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SMART PRONIOSOMAL TRANSDERMAL PLATFORMS FOR CONTROLLED LOCAL ANESTHETIC DELIVERY OF LIDOCAINE

Aditya Kumar*, Vivek Gupta, Jitendra Kumar Malik, Gyan Singh

Research Scholar, Faculty of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.

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***Corresponding Author: Aditya Kumar**
Research Scholar, Faculty of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.
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ABSTRACT

Localized pain control increasingly demands delivery systems that behave intelligently at the skin interface, delivering anesthetic precisely where needed while avoiding systemic spillover. Lidocaine, despite its clinical versatility, remains constrained by short duration of action and frequent reapplication when administered through conventional routes. Transdermal delivery offers an attractive alternative, yet the skin barrier and uncontrolled diffusion continue to limit therapeutic performance. Smart proniosomal transdermal platforms introduce a disruptive shift by coupling vesicular nanotechnology with skin-triggered self-assembly and controlled release behavior. Proniosomes are dry, storage-stable precursors that transform into niosomal vesicles upon hydration on the skin surface, generating a localized drug depot within the stratum corneum and viable epidermis. This review presents an integrative and forward-looking analysis of lidocaine-loaded proniosomal systems, focusing on formulation-driven control over vesicle architecture, interfacial dynamics, and anesthetic release profiles. The influence of surfactant chemistry, cholesterol content, and penetration enhancers on vesicle stability, drug entrapment, and dermal retention is critically examined. Advanced in vitro, ex vivo, and in vivo evaluation strategies are discussed to highlight prolonged anesthetic action, enhanced skin residency, and reduced systemic exposure. Beyond sustained delivery, proniosomal platforms enable modulation of spatial and temporal drug distribution, positioning them as precision-oriented systems rather than passive carriers. Emerging directions, including stimuli-responsive proniosomes, biointeractive excipients, and patient-adaptable designs, are highlighted as enablers of next-generation local anesthesia. Collectively, smart proniosomal transdermal systems redefine lidocaine delivery, offering a clinically compelling, scalable, and future-ready pathway for localized pain management in modern anesthetic and dermatological practice settings.

KEYWORDS: Proniosomes, transdermal drug delivery, lidocaine, smart vesicular systems, controlled local anesthesia.

1. INTRODUCTION

The pain management is also considered to be an essential part of clinical care and it is a broad concept that covers various acute and chronic conditions that can occur due to surgical operations, traumas, skin operations, and neuropathic diseases. Local anesthetics are one of the most important methods in pharmacology since it helps reduce local pain in the case of nerve conduction, being reversible, thus reducing the systemic effects and enhancing patient comfort.[1]

Local anesthetics such as lidocaine are considered to be one of the most commonly used due to its rapid action of effect, wide therapeutic use and established safety profile. It finds widespread use in minor surgery, dentistry, dermatology, and in the treatment and management of pain after surgery. However, these strengths are usually restricted by the fact that lidocaine has a short-acting period and requires repeated administration to ensure the desired analgesia.[2]

Lidocaine by conventional delivery methods (oral and injectable) is associated with a number of disadvantages, such as high first-pass metabolism, variable plasma levels, and the possibility of systemic toxicity such as central nervous system and cardiovascular adverse effects. Repeated dosing also reduces patient compliance and limits its effectiveness in local pain treatment in the case of longer application. These restrictions underscore the importance of developing alternative methods of delivery that can sustain therapeutic drug concentrations at the target location and reduce exposures to the body.[3]

The use of transdermal drug delivery has come out as a promising, convenient method of local anesthesia, and benefits of delivering drugs systematically, better patient compliance, and hepatic first-pass metabolism. Nevertheless, the stratum corneum has a very well-structured lipid layer which forms a very strong barrier hindering effective drug permeation and controlled delivery.[4]

In order to address these issues, smart vesicular carriers have attracted more interest. Among them, proniosomes have become next-generation transdermal platforms because they are more stable, can carry drugs in high loading and can be converted to niosomal vesicles upon hydration, thus providing the capability to deliver lidocaine locally and in controlled amounts.[5]

2. LITERATURE SEARCH METHODOLOGY

A detailed literature review was carried out to find the published scientific evidence connected with the smart proniosomal transdermal platforms in regards to the controlled delivery of lidocaine. The electronic databases such as PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar were searched to cover widely the research in pharmaceutical, biomedical, and formulation-oriented studies. To ensure consistency and clarity in interpretation of data, only articles written in English language were searched.[6]

Relevant keywords and Boolean operators were used to search and retrieve relevant studies. The key search terms were lidocaine, proniosomes, niosomes, transdermal drug delivery, vesicular drug delivery systems, delivery of local anesthesia and controlled release. To narrow down search results and make the literature retrieved relevant to the search query, these terms were used with Boolean operators like AND and OR. The reference lists of selected articles were also screened by hand to get more relevant studies.[7]

The inclusion criteria included original research articles as well as review papers concentrating on proniosomal or vesicular delivery of lidocaine or similar local anesthetic, formulation development study, and experimental studies with in vitro, ex vivo, and in vivo analyses. Articles that reported the preparation techniques, characterization variables, drug release, skin permeation, pharmacological efficiency, and safety issues were taken into account. The exclusion criterion was a non-English publication, conference abstracts, editorial, duplication studies, and those without sufficient experimental information.[8]

The literature retrieved was then systematically screened using titles and abstracts and full-text assessment was then done. Relevant information was expounded, critically evaluated, and themed thematically to offer coherent and structured review of the present progress in the delivery of proniosomal transdermal lidocaine.[9]

3. LIDOCAINE: PHYSICOCHEMICAL AND PHARMACOLOGICAL PROFILE

Lidocaine is a local anesthetic of amide type which has been a staple in clinical pain management over the last few decades. Its wide range of application, predictable pharmacologic action and established safety profile makes it one of the most widely used anesthetic agents in both the medical and pharmaceutical practice. Knowledge of the physicochemical and pharmacological properties of lidocaine is critical to the development of advanced delivery systems; especially transdermal systems directed to controlled and localized drug activity.[10]

3.1 Physicochemical Properties

Lidocaine is a weakly basic molecule with a relatively low molecular weight; thus, it is more likely to diffuse through biological membranes. The moderate lipophilicity of lidocaine combined with sufficient solubility in aqueous solution makes it a state of partitions well in the lipid-rich stratum corneum and the underlying hydrophilic layers of the skin. This dual solubility characteristic is a decisive attribute of an effective transdermal drug delivery.[11]

The pk a of lidocaine allows partial ionization at physiological pH, creating an equilibrium between ionized and unionize. The membrane is permeated by the unionized fraction and aqueous solubility and formulation stability by the ionized fraction.[12] The log P value of lidocaine also proves its capability of overcoming skin barriers and as such is a good drug to be incorporated in the vesicular delivery system. Nonetheless, quick diffusion of traditional topical preparations usually causes low retention by the skin and brief therapeutic actions. Such physicochemical limitations require carrier-based strategies, which can regulate drug release and improve the dermal localization.[13]

3.2 Pharmacological Action

Lidocaine can pharmacologically cause local anesthesia by reversible blockage of the neuronal cell membrane voltage-gated sodium channels. Lidocaine is effective by stabilizing the neuronal membrane and inhibiting the entry of sodium ions, which triggers and transmits action potential, culminating in the temporary loss of sensation on the part of the area of application. It is especially useful in clinical scenarios where they need immediate analgesia because of its fast onset of the activity.[14]

The most common use of lidocaine is in the local infiltration anesthesia, regional nerve block, topical anesthesia in dermatological and mucosal surgery, and in the management of postoperative pain. Although effective, the anesthetic effect of lidocaine is characterized by the relatively short-term duration of action because of its fast redistribution and

metabolism, which reduces its ability to be used during prolonged pain management without the necessity to repeat the injections.[15]

3.3 Limitations of Conventional Lidocaine Delivery

Oral and intravenous administration of lidocaine has a number of major disadvantages. Extensive hepatic clearance by the first-pass system restricts oral administer ability, which leads to low bioavailability and unstable plasma concentrations of drugs. Injections do not possess long-lasting effects, but injectable formulations are prone to quick absorption by the whole body and dose-related adverse effects, such as central nervous system toxicity and cardiovascular adverse effects.[16]

In addition, the relatively short biological half-life of lidocaine requires regular dosage or constant-rate infusion to sustain analgesic effects and this characteristic has adverse effects on patient compliance and systemic toxicity occurrence. These constraints underscore the necessity of establishing other delivery methodologies that will offer controlled, localized and sustained anesthetic effect and result in minimum systemic exposure hence the interest of exploring the smart transdermal and proniosomal delivery platforms.[17]

Table 1: Physicochemical and pharmacological properties of lidocaine relevant to transdermal delivery.[18]

Sr. No.	Parameter	Description / Relevance to Transdermal Delivery
1	Chemical class	Amide-type local anesthetic with stable pharmacological profile
2	Molecular formula	$C_{14}H_{22}N_2O$; supports formulation flexibility
3	Molecular weight	Low molecular weight, favorable for skin permeation
4	pKa	Weak base; partial ionization at physiological pH aids membrane diffusion
5	Log P (lipophilicity)	Moderate lipophilicity enables stratum corneum penetration
6	Aqueous solubility	Adequate solubility supports incorporation into vesicular systems
7	Skin permeability	Capable of diffusing through epidermal layers
8	Mechanism of action	Reversible blockade of voltage-gated sodium channels
9	Onset of action	Rapid onset, suitable for immediate local anesthesia
10	Duration of action	Short duration, necessitating controlled-release systems
11	Biological half-life	Relatively short; frequent dosing required in conventional delivery
12	Major limitations	Systemic absorption, toxicity risk, and poor retention at application site

4. PRONIOSOMES AS SMART TRANSDERMAL CARRIERS

Proniosomes are novel sophisticated vesicular delivery vehicles aimed to address the stability and handling problems that are linked with traditional nanocarriers. Their capability of integrating formulation stability with effective drug delivery in transdermal applications have made them intelligent platforms to deliver drugs in a controlled and localized manner specifically to drugs with a sustained action locally where the drug is applied like lidocaine.[19]

4.1 Concept and Composition of Proniosomes

Proniosomes are free-flowing or gel-based preparations that are made of non-ionic surfactants, which are then used in niosomal vesicles, when hydrated. They evolved out of the niosomes with the intention of solving problems caused by vesicle aggregation, drug leakage and poor shelf life of traditional vesicular dispersions. Proniosomes are also physically stable throughout storage in contrast to pre-hydrated vesicles, they are only converted into active vesicular systems when they are needed.[20]

The main components of the proniosomes are usually non-ionic surfactants, cholesterol, phospholipids and an appropriate hydration medium. The leading vesicle-forming agents are non-ionic surfactants that determine the size,

permeability and entrapment of the drug into the vesicles. Cholesterol is also added to make the bilayers rigid and stable to minimize drug leakage. The phospholipids enhance biocompatibility and contact with the skin lipids, and the hydration medium induces vesicle formation when coming into contact with the skin moisture. The cooperative ability between these components allows the delivery of drugs to be released in a controlled manner and an increase in dermal retention.[21]

4.2 Advantages of Proniosomes over Niosomes and Liposomes

Proniosomes have a number of benefits as compared to the traditional niosomes and liposomes. They exhibit physical and chemical stability, which is greatly enhanced by their high dry and metastable properties reducing fusion of vesicles and degradation of drugs during storage. Proniosomes are simple to manipulate, transport and scale, and thus can be used in an industrial and clinical setting. Also, the fact that they convert to vesicles upon reaching the point of application will guarantee increased localization of the drug, lower dosing rate, and increased patient compliance.[22]

4.3 Mechanism of Proniosome Formation and Skin Interaction

Proniosomal vesicles are formed at a high rate upon hydration of the skin moisture, or the presence of external aqueous phase, to form the niosomal vesicles. These vesicles interact with the stratum corneum by fluidizing the intercellular lipids, and improve the permeation of drugs. The vesicles are used as drug reservoirs, allowing the delivery of a sustained release and prolonged local action and reducing the overall absorption of the system, and therefore, proniosomes are the preferred vesicles to deliver lidocaine by the transdermal route.[23]

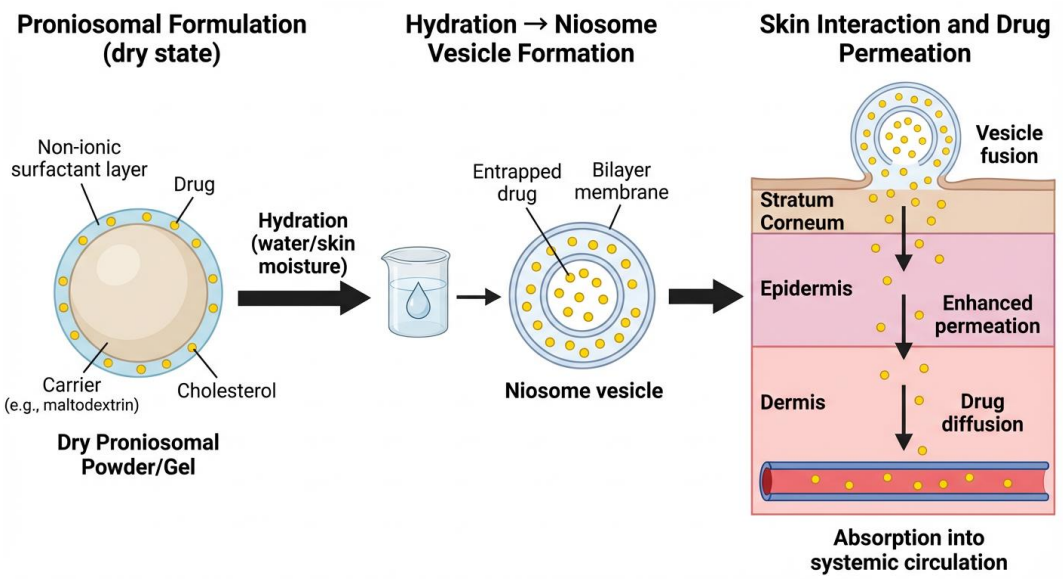

Figure 1: Schematic representation of proniosomal vesicle formation and skin interaction.[24]

5. FORMULATION STRATEGIES FOR LIDOCAINE-LOADED PRONIOSOMES

The effective formulation of lidocaine-loaded proniosomal systems is highly dependent on the design of the rational formulations and proper optimization on the variables of formulations. The correct choice of excipients, the proper method of preparation, and manipulation of formulation parameters are essential to the attainment of stable vesicles with a high degree of drug entrapment, controlled release, as well as increased skin permeation.[25]

5.1 Selection of Excipients

The choice of excipients plays a pivotal role in determining the physicochemical properties, stability, and performance of proniosomal formulations.

Surfactant type: The main vesicle-forming components of proniosomal include the specific surfactants that are not ionic. Sorbital esters and polyoxyethylene are typical examples of the best surfactant to use in this area because they are biocompatible and low toxicity, and capable of forming stable bilayers. Vesicle size, membrane permeability and efficiency of drug entrapment depend on the chemical nature and chain length of the surfactant. The loading and release behavior of lidocaine is therefore crucial to select a suitable surfactant.[26]

Cholesterol concentration: Cholesterol has been added to proniosomal preparations to improve the bilayer rigidity and stability. It stabilizes the membranes, lowers the vesicles leakage, and enhances the entrapment efficiency. Nonetheless, a high level of cholesterol can decrease the drug release and permeability, therefore, its level has to be optimally adjusted.[27]

Role of penetration enhancers: The penetration enhancers are also commonly added to allow lidocaine to penetrate through stratum corneum. These agents cause disruption of the lipid organization of the skin barrier enhancing drug permeation and dermal retention without causing severe irritation at optimal concentrations.[28]

5.2 Preparation Methods

Several techniques have been employed for the preparation of lidocaine-loaded proniosomes, each offering distinct advantages.

Coacervation phase separation method: This is the most popular method of which the surfactant, cholesterol and drug are dissolved in an appropriate solvent and then heated and hydrated under controlled conditions. It yields homogenous and stable proniosomal gels.[29]

Slurry method: In this process, a carrier material slurry containing a surfactant is dried to get proniosomal powder. This process is beneficial in mass production as well as enhanced storing capabilities.[30]

Spray coating technique: Here, the surfactant solution is sprayed onto a solid carrier, resulting in uniform coating and free-flowing proniosomes. This method offers precise control over formulation composition and scalability.[31]

5.3 Factors Affecting Vesicle Formation and Drug Loading

Surfactant HLB value: The Hydrophilic lipophilic balance (HLB) of the surfactant plays an essential role in the vesicle formation, size distribution and stability. Optimal HLB values of the surfactants prefer the formation of stable bilayers and preferable encapsulation of drugs.[32]

Drug-to-lipid ratio: The entrapment efficiency and release rate are dependent on the proportion between lipid constituents and lidocaine. An increase in lipid content tends to increase the drug encapsulation, though excess drug loading can cause vesicles to be destabilized.[33]

Hydration conditions: Vesicle size and uniformity is determined by hydration volume, temperature and duration. The maintenance of hydration under control fosters the efficient conversion of proniosomes to niosomes and the uniform delivery of drugs and interaction of drugs with the skin.[34]

Table 2: Formulation components and their role in lidocaine-loaded proniosomes.[35]

Sr. No.	Formulation Component	Role in Lidocaine-Loaded Proniosomes
1	Non-ionic surfactant	Primary vesicle-forming agent responsible for bilayer formation
2	Surfactant chain length	Influences vesicle size, permeability, and drug release rate
3	Surfactant HLB value	Determines stability, entrapment efficiency, and vesicle integrity
4	Cholesterol	Enhances bilayer rigidity and reduces drug leakage
5	Cholesterol concentration	Controls membrane fluidity and sustained release behavior
6	Phospholipids	Improve biocompatibility and interaction with skin lipids
7	Lidocaine	Active pharmaceutical ingredient providing local anesthetic effect
8	Drug-to-lipid ratio	Affects entrapment efficiency and vesicle stability
9	Penetration enhancers	Disrupt stratum corneum lipids to improve skin permeation
10	Hydration medium	Triggers conversion of proniosomes into niosomal vesicles
11	Organic solvent	Facilitates uniform mixing of formulation components during preparation
12	Solid carrier material	Improves flow properties and storage stability of proniosomal powder

6. CHARACTERIZATION AND EVALUATION PARAMETERS

Extensive characterization and assessment are needed to determine the performance, stability and therapeutic capability of lidocaine-loaded proniosomal transdermal system. The fact that drug release behavior, physicochemical properties and skin permeation properties determine the capacity of proniosomes to deliver anesthesia in a controlled and localized manner.[36]

6.1 Physicochemical Evaluation

Vesicle size and size distribution: Critical parameters that affect skin penetration, drug release and stability of proniosomal formulations are vesicle size. After hydration, the size and size distribution of resultant niosomal vesicles is normally measured by dynamic light scattering. Smaller, evenly dispersed vesicles prefer to interact better with the stratum corneum, and have a superior ability to penetrate the skin as well as provide a longer-lasting release of the drug. The values of polydispersity index are utilized to determine uniformity of sizes and homogeneity of formulations.[37]

Zeta potential: Zeta potential describes the amount of surface charge of vesicles and it is used to measure colloidal stability. Proniosomal formulations that contain high enough positive or negative values of zeta potential have lower aggregation of vesicles and are highly physically stable in the process of storage and use. The presence of surface charge can as well affect vesicle and skin interactions, which subsequently affects dermal penetration and retention of drugs.[38]

Entrapment efficiency: The highest percent of lidocaine entrapped in the vesical system and expressed as a percentage of the total drug content is the treatment efficiency. The desirable entrapment efficiency is to get the continuous drug release and the extension of local anesthetic effect. It is affected by composition of formulations, surfactant characteristics, cholesterol and the ratio of drugs to lipids.[39]

6.2 In Vitro Drug Release Studies

Studies on the in vitro drug release involve investigating the profile of lidocaine release in proniosomal formulations. Normally, these studies use diffusion cells or membrane cell-based models to model the diffusion behavior of drugs. Mathematical models are employed in analyzing release kinetics to establish the drug release mechanism, e.g. diffusion-controlled or matrix-controlled. There are usually patterns of controlled and sustained release in the proniosomal systems, which leads to improved anesthetic duration of action as well as decreased dosing schedules.[40]

6.3 Ex Vivo Skin Permeation Studies

Ex vivo skin permeation research offers essential data on the transdermal capability of proniosomal systems. Animal or human skin, which is excised, is often used as the means of assessing the permeation parameters of drugs. The retention of skin is research that evaluates the levels of lidocaine that are deposited in the various skin layers, which shows that the drug is deposited locally. Flux and permeability coefficients are used to determine the rate and the degree of transdermal transport. The increase in skin retention and permeation control are indicators of the efficacy of proniosomal carriers to deliver lidocaine to the skin with low systemic absorption.[41]

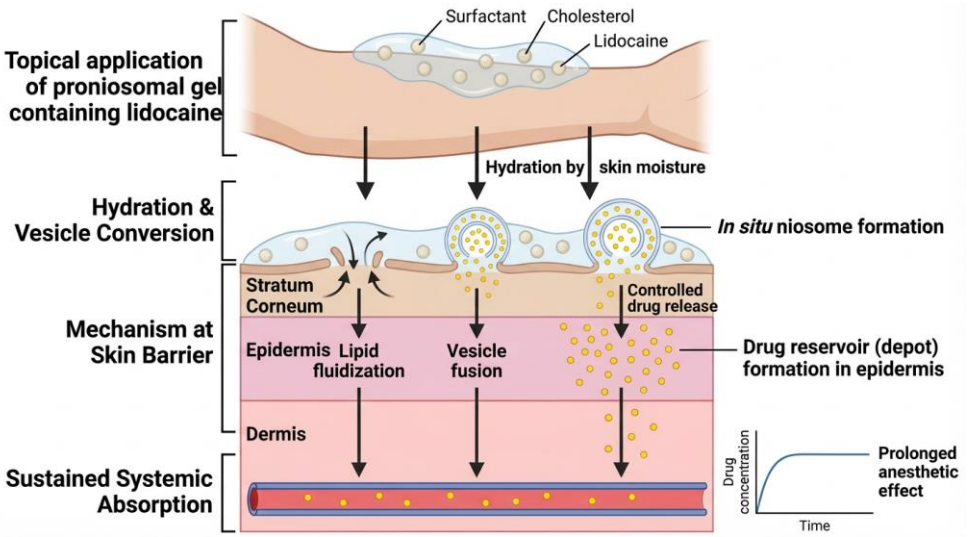

Figure 2: Mechanism of controlled transdermal delivery of lidocaine from proniosomal system.[42]

7. THERAPEUTIC PERFORMANCE AND SAFETY ASPECTS

Evaluation of therapeutic efficacy and safety is essential to establish the clinical relevance of lidocaine-loaded proniosomal transdermal systems. By enabling controlled and localized drug delivery, proniosomes aim to enhance anesthetic performance while minimizing adverse effects commonly associated with conventional formulations.[43]

7.1 Enhanced Local Anesthetic Effect

Proniosomal transdermal systems are important in enhancing the local anesthesia effects of lidocaine by delivering sustained concentration and extended residence at the drug delivery location. When hydrated the niosomal vesicles generated serve as a drug reservoir in the skin and this way the diffusion of lidocaine into underlying tissues is sustained. This regulated release effect causes long-term anesthetic effect as opposed to traditional topical preparations which normally have high rates of drug loss.[44]

The prolonged profile of release of proniosomes ensures that the frequency of reapplication is minimized and hence enhances patient compliance and comfort. Long-term anesthesia is especially beneficial in skin surgeries, pain management after surgery and in minor surgeries in which long-lasting analgesia is required without the need to take repeated doses or by intravenous injections.[45]

7.2 Skin Irritation and Toxicity Studies

The transdermal drug delivery systems need to consider skin safety. Skins irritation and toxicity are done in order to determine how well the proniosomal preparations are compatible with the skin. Such assessments are usually conducted through visual examination of erythema, edema or inflammation after topical use. Proniosomes containing Lidocaine typically exhibit excellent dermal tolerance due to the use of non-ionic surfactants which are biocompatible and the release of the drug is regulated.[46]

The same is affirmed by biocompatibility experiments, which show that proniosomal components do not cause any serious skin damage or inflammations. The low systemic absorption of lidocaine also helps to decrease the toxicity with the doses, which means a better safety profile.[47]

7.3 Comparison with Conventional Lidocaine Formulations

Proniosomal transdermal systems have better therapeutic performance compared to the conventional lidocaine creams, gels, and injections. They have long-lasting anesthetic effects, better skin retention, and decreased systemic exposure. These benefits can be translated into the increased safety, decreased dosing rate, and enhanced patient compliance, which makes proniosomes a potentially beneficial alternative to local pain treatment.[48]

8. MECHANISMS INVOLVED IN CONTROLLED LIDOCAINE DELIVERY

The controlled and localized delivery of lidocaine from proniosomal transdermal systems is governed by multiple complementary mechanisms that operate simultaneously at the formulation–skin interface. These mechanisms collectively enhance dermal retention, prolong anesthetic action, and minimize systemic exposure, distinguishing proniosomal systems from conventional topical formulations.

Vesicular Reservoir Effect

When the skin is hydrated on its surface, the proniosomes are converted into niosomal vesicles that serve as a localized drug reservoir in the stratum corneum and viable epidermis. These vesicles release lidocaine slowly in a regulated manner, and this sustains a constant concentration gradient across the skin. This reservoir effect is what extends the use of drugs at the site of action and avoids the rapid elimination hence prolonging local anesthesia.[49]

Stratum Corneum Lipid Fluidization

Proniosomal vesicles are in close contact with lipid matrix of stratum corneum. The surfactant constituents of proniosomes partially fluidize and rearrange intercellular lipids decreasing barrier resistance. This reversible temporary interruption is what increases the permeation of lidocaine without permanent destruction of the skin structure. Enhanced lipid fluidization enables enhanced penetration and even dispersion of the drug in the skin layers.[50]

Sustained Drug Diffusion

The rate of diffusion of lidocaine is controlled by the bilayer structure of niosomal vesicles which is a diffusion barrier. The diffusion of the vesicular core into the adjacent skin tissue is regulated, which means that the drug will be delivered

over an extended period of time without bursting out as it happens with standard formulations. This prolonged diffusion curve adds to the uniform effect of anesthesia in a long-acting manner.[51]

Reduced Systemic Absorption

By promoting localized drug deposition and controlled permeation, proniosomal systems limit the amount of lidocaine entering systemic circulation. Reduced systemic absorption lowers the risk of dose-related adverse effects, enhancing the overall safety profile of transdermal lidocaine therapy.[52]

9. FUTURE PERSPECTIVES

The further development of the proniosomal transdermal systems has great prospects to develop the localized anesthetic therapy. The next generation studies are anticipated to be on the incorporation of proniosomes in smart polymers and stimuli-reactive materials to attain on-demand and site-specific release of lidocaine. Thermo responsive, pH responsive or enzyme responsive polymers could be incorporated to enable the drug release to be induced by the physiological or pathological conditions and thereby increase the precision of the therapeutic and reduce unnecessary drug exposure.[53]

Although the results of the initial clinical studies of proniosomal systems have been promising, there are a number of issues with the application of the systems into clinical practice. Long-term safety, therapeutic efficacy and reproducibility in different patient groups need to be studied through comprehensive clinical works. Formulation parameters, quality control protocols should be standardized and performance in the different types of skin should be validated to achieve consistent clinical outcomes.[54]

The success of commercialization of proniosomal formulations is also largely dependent on scale-up and manufacturing. The establishment of affordable, reproducible and scalable production methods should be in line with the regulatory provisions of transdermal drug delivery systems. The approval will be based on the evidence of formulation stability, safety, and bioequivalence or superiority of existing products which will be achieved by conducting well-designed clinical trials.[55]

Moreover, proniosomal platforms have high potential of personalized pain management. Personalized anesthetic therapy might be achieved through the development of formulation composition, drug loading, and release profile based on patient issues, skin properties, and intensity of pain. This individual approach can potentially enhance treatment outcomes, patient satisfaction, and make proniosomal transdermal systems one of the major elements of future precision medicine in pain management practices.[56]

10. CONCLUSION

Proniosomal transdermal platforms represent a significant advancement in the field of localized drug delivery, offering a smart and efficient approach for overcoming the limitations associated with conventional lidocaine formulations. By combining the advantages of vesicular nanotechnology with the convenience of transdermal administration, proniosomes provide improved formulation stability, controlled drug release, and enhanced skin retention, making them particularly suitable for local anesthetic delivery.

The integration of lidocaine into proniosomal systems results in prolonged anesthetic action, reduced dosing frequency, and minimized systemic exposure. These benefits not only improve therapeutic efficacy but also enhance patient safety by lowering the risk of dose-related adverse effects commonly observed with oral and injectable administration.

Furthermore, the use of biocompatible non-ionic surfactants and optimized formulation components contributes to favorable dermal tolerance and overall safety.

As smart vesicular carriers, proniosomes enable precise modulation of drug release and spatial distribution within the skin, addressing the growing demand for localized and patient-centric pain management strategies. Their ability to form in situ vesicular reservoirs upon hydration further strengthens their potential to deliver sustained and effective anesthesia at the target site.

In conclusion, proniosomal transdermal systems emerge as a promising and future-ready platform for localized pain control. Continued research focused on formulation optimization, mechanistic understanding, and clinical validation is expected to accelerate their translation into clinically viable and commercially successful lidocaine therapies, ultimately enhancing the quality of pain management in modern clinical practice.

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REFERENCES

1. Falanga V, Isseroff RR, Soulika AM, Romanelli M, Margolis D, Kapp S, Granick M, Harding K. Chronic wounds. Nature Reviews Disease Primers, 2022 Jul 21; 8(1): 50.
2. Shah J, Votta-Velis EG, Borgeat A. New local anesthetics. Best Practice & Research Clinical Anaesthesiology, 2018 Jun 1; 32(2): 179-85.
3. Macfarlane AJ, Gitman M, Bornstein KJ, El-Boghdadly K, Weinberg G. Updates in our understanding of local anaesthetic systemic toxicity: a narrative review. Anaesthesia, 2021 Jan; 76: 27-39.
4. Samuel HS, Ekpan FM. Revolutionizing drugs administration: Techniques in drug delivery and development. Int J Biochem Physiol, 2023; 8(2): 1-5.
5. Bag J, Mukhopadhyay S, Nandi G, Tun HM. Next-generation composite vesicular systems: an in-depth review of proniosomes in advanced drug delivery. Drug Delivery, 2026 Dec 31; 33(1): 2614585.
6. Sahu S, Ghosh V, Jain P, Ajazuddin. Recent advancement of novel drug delivery systems for topical anaesthesia formulations. Current Nanomedicine, 2024 Oct 8.
7. Cammarano A, Iacono SD, Battisti M, De Stefano L, Meglio C, Nicolais L. A systematic review of microneedles technology in drug delivery through a bibliometric and patent overview. Heliyon, 2024 Dec 15; 10(23).
8. de Araujo DR, Ribeiro LN, de Paula E. Lipid-based carriers for the delivery of local anesthetics. Expert opinion on drug delivery, 2019 Jul 3; 16(7): 701-14.
9. Hu X, He T, Zhang D, Zhou C, Liang P. Nano-enabled delivery of anesthetics: mechanistic insights, technological advances and translational challenges. Journal of Materials Chemistry B., 2025; 13(43): 13844-66.
10. Eipe N, Gupta S, Penning JJ. Intravenous lidocaine for acute pain: an evidence-based clinical update. Bja Education, 2016 Sep 1; 16(9): 292-8.
11. Santa-Maria AR, Walter FR, Valkai S, Brás AR, Mészáros M, Kincses A, Klepe A, Gaspar D, Castanho MA, Zimányi L, Dér A. Lidocaine turns the surface charge of biological membranes more positive and changes the permeability of blood-brain barrier culture models. Biochimica et Biophysica Acta (BBA)-Biomembranes, 2019 Sep 1; 1861(9): 1579-91.

12. Logothetis DD. Pharmacology of Local Anesthetic Agents. Local Anesthesia for the Dental Hygienist, 2016 Feb 21; 28.
13. Caddeo C, Valenti D, Nácher A, Manconi M, Fadda AM. Exploring the co-loading of lidocaine chemical forms in surfactant/phospholipid vesicles for improved skin delivery. Journal of Pharmacy and Pharmacology, 2015 Jul; 67(7): 909-17.
14. Rashiq SA, Finucane TB. Nerve conduction and local anaesthetic action. Wylie and Churchill Davidson: A Practice of Anaesthesia. 7th ed. Florida: Boca Raton, 2003 Oct 31: 267-76.
15. Mysore V, Nischal KC. Guidelines for administration of local anesthesia for dermatosurgery and cosmetic dermatology procedures. Indian Journal of Dermatology, Venereology and Leprology, 2009 Aug 1; 75: 68.
16. Foong KW, Chaw SH, Lo YL, Loh PS. Population pharmacokinetics of intravenous lidocaine in adults: a systematic review. Clinical Pharmacokinetics, 2024 May; 63(5): 623-43.
17. Hoffman A, Stepensky D. Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy. Critical Reviews™ in Therapeutic Drug Carrier Systems, 1999; 16(6).
18. Marei HF, Arafa MF, Essa EA, El Maghraby GM. Lidocaine as eutectic forming drug for enhanced transdermal delivery of nonsteroidal anti-inflammatory drugs. Journal of Drug Delivery Science and Technology, 2021 Feb 1; 61: 102338.
19. Khatoon M, Shah KU, Din FU, Shah SU, Rehman AU, Dilawar N, Khan AN. Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug delivery, 2017 Nov 1; 24(2): 56-69.
20. Govindarajan S, Swamivelmanickam M, Nair SP, Sivagnanam S. A Comprehensive Study on Provesicular Drug Delivery System: Proniosomal Gel. Indian Journal of Pharmaceutical Sciences, 2022 Jan 1; 84(1).
21. Bachhav AA. Proniosome: A novel non-ionic provesicules as potential drug carrier. Asian Journal of Pharmaceutics (AJP), 2016 Sep 10; 10(03).
22. Khindri S, Aggarwal G, Hari Kumar SL. Role of niosomes and proniosomes for enhancing bioavailability of drugs. J Drug Deliv Ther, 2015 Jan 13; 5(1): 28-33.
23. Shah H, Nair AB, Shah J, Jacob S, Bharadia P, Haroun M. Proniosomal vesicles as an effective strategy to optimize naproxen transdermal delivery. Journal of Drug Delivery Science and Technology, 2021 Jun 1; 63: 102479.
24. Bouwstra JA, Honeywell-Nguyen PL, Gooris GS, Ponec M. Structure of the skin barrier and its modulation by vesicular formulations. Progress in lipid research, 2003 Jan 1; 42(1): 1-36.
25. Negi P, Singh B, Sharma G, Beg S, Katare OP. Biocompatible lidocaine and prilocaine loaded-nanoemulsion system for enhanced percutaneous absorption: QbD-based optimisation, dermatokinetics and in vivo evaluation. Journal of microencapsulation, 2015 Jul 4; 32(5): 419-31.
26. Uchegbu IF, Florence AT. Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. Advances in colloid and interface science, 1995 Jun 27; 58(1): 1-55.
27. Nsairat H, Ibrahim AA, Jaber AM, Abdelghany S, Atwan R, Shalan N, Abdelnabi H, Odeh F, El-Tanani M, Alshaer W. Liposome bilayer stability: emphasis on cholesterol and its alternatives. Journal of liposome research, 2024 Jan 2; 34(1): 178-202.
28. Hirata K, Mohammed D, Hadgraft J, Lane ME. Influence of lidocaine hydrochloride and penetration enhancers on the barrier function of human skin. International Journal of Pharmaceutics, 2014 Dec 30; 477(1-2): 416-20.
29. Veis A. A review of the early development of the thermodynamics of the complex coacervation phase separation. Advances in colloid and interface science, 2011 Sep 14; 167(1-2): 2-11.

30. Khudair N, Agouni A, Elrayess MA, Najlah M, Younes HM, Elhissi A. Letrozole-loaded nonionic surfactant vesicles prepared via a slurry-based proniosome technology: Formulation development and characterization. Journal of Drug Delivery Science and Technology, 2020 Aug 1; 58: 101721.
31. Ababei-Bobu A, Profire BȘ, Iacob AT, Chirliu OM, Lupașcu FG, Profire L. Niosomes as vesicular carriers: from formulation strategies to stimuli-responsive innovative modulations for targeted drug delivery. Pharmaceutics, 2025 Nov 14; 17(11): 1473.
32. Egan RW. Hydrophile-lipophile balance and critical micelle concentration as key factors influencing surfactant disruption of mitochondrial membranes. Journal of Biological Chemistry, 1976 Jul 25; 251(14): 4442-7.
33. Chountoulesi M, Naziris N, Pippa N, Demetzos C. The significance of drug-to-lipid ratio to the development of optimized liposomal formulation. Journal of liposome research, 2018 Jul 3; 28(3): 249-58.
34. Florence AT, Arunothayanun P, Kiri S, Bernard MS, Uchegbu IF. Some rheological properties of nonionic surfactant vesicles and the determination of surface hydration. The Journal of Physical Chemistry B., 1999 Mar 18; 103(11): 1995-2000.
35. Omar MM, Hasan OA, El Sisi AM. Preparation and optimization of lidocaine transferosomal gel containing permeation enhancers: a promising approach for enhancement of skin permeation. International journal of nanomedicine, 2019 Feb 26: 1551-62.
36. You P, Yuan R, Chen C. Design and evaluation of lidocaine-and prilocaine-coloaded nanoparticulate drug delivery systems for topical anesthetic analgesic therapy: a comparison between solid lipid nanoparticles and nanostructured lipid carriers. Drug Design, Development and Therapy, 2017 Sep 18: 2743-52.
37. Mokhtar M, Sammour OA, Hammad MA, Megrab NA. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. International journal of pharmaceutics, 2008 Sep 1; 361(1-2): 104-11.
38. Danaei M, Kalantari M, Raji M, Fekri HS, Saber R, Asnani GP, Mortazavi SM, Mozafari MR, Rasti B, Taheriazam A. Probing nanoliposomes using single particle analytical techniques: Effect of excipients, solvents, phase transition and zeta potential. Heliyon, 2018 Dec 1; 4(12).
39. Pathak P, Nagarsenker M. Formulation and evaluation of lidocaine lipid nanosystems for dermal delivery. Aaps Pharmscitech, 2009 Sep; 10(3): 985-92.
40. Steyn JD, Haasbroek-Pheiffer A, Pheiffer W, Weyers M, van Niekerk SE, Hamman JH, van Staden D. Evaluation of drug permeation enhancement by using in vitro and ex vivo models. Pharmaceuticals, 2025 Jan 31; 18(2): 195.
41. Nair RS, Billa N, Morris AP. Optimizing in vitro skin permeation studies to obtain meaningful data in topical and transdermal drug delivery. AAPS PharmSciTech, 2025 May 29; 26(5): 147.
42. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. Journal of controlled release, 1998 Jul 31; 54(2): 149-65.
43. Leon MM, Maștaleru A, Oancea A, Alexa-Stratulat T, Peptu CA, Tamba BI, Harabagiu V, Grosu C, Alexa AI, Cojocaru E. Lidocaine–Liposomes—a promising frontier for transdermal pain management. Journal of Clinical Medicine, 2024 Jan 3; 13(1): 271.
44. Shipton EA. Advances in delivery systems and routes for local anaesthetics. Trends in Anaesthesia and Critical Care, 2012 Oct 1; 2(5): 228-33.

45. Malabade S, Salve P, Shirke PS. Formulation of nanogel loaded with Lantana montevidensis-incorporated silver nanoparticles: A bio-inspired approach to rheumatoid arthritis therapy. Journal of Pharmaceutical Innovation, 2025 Apr; 20(2): 57.
46. Alkilani AZ, Nasereddin J, Hamed R, Nimrawi S, Hussein G, Abo-Zour H, Donnelly RF. Beneath the skin: a review of current trends and future prospects of transdermal drug delivery systems. Pharmaceutics, 2022 May 28; 14(6): 1152.
47. Helmy NA, Abdel Aziz EA, Raouf MA, Korany RM, Mansour DA, Baraka SM, Hassan AA, Gomaa E, Faisal MM, Basha WA, Fahmy EM. Revealing the impact of tadalafil-loaded proniosomal gel against dexamethasone-delayed wound healing via modulating oxido-inflammatory response and TGF-β/Macrophage activation pathway in rabbit model. PloS one, 2025 Jan 7; 20(1): e0315673.
48. Rahimpour Y, Kouhsoltani M, Hamishehkar H. Proniosomes in transdermal drug delivery. Current pharmaceutical design, 2015 Jun 1; 21(20): 2883-91.
49. Muzzalupo R. Niosomes and proniosomes for enhanced skin delivery. InPercutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Nanocarriers, 2016 Jan 5 (pp. 147-160). Berlin, Heidelberg: Springer Berlin Heidelberg.
50. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Critical reviews™ in therapeutic drug carrier systems, 1996; 13(3-4).
51. Carafa M, Santucci E, Lucania G. Lidocaine-loaded non-ionic surfactant vesicles: characterization and in vitro permeation studies. International journal of pharmaceutics, 2002 Jan 1; 231(1): 21-32.
52. Santamaria CM, Woodruff A, Yang R, Kohane DS. Drug delivery systems for prolonged duration local anesthesia. Materials Today, 2017 Jan 1; 20(1): 22-31.
53. Singh J, Nayak P. pH-responsive polymers for drug delivery: trends and opportunities. Journal of polymer science, 2023 Nov 15; 61(22): 2828-50.
54. Radha GV, Rani TS, Sarvani B. A review on proniosomal drug delivery system for targeted drug action. Journal of basic and clinical pharmacy, 2013 Mar; 4(2): 42.
55. Türeli NG, Türeli AE. Upscaling and GMP production of pharmaceutical drug delivery systems. InDrug delivery trends, 2020 Jan 1 (pp. 215-229). Elsevier.
56. Jeong JO, Kim M, Kim S, Lee KK, Choi H. Advanced hydrogel systems for local anesthetic delivery: Toward prolonged and targeted pain relief. Gels, 2025 Feb 12; 11(2): 131.