Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

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

Proniosomal Formulations: A Versatile Platform for Enhanced Topical Drug Delivery

Vaibhav Tiwari[1], Ramsha Aslam[2*], Disha Dutta[3*]
[1,2*,3*]Devsthali Vidyapeeth College of Pharmacy, Rudrapur Uttarakhand, India

Article Information
Received: 20-10-2025
Revised: 14-11-2025
Accepted: 24-11-2025
Published: 21-12-2025

Keywords
Proniosomes, Niosomes, Vesicular carriers, Topical drug delivery, Controlled release, Dermatology

ABSTRACT
Topical drug delivery remains a preferred route for treating dermatological disorders due to its ability to bypass first-pass metabolism and provide localized therapeutic action. However, conventional formulations often suffer from poor penetration, instability, and limited bioavailability. Vesicular carriers such as liposomes, niosomes, ethosomes, and transfersomes have been explored to overcome these barriers, yet challenges in stability and scalability persist. Proniosomes, dry surfactant-coated carrier particles that readily hydrate to form niosomes, represent a versatile advancement in this field. Their unique composition enhances entrapment efficiency, improves drug stability, and facilitates controlled release of both hydrophilic and lipophilic agents. This review highlights the development, structure, preparation methods, and physicochemical characterization of proniosomes, while emphasizing their advantages over conventional vesicular systems. Applications in dermatology, anti-inflammatory therapy, antimicrobial delivery, and cosmetic formulations are discussed alongside comparative insights. By consolidating current progress and identifying future challenges, this article underscores proniosomes as a promising platform for enhanced topical drug delivery and encourages further translational research toward clinical adoption.

1. INTRODUCTION:

Skin is a highly effective, very well route for drug delivery which avoids many of the disadvantages of the oral, inhalation, and parenteral methods. [1] The largest organ in the body, the skin is composed of its outermost layer, the dermis, and subcutaneous tissues (Figure 1). It also includes auxiliary organs like sebaceous glands and hair follicles. External factors, stress, sleep difficulties, and many more characteristics are only a few variables that could disrupt the skin barrier. As society keeps evolving and people's habits and their surroundings change, skin diseases have grown increasingly widespread in recent years. With an incidence rate around 25%, skin diseases are presently the fourth most frequent non-fatal disease in the globe. [2,3]

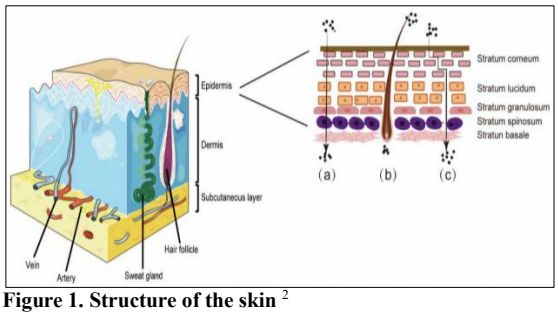

Figure 1. Structure of the skin [2]

The skin controls the in and outflow of several substances, avoiding moisture loss and maintaining body temperature to keep equilibrium as homeostasis inside the body. [4,5] Almost one third of the worldwide population suffers from by skin problems, which are the second most prevalent cause of humanity's diseases. Their influence is sometimes underestimated in spite of this. The expense of skin illnesses is increased by the high prevalence of skin conditions, prolonged morbidity, disability-adjusted life, which includes extreme itching, including in the case regarding atopic dermatitis when chronic inflammatory skin

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

ailments like inflammatory psoriasis, and the high cost of innovative treatments like biologics. [6] Some health systems may be fiscally endangered by the high prevalence of carcinoma of the skin and the related treatment expenditures. Atopic dermatitis, which ranks 15th among all nonfatal illnesses, is the source of the greatest burden among skin conditions. Acne is a very frequent inflamed dermatosis that is especially common in women and teens. Psoriasis is believed to afflict roughly 2–4% of humans in western nations. [4] Therefore, topical therapy is an effective way to treat many conditions, but it requires a deep understanding of the skin as a barrier. Skin is a complex membrane with three layers: the dermis (outermost layer), the intermediate layer dermis (contains numerous connective fibers, receptors for senses, and sweaty glands), and the outermost layer of which is the layer beneath the dermis (includes adipose tissue and links the other body skin layers provide support).[7]

Researchers think highly of the transdermal route is frequently utilized. Previous research indicates that over 70% of doctors and patients choose this for skin-related problems. [8] This is primarily because the TDDS offers distinct benefits over ingested and topical medicines, including [2] direct actions on the skin, high bioavailability, and avoidance of the liver's first-pass impact; [8] maintenance of a steady blood concentration avoiding peak and fall effects; [8] minimal frequency with general adverse consequences; [9] good patient compliance and [10] the capacity to quickly stop giving medication. The primary drawbacks of TDDSs are [2] restricted penetration accuracy, [3] limited tissue saturation maintenance length, [3] high dosage frequency, and [9] quick skin irritation. TDDSs still barely reach the anticipated effectiveness. The effectiveness of medicine penetration and precision administration has significantly improved over the past few decades due to quickly developing drug delivery technologies.

Vesicular pathways have been intensively researched as channels for percutaneous and transdermal medication delivery. It is commonly known that they improve medication penetration. [11] Because liposomes are bilayered lipid gels made mostly of cholesterol and phospholipids, they may also be able to pass through the skin barrier. [12] It is known that drugs encapsulated in lipid vesicles made of phospholipids while nonionic surfactant can enter and pass through the skin. Liposomes have been thoroughly studied for their possible use in pharmaceutics, including drug delivery for drug targeting, controlled release, or enhancing solubility, due to their capacity to transport a wide range of medications. [13–16] It has been found that liposomes, transferosomes, ethosomes, and niosomes provide improved permeability across stratum corneum barriers.

Proniosomes are dry formulation of aqueous soluble carrier particles and are coated with surfactant. They are hydrated to produce niosomal distribution immediately before being agitated in hot aqueous solution for a few minutes. The main purpose of developing managed and focused release prescription form is that enhance the therapeutic impact of medication boost drug safety window of high potency pharmaceuticals by the raises plasma levels and also minimize adverse effects. [17] This review focuses on proniosomal formulation as a very advanced topical delivery system which can work fast with more accuracy as compares to other routes.

1.1 Topical Drug Delivery Systems

Topical medicines have a lengthy history. Egyptians, Chinese, and Babylonians employed ointments and salves produced from plant, mineral, or animal extracts several thousand years ago to treat a variety of illnesses. [18-20] During the age of using natural remedies to cure ailments, external treatment is one of the most crucial ways of treating diseases. [21-23] Conventional topical medication development procedure. The research process is separated into four facets: topical medicine boasts a long history, topical medications play a significant role, (Figure 2) the ancient Egyptians can increase the efficacy of topical pharmaceuticals, and topical drugs have entered a new age. [24]

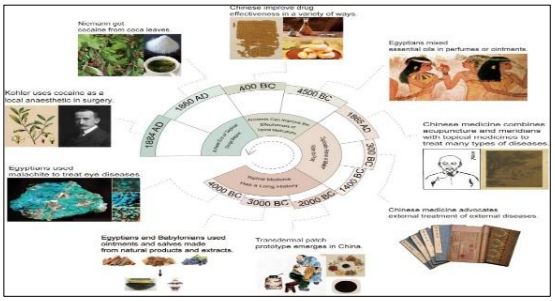

Figure 2. Development of topical medication [24]

A drug's bioavailability can be affected by both internal and external factors. The specificity of a medication's target receptors, an individual's distinct physiology (including genetic polymorphisms), the drug's mode of administration, the site of medication absorption, and the necessary metabolic steps to stimulation can all have an intrinsic impact on a drug's bioavailability. Drug interactions with pharmaceuticals and concurrent food of substance metabolic processes are examples of extrinsic factors that alter drug bioavailability. [25]

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

1.2. Vesicular Carriers

Water-filled colloidal particles are referred to as vesicles. The walls of individual vessels are made out of multiple layers of hydrophilic molecules. In the presence of sufficient water, these conductive chemicals can form any one (unilamellar evs) or several (multilamellar vesicles) annular bilayers. [26]

1.2.1. Liposomes

The discovery that enclosed lipid bilayer vesicles (Figure 3) spontaneously form in water led to the coining of the name "liposome" in the 1960s. [27-29]

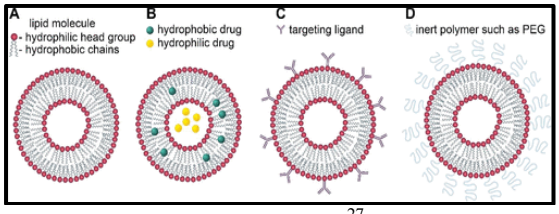

Figure 3. Representation of Liposome[27]

The potential about liposomes being drug delivery vehicles was realized almost immediately since their development.

For example, it was discovered that roughly 40% of small-molecule medicines for cancer therapy display low solubility within water, hence the benefits of medication delivery systems that can encapsulating these compounds and improving their aqueous properties was instantly realized. Liposomes served as the earliest nanotechnology transportation platform to successfully go from idea to clinical use, with a number of authorized pharmaceutical formulations. For instance, Doxil, a lipid nanoparticle version of the anticancer chemical doxorubicin used to treat ovarian cancer, was the first liposomal medication to be licensed.[30]

1.2.3. Niosomes

Niosomes are the special bilayer lipid nanostructure created with the assistance of the self-aggregation that occurs in a non-ionic surfactant. Initially, it had been produced by the L'Oreal corporation for its cosmetic use in 1975. After a period of development in 1980, implants have been deployed as medication delivery devices (Figure 4). [31]

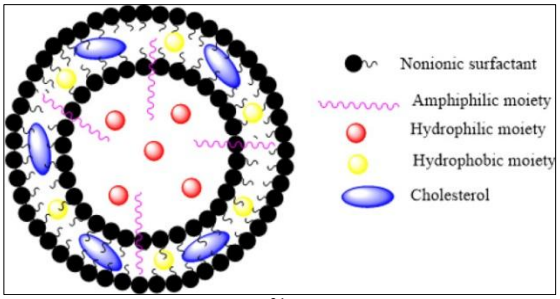

Figure 4. Design of Niosomes [31]

1.2.4. Ethosomes:

The content of ethosomes can be used to categorize them.

Table 1 displays the main distinctions between different ethosomes for transdermal medication administration. [32]

Sl. No.	Parameter	Classical ethosomes	Binary ethosomes	Transethosomes
1	Composition	1. Phospholipids	1. Phospholipids	1. Phospholipids
		2. Ethanol	2. Ethanol	2. Ethanol
		3. Stabilizer	3. Propylene glycol (PG) or other alcohol	3. Edge activator (surfactant) or penetration enhancer
		4. Charge inducer	4. Charge inducer	4. Charge inducer
		5. Water	5. Water	5. Water
		6. Drug/agent	6. Drug/agent	6. Drug/agent
2	Morphology	Spherical	Spherical	Regular, irregular spherical shapes
3	Size	Small than classical liposomes	Almost Equal or smaller than others	based on type, concentration of penetration enhancer or edge activator used
4	Entrapment efficiency	Superior than traditional liposomes	Often higher than traditional ethosomes	Higher than the majority of typical ethosomes
5	Skin permeation	larger than traditional liposomes	on pair with or superior to traditional ethosomes	higher than traditional ethosomes
6	Stability	More robust than traditional liposomes	Stabler than classical ethosomes	There was no clear trend found

1.2.5. Transfersomes

Compared to subcutaneous or just intramuscular routes, the transdermal route is simpler to administer vaccines; additionally, transcutaneous immunization exhibits superior immunogenicity [33]. Nanoparticles with a diameter of roughly 100 nm are of particular interest because they can enter hair follicles and transfer antibodies to APCs, such as epidermal Langerhans cells. Particle-based vaccinations administered transdermally may need skin preparation, such as electroporation, sonophoresis, laser ablation, or skin abrasion, to increase the particles' permeability; nonetheless, this can be an extremely invasive and rare procedure. Transfersomes can be employed for transdermal vaccine distribution as an alternative to these invasive techniques since they can alter their form as the medication is being delivered and transported across the skin (Fig. 4) [34]. Their movement through the skin is owing to the osmotic

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

force or to the moisture.

1.3. Proniosomes

Proniosomes are result of nonionic surfactants simply manufactured by dissolving the ingredient in question in a small quantity of an appropriate solvent and a tiny amount of water. Typically, proniosomes may contain different nonionic surfactants including span 20, 40, 60, 80 along with 85, tween 20, 40, 80; lecithin, alcohol (ethanol, methanol, isopropyl alcohol, etc.); and chloroform. Chemical property of surfactants determines drug trapping efficiency. Higher entrapment efficiency results from lengthening the alkyl chain. [35] Additionally, it has been shown that the medication is most entraped in spans with the greatest phase transition temperature and vice versa. [35] Additionally, it has been reported that spans with the highest temperature of phase transition offer highest entrapment for the medicinal product and vice versa. [36] Drug can be entrapped toward proniosomes made of tweens, but the encapsulation efficiency was comparatively low when compared to those made of spans. [37] The majority of surfactants used to create nonionic surfactant vesicles exhibit a low fluid solubility. However, in the presence of cholesterol, freely soluble non-ionic surfactants like tween may hydrate and form micelles. [38]

1.3.1. Structure

They are tiny lamellar structures, angled structures, and blackish structures, while their position is semi-transparent, yet semi-solid gel-like structures (Figure 5). Consistent with their manner of preparation, proniosomes may unilamellar, multi-lamellar. They even have a bilayer in the center of them with hydrophobic chains facing each other inside the bilayer amid the vesicles and hydrophilic ends exposed on the surface. Bilayer comprises of non-ionic surface-active chemicals. In order to form a bilayer particle molecule, the non-ionic surfactant's hydrophilic ends are oriented toward the exterior while its hydrophobic ends are oriented in reverse order. Hydrophilic pharmaceuticals are inserted at periods in the region encompassed within the vesicle along with the hydrophobic type of medication is placed within the bilayer. [39]

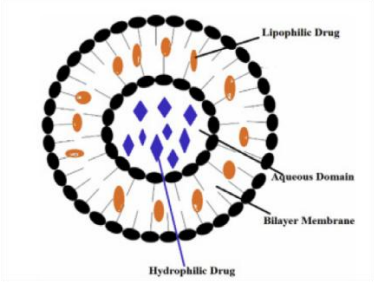

Figure 5. Structure of Proniosome [39]

1.3.2. Materials

These are result of nonionic surfactants simply manufactured by combining the surfactant in just enough of an appropriate carrier and least amounts of water. Typically, contain different non-ionic surfactants including span 20, 40, 60, 80 and 85, tween 20, 40, 80; lecithin, alcohol as chloroform. Chemical structure of lubricants determines drug trapping efficiency. Higher entrapment efficiency results from lengthening the alkyl chain. [40] Additionally, it has been shown that the medication is most entraped in spans with the greatest phase transition temperature and vice versa. [41] Drug may be encapsulated then comprised of tweens, although the encapsulation success was comparatively poor particularly compared to those made of spans. [42] The majority of surfactants utilized to generate nonionic surfactant nanoparticles have minimal aqueous solubility. However, in the presence of cholesterol, readily soluble nonionic surfactants like tween may hydrate and form micelles. [43] Vesicle stability и permeability may be impacted by the content of cholesterol in formulations. [44–45] Lecithin can also be mixed with cholesterol and nonionic surfactant in these compositions. Formulations using lecithin boost the encapsulation efficiency of pharmaceuticals compared to formulation including cholesterol solely. [46] However, encapsulating lecithin into a formulation necessitates particular preparation and storage conditions, making the product less stable and more costly. [44] As previously mentioned, only need a little amount of a suitable solvent to dissolve surfactants, such as ethanol, methanol, isopropyl alcohol, and chloroform.

1. **Surfactants**: Surfactants, notably non-ionic ones, are the fundamental structural elements used in the formation. Due to their polar head its non-polar tail, these surfactants are charge-free. As a result, they are more stable, poisonous, and compatible than other surfactants. Non-ionic surfactants increase the solubility plus permeability of medications through their wet and emulsifying properties. The lipophilic–hydrophilic balance (HLB) value is crucial for choosing surfactants and HLB value within 4 and 8 is consistent with vesicle production. It is difficult with hydrophilic surfactants to attain a high concentration on account of the elevated liquid solubility with hydrophilic surfactants. Therefore, aggregation of conglutination to produce a laminated structure is likely lacking. [47]

2. **Cholesterol**: Cholesterol may interact with surfactants that are not ionizing and controls

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

the physical et structural features.[48] It regulates medication penetration through the membrane and increases the membrane's stiffness and stability. The precise quantity of cholesterol needed to create also depends on the HLB value in the surfactants. When the HLB score is above 10, the amount contains cholesterol should be boosted to cover the bigger groups. 4]

3. **Lecithin**: In the creation, lecithin, a phospholipid, serves as a membrane stabilizer. Soy and egg lecithin are the most often utilized lecithins in the formulation. It has been claimed that hydrogenated-type lecithins offer benefits over non-hydrogenated lecithins, including greater cholesterol stiffness and assistance in the production of tight vesicles. [50]

4. **Hydration media**: Generally, the hydration medium utilized is phosphate buffer. Depending on how soluble of the encapsulated medicine, the pH of the buffering substance is determined. [51]

5. **Organic solvent**: its solvent can function as a penetration booster. It also considerably impacts the physical dimensions of the vesicles that are produced. The size of the particle and penetration rate of the medication in formulations are regulated by the kind of alcohol. Different alcohols are used to create vesicles of varying sizes because they are arranged as follows: >> isopropanol < butanol < propanol < ethanol.[52]

6. **Carrier material**: In proniosomal formulations, the medication is accommodated by carrier materials. Carriers ought to be safe, non-toxicity, free-flowing qualities. [53]

1.3.3. Preparation:

Some of the procedures, which were described for the preparation are as follows:

1. **Coacervation method**: Using this procedure, a wide-mouth glass vase is filled with a precisely measured amount of medication, surfactant, cholesterol, and lecithin. After adding enough ethanol as a solvent, the liquid was heated to between 50 and 60 degrees Celsius in a water bath. To stop the solvent from evaporating, a lid is placed over the glass vial's open end. This mixture was heated over a water bath at 50–60°C until the medication dissolved inside of the surfactant mixture after adding the water-soluble phosphate buffer pH 7.4. Either chill the mixture in room temperature or add an appropriate gelling component to the hot liquid and drop it on an ice bath to create the proniosomal gel. [54]

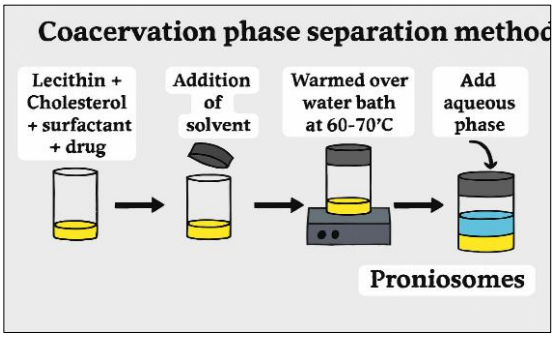

Figure 6. Shows coacervation process [66]

2. **Slurry method:** Chloroform: methanol (2:1) was used to create a 250 µmol storage solution of membrane stabilizer and surfactant. A 100 ml round-bottom flask holding the carrier material was filled with a specific volume of stock solution and medication dissolved in a chloroform: methanol (2:1) solution. If there is less surfactant loading, more organic solvent solution is added to create a slurry. The flask was coupled to a centrifugal flash evaporation device, wherein evaporates solution at 60 -70 rpm, whose temperature were 45 ± 2°C, plus a lowered pressure was set at 600 mmHg til the bulk in the flask resembled a dry, freely moving solution. These materials had been dehydrated in a desiccator 24/7 at room temperature underneath vacuum. [54]

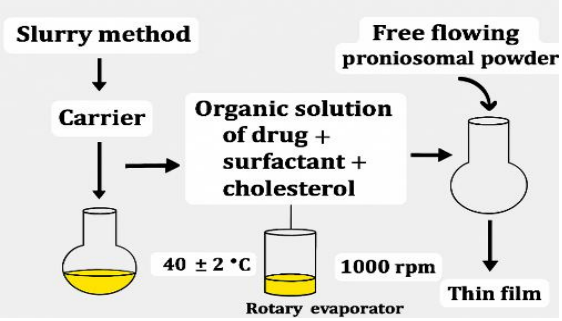

Figure 7. Steps of Slurry method [66]

3. **Slow spray coating method:** A one hundred ml round bottom flask with the necessary amount of carrier may be fitted to the rotary evaporator. The evaporator must be emptied, and the rotating keg can be spun in a solution of water underneath vacuum between 65-70°C for 15-20 minutes. This method is continued until the entire surfactant water has been administered. The evaporation should continue until the powder is fully dry. [55, 56]

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1489-1496
DoI-10.004687/1000-9035.2025.193

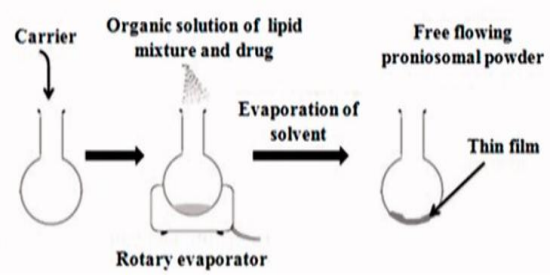

Figure 8. Spray coating method [66]

1.3.4. Advantages [57]

1. Eliminating physical stability issues such as aggregation, fusion, and niosome leakage.
2. Avoiding hydrolysis of encapsulated pharmaceuticals, which would shorten the period of storage of the dispersed.
3. Avoid first-pass metabolism.
4. Reduce adverse effects.
5. Improve bioavailability and stability issues.

1.3.5. Applications

Application Type	Description	Reference No
As carriers	Niosomes have been used as carriers for iobitridol, a diagnostic agent for X-ray imaging. Topical niosomes may act as solubilization matrices, local depots for sustained release of dermally active compounds, penetration enhancers, or rate-limiting membrane barriers for modulating systemic drug absorption.	[58]
Peptide drug delivery	Niosomes help protect peptides from gastrointestinal enzymatic breakdown. An in vitro study on oral delivery of a vasopressin derivative entrapped in niosomes showed significantly increased peptide stability.	[59]
Sustained release	Niosomes enable sustained release for drugs with low therapeutic index and poor water solubility, maintaining their circulation levels via encapsulation.	[60]
Other applications	Include vaccine delivery, anti-neoplastic agents, cosmetic delivery, hormone delivery, etc.	—
Proniosome advantages	Proniosome powders are preferred over lyophilized powders due to better drug stability. Studies show proniosomes are superior to niosomes in terms of room temperature storage and reduced drug leakage.	[61]

1.3.6. Characterization Techniques

1. Angle of Repose: It was determined using both the funnel and cylinder methods. [62]

2. Cylinder method: The powder was placed into a cylinder and fastened in place so that the cylinder's outflow aperture was 10 cm above the surface. The powder ran down in the cylinder, forming a cone on its outermost layer. [62]

3. SEM: Its particle size is an important aspect. The surface appearance, size distribution was examined using SEM. A double-sided tape was applied on aluminum stubs, and powder was dispersed over it. The aluminum stub was put in the vacuum area of a scanning electron microscope. The samples morphological characteristics were determined using a gaseous secondary electron detector XL 30. [63]

4. Optical microscopy: Niosomes were put on glass slides and examined using a microscope. The microscope offers a magnification of ×1200 for morphological examination after adequate dilution. The photomicrograph was taken from the microscope with a digital Single lens reflex (SLR) camera. [63]

5. Entrapment Efficiency: The unentrapped medication was separated from the niosomal solution using an extensive dialysis and centrifugation process. The niosomal solution was transferred to a dialysis tube with an osmotic cellulose membrane firmly connected to one side. The dialysis tube had been submerged in 100 ml saline buffer during a specific pH and swirled using a magnetic stirrer. The niosomal slurry and unentrapped medication were separated into the medium using an osmotic cellulose membrane. After 6 hours of rigorous dialysis, optical density results were obtained, and the entrapped drug was estimated using the UV spectrophotometric technique. [64]

6. In Vitro studies: The receptor compartment had a 20 ml capacity. The donor and receptor compartments were separated by the dialysis membrane and human cadaver skin. On one side of the membrane, a measured quantity of proniosomal gel was applied. A magnetic stirrer was used to continuously rotate the receptor media, which included phosphate buffer pH 7.4, at a speed of 50 rpm. To keep the temperature at 37±0.5°C, a water jacket was placed around the receptor chamber. One milliliter was taken out at each sample interval throughout the course of 24 hours, and equal quantities of new receptor fluid were added each time. Samples that were removed were examined using the furfural test of NS at 277 nm using a UV-visible double beam spectrophotometer. [65]

Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes have been tested to encapsulate

lipophillic as well as hydrophilic drug molecules. The use of proniosomal carriers results in delivery of high concentrations of active agent(s) to/through skin, regulated by system composition and their physical characteristics. Hence, enhanced delivery of bioactive molecules through skin by means of proniosomal carrier opens new challenges and opportunities for the development of novel improved therapies. So, comparatively Proniosome contain better structure, constituents and duration of action along with its sustainability.

CONCLUSION:

Extensive research reported on proniosomes evident their effectiveness in drug delivery and targeting. Proniosomes are suitable carrier system for the delivery of wide variety of drugs through different routes, such as oral, parenteral, dermal, transdermal, ocular, vaginal, mucosal pulmonary, and nasal effectively. Proniosomes are extensively employed in oral and transdermal delivery of wide variety of drugs. In oral delivery, they predominantly used to improve the bioavailability and absorption from the gastrointestinal tract. Moreover, they have a promising role in transdermal delivery because of their penetration enhancing properties, non-toxicity, and drug release modulation properties. Proniosomal formulations have emerged as a stable, efficient, and patient-friendly alternative to conventional vesicular carriers for topical drug delivery. Their ability to encapsulate diverse therapeutic agents, improve penetration through the skin barrier, and provide controlled release makes them highly versatile. Compared to liposomes and niosomes, proniosomes offer superior stability, ease of storage, and better reproducibility. Despite these advantages, challenges such as large-scale manufacturing, regulatory validation, and long-term clinical evaluation remain. Future research should focus on optimizing formulation strategies and expanding therapeutic applications, positioning proniosomes as a next-generation platform for safe and effective topical drug delivery.

REFERENCES:

1. Kamble, P.; Sadarani, B.; Majumdar, A.; Bhullar, S. Nanofiber Based Drug Delivery Systems for Skin: A Promising Therapeutic Approach. J. Drug Delivery Sci. Technol. 2017, 41, 124−133.
2. Qu, F.; Geng, R.; Liu, Y.; Zhu, J. Advanced nanocarrier- and microneedle-based transdermal drug delivery strategies. *Theranostics* **2022**, *12*, 3372–3406.
3. Jee, M.H.; Mraz, V.; Geisler, C.; Bonefeld, C.M. γδ T cells and inflammatory skin diseases. *Immunol. Rev.* **2020**, *298*, 61–73.
4. Seth, D.; Cheldize, K.; Brown, D.; Freeman, E. F. Global Burden of Skin Disease: Inequities and Innovations. Curr. Dermatol. Rep. 2017, 6 (3), 204−210.
5. Schäfer-Korting, M.; Mehnert, W.; Korting, H.-C. Lipid Nanoparticles for Improved Topical Application of Drugs for Skin Diseases. Adv. Drug Delivery Rev. 2007, 59 (6), 427−443.
6. Flohr, C.; Hay, R. Putting the burden of skin diseases on the global map. Br. J. Dermatol. 2021, 184 (2), 189−190.
7. Gorzelanny, C.; Mess, C.; Schneider, S. W.; Huck, V.; Brandner, J. M. Skin Barriers in Dermal Drug Delivery: Which Barriers Have to Be Overcome and How Can We Measure Them? Pharmaceutics 2020, 12 (7), 684.
8. Shah, P.; Goodyear, B.; Dholaria, N.; Puri, V.; Michniak-Kohn, B. Nanostructured Non-Ionic Surfactant Carrier-Based Gel for Topical Delivery of desoximetasone. *Int. J. Mol. Sci.* **2021**, *22*, 1535.
9. Mahant, S.; Kumar, S.; Nanda, S.; Rao, R. Microsponges for dermatological applications: Perspectives and challenges. *Asian J. Pharm. Sci.* **2020**, *15*, 273–291.
10. Guy, R.H. Transdermal drug delivery. *Handb. Exp. Pharmacol.* **2010**, *197*, 399–410.
11. R. Schreier, J. Bouwstra, J. Control. Release, 1994, 30, 1-15.
12. R. Barber, P. Shek, Liposomes as a topical ocular drug delivery system In: A. Rolland (Ed.), Marcel Dekker, New York, NY, 1993, 1-20.
13. P. Couvreur, E. Fattal, A. Andremont, Pharm. Res., 1991, 8, 1079-1086.
14. S. Kim, Drugs, 1993, 46, 618-638.
15. D. Booser, G. Hortobagyi, Drugs, 1994, 47, 223-258.
16. G. Gregoriadis, A. Florence, M. Harish, Liposomes in drug delivery, Harwood academic publishers, Langhorne, PA, 1993, 1085-1094.
17. Santosh Kumar, Harikesh mouray. (An overview on advance vesicles formulation as a drug carrier for N.D.D.S) European journal of biomedical and pharmaceutical science, 2018; 5(2): 292-303.
18. Lima, W. G., Brito, J. C. M., and da Cruz Nizer, W. S. (2021). Bee products as a source of promising therapeutic and chemoprophylaxis strategies against COVID-19 (SARS-CoV-2). Phytotherapy Res. PTR 35 (2), 743–750. doi:10. 1002/ptr.6872
19. Metwaly, A. M., Ghoneim, M. M., Eissa, I. H., Elsehemy, I. A., Mostafa, A. E., Hegazy, M. M., et al. (2021). Traditional ancient Egyptian medicine: a review. Saudi J. Biol. Sci. 28 (10), 5823–5832. Doi: 10.1016/j.sjbs.2021.06.044.
20. Roberts, M. S., Cheruvu, H. S., Mangion, S. E., Alinaghi, A., Benson, H. A. E., Mohammed, Y., et al. (2021). Topical drug delivery: history, percutaneous absorption, and product development. Adv. drug Deliv. Rev. 177, 113929. doi: 10.1016/j.addr.2021.113929.
21. Pastore, M. N., Kalia, Y. N., Horstmann, M., and Roberts, M. S. (2015). Transdermal patches: history, development and pharmacology. Br. J. Pharmacol. 172 (9), 2179–2209. doi:10.1111/bph.13059
22. Chen, S. (2016). The external treatment theory and Application about "Yellow Emperor's Inner Canon" bachelor's degree. China: Liaoning University of Traditional Chinese Medicine.
23. Zheng, H. L., and Zhang, Y. C. (2017). Elementary analysis on external treatment in Li Yue pian wen. J. Clin. Acupunct. Moxibustion 33 (5), 78–80.
24. Grzybowski, A. (2008). Cocaine and the eye: a historical overview. Ophthalmol. J. Int. d'ophtalmologie. Int. J. Ophthalmol. Zeitschrift fur Augenheilkunde. 222 (5), 296–301. doi:10.1159/000140625.
25. Martinez MN, Amidon GL. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. J Clin Pharmacol. 2002 Jun;42(6):620-43.
26. Hashizume M, Inoue H, Katagiri K, Ikeda A, Kikuchi J-I. Cerasome as an Organic-Inorganic Vesicular Nanohybrid: Characterization of Cerasome-Forming Lipids having a Single or a Dual Trialkoxysilyl Head. Journal of Sol-Gel Science and Technology. 2004; 31(1): 99-102.
27. Bangham, A. D.; Standish, M. M.; Watkins, J. C. Diffusion of Univalent Ions across Lamellae of Swollen

Phospholipids. *J. Mol. Biol.* **1965**, *13*, 238– 252, DOI: 10.1016/S0022-2836(65)80093-6
28. Gregoriadis, G. Liposomes in Drug Delivery: How It All Happened. *Pharmaceutics* **2016**, *8*, 1– 5, DOI: 10.3390/pharmaceutics8020019.
29. Weissig, V. Liposomes Came First: The Early History of Liposomology. In *Liposomes: Methods and Protocols*, 2nd ed.; D'Souza, G. G. M., Ed.; Humana Press: New York, **2017**; Vol. 1522, pp 1– 15.
30. Working, P. K.; Dayan, A. D. Pharmacological-Toxicological Expert Report. Caelyx. (Stealth Liposomal Doxorubicin Hcl). *Hum. Exp. Toxicol.* **1996**, *15*, 751– 785
31. M.N. Azmin, A.T. Florence, R.M. Handjani-Vila, J.F.B. Stuart, G. Vanlerberghe, J.S. Whittaker. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J. Pharm. Pharmacol., 37 (1985), pp. 237-242.
32. Abdulbaqi I.M., Darwis Y., Khan N.A.K., Assi R.A., Khan A.A. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. Int. J. Nanomed. 2016; 11:2279–2304. doi: 10.2147/IJN.S105016.
33. Dewangan HK, Tomar S. Nanovaccine for transdermal delivery system. J Drug Delivery Sci Technol. 2022; 67:102988.
34. 81.Simrah HA, Usmani SA, Izhar MP. Transfersome, an ultra-deformable lipid-based drug nanocarrier: an updated review with therapeutic applications. Naunyn Schmiedebergs Arch Pharmacol. 2023.
35. 82.Piumitali B, Neeraj U, Jyotivardhan J. Transfersome– a nanoscience in transdermal drug delivery and its clinical advancements. Int J Nanosci. 2020;19(4):1950033.
36. Y. Hao, F. Zhao, N. Li, Y. Yang, K. Li, Int. J. Pharm., 2002, 244, 73-80.
37. T. Yoshioka, B. Sternberg, A.T. Florence, Int. J. Pharm., 1994, 105, 1-6.
38. J,Y, Fang, S.Y. Yu, P.C. Wu, Y.B. Huang, Y.H. Tsai, Int. J. Pharm., 2001, 215, 91-99.
39. Walve JR, Rane BR, Gujrathi NA, Bakaliwal SR, Pawar SP. Proniosomes: a surrogate carrier for improved transdermal drug delivery system. Int J Res Ayurveda Res. 2011; 2:743-750.
40. Y. Hao, F. Zhao, N. Li, Y. Yang, K. Li, Int. J. Pharm., 2002, 244, 73-80.
41. T. Yoshioka, B. Sternberg, A.T. Florence, Int. J. Pharm., 1994, 105, 1-6.
42. J, Y, Fang, S.Y. Yu, P.C. Wu, Y.B. Huang, Y.H. Tsai, Int. J. Pharm., 2001, 215, 91-99.
43. I.F. Uchegbu, S, P, Vyas, Int. J. Pharm., 1998, 172, 33-70.
44. M. Mokhtar, O.A. Sammour, M.A. Hammad, N.A. Megrab, Int. J. Pharm., 2008, 361, 104-111.
45. Rogerson, J. Commings, A.T. Florence, J. Microcapsul., 1987, 4, 321-328.
46. A.F. Azarbayjani, E.H. Tan, Y.W. Chan, S.Y. Chan, Biol. Pharm. Bull., 2009, 32(8),1453-1458.
47. Sivaprasad SN, Kumar PL, Srinivas M, Brahmaiah B, Nama S. Proniosome: a novel approach to vesicular drug delivery system. Int J Drug Discov. 2013; 3:85-90.
48. Nasseri B. Effect of cholesterol and temperature on the elastic properties of niosomal membranes. Int J Pharm. 2005; 300:95-101.
49. Uchegbu IF, Vyas SP. Non-ionic surfactant-based vesicles (niosomes) in drug delivery. Int J Pharm. 1998; 172:33-70.
50. Morakul B, Junyaprasert VB. Proniosomes: an effective carrier for dermal and transdermal delivery. Songklanakarin J Sci Technol. 2020; 42:1171-1186.
51. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: a review on niosomal research in the last decade. J Drug Deliv Sci Technol. 2020;56: Part A:101581.
52. Sahoo RK, Biswas N, Guha A, Kuotsu K. Maltodextrin based proniosomes of nateglinide: bioavailability assessment. Int J Biol Macromol. 2014; 69:430-434.
53. Akhilesh D, Faishal G, Kamath JV. Comparative study of carriers used in proniosomes. Int J Pharm Chem Sci. 2012; 1:164-173.
54. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release., 1998; 54: 149–65.
55. Mishra A, Kapoor A, Bhargava S. Proniosoml gel as a carrier for improved transdermal drug delivery. Asian J Pharm Life Sci. 2011; 1:370–9. [Google Scholar]
56. Sankar V, Ruckmani K, Durga S, Jailani S. Proniosomes as drug carriers. Pak J Pharm Sci. 2010; 23:103–7.
57. Dufes C, Gaillard F, Uchegbu IF, Schatzlein AG, Olivier JC, Muller JM. Glucose-targeted niosomes delivervasoactive intestinal peptide (VIP) to the brain. Int J Pharm. 2004; 285: 77–85.
58. Akul Mehta, PharmaXChange_info-Articles –Niosomes.
59. Baillie AJ, Coombs GH and Dolan TF, Non-ionic surfactant vesicles, niosomes, as delivery system for the antileishmanial drug, sodium stribogluconate, J. Pharm. Pharmacol., 1986; 38:502-505
60. Baillie AJ, Coombs GH and Dolan TF, Non-ionic surfactant vesicles, niosomes, as delivery system for the antileishmanial drug, sodium stibogluconate. Pharm. Pharmacol., 1986; 38:502-505.
61. Ruckmani K, Sankar V, Sivakumar M. (2010). Tissue distribution, pharmacokinetics and stability studies of zidovudine delivered by niosomes and proniosomes. J Biomed Nanotechnol 6:43–51.
62. Mishra A, Kapoor A, Bhargava S. Proniosoml gel as a carrier for improved transdermal drug delivery. Asian J Pharm Life Sci 2011; 1:370-9.
63. Kakkar R, Rao R, Kumar DN. Formulation and characterisation of valsartan proniosomes. Maejo Int J Sci Technol 2011; 5:146-58.
64. Kapil S, Rao R, Saini V. Preparation and evaluation of lornoxicamniosomal gel. Int Res J Pharm 2012; 3:378-83.
65. Sharma, Y., Mittal, A., Pandey, P., Kumar, N., & Bhati, T. (2024). Formulation and evaluation of proniosomal gel of neomycin sulphate. HIMT College of Pharmacy Journal, Greater Noida, U.P.
66. Khatoon, Maryam & Shah, Kifayat Ullah & Khan, Fakhar & Shah, Shefaat Ullah & Rehman, Asim.ur & Dilawar, Naz & Khan, Ahmad. (2017). Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug Delivery. 24. 10.1080/10717544.2017.1384520.