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Review Article

ENHANCING TRANSDERMAL DELIVERY OF POORLY WATER-SOLUBLE NSAIDS: EFFECTIVE STRATEGIES

PRACHI SHARMA[1,2*], ASHISH AGGARWAL[1], SHUBHAM TANDON[2]

[1]Faculty of Pharmacy Mandsaur University, Mandsaur, India. [2]St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT (R. E. C.), Jalandhar-Amritsar bypass NH-1 jalandhar-144011, Punjab, India

*Corresponding author: Prachi Sharma; *Email: prachi26sharma85@gmail.com

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ABSTRACT

Transdermal drug delivery offers significant advantages for administering non-steroidal anti-inflammatory drugs (NSAIDs) and anti-complementary drugs, particularly those with poor water solubility. This delivery route bypasses first-pass metabolism and gastrointestinal degradation, enhancing bioavailability and patient compliance. However, the stratum corneum, the outermost layer of the skin, poses a formidable barrier to drug permeation. To address this challenge, several innovative strategies have been developed to improve the transdermal delivery of these poorly soluble drugs.

Chemical enhancers, such as alcohols, fatty acids, and surfactants, can disrupt the lipid structure of the stratum corneum, increasing drug solubility and permeability. Nanoformulations, including liposomes, niosomes, solid lipid nanoparticles, and nanoemulsions, enhance drug solubility, provide protection against degradation, and facilitate controlled release with deeper skin penetration. Prodrugs, designed to convert into the active drug within the skin, can improve solubility and permeability. Physical methods like microneedles, iontophoresis, and phonophoresis create micropores or use electrical and ultrasound waves to enhance permeation without compromising skin integrity.

Cyclodextrins form inclusion complexes with drugs, boosting solubility and stability. Hydrogels and polymer-based formulations create a moist environment for sustained drug release and better absorption. Co-solvents and surfactants, such as ethanol and DMSO, further enhance solubility and disrupt the stratum corneum to facilitate drug penetration. Electroporation and thermal ablation transiently disrupt the skin barrier, significantly improving drug permeation.

These strategies, individually or in combination, hold promise for optimizing the transdermal delivery of poorly water-soluble NSAIDs and anticomplementary drugs, ensuring effective therapeutic outcomes and improved patient compliance.

Keywords: Transdermal drug delivery, NSAIDs, Anticomplementary drugs, Poorly water-soluble drugs, Chemical enhancers

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INTRODUCTION

The goal of every pharmaceutical researcher and industry is to develop a safe and efficient drug delivery system. Transdermal patches facilitate the controlled release of active ingredients through the skin into systemic circulation. Controlled-release drug forms, such as microcapsules, nanoparticles, liposomes, chitosan, vancomycin microspheres, and encapsulated biopolymers, are increasingly important in therapy. They offer significant advantages by releasing active substances slowly over an extended period with a single administration, enhancing patient convenience [1]. The transdermal route of drug delivery offers both local and systemic therapeutic effects, making it an appealing alternative to oral administration [2]. Oral treatment requires regular dosing to maintain therapeutic drug levels, causing fluctuations that can lead to side effects or therapeutic failure, with significant drug loss and the need for close monitoring to prevent overdose. Transdermal delivery overcomes these issues by bypassing hepatic first-pass elimination maintaining steady, therapeutic drug levels without the risks of intravenous infusion [3]. Transdermal drug delivery systems utilize the skin to administer drugs, which are absorbed into the bloodstream and circulate throughout the body. This method works for both hydrophilic and hydrophobic drugs. The benefits of transdermal delivery have driven pharmaceutical research to focus on enhancing drug permeation by modifying or breaching the stratum corneum [4].

Inflammation is the body's response to harmful stimuli, infection, or trauma, characterized by redness, swelling, pain, heat, and loss of function. This process is regulated by various chemical mediators such as kinins, eicosanoids, complement proteins, histamine, and monokines. NSAIDs are widely used for conditions like osteoarthritis, soft-tissue injuries, and fractures and are effective for postoperative pain [5].

NSAIDs are used to manage both acute and chronic pain and come in various forms, including non-steroidal anti-inflammatory drug (NSAID) patches, opioid patches, local anesthetic patches, capsaicin patches, and nitroglycerine patches. These are commonly utilized in pediatric practice. NSAID patches are widely used for treating both chronic and acute musculoskeletal conditions due to their local action, avoiding central adverse effects and cognitive defects. Common NSAID patches include ketoprofen, diclofenac, flurbiprofen, and piroxicam. Topical NSAIDs aim to minimize systemic adverse effects and improve compliance [6].

This reviews highlight the broad therapeutic applications of TDDS, such as in pain management and hormone replacement therapy, and help identify potential new applications (Guy and Hadgraft, 2003). Scientific and technical challenges, such as the skin's barrier properties and drug formulation issues, are also addressed in reviews, helping to overcome limitations and improve system effectiveness [7]. Lastly, a comprehensive review integrates knowledge from various fields, fostering interdisciplinary collaboration and providing a holistic view that can inspire new ideas and innovations [8].

NSAIDS patches in pain management

A systematic review of topical NSAIDs for acute musculoskeletal conditions involving 3,455 subjects found that these preparations provide effective pain relief without the systemic adverse events associated with oral NSAIDs. The 1% diclofenac

epolamine patch, commonly used for acute pain in epicondylitis and ankle sprains, shows a reduction in pain scores within 3 h, with minimal systemic side effects due to low systemic transfer. Ketoprofen patches and gels, besides inhibiting COX, stabilize lysosomal membranes and antagonize bradykinin. They are well-tolerated, with side effects limited to the skin. Piroxicam patches offer good analgesic and antipyretic effects for conditions like rheumatoid arthritis, osteoarthritis, and post-operative pain thanks to their high solubility and permeation-enhancing properties [6].

Preference of patches over oral pain management

Oral pain medications are commonly prescribed, but they come with significant concerns, including serious side effects and the risk of abuse and addiction (table 1). Patients often take multiple pills daily for different types of pain, which can be overwhelming and lead to non-compliance. Commonly prescribed oral medications include NSAIDs, acetaminophen, narcotics, muscle relaxants, tricyclic antidepressants, and anticonvulsants like gabapentin. Despite their effectiveness, long-term use presents challenges for both prescribers and patients [9].

Table 1: Typical side effects of oral pain medications

S. No.	Oral pain medication	Common side effects
1.	NSAIDS	GI toxicity and complications such as bleeding, perforation, and ulcers; nephrotoxicity, cardiovascular disease, and cartilage degeneration
2.	Acetaminophen	Toxic ingestion: renal insufficiency and acute liver
3.	Narcotics (Opioids)	CNS effects such as sedation and decreased
4.	Muscle relaxants	CNS effects such as dizziness and drowsiness
5.	Tricyclic antidepressants	CNS effects such as constipation, dry mouth, and tachycardia

Barriers

The skin, the body's largest organ, offers a painless way to deliver drugs but has evolved to block toxins and minimize water loss, making it poorly permeable to foreign molecules. The stratum corneum, the top 15 µm layer, is key to this barrier, consisting of lipid-rich matrices and corneocytes (0.2–0.4 µm thick, 40 µm wide) held together by corneodesmosomes. These lipids, mainly ceramides, cholesterol, and fatty acids, form protective multi-lamellar bilayers. The stratum corneum, which renews every two to four weeks, is repaired by cellular secretion of lamellar bodies when its barrier is disrupted [10].

Drug penetration pathway

Drug penetration into the skin occurs through three main pathways: transcellular, paracellular lipid, and transappendageal routes.

- **Transcellular route:** The drug molecules pass through both keratinocytes and lipids in a direct path to the dermis.
- **Paracellular route:** This is the most common pathway, where drugs remain within lipid moieties and linger around keratin. It's easier for lipid-soluble drugs to penetrate through this route compared to proteins.
- **Transappendageal route:** This pathway involves the creation of continuous channels for drug permeation, but it's easily hindered by the presence of hair follicles and sweat ducts [11].

Strategies for enhancing permeation

Transdermal delivery often faces challenges in permeating the active moiety through the skin. Various strategies have been studied to enhance this permeability. These strategies work through three main mechanisms:

1. Altering the physicochemical properties of the stratum corneum.

2. Changing the hydrating properties of the stratum corneum.

3. Modifying the structure of lipids and proteins in the intercellular channels via carrier mechanisms.

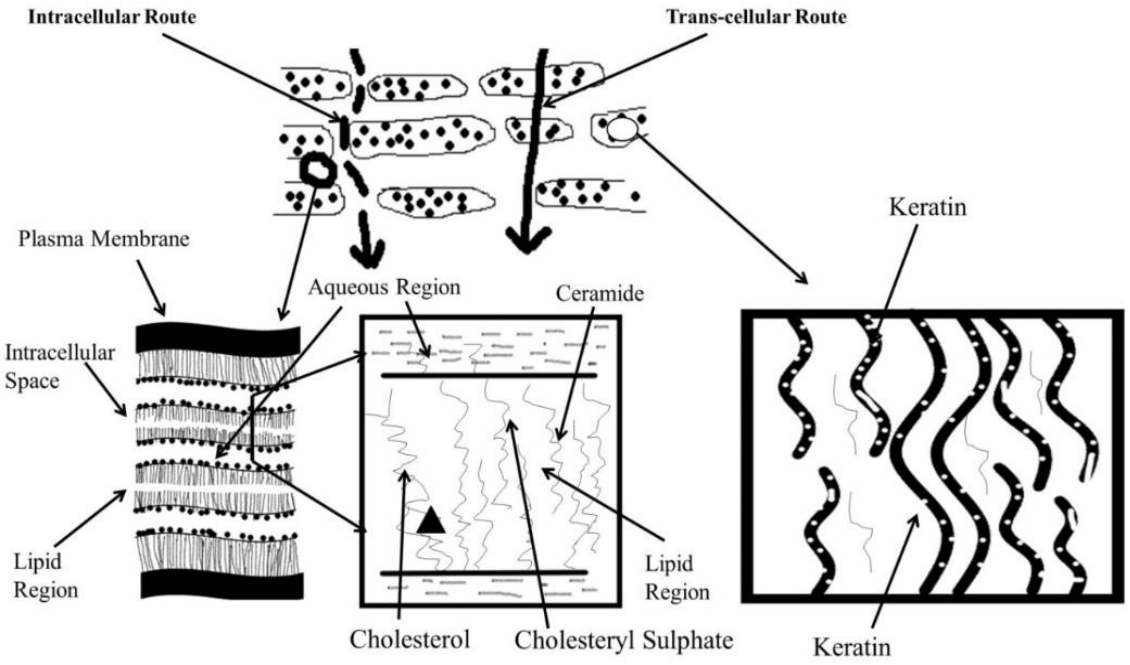

Fig. 1: A diagrammatic representation of the stratum corneum illustrates the intercellular and transcellular routes of penetration for drugs [12]

Drug/vehicle interaction and selection

The active ingredient should be carefully selected based on pharmacological or physicochemical properties. Ideal properties for drug selection include:

-Molecular weight less than 600 Da for high diffusion coefficient.
-Good solubility in both oil and water.
-Adequate partition coefficient (1–3).
-Melting point below 200 °F.
-Stability, ensuring it does not metabolize in the skin.

While charged molecules typically cannot permeate the skin, the lipophilic ion pair technique can enhance epidermal penetration of such molecules.

Eutectic mixtures

Lowering the melting point of a substance enhances its solubility in skin lipids, thereby improving skin permeation. Eutectic mixtures, composed of two components at a specific ratio, inhibit the crystalline phase, resulting in a lower melting point than the individual components. Examples include ibuprofen with terpenes and menthol with methyl nicotine. These mixtures are particularly useful for topical NSAIDs like meloxicam, which lacks a market-available topical form. A formulation with thymol as a penetration enhancer showed a significant permeation rate in studies.

Horny layer modification

Hydration is key for enhancing the permeation of both hydrophilic and hydrophobic drugs. The stratum corneum typically contains 10-20% water. Hydrating the epidermis causes keratin swelling, disrupts lipid packing, and alters both polar and non-polar routes, thus improving permeability.

Chemical enhancers

Chemical enhancers improve skin permeation by disrupting the stratum corneum's lipid structure, interacting with intercellular proteins, or enhancing drug partitioning into the stratum corneum. Ideal enhancers are non-toxic, non-allergenic, fast-acting, predictable in duration, unidirectional, and compatible with both excipients and drugs [12].

Novel chemical enhancers

Ceramide analogs

The stratum corneum (SC) lipids comprise ceramides, cholesterol, fatty acids, and some cholesterol sulfate. Ceramides are crucial for the SC's barrier function, being amphiphilic molecules with two long hydrocarbon tails and a polar acylamide head. Vávrová *et al.* hypothesized that enhancers with structural similarities to ceramides could integrate into the ceramide bilayers, disrupting the lipid barrier. They synthesized ceramide analogs with polar heads based on L-serine and glycine, investigating the relationship between these polar head properties and their enhancement activity [13].

Azone analogs

Azone (1-dodecylazacycloheptan-2-one or laurocapram) is the first molecule specifically designed as a skin permeation enhancer. It enhances the transdermal absorption of various drugs, likely by interacting with the lipid domains of the stratum corneum (SC). Azone's 'soup spoon' structure allows it to partition into bilayer lipids, where it disrupts the organized lipid packing, either by dispersing within the lipids or forming separate domains. Despite its effectiveness, Azone is not FDA-approved due to minor side effects, but it is listed in the Chinese Pharmacopoeia and extensively used in China. To optimize its properties, researchers have synthesized hundreds of Azone analogs, providing valuable insights into molecular design for enhanced skin permeation [13].

Menthol derivatives

Terpenes, especially menthol, are widely studied as transdermal permeation enhancers. Menthol is known to disrupt the lipid organization in the stratum corneum (SC), enhancing permeation. Despite its efficacy and low skin irritation, menthol's use is limited by its strong odor and high volatility. To address these issues, numerous menthol derivatives have been synthesized, aiming to find candidates with improved properties suitable for transdermal drug delivery systems (TDDS) [13].

Enhancing nanoformulation penetration: exploring penetration enhancers

This comprehensive review delves into the exploration of penetration enhancers in nanoformulations for topical drug delivery. Spanning literature from 1990 to May 2020, the study analyzed data from PubMed, Scopus, Google Scholar, and Web of Science databases. Key search terms included "skin permeation," "nanoparticles," and various nanoparticle types such as nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and polymeric nanoparticles.

Nanoparticles offer distinct advantages in topical drug delivery, including enhanced drug deposition, improved stability, and controlled release. Lipid-based nanoparticles like nanoemulsions, SLNs, NLCs, liposomes, and niosomes are favored due to their versatility across administration routes and their ability to boost skin permeation through surfactant-mediated enhancement.

Solid Lipid Nanoparticles (SLNs) represent the first generation of lipid-based nanocarriers, offering biocompatibility and low toxicity. SLNs act as adhesive and occlusive topical drug delivery systems, forming a uniform layer on the stratum corneum and enhancing drug penetration.

Nanostructured Lipid Carriers (NLCs), the second generation of lipid nanoparticles, blend solid and liquid lipids to enhance drug protection, controlled release, and bioavailability. NLCs exhibit occlusive properties and small particle size, facilitating adhesion to the stratum corneum and increasing drug penetration depth.

Liposomes, composed of lipid bilayers enclosing an aqueous core, enable controlled drug release and localized deposition in skin layers. Liposomes target hair follicles and facilitate transdermal drug delivery, with smaller vesicles showing superior penetration.

Polymeric nanoparticles, with diameters below 1000 nm, serve as effective topical nanocarriers by masking the physicochemical properties of drugs. They utilize natural and synthetic polymers like chitosan for biocompatibility and low toxicity, enhancing drug penetration and minimizing further skin penetration, particularly in sunscreen delivery.

Natural-based nanoparticles harness the benefits of ingredients like Illip butter and Calendula oil for skin hydration, anti-inflammatory, and healing effects. These nanoparticles encapsulate pharmaceuticals for targeted skin delivery, providing enhanced therapeutic outcomes [14].

Advancing transdermal delivery through physical techniques

To enhance transdermal drug delivery, various physical techniques surpass the limitations of chemical penetrators. Novel formulations like nanoparticles, liposomes, and transferosomes offer improved absorption without side effects. Advanced technologies such as microneedles, sonophoresis, iontophoresis, electroporation, and lasers directly alter skin structure, enhancing absorption safely and effectively. These methods ensure high bioavailability, making them preferable for promoting drug absorption through the skin [15].

Role of some important penetration enhancers to improve transdermal permeation of drugs

The essential role of hydrogels in transdermal drug delivery systems

Wound healing

A wound is any disruption or break in the skin caused by medical conditions, physiological disorders, or trauma. Healing is considered complete when the tissue returns to its normal appearance, structure, and function within a reasonable time. Wounds are categorized by skin layer involvement: superficial wounds affect only the epidermis, partial thickness wounds affect the epidermis and deeper dermis layers, and full-thickness wounds involve deeper tissues and subcutaneous layers [16].

Table 2: Leading developers and commercializes of skin permeability technologies

Technologies	Company	Product	Mechanism
Low-frequency sonophoresis/Sensing	Echo Therapeutics, Inc.	Symphony Continuous Glucose Monitor	Glucose monitoring by interstitial fluid after skin permeability
	Becton Dickinson/Sanofi Pasteur	Intanza	Prefillable injection system utilizing the microneedle for delivery of vaccine against seasonal influenza
Microneedles	Corium International, Inc.	MicroCor	Dissolvable microneedle device
	NanoPass Technologies, Ltd.	MicronJet	Hollow microneedle device
	Seventh Sense Biosystems, Inc.	TAP 20 °C	Microneedle penetration of the skin followed by application of vacuum for blood extraction
	TheraJect	TheraJect Patch	Dissolvable microneedle
	Valeritas, Inc.	Micro-Trans	Microneedle device
	Vaxxas, Inc.	The Nanopatch	Vaccine-coated microneedle device
Electrical techniques	ZosanoPharma	ZP Patch	Drug-coated microneedle patch
	Ichor Medical Systems	TriGrid Delivery System	Electroporation platform for vaccination
	Inovio Pharmaceuticals, Inc.	Cellectra	Electroporation platform for vaccination
	NuPathe, Inc.	Zecuit	Iontophoresis-facilitated delivery of sumatriptan for acute treatment of migraines
	OncoSec Medical, Inc.	OncoSec Medical System	Electroporation platform for vaccination
	NB Therapeutics	Iontophoresis Platform	Iontophoresis-facilitated delivery of terbinafine HCl for the treatment of toenail fungus

Table 3: Assessing various physical technologies for drug delivery

Physical energy poration	Electric field electroporation	Magnetic field MNP	Temperature thermoporation	Ultrasound sonoporation	Light optoporation
Limitations	Narrow range of clinically safe electric field parameters (refer to current standards for safety levels)	Limited drug carrying capacity of magnetic field due to their biodistribution Narrow range of magnetic field	Low penetration depth (since only applied topically so far)	Sonoporation devices have poor calibration in terms of the amount of ultrasound energy emitted	Limited time duration between optoporation and drug delivery
Disadvantages	Irreversible electroporation, cell death with high fields	Aggregation of MNP can cause embolization	Excess heat can induce thermohemolysis	Shear forces may induce rupture of cells	Excessive inflammation, postinflammatory, and hyperpigmentation
Advantages	Inexpensive and simple-to-perform Drugs are easy to overcome the cell membrane barrier	Electromechanical coupling effect	Cytotoxicity increases with the increased concentrations of MNP Noninvasive nature of the magnetic field.	Relies on electric field to heat up the filaments; therefore, the disadvantages of electric field applies Noninvasive nature of low heat compared to EP	Less invasive compared to EP Instant impermeabilization after ultrasound exposure

Hydrogel-based patches

They have gained prominence due to their unique properties. Synthesized from hydrophilic polymers, hydrogels can hold 10-20% up to 1000 times their dry weight in water, enhancing skin elasticity and moisturization. Made from natural or synthetic polymers, these patches effectively hydrate the stratum corneum, facilitating enhanced drug delivery. Their adhesive nature aids in removing dead skin upon peeling. Hydrogels provide excellent mechanical properties for transdermal drug delivery systems (TDDS) and can be designed for sustained drug release. Additionally, hydrogel patches offer a cooling effect at the application site, making them ideal for topical use [16].

The role of cyclodextrins in transdermal drug delivery systems (TDDS)

Cyclodextrin complexes enhance drug permeation in transdermal drug delivery systems (TDDS). For example, a piroxicam-β-cyclodextrin complex increased drug flux threefold across mouse skin. These complexes, formed with enhancers like quaternary ammonium salts, raise their critical micellar concentration, reducing toxicity. Transdermal absorption of alprostadil (AP) from β-cyclodextrin and O-carboxymethyl-O-ethyl-β-cyclodextrin (CME-β-CD) complexes was studied using HPE-101 as a permeation enhancer. The combination of CME-β-CD and HPE-101 significantly improved drug bioavailability, with the latter complex achieving ten times higher flux [17].

Table 4: Role of cyclodextrin complexes in drug penetration [18]

Improvement	Drug
Enhanced solubility of drugs	Miconazole
Enhanced stability of drugs	Miconazole
Enhanced permeation of drugs through Stratum corneum	Dihydroepiandrosterone, Oxybenzone Gliquidone, Levosimendan Dexamethasone, Hydrocortisone 5-Fluorouracil, Insulin Ethyl 4-biphenylyl acetate
Sustained release of drugs through the vehicle	Piroxicam
Reduced side effects	Ketoprofen

The role of solvents and co-solvents in transdermal drug delivery systems (TDDS)

Solvents like water, alcohols, methanol, and ethanol enhance penetration by swelling the polar pathway and fluidizing lipids. Miscellaneous chemicals, such as urea and N, N-dimethyl-m-toluamide, act as hydrating and keratolytic agents. Alkanes, alcohols, glycerides, and glycols, including ethanol and propylene glycol, serve as effective transdermal penetration enhancers. Azone, a lipophilic material, disrupts lipid packing to improve drug transport. Fatty acids and esters, such as oleic acid, enhance percutaneous absorption. Pyrrolidones, sulphoxides like DMSO, and surfactants also increase permeability. Terpenes and essential oils, such as L-menthol and eucalyptus oil, significantly boost skin absorption by forming eutectic mixtures.

CONCLUSION

Transdermal drug delivery systems present a compelling alternative for the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and anticomplementary drugs, particularly those with poor water solubility. This delivery route bypasses the limitations of oral administration, such as first-pass metabolism and gastrointestinal degradation, thereby enhancing bioavailability and patient compliance. However, the stratum corneum remains a significant barrier to drug permeation, necessitating innovative strategies to enhance transdermal drug delivery.

Chemical enhancers, such as alcohols, fatty acids, and surfactants, disrupt the lipid structure of the stratum corneum, increasing both drug solubility and permeability. Nanoformulations, including liposomes, niosomes, solid lipid nanoparticles, and nanoemulsions, not only enhance drug solubility but also provide protection against degradation and facilitate controlled release with deeper skin penetration. Prodrugs, designed to be converted into active drug within the skin, further improve solubility and permeability, optimizing therapeutic outcomes.

Physical methods, such as microneedles, iontophoresis, and phonophoresis, create micropores or utilize electrical and ultrasound waves to enhance drug permeation without compromising skin integrity. Cyclodextrins form inclusion complexes with drugs, boosting their solubility and stability. Hydrogels and polymer-based formulations create a moist environment conducive to sustained drug release and improved absorption. Co-solvents and surfactants, like ethanol and DMSO, further enhance solubility and disrupt the stratum corneum, facilitating drug penetration. Additionally, techniques such as electroporation and thermal ablation transiently disrupt the skin barrier, significantly improving drug permeation.

Individually or in combination, these strategies offer promising solutions for optimizing the transdermal delivery of poorly water-soluble NSAIDs and anticomplementary drugs. By overcoming the formidable barrier of the stratum corneum, these methods ensure effective therapeutic outcomes and improved patient compliance, heralding a new era in transdermal drug delivery technology.

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All authors have contributed equally

CONFLICT OF INTERESTS

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REFERENCES

1. Dumitriu Buzia O, Paduraru AM, Stefan CS, Dinu M, Cocoş DI, Nwabudike LC. Strategies for improving transdermal administration: new approaches to controlled drug release. Pharmaceutics. 2023 Apr 7;15(4):1183. doi: 10.3390/pharmaceutics15041183, PMID 37111667, PMCID PMC10143057.
2. Al Hanbali OA, Khan HM, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: design and current approaches to painless drug delivery. Acta Pharm. 2019;69(2):197-215. doi: 10.2478/acph-2019-0016, PMID 31259729.
3. Rastogi V, Yadav P. Transdermal drug delivery system: an overview. Asian J Pharm. 2012;6(3):161-70. doi: 10.4103/0973-8398.104828.
4. Ramadon D, McCrudden MT, Courtenay AJ, Donnelly RF. Enhancement strategies for transdermal drug delivery systems: current trends and applications. Drug Deliv Transl Res. 2022;12(4):758-91. doi: 10.1007/s13346-021-00909-6, PMID 33474709.
5. Vikrant A, Arya ML. A review on anti-inflammatory plant barks. Int J Pharm Tech Res. 2011;3(2):899-908.
6. Mathews LM. Management of pain using transdermal patches. Asian J Pharm Clin Res. 2016:9(6):32-5. doi: 10.22159/ajpcr.2016.v9i6.13775.
7. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. doi: 10.1038/nbt.1504, PMID 18997767.
8. Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Adv Drug Deliv Rev. 2004;56(5):619-58. doi: 10.1016/j.addr.2003.10.026, PMID 15019750.
9. Branvold A. Pain management therapy: the benefits of compounded transdermal pain medication. J Gen Pract. 2014;02(6):1000188. doi: 10.4172/2329-9126.1000188.
10. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004;3(2):115-24. doi: 10.1038/nrd1304, PMID 15040576.
11. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug Deliv. 2016;23(2):564-78. doi: 10.3109/10717544.2014.935532, PMID 25006687.
12. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005;2(1):23-33. doi: 10.2174/1567201052772915, PMID 16305405.
13. Chen Y, Quan P, Liu X, Wang M, Fang L. Novel chemical permeation enhancers for transdermal drug delivery. Asian J Pharm Sci. 2014;9(2):51-64. doi: 10.1016/j.ajps.2014.01.001.
14. Ghasemiyeh P, Mohammadi Samani S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: advantages and disadvantages. Drug Des Devel Ther. 2020;14:3271-89. doi: 10.2147/DDDT.S264648, PMID 32848366.
15. Gao Y, DU L, LI Q, LI Q, Zhu L, Yang M. How physical techniques improve the transdermal permeation of therapeutics: a review. Medicine (Baltimore). 2022;101(26):e29314. doi: 10.1097/MD.0000000000029314, PMID 35777055.
16. Ahsan A, Tian WX, Farooq MA, Khan DH. An overview of hydrogels and their role in transdermal drug delivery. Int J Polym Mater Polym Biomater. 2021;70(8):574-84. doi: 10.1080/00914037.2020.1740989.
17. Gupta MM, Singh S, Jindal R, Patidar S. Role in transdermal drug delivery system skin : a barrier permeation for. International Journal of Comprehensive Pharmacy Penetration Enhancers. 2012;03(9):1-8.
18. Cyclodextrins in delivery systems: applications scientific fig. On ResearchGate. Available from: https://www.researchgate.net/figure/cyclodextrins-in-transdermal-drug-delivery-system_tbl4_51545265. [Last accessed on 06 Jun 2024].