava and Dashora 2022	Thecore objective of this study is to mitigate the adverse effects associated with oral dexketoprofen by employing encapsulation techniques with non-ionic surfactants. The preformulation phase encompasses a comprehensive analysis involving techniques such as FTIR to ascertain the compatibility of components. Additionally, various critical parameters like Polydispersity Index (PDI), zeta potential, drug release profiles, encapsulation efficiency, and drug content are meticulously evaluated across different formulations. The proniosomal gel formulation displays promising attributes, including robust stability, drug release profiles conforming to zero-order kinetics, and notably high encapsulation efficiency. These positive findings lay a foundation for the potential effectiveness of the proniosomal gel in delivering dexketoprofentransdermally.To further validate the therapeutic potential and aptness of the transdermal drug delivery, subsequent in-vivo studies are suggested. These studies would not only assess the pharmacological activity but also provide insight into the efficacy and appropriateness of the drug release mechanism through the skin. This comprehensive approach holds promise in advancing the utilization of dexketoprofen for transdermal applications while minimizing the associated risks of oral administration.
4	Mahajan *et al* 2021	The study encompassed the preparation of ten distinct proniosomal gel formulations, each employing different combinations of non-ionic surfactants, cholesterol, and lecithin. These formulations were subject to rigorous characterization involving the assessment of multiple parameters, including particle size, entrapment efficiency, drug content, and in vitro drug permeation. Following meticulous experimentation, the formulation that exhibited optimal attributes, denoted as C5MF8, emerged as the preferred choice. This optimized formulation demonstrated noteworthy characteristics, encompassing sustained drug release profiles, potent antifungal activity, and elevated drug permeation in comparison to a commercially available cream formulation. Importantly, Fourier transform infrared spectroscopy analyses reaffirmed the harmonious compatibility of the drug with the chosen excipients.A standout feature of the proniosomal gel was its role as a controlled release drug carrier, effectively extending drug release over an extended period. This controlled release mechanism exhibited the capability to sustain drug release for an extended duration, signifying its potential to enhance therapeutic efficacy and minimize dosage frequency. Overall, the study underscores the potential of the proniosomal gel as a promising platform for controlled and sustained drug delivery, showcasing advantages over conventional formulations.
5	Soliman *et al* 2022	The primary focus of the research paper is centered on the development and thorough characterization of transethosomes (TEs) with the potential to serve as an effective delivery system for Amlodipine besylate (DKT), aimed at transdermal pain management. The study implements a factorial design methodology to systematically evaluate the impact of various independent variables on critical parameters such as solubilization efficiency, vesicle size, and release efficiency.To assess the performance of the developed transethosomes, the study employs the dialysis bag method to analyze the in vitro release profile of DKT from the TEs. The results of this analysis reveal a controlled release pattern that extends over a span of 8 hours, showcasing the promising potential of transethosomes as a sustained drug delivery platform.Furthermore, the study identifies an optimized formulation of transethosomes, labeled as F1, which exhibits notable advantages over conventional DKT solution. Specifically, this optimized formulation showcases enhanced skin permeation capabilities, thereby potentially enhancing drug absorption. Additionally, the formulated TEs demonstrate improved stability in comparison to the standalone DKT solution. These findings collectively propose the transethosomal delivery system as a promising alternative for efficient and controlled transdermal delivery of DKT, thereby highlighting its potential in the realm of pain management.
7	Kapoor*et al*2001	Amlodipine (AM) is a third-generation dihydropyridine calcium channel antagonist that is commonly used for the treatment of angina and hypertension. Despite its therapeutic benefits, AM faces challenges related to its poor aqueous solubility and low permeability through the gastrointestinal tract (GIT), which in turn results in low bioavailability. This limitation restricts the drug's effective delivery to its intended therapeutic targets, such as the heart and cardiac smooth muscles. AM is a weak base and predominantly exists in its ionized form, which contributes to its low permeability within the pH range of the gastrointestinal environment. Notably, the oral bioavailability of amlodipine free base is lower in comparison to amlodipine salt. To address these challenges, a formulation strategy known as Amlodipine Loaded Nano Lipid Carriers (AMNLCs) was explored. The optimization of AMNLCs was carried out using a statistical experimental design

		called Box-Behnken design (BBD). This design involved three independent variables: X1 (Peceol), X2 (glycerylmonostearate), and X3 (tween 80), each with three levels (low, medium, and high). The impact of these variables on dependent responses—namely, Y1 (particle size), Y2 (flux), and Y3 (encapsulation efficiency)—was observed and analyzed. BBD was chosen for optimization due to its efficiency in requiring fewer experimental runs compared to other designs like the central composite design. The optimization process was facilitated using specialized software called Design Expert. The ultimate goal was to create an optimized nano lipid carrier formulation for amlodipine. The optimized formulation of AMNLCs was then subjected to various analyses to evaluate its properties. These analyses included studying the morphology of the carriers, assessing in-vitro drug release behavior, investigating in-vivo absorption characteristics, and examining the interaction of the formulation with the skin. In summary, the study focused on enhancing the bioavailability and delivery efficiency of amlodipine through the development of nano lipid carriers. The Box-Behnken design was employed for optimization, resulting in an optimized formulation that was extensively characterized for its properties and potential for effective drug delivery.
8	Wangding Lu *et al*2014	The paper discusses the development of a metered dose transdermal spray (MDTS) formulation for the transdermal delivery of dexketoprofen (DE). The in vitro release of DE from different formulations was evaluated, and various parameters such as spray pattern, pump seal efficiency, and dose uniformity were assessed. The optimized formulation contained 7% DE, 7% isopropyl myristate (IPM), and 93% ethanol, and showed good skin permeation and drug concentration. In vivo pharmacokinetic studies in rats showed that the optimized MDTS formulation had a more sustainable plasma concentration profile compared to the Fenli group.
9	Mohanty *et al* 2022	The paper develops and optimizes esomeprazole loaded proniosomes (EZL-PNs) to improve bioavailability and therapeutic efficacy.The study utilized 33 box-Behnken statistical design software to optimize the formulation and evaluate its effects on vesicle size, entrapment efficiency, and drug release. The optimized EZL-PNs formulation showed a vesicle size of 616 ± 13.21 nm and an entrapment efficiency of 81.21 ± 2.35%.The formulation exhibited sustained release of EZL and enhanced flux in ex vivo gut permeation compared to pure EZL.In vivo results showed a 4.02-fold enhancement in bioavailability and 61.65% protection in ulcer compared to pure EZL dispersion. The study concludes that the developed EZL-PNs formulation could be a promising alternative delivery system for esomeprazole, enhancing its oral bioavailability and antiulcer activity.
10	Mamatha *et al* 2010	The present investigation aimed to deliver lercanidipine hydrochloride (LRDP) transdermally via patches to overcome the poor oral bioavailability and erratic oral absorption of the drug.The study involved formulating transdermal polymeric films with Eudragit RL100 (ERL) and hydroxypropyl methyl cellulose (HPMC) containing LRDP, using d-limonene as a permeation enhancer.The transdermal patches were found to be non-irritant and suitable for further pharmacokinetic and pharmacodynamic studies in humans or animals.
11	Trivedi and Goyal 2020	The paper discusses the formulation and evaluation of transdermal patches containing Amlodipine besylate, a NSAID used as an analgesic and anti-inflammatory drug. The transdermal patches were prepared using polymers such as ethyl cellulose, HPMC, and ERS 100 in different ratios, with formulation F6 (HPMC: EC in ratio 4:1) showing the maximum drug release of 85.77% in 24 hours. The solubility study revealed that Amlodipine besylate is freely soluble in water and DMSO and sparingly soluble in methanol. The drug also has a hydrophobic nature, making it suitable for transdermal drug delivery.
12	Ghanbarzadeh *et al*. 2014	The objective of the study was to formulate and evaluate a niosomal formulation of Ibuprofen as a transdermal drug delivery system.The niosomes were prepared using a modified ethanol injection method with specific surfactants and cholesterol ratios. The vesicles were characterized for various parameters such as entrapment efficiency, particle size, and in vitro release.Skin permeation studies were conducted using a modified Franz diffusion cell, and the results showed that both niosomal and liposomal formulations enhanced drug permeation and accumulation in the skin compared to a conventional gel formulation.The study concluded that niosomal formulations could be a promising carrier for transdermal delivery of Ibuprofen.
13	Verma *et al* 2016	The paper discusses the use of proniosomes, a type of vesicular delivery system, to sustain systemic exposure and therapeutic effect of the anti-inflammatory drug flurbiprofen after intravenous delivery. Proniosomes are dehydrated powder or gel formulations that spontaneously form niosomes (vesicles) on hydration with aqueous media. The proniosomes were found to successfully sustain drug release, pharmacokinetics, and the anti-inflammatory effect of flurbiprofen in an acute model of inflammation. The study demonstrates that hydrated proniosomes can provide prolonged systemic drug exposure and a sustained therapeutic effect, making them a novel approach for treating acute pain and inflammation. The proniosomes have the potential to be administered as a single intravenous dose, providing relief for several days and reducing fluctuations in therapy. Similar systems loaded with different drugs have potential applications in anesthesia, anti-infective, antiemetic, and cancer therapy.
14	Yen *et al*.	The paper focuses on the preparation and characterization of niosomes loaded with diclofenac (DiC)

	2020	for transdermal administration.The niosomes were found to be spherical particles with an average size of less than 100 nm and a polydispersity index (PDI) smaller than 0. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and field emission scanning electron microscopy were used to investigate the niosomal vesicles.Ex vivo and in vivo studies on rats demonstrated that the niosomal hydrogel improved the amount and rate of DiC transport through the skin and increased drug concentration in the muscle compared to the commercial drug.The cumulative amount of DiC permeated through excised rat skin was calculated, and it was observed that DiC from the niosomal hydrogel could permeate through the skin and subcutaneous tissue and reach the blood.
15	Patil *et al* 2021	The paper states that etodolac, a drug used for acute pain and inflammation, has low solubility and can cause gastric disturbances when administered orally. Therefore, the development of a topical vesicular formulation is encouraged. The study used a coacervation-phase separation method to develop an etodolac-loaded vesicular system using non-ionic surfactants, cholesterol, and soy lecithin. The formulations were characterized for vesicle size, zeta potential, entrapment efficiency, in-vitro permeation, ex-vivo permeation, and anti-inflammatory activity. The optimized proniosomal gel formulation was found to be stable and showed excellent permeation capacity, suggesting its potential for improving the delivery of etodolac to the skin
16	Shah *et al* 2019	The study aimed to evaluate the potential of an optimized proniosomal gel for transdermal delivery of lornoxicam, comparing it with oral therapy, to improve clinical efficacy and reduce gastric adverse effects.The proniosomal gel formulation (F19) exhibited nano size with high entrapment efficiency, adequate zeta potential, greater transdermal flux, and better stability. It showed distinct release profile and steady lornoxicam release through Fickian diffusion. Transdermal administration of F19 significantly inhibited carrageenan-induced hindpawedema in rats compared to oral lornoxicam group. The concentration of span 60 and cholesterol had a significant effect on entrapment efficiency, with an increase in span 60 concentration improving the percentage entrapment efficiency
17	Ammar *et al* 2011	Proniosomes, a vesicle delivery concept, have been explored as a carrier system for transdermal delivery of tenoxicam. Lecithin-free proniosomes prepared from Tween 20: cholesterol (9:1) showed high stability, drug entrapment efficiency, and release efficiency. In vivo studies on male rats showed that the tenoxicam-loaded proniosomal formula had higher anti-inflammatory and analgesic effects compared to oral market tablets. Stability studies revealed that proniosomal formulations prepared with distilled water were the most stable, followed by buffer preparations and those prepared using glycerol. In vitro release studies showed that the selected proniosomal gel formulations had high drug entrapment levels and release rates. Release efficiency was calculated using the trapezoidal method.
18	Tahreen *et al*2020	The study aimed to develop a proniosomal gel loaded with clozapine for transdermal drug delivery, with the goal of improving the drug's bioavailability and reducing adverse drug reactions.The proniosomal gel formulation was optimized based on particle size, entrapment efficiency, polydispersity index, and zeta potential. The optimized formulation showed high entrapment efficiency, small particle size, and stable properties.In vitro release studies demonstrated sustained release of clozapine from the proniosomal gel, while ex vivo permeation studies showed significant drug permeation through the stratum corneum. The optimized gel was also analyzed for pH, spreadability, bioadhesion, and rheology, indicating its suitability for transdermal administration.
19	Chavan *et al* 2012	The paper discusses the use of proniosomes as a drug carrier system for transdermal delivery of lornoxicam, a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatic diseases. Proniosomes are versatile vesicle delivery systems that offer an alternative approach for transdermal drug delivery. The proniosomal gel bases were prepared and characterized, and their drug entrapment efficiency, stability, and in vitro drug release were assessed. The proniosomal gel was prepared by hydrating proniosomes and then converting the dispersion into a gel. This gel was mixed with carbopol gel as a base and stored for further use. The release of lornoxicam from the proniosomal gel was studied using different mathematical models, including the Higuchi model and first-order kinetics. The findings indicated that proniosomes have the potential to be an alternative approach for transdermal delivery of lornoxicam, offering a promising option with fewer side effects compared to oral administration.
20	Akhilesh *et al* 2012	The paper discusses the drawbacks of niosomes as a drug delivery system and introduces proniosomes as a solution to these issues. The study compares different carriers, such as maltodextrin, sorbitol, lactose, mannitol, magnesium aluminum silicate, and microcrystalline cellulose, for the preparation of proniosomes. Proniosome-derived niosomes using maltodextrin as the carrier are as good as or even better than conventional niosomes. Maltodextrin particles can be coated with surfactant by adding surfactant in organic solvent to dry maltodextrin and evaporating the solvent, resulting in hollow blown maltodextrin particles with a thinner surfactant coating for more efficient rehydration.
21	Varsha *et al* 2019	This review focuses on Proniosome as they offer versatile drug delivery for both hydrophilic and hydrophobic drugs, improving oral bioavailability, targeting drugs to specific sites, and achieving

		controlled release action while reducing toxic effects. Proniosomes have been found to be more stable during sterilization and storage than niosomes, making them promising drug carriers for the future. They have been used in various clinical applications, including transdermal delivery of captopril for hypertension treatment, non-invasive delivery of furesamide for diabetes, and protection of peptides from gastrointestinal breakdown.
22	Choudhury *et al* 2021	The paper discusses the use of transdermal patches as an anti-inflammatory agent, focusing on drugs such as Diclofenac sodium, Lornoxicam, Aceclofenac, Ibuprofen, Repaglinide, Atenolol, and Stavudine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain and inflammation but can have various side effects. Transdermal delivery of these drugs can avoid hepatic first-pass effect, gastric irritation, and deliver the drug for an extended period at a sustained level.The basic components of transdermal patches include a polymer matrix, drug reservoir, active ingredient, permeation enhancers, backing laminates, adhesives, plasticizers, and solvents. The development of efficient transdermal administration of NSAIDs can increase local concentrations and reduce side effects associated with oral administration.
23	Aboumaneie*t al*2020	The paper discusses the design and development of a proniosomal transdermal drug delivery system of caffeine for the management of migraine.The system was characterized in vitro and labeled with 131I for in vivo biodistribution studies.The optimized proniosomal system was fabricated into a transdermal patch. Radioiodination of caffeine was performed successfully, and in vivo biodistribution studies showed that the proniosomal system increased the residence of caffeine in the blood and improved its targeting capacity to the brain.Theproniosomal system represents a promising transdermal drug delivery system for caffeine, overcoming challenges faced by oral delivery
24	Kumar *et al* 2016	The study compares the effectiveness of proniosomal powder and gel formulations of flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID) used for pain and inflammation relief in arthritis. Various surfactants like span 20, 40, 60, 80, and brij 35 were used in the formulations, with the best results obtained with the formulation containing an equimolar ratio of brij 35 and cholesterol. The proniosomal gel formulation showed higher entrapment efficiency and in vitro drug release compared to the powder formulation. The study also investigated the kinetics and mechanism of drug release from the proniosomal formulations, with the gel formulation following zero order kinetics and exhibiting sustained release.
25	Chowdary *et al* 2013	The research paper focuses on the formulation and evaluation of proniosomal gels containing ibuprofen for sustained drug release. Different proniosomal gels were formulated using Span 20/Span 80 and soya lecithin, with cholesterol concentration kept constant. The encapsulation efficiency of ibuprofen in the proniosomal gels was evaluated, and it was found to be higher in formulations containing Span 20. The vesicular diameter of the proniosomes depended on the type of non-ionic surfactant used, with proniosomes prepared using Span 80 having a smaller diameter. The proniosomal gel formulation PN3, containing Span 20, exhibited prolonged ibuprofen release profiles and showed a Fickian diffusion mechanism. The results suggest that the proniosomal gel could be an effective transdermal delivery system for ibuprofen.
26	Puglia *et al*. 2013	The paper discusses the use of colloidal drug delivery systems (CDDS) in the topical administration of NSAIDs for musculoskeletal pain and inflammation. CDDS improve drug residence in the skin and allow sustained and controlled release of the drug compared to conventional topical formulations. The use of nanocarriers, such as micro and nanoemulsions, vesicular carriers, and nanoparticles, is highlighted as novel high-efficiency delivery systems for NSAIDs in topical applications. Safety concerns regarding the use of nanocarriers in topical drug administration are mentioned, particularly related to their dimensions and potential to cross biological membranes and interfere with biological processes. The formulation of topical dosage forms for NSAIDs is considered a logical pharmaceutical development to limit systemic exposure and reduce adverse effects associated with systemic NSAID therapy.

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